CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215192Orig1s000

INTEGRATED REVIEW

CLINICAL REVIEW

Application Type	NDA resubmission
Application Number(s)	NDA 215192
Priority or Standard	Priority
Submit Date(s)	09/27/2023
Received Date(s)	09/27/2023
PDUFA Goal Date	03/27/2024
Division/Office	DNH/OCHEN
Reviewer Name(s)	Andrew Dmytrijuk (Primary Clinical Reviewer) Carrie Diamond (Clinical Team Lead)
Review Completion Date	Electronic Stamp
Established/Proper Name	Vadadustat
(Proposed) Trade Name	VAFSEO
Applicant	Akebia Therapeutics
Dosage Form(s)	Tablets: 150 mg, 300 mg and 450 mg
Applicant Proposed Dosing Regimen(s)	The recommended starting dose is 300 mg QD
Applicant Proposed Indication(s)/Population(s)	The treatment of anemia associated with chronic kidney disease in adults on dialysis. Limitations of Use Not indicated for use: • As a substitute for transfusion in patients requiring immediate correction of anemia. • For use in patients with anemia associated with CKD not on dialysis.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	VAFSEO is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least three months. Limitations of Use VAFSEO has not been shown to improve quality of life, fatigue, or patient well-being. Not indicated for use: • As a substitute for transfusion in patients requiring immediate correction of anemia. • For use in patients with anemia associated with CKD not on dialysis.

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Glossary

AC	advisory committee
ACS	acute coronary syndrome
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BMI	body mass index
CABG	coronary artery bypass graft
CDER	Center for Drug Evaluation and Research
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CRF	case report form
CRL	complete response letter
CRT	clinical review template
CSR	clinical study report
DD	dialysis dependent
DHN	Division of Hepatology and Nutrition Drugs
DILI	drug-induced liver injury
DMEP	Division of Metabolism and Endocrinology Products
DNH	Division of Nonmalignant Hematology
DV	Device
EPPV	Early Post-marketing Phase Vigilance
ESA	erythropoietin stimulating agent
EU	European Union
FDA	Food and Drug Administration
FDRR	formal dispute resolution request
FMQ	FDA Medical Query
GI	gastrointestinal
Hb	hemoglobin
HD	hemodialysis
HF	heart failure
HIF-PH	hypoxia inducible factor-prolyl hydroxylase
HR	hazard ratio
IR	Information Request
IRD	incidence rate difference
ISS	integrated summary of safety

J-RMP	Japan-Risk Management Plan
LOU	limitation of use
MACE	major adverse cardiovascular events
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MF	malfunction stenosis
MI	myocardial infarction
Min	minimum
MTPC	Mitsubishi Tanabe Pharma Corporation
N	number
NDA	new drug application
ND	non-dialysis dependent
OCC	occlusion
OCHEN	Office of Cardiology, Hematology, Endocrinology and Nephrology
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PICC	peripherally inserted central catheter
PI	package insert
PMC	postmarketing commitment
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	postmarketing requirement
PMS	post-marketing surveillance
PSUR	Periodic Safety Update Report
PT	preferred term
QD	once daily
RBC	red blood cell
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	standard deviation
SH	shunt
SOC	system organ class
ST	shunt thrombosis
TA	transaminase
TB	total bilirubin
TE	thromboembolism
TEAE	treatment emergent adverse event
TIW	three times weekly
ULN	upper limit of normal
US	United States
VAT	vascular access thrombosis

1. Executive Summary

1.1. Summary of Regulatory Action

Akebia Therapeutics originally submitted their New Drug Application (NDA) for marketing approval of vadadustat for the treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis and not on dialysis on March 29, 2021. Vadadustat is an oral inhibitor of hypoxia inducible factor-prolyl hydroxylase (HIF-PH). During the initial review cycle of the application, we concluded that the data did not support a favorable benefit-risk assessment of vadadustat for the proposed indications. The Applicant received a Complete Response Letter (CRL) on March 29, 2022. The reasons for the CRL are summarized below in Section 2, Regulatory History, of this review. The Applicant submitted a formal dispute resolution request (FDRR) on October 24, 2022 in response to the CRL. The Applicant, stated in the appeal, that they are now only seeking an indication in the dialysis dependent (DD)-CKD population. On May 26, 2023, the Agency issued a Formal Dispute Resolution Appeal Denied letter, however a path forward was provided as described in Section 2, Regulatory History.

On September 27, 2023, the Applicant submitted a response to the CRL, addressing the deficiencies listed in the CRL that were applicable to the DD-CKD population and modified the indication statement to the treatment of anemia associated with chronic kidney disease in adults on dialysis only. This resubmission review focuses only on the review of the deficiencies identified in the CRL for the DD-CKD population, updated safety information, labeling and postmarketing requirements.

The Applicant established substantial evidence of effectiveness for the proposed indication with two adequate and well-controlled trials, Study AKB-6548-CI-0016 (INNO2VATE 1) and Study AKB-6548-CI-0017 (INNO2VATE 2) that demonstrated non-inferiority of vadadustat to darbepoetin alfa (an approved erythropoietin stimulating agent (ESA)), based on hemoglobin (Hb) response in the DD-CKD populations.

Similar to the other approved HIF-PH inhibitor and to ESAs, vadadustat has a risk of death, myocardial infarction (MI), stroke, venous thromboembolism (TE) and thrombosis of vascular access. Vadadustat also has a risk of gastrointestinal erosion (which is also labeled for the other approved HIF-PH inhibitor) and an additional risk of hepatoxicity, both of which are addressed in labeling.

This application resubmission was reviewed by a multidisciplinary review team. The Applicant has adequately addressed all deficiencies in the CRL for the indication of anemia of DD-CKD. All other safety and efficacy review issues were resolved in the original review of the application, see finalized review in DARRTS on March 29, 2022. Each discipline recommends approval, and the signatory authority concurs that the application should be approved. The overall benefit-risk profile is favorable as described in the Benefit-Risk Framework below.

1.2. Benefit-Risk Assessment

1.2.1. Benefit-Risk Framework

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic kidney disease (CKD) is a progressive condition that results in decreased kidney function due to irreversible kidney damage. • The prevalence of CKD in the U.S. adult population is ~15%, with an estimated 17.2 million having advanced CKD. • Patients with CKD may be on dialysis or not on dialysis, and those with advanced CKD are commonly awaiting kidney transplant as a definitive therapy for their disease. • Anemia is a common, early and progressive complication of CKD, affecting ~90% of patients with advanced CKD, regardless of dialysis status. • Anemia in CKD is caused by decreases in production of erythropoietin (EPO) due to progressive loss of EPO-producing cells in the diseased kidney, iron deficiency from inadequate intake or absorption, and chronic inflammation. • CKD is associated with increased risk of cardiovascular disease, morbidity due to symptomatic anemia, and mortality due to cardiac disease, stroke, and renal-associated causes.	CKD is a prevalent and serious disease with significant morbidity and mortality. It is associated with increased risk of cardiovascular disease, anemia and anemia-related signs and symptoms. Untreated anemia of CKD may lead to a variety of signs and symptoms, including fatigue, dyspnea, tachycardia, myocardial ischemia and decreases in cognitive function and mental acuity, resulting in significant morbidity and mortality.
Current Treatment Options	• Red blood cell (RBC) transfusions are used mainly for acute and life-threating anemia, and are associated with risk of transmission of infection, alloimmunization, iron overload, and allergic reactions. • Several erythropoiesis stimulating agents (ESAs) – Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta (epoetin beta)) and Retacrit (epoetin alfa-epbx) – are injectable therapies approved for the treatment of anemia in patients with CKD, on dialysis and not on	ESAs are considered the current standard therapy for the treatment of anemia in patients with CKD, while RBC transfusions are mainly considered in acute scenarios. An oral HIF-PH inhibitor was recently approved for anemia in patients with DD-CKD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dialysis. ○ All ESA labels contain a boxed warning for increased risk of cardiovascular mortality and morbidity associated with targeting a higher hemoglobin (Hb) value, compared to a lower Hb value. There is no identified trial-based Hb target value, ESA dose, or dosing strategy that does not increase these risks. ○ The general dosing recommendations for ESAs is to use the lowest dose sufficient to reduce the need for RBC transfusions, while targeting a Hb value less than 11 g/dL. • Jesduvroq (daprodustat), is an oral HIF-PH inhibitor, approved in 2023 for the treatment of anemia due to CKD in adults who have been receiving dialysis for at least four months. ○ Similar to ESAs, daprodustat has a boxed warning for increased mortality, myocardial infarction, stroke, and thromboembolism. ○ Daprodustat also has a risk of hospitalization for heart failure (particularly in those with a history of heart failure) and of gastrointestinal erosions.	ESAs (and presumably HIF-PH inhibitors) are associated with cardiovascular mortality and morbidity when higher Hb values (>11 g/dL) are targeted, compared to lower Hb values. RBC transfusions are associated with foreign antigen exposure that may result in alloimmunization, thus RBC transfusions may impact a patient's eligibility for a kidney transplant. Currently there is only one oral therapy option for patients with DD-CKD. Additional safe and effective orally available therapies will add to the armamentarium for patients with anemia of CKD. These therapies will allow patients to avoid the need for transfusion and its potential impact on transplant eligibility and allow for a more convenient route of administration that avoids ESA injections.
Benefit	• Hematologic response and reduction in RBC transfusions have been used to establish efficacy for traditional approval for drugs intended to treat anemia of CKD. • Two adequately designed and powered, phase 3, randomized, active-controlled, open-label, clinical trials were conducted in patients with DD-CKD. • These trials showed that that vadadustat was non-inferior to darbepoetin alfa (an approved ESA) in raising and maintaining the Hb in patients with DD-	Based on Studies CI-0016 and CI-0017, the benefits of vadadustat in adults with DD-CKD include raising and maintaining Hb that is expected to improve or maintain improvement in the signs and symptoms of anemia as well as reduce the need for RBC transfusions, a procedure that carries risks for infection, transfusion related reactions, and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	CKD from baseline to the primary efficacy period (weeks 24 to 36) and from baseline to the secondary efficacy period (weeks 40 to 52). • There was a higher incidence of RBC transfusions with vadadustat compared to darbepoetin alfa (7.3% vs. 4.3% in Trial 0016; 7.5% vs. 6.3% in Trial 0017). The non-inferiority conclusion on Hb response remained robust to sensitivity analyses that treated Hb values as missing within four weeks after rescue therapy. The higher RBC transfusion incidence did not translate into an increase in the rate of renal transplant rejection.	alloimmunization and potentially graft rejection. The Applicant did not demonstrate any other benefits of vadadustat on how patients feel, function or survive. Vadadustat will provide the convenience of an oral option that some may prefer. Vadadustat should not be used in patients with anemia associated with CKD not on dialysis (see original review for unfavorable benefit/risk assessment in that population).
Risk and Risk Management	• Major adverse cardiac events (MACE) and thromboembolism (TE) were key safety endpoints, based on the safety profile of ESAs, given their similarities to the HIF-PH inhibitor drug-class in mechanism of action. • Vadadustat was non-inferior to darbepoetin alfa on the time to first occurrence of MACE in adults with anemia due to CKD who were on dialysis. • The analysis of the adjudicated data for TE events showed an increased risk of time to first TE that was more apparent in the U.S. DD-CKD population. The TE finding was driven by an imbalance in vascular access thrombosis, which accounted for more than 80% of the adjudicated TE events. However, additional analyses showed a similar total number of vascular access thromboses in the vadadustat and darbepoetin alfa groups and similar rates of access abandonment and revascularization procedures.	The safety database for vadadustat was adequate to evaluate safety of the proposed dosing regimen in the intended patient population. Because the trials demonstrated non-inferiority on MACE with respect to the ESA comparator, a similar boxed warning as used for ESAs will be included in the vadadustat labeling for the increased risk of death, myocardial infarction, and stroke. Vadadustat will also include a Boxed Warning for venous TE and thrombosis of vascular

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In the premarketing database, there was one probable Hy's Law case and several other cases of probable drug-induced liver injury (DILI) not meeting Hy's Law. We concluded that there is a hepatocellular injury risk with the use of vadadustat in patients with CKD. Studies CI-0036 and CI-0039, along with the post-marketing experience from Japan (where (b) (4) patients have been exposed to vadadustat), did not identify additional serious cases of DILI, such as DILI-related death, liver transplantation, or liver failure. • There were no treatment differences disfavoring vadadustat compared to ESA for other known risks of ESAs, including seizures, hypertension, and malignancy. • In the NDD-CKD population vadadustat was not non-inferior to darbepoetin on MACE. Other risks of vadadustat identified in the DD-CKD population were similar in the NDD-CKD population.	access like that of ESAs. It is possible that vadadustat may increase the risk of time-to-first vascular thrombosis compared to that of darbepoetin alfa, however, this finding is not seen in all analyses and there does not appear to be an apparent increase in the complications of vascular access thrombosis. The risk of time-to-first vascular access thrombosis with vadadustat compared to darbepoetin alfa will be included in labeling and this risk will be further assessed in a required postmarketing study. In patients with CKD, the use of vadadustat is associated with hepatocellular injury risk. The risk of serious liver injury appears rare and should be able to be closely monitored given the frequent monitoring of patients on dialysis. The risk mitigation strategy (monitoring liver tests at baseline and monthly for the first six months, discontinuing vadadustat if liver test abnormalities develop, and a recommendation to not use vadadustat in patients with cirrhosis or active, acute hepatitis) will be described in the Warnings and Precautions of the label and this risk will also be included in the Medication Guide. This risk will also be further assessed with enhanced pharmacovigilance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Additional risks described in the Warnings and Precautions section of the label include hypertension, seizures, and malignancy. These are adverse reactions associated with ESAs and also occurred in patients who were randomized to vadadustat, therefore, we were unable to conclude that vadadustat differs from ESAs with regard to these safety risks. Vadadustat will also include a Warning and Precaution for gastrointestinal erosions, which were also seen with the other approved HIF-PH inhibitor. This risk appears slightly increased with vadadustat compared to darbepoetin alfa, but serious gastrointestinal erosions were similar between treatment groups. Postmarketing requirements (PMRs) will be issued at the time of approval to assess the longer-term safety of vadadustat.

*A substantial portion of the text in the benefit-risk framework was taken directly from the original NDA review, see finalized review in DARRTS dated March 29, 2022.

1.2.2. Conclusions Regarding Benefit-Risk

Chronic kidney disease (CKD) is a progressive and irreversible condition that affects many U.S. adults. Patients with CKD may become dialysis-dependent, and those with advanced CKD are commonly awaiting kidney transplant as definitive therapy. Anemia is a common and chronic complication in CKD and is associated with significant morbidity and mortality.

The efficacy and safety of vadadustat, an oral HIF-PH inhibitor that increases endogenous production of erythropoietin, was evaluated in four randomized, open-label trials that used darbepoetin alfa (an approved ESA) as the active comparator. This benefit-risk assessment will focus on the DD-CKD trials as the Applicant is no longer seeking an indication in the non-dialysis dependent CKD (NDD-CKD) population due to an unfavorable benefit-risk assessment in that population. Specifically, vadadustat was not non-inferior to darbepoetin alfa on MACE in patients with NDD-CKD (refer to the original NDA review finalized in DARRTS on March 29, 2022 for further details). A limitation of use (LOU) for the NDD-CKD population will be included in the approved label, along with a warning listing serious adverse reactions (SARs) that occurred in the NDD-CKD population.

Vadadustat demonstrated noninferiority to darbepoetin alfa in raising and maintaining Hb, up to a treatment period of at least 52 weeks, in patients with anemia and DD-CKD. Vadadustat's effects on Hb are expected to improve or maintain improvement on signs and symptoms of anemia and reduce the need for RBC transfusions, a procedure that carries risks for infection, transfusion related reactions and alloimmunization.

Most of the risks of vadadustat are known risks for ESAs; therefore, in the context of similar effectiveness as the approved ESA, darbepoetin alfa, vadadustat has a favorable benefit-risk assessment with regard to these risks with labeling similar to that of the ESAs and also provides the convenience of an oral dosage form that some patients may prefer.

There are two risks of vadadustat that are not risks of ESAs – hepatotoxicity and gastrointestinal erosions – that need to be factored into vadadustat' s benefit-risk assessment.

In the premarketing application, we identified several cases of probable drug-induced liver injury (DILI), including one Hy's Law case. Therefore, we conclude that vadadustat has a risk for DILI. However, postmarketing surveillance of approximately (b) (4) patients treated following the approval of vadadustat in Japan did not identify serious DILI cases such as DILI fatalities, liver failure, or liver transplantation. We conclude that the risk of serious DILI appears to be low and that the routine close monitoring of patients on dialysis makes it feasible to regularly assess liver tests and discontinue vadadustat if liver test elevations occur. We will continue to assess the risk of liver toxicity postmarketing with enhanced pharmacovigilance.

Daprodustat, the other approved HIF-PH inhibitor has a risk of hospitalization for heart failure (particularly in patients with a history of heart failure) and of gastrointestinal erosions.

Vadadustat also appears to have a risk of gastrointestinal erosions, but there was not an apparent increase in risk of hospitalization for heart failure compared to darbepoetin alfa. The risk of gastrointestinal erosions with vadadustat can be mitigated with recommendations in labeling such as considering this risk in patients at increased risk for erosions and informing patients to immediately report signs and symptoms of erosions or gastrointestinal bleeding, similar to the approach used with daprodustat.

Having vadadustat available will provide healthcare prescribers with another oral option for treating anemia of CKD in dialysis-dependent patients, and for those who wish to use an oral option, and allow health care providers to choose the drug that they think is best suited for their patient.

2. Regulatory History

Akebia Therapeutics originally submitted their NDA for the treatment of anemia associated with CKD in adults on dialysis and not on dialysis on March 29, 2021. The Applicant received a CRL on March 29, 2022. The reasons for the CRL are briefly summarized below, see finalized CRL in DARRTS for further details.

Deficiencies identified in the CRL:

Benefit:

- There was higher use of rescue therapy for worsening anemia with vadadustat compared to darbepoetin alfa, particularly for ESA rescue in the NDD-CKD population and for ESA and RBC transfusion rescue in the DD-CKD population.
- Increased use of RBC transfusion rescue therapy could potentially impact alloreactivity, a risk factor for renal allograft rejection in patients who undergo kidney transplantation.

Risk:

- In the NDD-CKD population primary analysis, non-inferiority was not established for vadadustat compared to darbepoetin alfa on the primary safety endpoint of adjudicated MACE – a composite of all-cause mortality, non-fatal MI and non-fatal stroke.
- In the DD-CKD population, there was an increased risk for adjudicated TE events (mostly VAT) with vadadustat compared to darbepoetin alfa, this risk was more pronounced in the U.S. subgroup.
- There was a risk for DILI with the use of vadadustat in patients with CKD. This conclusion was based on one Hy's Law case, at least seven cases of probable DILI with significant elevation in ALT without jaundice, and an imbalance in ALT elevations with vadadustat compared to darbepoetin alfa.

As a path forward, the Agency recommended that the Applicant conduct new clinical trial(s) that establish a favorable benefit/risk assessment of vadadustat in a specific patient population or with a different dosing regimen. In addition, the Applicant also needed to propose and assess

a strategy that successfully mitigates the risk of hepatotoxicity with the use of vadadustat in patients with CKD.

Type A End of Review Meeting

On July 22, 2023, a Type A End of Review Teleconference was held to discuss the deficiencies in the CRL and potential path forward. Key responses from the meeting are listed below, see finalized meeting minutes in DARRTS for further details.

- At the meeting, the Agency acknowledged that the non-inferiority of vadadustat on change from baseline in Hb remained robust to sensitivity analysis accounting for rescue therapy use. Therefore, provided the Applicant could provide adequate reassurance that the imbalance in RBC transfusion does not lead to an adverse impact on renal allograft rejection, the Agency agreed that the rescue therapy results would not be an approvability issue.
- The Agency reiterated the concern regarding the risk of TE events with vadadustat, compared to darbepoetin alfa, driven by an increased risk of VAT occurrence in the DD-CKD population. The Agency emphasized that fistula/graft abandonment is a major clinical consequence of VAT and can have dire effects for DD-CKD patients, who rely on their access for survival.
- The Agency continued to state their concern regarding the clinically significant risk for DILI due to a Hy's Law case and other probable DILI cases. The Applicant presented their proposal of frequent laboratory monitoring to mitigate the identified DILI risk associated with vadadustat.
- The Applicant proposed to restrict the indication to DD-CKD patients.
- The Agency stated vadadustat has an unfavorable benefit-risk profile in the DD-CKD population and continued to recommend the path forward options described in the CRL, which included conducting new clinical trial(s).

Formal Dispute Resolution Request

The Applicant submitted a formal dispute resolution request (FDRR) to the Office of New Drugs (OND) on October 24, 2022. The appeal concerned the March 29, 2022, CRL issued by the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN). The Applicant, stated in the appeal, that they are now only seeking an indication in the DD-CKD population. On May 26, 2023, Peter Stein, MD, the deciding authority, issued a Formal Dispute Resolution Appeal Denied letter. In the letter, he concluded that the issues in the CRL related to vadadustat effectiveness will be resolved if submitted data confirm no differences in renal transplant rejection. In addition, he concluded that the risk of VAT could be addressed in labeling. The Appeal was denied due to the unresolved safety concern of DILI. However, Dr. Stein concluded that this concern could potentially be addressed if there were reassuring postmarketing hepatic safety data from vadadustat in Japan.

Type A End of Dispute Meeting

A face-to-face meeting was held with the Applicant on July 17, 2023, to discuss the planned resubmission following the appeal denied letter. At the meeting, the Applicant outlined the

Japanese postmarketing safety data that would be submitted to address the DILI deficiency in the CRL, along with the content and structure of the planned NDA resubmission.

3. Summary of Data Included in the Resubmission and Approach to the Review

The Approach to this review included addressing deficiencies identified in the CRL, assessing adverse events of special interest that were not previously analyzed (gastric erosions and heart failure leading to hospitalization, which were identified with another member of the class) in the original review, safety analyses of studies not previously reviewed (Studies CI-0036 and CI-0039) and safety analyses of the Japanese postmarketing database. An outline of pertinent information submitted with this vadadustat NDA resubmission is summarized below.

Akebia's Response to the CRL Document

Akebia submitted a Complete Response to address the deficiencies in the CRL.

- The Applicant states they will only seek an indication in the DD-CKD population and will have a Limitation of Use about not using in the NDD-CKD population to address the deficiency of the unfavorable benefit-risk profile in the NDD-CKD population.
- The Agency listed the concern regarding higher use of ESA and RBC transfusion rescue therapy in vadadustat treatment groups than darbepoetin alfa treatment groups and the potential for transfusions to impact alloreactivity and renal allograft rejection. To address this concern, the Applicant highlighted prespecified sensitivity analyses in both Study CI-0016 and Study CI-0017 of the primary and key secondary endpoints pertaining to rescue in which all pre-visit hemoglobin values within four weeks of administration of rescue therapy were set to missing. In addition, the Applicant provided the rate of renal transplant rejection.
- To address the concern of an increased risk for adjudicated TE events (driven by VAT) in the DD-CKD population, the Applicant submitted rates of access abandonment and revascularization procedures.
- To address the risk of DILI the Applicant submitted a safety update report and Japanese postmarketing data (details are discussed below).

Safety Update Report

A Safety Update Report which summarizes all the available safety data for vadadustat since the 120-Day Safety Update Report that was submitted for the initial NDA. The reporting period for this report is from February 26, 2021 to June 28, 2023 for any ongoing/completed clinical studies. During the reporting period, 2 Akebia-sponsored clinical studies of vadadustat in patients with DD-CKD completed enrollment (Study AKB-6548-CI-0036 [MO2DIFY] referred to as Study CI-0036 and Study AKB-6548-CI-0039 [FO2CUS] referred to as Study CI-0039). There were no other Akebia-sponsored ongoing studies with vadadustat during the reporting period. This safety update report included a summary of cumulative data for all patients from Study CI-0036 and Study CI-0039 for disposition, demographics, and treatment-emergent adverse events

(TEAEs). Patient narratives and case report forms (CRFs) were included for deaths due to TEAEs, serious TEAEs, and TEAEs leading to discontinuation of study drug. Worldwide post-marketing safety data from Japan for TEAEs reported are also provided in this report.

Japan Vadadustat Post-Marketing Safety Data

Japan vadadustat postmarketing safety data were submitted to primarily address the risk of DILI.

Akebia's development partner Mitsubishi Tanabe Pharma Corporation (MTPC) obtained approval for vadadustat (VAFSEO) in Japan on June 29, 2020 for the treatment of anemia due to CKD in both dialysis dependent and non-dialysis dependent adults. As required for all new drugs approved in Japan, MTPC created and maintains a local risk management plan (J-RMP) for Vafseo which was agreed with Japan's regulatory agency – the Pharmaceuticals and Medical Devices Agency (PMDA). The key elements in the J-RMP are comprised of the Early Post-marketing Phase Vigilance (EPPV) phase of the approved drug and collection of spontaneous adverse drug events, data generation from a post-marketing surveillance (PMS) observational study (VIOLET Study), and submission of aggregate data and other safety updates in Periodic Safety Update Reports (PSURs). The results of these 4 elements were included in the vadadustat resubmission with a reporting period of August 26, 2020 to June 28, 2023. In addition, there were two Phase 4 studies conducted by MTPC in Japan: MTPC-2020-002 – "Transition of Hb values after switching from ESA to vada in hemodialysis (HD)" (study complete) and MTPC-2020-004, "An exploratory study of vadadustat on metabolic parameters in patients with anemia in non-dialysis dependent chronic kidney disease complicated with type 2 diabetes" (study complete). The adverse events (AEs) from these two studies have been included in the resubmission.

Additional Clinical Studies

Two additional studies were completed by the Applicant in the DD-CKD population. These studies provide supportive safety information. Both studies explore an alternative (three times a week) dosing regimen of vadadustat.

Study AKB-6548-CI-0036 (MO2DIFY or Study CI-0036) was a Phase 3b, randomized, open-label, active controlled study of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in patients requiring hemodialysis, after conversion from ESA therapy in the U.S. and EU. The Applicant submitted a clinical study synopsis, study protocol, statistical analysis plan (SAP), patient narratives and CRFs, along with datasets.

Study AKB-6548-CI-0039 (FO2CUS or Study CI-0039) was a Phase 3b, randomized, open-label, active controlled study evaluating the efficacy and safety of dose conversion from a long-lasting ESA i.e., epoetin beta (Mircera®), to three times weekly (TIW) oral vadadustat for the maintenance treatment of anemia in patients requiring hemodialysis in the U.S. The Applicant

submitted a clinical study synopsis, study protocol, SAP, patient narratives and CRFs, along with datasets.

4. Deficiencies Identified in the CRL

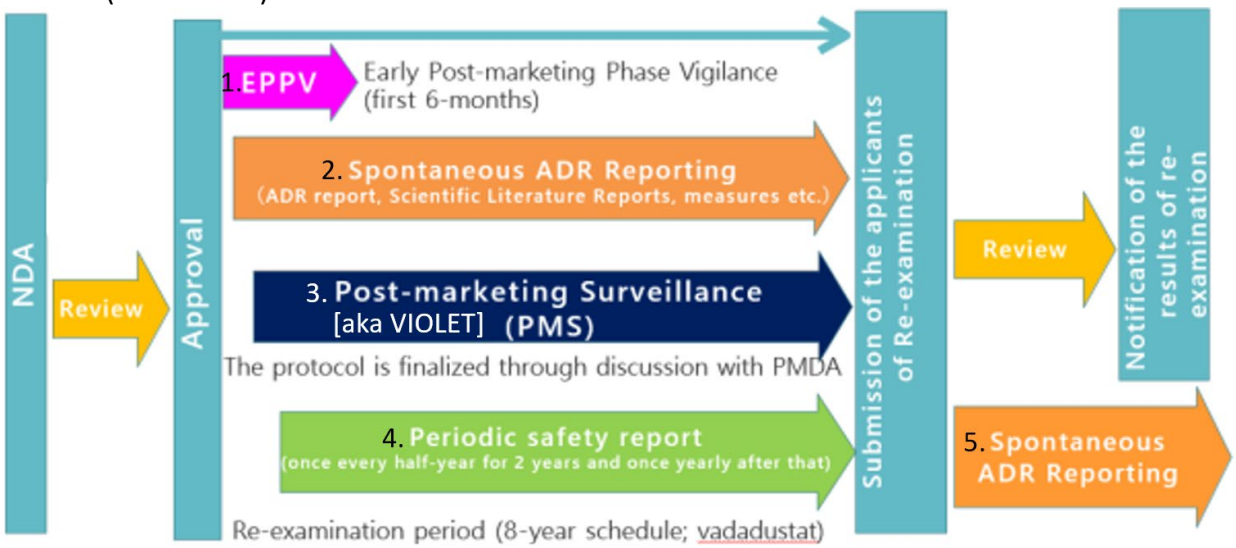
4.1. Drug Induced Liver Injury (DILI)

Background:

Drug induced liver injury is a substantial risk identified in the CRL for vadadustat. This conclusion is based on one Hy's Law case, at least seven cases of probable DILI with significant elevation in ALT without jaundice, and a small imbalance in ALT elevations with vadadustat compared to darbepoetin alfa. In addition, there was a concern that patients in the real-world setting may not be as closely monitored (e.g., with liver tests) as in clinical trials and therefore this risk may be underestimated, in particular because of the convenience of an orally administered drug. In accordance with the FDRR decision, the Applicant submitted additional postmarket experience to show that serious DILI is a very rare event and liver monitoring could be feasible.

The new data that we evaluated to address the DILI concern includes the two RCTs mentioned above (Studies CI-0036 and CI-0039, see Sections 12.1 and 12.2 for further details on the study design) that enrolled approximately 500 DD-CKD subjects in the U.S. and EU, and the postmarketing surveillance of (b) (4) subjects treated following product launch in Japan. As required for all new drugs approved in Japan, the Applicant maintains a risk management plan for vadadustat, including: 1) Early Postmarketing Phase Vigilance (EPPV), 2) routine pharmacovigilance (i.e., postmarketing spontaneous reports and Periodic Safety Update Reports) and 3) a PMS observational study (VIOLET), a prospective, single-arm, long-term surveillance study to evaluate the safety and efficacy of long-term administration of vadadustat (Figure 1).

Figure 1: Schematic of Data Sources from the Japanese pharmacovigilance program.



Source: DHN DILI team review

Analysis:

The Division of Hepatology and Nutrition Drug (DHN) DILI Team assessed the hepatotoxicity risk based on data in this resubmission. The Division of Epidemiology-1 (DEPI-1) also assessed the Japanese pharmacovigilance program.

DHN DILI Team Review

The DILI Team concluded that the application can be approved for the DD-CKD population if the primary review team confirms efficacy and need are otherwise favorable and labeling includes hepatotoxicity risk. See finalized review in DARRTS dated March 8, 2024. Key points from the review are summarized below.

Studies CI-0036 and CI-0039

In Studies CI-0036 and CI-0039, there were no serious DILI cases nor reports of liver failure, liver transplantation, or death amongst subjects with hepatobiliary AEs. In addition, there was no obvious imbalances suggesting vadadustat liver injury by hepatotoxicity AESI or preferred terms (Table 1). No vadadustat subjects met Hy's Law criteria by total bilirubin (TB) >2x upper limit of normal (ULN) and transaminase (TA) elevation >3x ULN criteria. Three vadadustat subjects and one ESA subject had ALT >3x ULN in Study CI-0039, but TA elevations were less than 8x ULN without jaundice in these cases. There was no excess of ALT or AST elevations >5x ULN for vadadustat relative to ESA. There was no excess of alkaline phosphatase (ALP) or TB at least >2x ULN for vadadustat relative to the ESA comparator.

Table 1. Summary of Liver Safety from Studies CI-0036 and CI-0039

	Study CI-0036			CI-0039		
Disposition	319 randomized 317 safety population 171 completed treatment			456 randomized 456 safety population 315 completed treatment		
Arm	**VDA QD N=105 n (%)**	**VDA TIW N=104 n (%)**	**Darbepoetin N=108 n (%)**	**VDA 600 mg N=151 n (%)**	**VDA 900 mg N=150 n (%)**	**Peg EPO N=150 n (%)**
Hepatotoxicity (AESI)	4 (3.8)	3 (2.9)	5 (4.6)	4 (2.6)	7 (4.7)	6 (4)
Investigations (Preferred terms)*	3 (2.9)	1 (1)	2 (1.9)	1 (0.7) (INR increase)	4 (2.7)	4 (2.7) (1 bilirubin increase; 1 INR increase)
Hepatobiliary disorders^	1 (1)	1 (1) (cirrhosis)	3 (2.8) (1 cirrhosis)	3 (2.0) (1 cirrhosis)	1 (0.7) (cirrhosis)	1 (0.7)

Source: DHN DILI Consult Review
VDA = vadadustat; AESI = adverse event of special interest; QD = daily; TIW = thrice weekly; EPO = erythropoietin; Peg = polyethylene glycol.
*Preferred terms: Increases in ALT, AST, liver function test, hepatic enzyme, transaminase, bilirubin, or INR.
Hepatobiliary disorders: hypertransaminasemia, hepatomegaly, cyst, steatosis, cirrhosis.

Japanese Postmarketing Database

In the Japanese postmarketing database, there were no DILI deaths, transplants, or liver failures attributable to vadadustat by AE terms. However, the subject level data were routinely inadequate to adjudicate for DILI, and there were no comparator arms in these data sources.

In the EPPV program there was one case of hepatitis listed as a serious adverse reaction among 4000 exposures, however there was not enough subject level data to adjudicate the AE.

In the source of spontaneous adverse drug reaction (ADR) reports, hepatobiliary ADRs represented 1.3% of all AE reports. Of the 46 AEs under the hepatobiliary system organ class (SOC), 14 were serious, but none resulted in liver transplant, liver failure or death. The number of hepatobiliary AEs leading to discontinuation was not provided, but only five hepatobiliary AEs were reported overall, two of which were considered “serious.” Of these five, one was a portal vein thrombosis and one was Budd-Chiari syndrome. Neither of these are pertinent to hepatocellular DILI risk. Therefore, 0.16% (3 of 1847) of subjects may have discontinued vadadustat for a DILI in the worst-case scenario. Case level data were typically inadequate for DILI adjudication.

As of June 28, 2023, 2262 subjects registered in the VIOLET study, of which 1847 (82%) are in the safety population. In total, the DD-CKD population included 142 patients on peritoneal dialysis and 472 patients on hemodialysis. The Applicant provided case details for four cases from VIOLET, three that met the biochemical criteria for Hy’s law and one that had an AST >10x ULN without jaundice. The DHN DILI team did not attribute any of these cases to DILI (Table 2).

In the five PSURs, hepatotoxicity AESIs occurred in less than 1% of patients and adjudication was not possible due to limited case level data.

Table 2: Four Cases from VIOLET that met Hy’s Law Biochemical Criteria or had a Serum Transaminase >10 X ULN

Subject ID	Causality Score^	Alternate Cause	Age (y)/Sex/Race	Hy's Law	Latency (da)	Peak values		
						AST (U/L)	ALT (U/L)	R value
(b) (6)	5 or 6	Herbal liver injury	65/M/Asian	No	65	995	881	2.62
	5	Undiagnosed liver disease, CHF, pancreatic cancer	93/F/Asian	No	318	129	72	0.46
	5	CHF, Herbal liver injury	84/M/Asian	No	25	121	31	0.35
	4 or 6	Possible muscle or ischemic injury; limited data	74/M/Asian	No	29	2456	441	65*

CHF = chronic heart failure (leading to congestive hepatopathy);
R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values > 5; mixed: 2-5; cholestatic: R-value < 5
^1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate
*R-value based on AST

Source: DHN DILI Consult Review

The DHN DILI team supports approval of vadadustat. As stated in the finalized consult review, "This conclusion was based on no additional cases of Hy's Law or serious DILI were observed among the 500 vadadustat treated subjects in the two additional RCTs from the US and Europe, bringing the overall DILI rate to approximately 0.16% and 0.02% for Hy's Law cases. We saw no imbalance in liver analyte elevations between the study drug and comparator, erythropoiesis-stimulating agents, in these two trials. We did not identify DILI fatalities or liver transplantations in the Japanese pharmacovigilance program, encompassing (b) (4) new uses of VDA, but our overall assessment is obfuscated by lack of adequate case level data as well as differences in clinical practice between Japan and the US."

The DILI team recommended labeling for hepatotoxicity risk and implementing enhanced pharmacovigilance to monitor for hepatotoxicity. The DILI team recommended liver enzyme monitoring at baseline and monthly during the first few months of use of vadadustat and that use of vadadustat in patients with cirrhosis or active, acute liver disease should be discouraged.

Division of Epidemiology-1

The DEPI-1 team concurred with the DHN DILI team and that vadadustat can be approved. See finalized review in DARRTS dated March 4, 2024, a summary of the review is provided below.

DEPI-1 evaluated the Japanese postmarketing data. Although a final clinical study report from the VIOLET study was not currently available, an interim report described data collected from November 24, 2020 (study start date) through June 28, 2023. A total of 2,262 patients from 431 sites enrolled in the VIOLET PMS study, of which 1,847 were included in the safety analysis. The mean dosing period was 202 days. Baseline characteristics of the study population, along with exposure information is provided in the tables below. DEPI-1 sent an information request (IR) to

the PMDA asking for an update on their review of the most recent safety report for vadadustat. In his response dated February 22, 2024, Dr. Uyama indicated that as of the cut-off February 18, 2024, PMDA's review has not identified any cases of hepatic failure, liver transplant, or death due to DILI.

Table 3. Baseline Demographic and Clinical Characteristics- VIOLET Study

Patient characteristics	Overall (n=1,847)	Dialysis-dependent (n=614)
Male	999 (54.1%)	398 (64.8%)
Age, years (mean±standard deviation)	74.2±13.3	67.7±13.6
Stage of CKD		
Non-dialysis-dependent CKD	1,233 (66.8%)	0 (0)
Peritoneal dialysis-dependent CKD	142 (7.7%)	142 (23.1%)
Hemodialysis-dependent CKD	472 (25.5%)	472 (76.9%)
Dialysis period, years	5.23±6.17	5.23±6.17
Duration of renal anemia, years	2.66±4.36	4.31±5.04
Switched from ESA preparations	396 (21.4%)	247 (40.2%)

Source: Vadadustat Japan VIOLET Study Interim Results. June 28, 2023. Page 29. Attachment 1-5.

Note: Dialysis-dependent population (n=614) is a subset of total patients included in the safety analysis (n=1,847)

Table 4. Dose and Duration of Vadadustat Exposure- VIOLET Study

	Overall (n=1,847)	Dialysis-dependent (n=614)
Initial dose of vadadustat		
150 mg/day	146 (7.9%)	33 (5.4%)
300 mg/day	1,673 (90.6%)	563 (91.7%)
450 mg/day	15 (0.8%)	10 (1.6%)
600 mg/day	10 (0.5%)	6 (1.0%)
Mean dosing period of vadadustat, days	201.8±138.5	175.4±124.2
Mean dosage of vadadustat, mg/day	315.4±88.9	346.5±103.1
Dosing discontinued/ended (patients)	528 (28.6%)	213 (34.7%)
Reasons for discontinuation		
Ineffective/inadequate efficacy	99 (5.4%)	76 (12.4%)
AEs/ADRs	162 (8.8%)	61 (9.9%)
Hospital transfer	94 (5.1%)	25 (4.1%)
Renal transplant	3 (0.2%)	1 (0.2%)
Patient preference	52 (2.8%)	16 (2.6%)

Source: Vadadustat Japan VIOLET Study Interim Results. June 28, 2023. Page 26-29. Attachments 1-3 and 1-4.

In their review, DEPI-1 states that the postmarketing surveillance programs initiated by Akebia and its partners are being conducted in alignment with local regulations and standards for pharmacovigilance. Overall, these programs appeared to be appropriately designed for the purpose of monitoring the safety of vadadustat and AEs/ADRs of special interest (e.g., hepatic function disorder) in routine clinical practice. Based on information provided by Akebia in the vadadustat resubmission application, postmarketing surveillance in Japan appears to have been conducted in compliance with the local regulations.

The DEPI-1 team cautioned that estimation of incidence of AESIs, including hepatotoxicity in the VIOLET study is limited by data quality issues in the interim report, including: 1) unknown missing data, 2) likely misclassification of AESIs based on inconsistent MedDRA coding and lack of pre-specified AESI case definitions, and 3) inconsistent case counts. However, the number of hepatobiliary serious adverse events (SAEs) reported during marketed experience in Japan appears small based on available data. The surveillance program overall demonstrates feasibility of liver monitoring in the setting of anemia of CKD, and supports considerations for safe use in the DD-CKD population. In light of PMDA's assessment of postmarketing safety data over a three year period, the team stated it is reasonable to conclude that the safety profile of vadadustat is consistent with product labeling in Japan.

Conclusion

The clinical review team concurs with the assessment by DHN DILI and DEPI-1 teams. In summary, no additional adjudicated DILI cases were identified in Studies CI-0036 and CI-0039. In addition, no serious DILI cases, including DILI death, liver transplantation, or liver failure were identified in the Japanese postmarketing experience involving approximately (b) (4) treated patients, however, these data should be interpreted with caution given the lack of patient level data. In addition, the applicability of the Japanese data to the US population remains uncertain given differences in medical practice and genetic differences that may predispose a person to DILI.

Hepatotoxicity remains a risk as evident by cases of DILI identified in the original NDA submission, including a case of Hy's Law in DD-CKD studies. However, given that this risk appears to be a rare event and postmarketing experience from Japan demonstrates the feasibility of monitoring for liver toxicity, this risk can be managed in labeling. Patients with DD-CKD are monitored by medical professionals closely and have frequent interactions, therefore monthly liver enzyme monitoring for the first 6 months should be achievable. In addition, enhanced pharmacovigilance to further assess the risk of hepatotoxicity is recommended.

4.2. Vascular access thrombosis

Background

Adjudicated TE events, driven by VAT, was identified as a key safety concern in the CRL for patients with DD-CKD treated with vadadustat. This risk appeared more concerning in the U.S. subgroup.

To address this deficiency, the Applicant submitted additional data that include the number of events of VAT per patient and rates of access abandonment and revascularization procedures in Studies CI-0016 and CI-0017. In addition, the Applicant has proposed to address this risk with a boxed warning for TE events, including VAT, and a description of TE events in Section 6 of the label.

Analysis

Total VAT Events

As stated in the CRL, in the pooled DD-CKD studies (Studies CI-0016 and CI-0017), the estimated hazard ratio (HR) for the time-to-first adjudicated VAT event was 1.28 (95% CI: 1.00, 1.63). In addition, a higher proportion of patients in the vadadustat group experienced a TE, 8.7% of vadadustat patients had an adjudicated TE event compared to 7.8% in the darbepoetin alfa groups. However, the total number of VAT events, was similar between treatment groups, there were 212 VAT events in the vadadustat group and 214 VAT events in the darbepoetin alfa group (Table 5).

Table 5. Time to Multiple VAT Events, DD-CKD Safety Population

Statistics	Vadadustat N=1947	Darbepoetin alfa N=1955
Number of events	212	214
Number of events per Subject	146	120
Mean (SD)	1.5 (1.03)	1.8 (1.95)
Median (Min, Max)	1 (1, 9)	1 (1, 13)
Time to Event (weeks)		
Mean (SD)	48 (34.4)	51.1 (35.8)
Median (Min, Max)	42.1 (1, 134.7)	48.2 (0.6, 154.3)
Hazard Ratio* (95% CI)	1 (0.8, 1.2)	

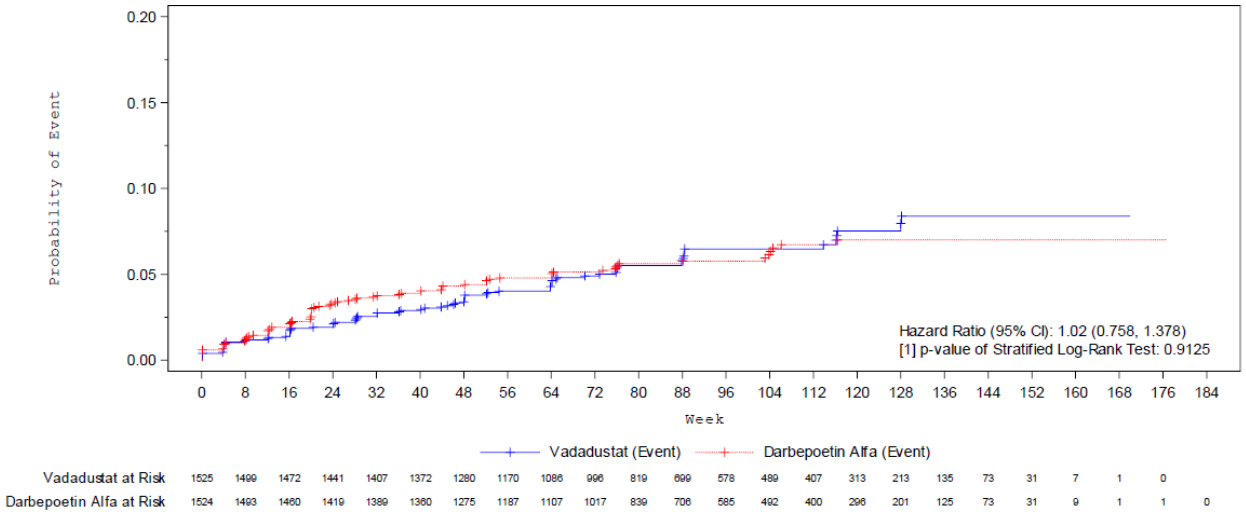
Source: Applicant's Response Document to the CRL
Abbreviations: SD= standard deviation, min=minimum, max= maximum, CI= confidence interval
*Hazard ratio for time-to-multiple VAT events

Access Abandonment

The Applicant acknowledged one of the most direct and consequential results of VAT is fistula/graft abandonment. With abandonment, there is the need to catheterize patients for dialysis access, and the need for surgical placement of a new permanent vascular access (i.e.,

change dialysis type). The Kaplan-Meier curves below show that the proportion of subjects transitioning from a fistula or graft to another dialysis access are overlapping and crossing, illustrating that there is no difference between treatment groups in the risk of access abandonment (Figure 2). The analysis was based on patients whose dialysis type was changed from arteriovenous fistula at baseline to either arteriovenous graft, temporary catheter or tunneled dialysis catheter or dialysis type was changed from arteriovenous graft at baseline to either temporary catheter or tunneled dialysis catheter. Change in dialysis type was reported in 3.6% of patients in the vadadustat treatment group and 4.2% of patients in the darbepoetin alfa treatment group at Week 52 (Table 6). The rates of change in dialysis type were similar between the vadadustat and darbepoetin alfa groups at weeks 104 and 156, although these results are difficult to interpret due to the smaller number of events with onset after Week 52. Rates of change in dialysis type were slightly higher with vadadustat compared to darbepoetin alfa in the U.S. subgroup (Table 7).

Figure 2. Kaplan-Meier Curve of Time to Change of Dialysis Type in DD-CKD Population (Safety Analysis Set) - Studies CI-0016 and CI-0017



Source: Applicant's End of Review Meeting Type A Meeting Briefing Document, independently confirmed by FDA statistical reviewer

Table 6. Time to Change of Dialysis Type in DD-CKD Population (Safety Analysis Set)- Studies CI-0016 and CI-0017*

Parameter	Vadadustat N=1525	Darbepoetin alfa N=1524
Number of patients with events		
n (%)	87 (5.7)	86 (5.6)
Number of patients censored		
n (%)	1438 (95.3)	1438 (94.4)
Time to first event (weeks)		
n (%)	87 (5.7)	86 (5.6)

Mean (SD)	43.5 (34.3)	32.1 (30.1)
Median (Min, Max)	40.2 (0.1, 128.1)	20.1 (0.1, 116.4)
Time to last contact (weeks)		
n (%)	1438 (95.3)	1438 (94.4)
Mean (SD)	87.3 (35)	88 (34.4)
Median (Min, Max)	85.1 (0.9, 170)	86.9 (0.7, 176.4)
Cumulative incidence (C_{in}) [1]		
52 weeks, n (%)	55 (3.6)	65 (4.2)
C_{in} (95% CI)	0.038 (0.029, 0.0489)	0.044 (0.035, 0.056)
104 weeks, n (%)	81 (5.3)	82 (5.4)
C_{in} (95% CI)	0.065 (0.052, 0.080)	0.061 (0.049, 0.076)
156 weeks, n (%)	87 (5.7)	86 (5.6)
C_{in} (95% CI)	0.084 (0.065, 0.108)	0.07 (0.056, 0.088)

Source: Applicant's End of Review Meeting Type A Meeting Briefing Document, independently confirmed by FDA statistical reviewer
* Time to change of dialysis type from arteriovenous fistula at baseline to either arteriovenous graft, temporary catheter or tunneled dialysis catheter or dialysis type from arteriovenous graft at baseline to either temporary catheter or tunneled dialysis catheter. Safety analysis set with baseline dialysis type as arteriovenous fistula or arteriovenous graft
[1] Based on non-parametric analysis and log-rank test is stratified by study.
Note: Baseline dialysis type is defined as the last dialysis type prior to first dose date.
Abbreviations: n, number; SD, standard deviation; min, minimum; max, maximum; CI, confidence interval

Table 7. Time to Change of Dialysis Type Safety Analysis Set in DD-CKD Population (U.S. Subgroup)*; Studies CI-0016 and CI-0017

Parameter	**Vadadustat N=942**	**Darbepoetin alfa N=931**
Number of patients with events		
n (%)	51 (5.4)	43 (4.6)
Number of patients censored		
n (%)	891 (94.6)	888 (94.4)
Time to first event (weeks)		
n (%)	51 (5.4)	43 (4.6)
Mean (SD)	50.5 (37.3)	42.2 (31.8)
Median (Min, Max)	46.4 (0.1, 128.1)	36.6 (0.1, 116.4)
Time to last contact (weeks)		
n (%)	891 (94.6)	888 (94.4)
Mean (SD)	97.4 (36.7)	98.4 (34.7)
Median (Min, Max)	103 (1.3, 170)	102 (2.1, 176.4)
Cumulative incidence (C_{in}) [1]		
52 weeks, n (%)	30 (3.2)	27 (2.9)

C_{in} (95% CI)	0.034 (0.024, 0.0479)	0.03 (0.021, 0.044)
104 weeks, n (%)	45 (4.8)	40 (4.3)
C_{in} (95% CI)	0.056 (0.042, 0.074)	0.048 (0.035, 0.065)
156 weeks, n (%)	51 (5.4)	43 (4.6)
C_{in} (95% CI)	0.076 (0.056, 0.103)	0.056 (0.041, 0.075)

Source: Applicant's End of Review Meeting Type A Meeting Briefing Document, independently confirmed by FDA statistical reviewer
* Time to change of dialysis type from arteriovenous fistula at baseline to either arteriovenous graft, temporary catheter or tunneled dialysis catheter or dialysis type from arteriovenous graft at baseline to either temporary catheter or tunneled dialysis catheter. Safety analysis set with baseline dialysis type as arteriovenous fistula or arteriovenous graft
[1] Based on non-parametric analysis and log-rank test is stratified by study.
Note: Baseline dialysis type is defined as the last dialysis type prior to first dose date.
Abbreviations: n, number; SD, standard deviation; min, minimum; max, maximum; CI, confidence interval

Revascularization Procedures

In the DD-CKD population, the rates of revascularization procedures, were similar between treatment groups. In the pooled DD-CKD population, rates of revascularization procedures were reported in 11.4% of patients in the vadadustat treatment group and 12.9% of patients in the darbepoetin alfa treatment group.

In Study CI-0016, revascularization procedures occurred in 14 (7.8%) patients and 12 (6.5%) patients in the vadadustat and darbepoetin alfa groups, respectively. In total, 6 (3.4%) patients had revascularization procedures of the arteriovenous graft and 4 (2.2%) patients had revascularization procedures of the arteriovenous fistula in the vadadustat group, compared to 3 (1.6%) patients and 6 (3.2%) patients in the darbepoetin alfa group respectively. Arteriovenous graft revascularization procedures were marginally higher in the vadadustat group whereas arteriovenous fistula revascularizations were marginally higher in the darbepoetin alfa group (See Table 8). Overall, there do not appear to be differences between treatment groups in arteriovenous graft/fistula revascularizations.

Table 8: Summary of Revascularization Procedures Safety Population (AKB-6548-CI-0016)

Parameter	**Vadadustat N=179 N (%)/E**	**Darbepoetin alfa N=186 N (%)/E**
Any Revascularization Procedures Associated with an AE	13 (7.3)/19	8 (4.3)/16
Any Revascularization Procedures	14 (7.8)/20	12 (6.5)/25
CABG	2 (1.1)/2	0/0
PICC	1 (0.6)/1	1 (0.5)/1
Carotid Revascularization	0/0	0/0
Peripheral (Arterial) Revascularization	1 (0.6)/2	0/0
Peripheral (venous) Revascularization	0/0	0/0
Renal Artery Revascularization	0/0	0/0
Abdominal Aortic	0/0	0/0

Parameter	Vadadustat N=179 N (%)/E	Darbepoetin alfa N=186 N (%)/E
Aneurysm Revascularization and /or Repair		
Arteriovenous graft Elective Therapeutic	6 (3.4)/11 2 (1.1)/2 4 (2.2)/9	3 (1.6)/8 1 (0.5)/1 3 (1.6)/7
Arteriovenous fistula Elective Therapeutic	4 (2.2)/4 1 (0.6)/1 3 (1.7)/3	6 (3.2)/7 2 (1.1)/3 4 (2.2)/4
Other	0/0	5 (2.7)/9

Source: Applicant's Clinical Study Report (CSR), confirmed by the FDA Statistical Reviewer
Abbreviations: n (%) = number (percent) of patients with revascularization procedures, E = number of revascularization procedures, CABG= Coronary Artery Bypass Graft, PICC= Peripherally Inserted Central Catheter

In Study CI-0017, there were 208 (11.8%) patients and 240 (13.6%) patients with revascularization procedures in the vadadustat and darbepoetin alfa groups, respectively. In total, 44 (2.5%) patients had arteriovenous graft revascularization and 84 (4.8%) patients had arteriovenous fistula revascularization in the vadadustat group compared to 34 (1.9%) patients and 96 (5.4%) patients in the darbepoetin alfa group. The percentage of patients with arteriovenous graft revascularization procedures was slightly higher with vadadustat compared with darbepoetin alfa, although the total number of these events was higher with darbepoetin alfa. In contrast, the percentage of patients with arteriovenous fistula revascularization procedures was slightly higher with darbepoetin alfa compared with vadadustat, although the total number of these events was higher with vadadustat (See Table 9). Overall, there do not appear to be differences between treatment groups in arteriovenous graft/fistula revascularizations.

Table 9: Summary of Revascularization Procedures Safety Population (AKB-6548-CI-0017)

Parameter	Vadadustat N=1768 N (%)/E	Darbepoetin alfa N=1769 N (%)/E
Any Revascularization Procedures Associated with an AE	191 (10.8)/342	225 (12.7)/402
Any Revascularization Procedures	208 (11.8)/372	240 (13.6)/436
CABG	12 (0.7)/12	14 (0.8)/14
PICC	5 (0.3)/5	3 (0.2)/3
Carotid Revascularization	3 (0.2)/3	3 (0.2)/3
Peripheral (Arterial) Revascularization	23 (1.3)/28	31 (1.8)/36
Peripheral (venous) Revascularization	7 (0.4)/7	9 (0.5)/10
Renal Artery Revascularization	1 (0.1)/1	0/0
Abdominal Aortic Aneurysm Revascularization and /or Repair	2 (0.1)/2	0/0

Parameter	Vadadustat N=1768 N (%)/E	Darbepoetin alfa N=1769 N (%)/E
Arteriovenous graft	44 (2.5)/73	34 (1.9)/115
Elective	17 (1.0)/24	13 (0.7)/19
Therapeutic	32 (1.8)/49	28 (1.6)/96
Arteriovenous fistula	84 (4.8)/163	96 (5.4)/147
Elective	31 (1.8)/48	38 (2.1)/56
Therapeutic	59 (3.3)/115	61 (3.4)/91
Other	58 (3.3)/78	85 (4.8)/108

Source Applicant's CSR, confirmed by FDA Statistical Reviewer
n (%) = number (percent) of patients with revascularization procedures, E = number of revascularization procedures, CABG= Coronary Artery Bypass Graft, PICC= Peripherally Inserted Central Catheter

Conclusion

A concerning signal of TE events, in particular VAT was identified in the safety analysis of Studies CI-0016 and CI-0017. VAT can have serious clinical consequences as occlusion of dialysis access sites can impact the ability of patients to maintain life-saving dialysis. However, an increase in the HR for VAT is an isolated one among the large number of CV and TE event analyses, raising the risk of a type I error. It is notable that while time to first VAT demonstrated an increased risk in the vadadustat arm, the total number of VAT events between treatment arms was similar. The Applicant conducted additional analyses demonstrating that serious consequences of VAT such as access abandonment and need for graft/fistula revascularization procedures were observed at similar rates in the vadadustat group and darbepoetin alfa group. However, in the US subgroup, the rates of access abandonment were slightly higher in the vadadustat group compared to the darbepoetin alfa group.

Given the totality of evidence, we conclude there is an increased risk of TE events and VAT with vadadustat, however, not all the analyses support that the risk of VAT and its consequences are higher with vadadustat compared to darbepoetin alfa. These risks can be adequately managed in labeling. The label will include a boxed warning that includes VTE and VAT, along with an increased risk of death, MI, and stroke. The risk of thrombotic vascular events will be further described in Section 6 of the label. Section 6 of the label will describe the rates of adjudicated thrombotic vascular events. The number of patients with event (%) and rate per 100-person year of adjudicated thrombotic vascular events (fatal and non-fatal) in the DD-CKD population (Studies CI-0016 and CI-0017) are 9.0 per 100-person year for the vadadustat arm, 8.7 per 100-person year for the darbepoetin alfa arm. Rates of thrombotic events are described below (Table 10).

Table 10. Adjudicated Thrombotic Vascular Events in Patients with DD-CKD (Fatal and Non-fatal Events)*

Event	VAFSEO (N = 1947) Rate per 100 PY**	Darbepoetin Alfa (N = 1955) Rate per 100 PY**
Vascular access thrombosis	4.8	3.9
Myocardial infarction	2.9	2.8
Stroke	1.1	1.4
Deep vein thrombosis	0.5	0.6
Pulmonary embolism	0.2	0.3
Arterial thrombosis	0.2	0.1

Source: Division of Biometrics (DB) 7 Statistical reviewer
Abbreviations: N= number, PY= person-year, %= percent
*These data are not an adequate basis for comparison of rates between the study drug and active control.
** Based on time to first event analysis.

4.3. Use of Rescue for Anemia

Background

The CRL acknowledged that vadadustat demonstrated non-inferiority to darbepoetin alfa on the primary endpoint of change from baseline in Hb and the key secondary endpoint measuring durability of that effect in Studies CI-0016 and CI-0017 (INNO2VATE) but raised a concern regarding higher use of ESA and RBC transfusion rescue therapy in vadadustat treatment groups than darbepoetin alfa treatment groups and the potential for transfusions to impact alloreactivity and renal allograft rejection.

Analysis

ESA Rescue

The Applicant clarified that higher rate of ESA rescue in the vadadustat group was artifactual and likely due to the definitions of ESA rescue therapy. In the vadadustat treatment group, any receipt of ESA was deemed rescue therapy. In contrast, in the darbepoetin alfa treatment group, rescue was defined as receipt of any ESA other than darbepoetin alfa. To address this issue the Applicant conducted additional post-hoc analyses in which rescue for the darbepoetin alfa group was defined as increased doses of the ESA for worsening anemia in the same time periods (Table 11 and Table 12). Using increased doses of darbepoetin alfa as the ESA rescue therapy definition in the darbepoetin alfa group, showed that ESA rescue occurred at similar or higher rates in the darbepoetin alfa group.

Table 11. Patients Receiving ESA Rescue in Study CI-0016

Period	Vadadustat N=179 n/N (%)	Darbepoetin Alfa[i] N=186 n/N (%)	Darbepoetin Alfa Including ≥50% Increase as Rescue N=186 n/N (%)	Darbepoetin Alfa Including ≥100% Increase as Rescue N=186 n/N (%)
Weeks 2–8	10/179 (5.6)	1/186 (0.5)	40/186 (21.5)	13/186 (7)
Weeks 10–20	25/169 (14.8)	3/177 (1.7)	35/177 (19.8)	16/177 (9)
Weeks 24–36	23/156 (14.7)	5/169 (3)	42/169 (24.9)	19/169 (11.2)
Weeks 40–52	19/125 (15.2)	4/140 (2.9)	27/140 (19.3)	13/140 (9.3)
Weeks 64–EOS	16/78 (20.5)	4/82 (4.9)	25/82 (30.5)	19/82 (23.2)

[i] narrow ESA rescue defined as rescue for worsening anemia with ESA medication
Abbreviations: EOS, end-of-study; ESA: erythropoiesis-stimulating agent
Source: Applicant's table derived from CSR-0016 Table 30, CSR-0016 Table 31, and CSR-0016 Table 32

Table 12. Patients Receiving ESA Rescue in Study CI-0017

Period	Vadadustat N=1777 n/N (%)	Darbepoetin Alfa[i] N=1777 n/N (%)	Darbepoetin Alfa Including ≥50% as Rescue N=1777 n/N (%)	Darbepoetin Alfa Including ≥100% as Rescue N=1777 n/N (%)
Weeks 2–8	169/1768 (9.6)	22/1769 (1.2)	539/1769 (30.5)	246/1769 (13.9)
Weeks 10–20	297/1647 (18.0)	58/1712 (3.4)	537/1712 (31.4)	279/1712 (16.3)
Weeks 24–36	253/1473 (17.2)	73/1612 (4.5)	507/1612 (31.5)	301/1612 (18.7)
Weeks 40–52	273/1306 (20.9)	95/1486 (6.4)	453/1486 (30.5)	260/1486 (17.5)
Weeks 64–EOS	256/961 (26.6)	133/1185 (11.2)	490/1185 (41.4)	321/1185 (27.1)

[i] narrow ESA rescue defined as rescue for worsening anemia with ESA medication
Abbreviations: EOS, end-of-study; ESA: erythropoiesis-stimulating agent
Source: Applicant's table derived from CSR-0017 Table 31, CSR-0017 Table 32, and CSR-0017 Table 33

RBC Transfusion Rescue

The Applicant conducted an analysis of kidney transplant rejection using the preferred terms "kidney transplant rejection" and "transplant rejection" among patients enrolled in the pooled DD-CKD studies (CI-0016 and CI-0017) in which end of treatment was due to kidney transplant. The table below shows that there were very few reports of renal transplant rejection and minimal differences in the rate of renal transplant rejection over similar exposure durations. In the DD-CKD pooled population, 2.5% of patients and 3.8% of patients in the vadadustat and darbepoetin groups, respectively, had transplant rejection.

Table 13: Transplant Rejection – Pooled DD-CKD Population

System Organ Class (SOC) Preferred Term (PT)	Vadadustat N=120 PY = 114.1		Darbepoetin Alfa N = 105 PY 112.4		Total N= 228 PY = 226.6	
	n (%)	E (E*100/PY)	n (%)	E (E*100/PY)	n (%)	E (E*100/PY)
Immune System Disorders	3 (2.5)	3 (2.6)	4 (3.7)	4 (3.6)	7 (3.1)	7 (3.1)

System Organ Class (SOC) Preferred Term (PT)	Vadadustat N=120 PY = 114.1		Darbepoetin Alfa N = 105 PY 112.4		Total N= 228 PY = 226.6	
Kidney Transplant Rejection	1 (0.8)	1 (0.9)	4 (3.7)	4 (3.6)	5 (2.2)	5 (2.2)
Transplant Rejection	2 (1.7)	2 (1.8)	0	0	2 (0.9)	2 (0.9)

Source code: Applicant's table from Integrated Summary of Safety (ISS) confirmed by statistical reviewer using adae.xpt and adsl.xpt in the original submission (SN 000)
Abbreviations: AE = Treatment-Emergent adverse events coded using MedDRA version 23.0; n (%) = number (percent) of patients with events; E (E*100/PY) = number of events (events rate per 100 patient years); PY = sum of ((Date Last Known Alive – Date of Transplant + 1) / 365.25) and End of Treatment Date is used when Date of Transplant is missing

Conclusion

The CRL listed the use of rescue therapies, in particular blood transfusions as a deficiency. Regarding the increased use of ESA rescue in the vadadustat arm, the reviewer agrees with the Applicant that the definition of ESA rescue may have artificially decreased the rate of ESA rescue in the darbepoetin alfa arm as it did not capture substantial increases in darbepoetin alfa doses (i.e., above the US package insert ((USPI) recommendations). More convincing is the pre-specified sensitivity analyses that were performed for both the primary and secondary efficacy endpoints in which all hemoglobin values obtained within four weeks of administration of rescue therapy were set to missing and vadadustat remained non-inferior to darbepoetin alfa (see detailed analyses in the original NDA review). In addition, the Applicant has provided additional data of transplant rejection rates which shows that blood transfusions did not lead to increased rates of renal allograft rejection in the vadadustat group. This analysis provides reassurance that the RBC transfusions did not lead to adverse impact on renal allograft rejection.

The clinical reviewer considers the deficiency of increased rescue therapy use in the vadadustat arm resolved.

5. Adverse Events of Special Interest

The review team conducted additional safety analyses for gastric erosions and heart failure leading to hospitalization in the DD-CKD population, as these safety signals have been identified in the other approved HIF-PH inhibitor.

5.1. Gastric Erosions

Daprodustat, another HIF-PH inhibitor has a Warning in the label for gastric erosions. Due to concerns that this may be a class effect, the clinical and statistical reviewers assessed the data from the INNO2VATE trials (CI-0016 and CI-0017) for this safety signal.

As stated in the finalized statistical review (See review in DARRTS dated February 23, 2024), "In

the INNO2VATE trials narrowly defined gastrointestinal erosion events occurred more frequently in the vadadustat arm than the darbepoetin arm (4.0 per 100 PY versus 3.3 per 100 PY). The estimated IRD (95% CI) and HR (95% CI) were 0.72 per 100 PY (-0.23 per 100 PY, 1.67 per 100 PY) and 1.23 (0.94, 1.59), respectively (Table 14). This risk was mainly driven by gastrointestinal hemorrhage, gastritis erosive, melena in both arms (Table 16). A larger proportion of subjects in the vadadustat arm had serious gastrointestinal erosion events compared to those in the darbepoetin arm (2.1 per 100 PY versus 2.0 per 100 PY). ” Note, however, that the serious GI erosion results are unstable because of the small difference between treatment groups (2 patient difference). The rate of RBC transfusion for GI hemorrhage was lower in the vadadustat arm (Table 15).

Table 14. Risk of Gastrointestinal Erosion- INNO2VATE Trials, Pooled DD-CKD Safety Population

Endpoint	**Vadadustat N= 1947**				**Darbepoetin alfa N=1955**					
	n	%	PY	IR	n	%	PY	IR	IRD (95% CI)	HR (95% CI)
GI Erosion (Narrow FMQ)	124	6.4	3099	4.0	103	5.3	3144	3.28	0.72 (-0.23, 1.67)	1.23 (0.94, 1.59)
Serious GI Erosion (Narrow FMQ)	67	3.4	3154	2.1	65	3.3	3181	2.0	0.08 (-0.63, 0.79)	1.05 (0.8, 1.5)

Note: Group terms were used for GI erosion, see Appendix 12.5 for further details.
Source: DB7 Statistical Review
Abbreviations: n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; HR: hazard ratio; 95% CI: 95% confidence interval; GI, gastrointestinal

Table 15. Number and Proportion of Subjects with RBC Transfusion for Any Reason +/- 7 Days from GI Hemorrhage Event, INNO2VATE Trials, Pooled DD-CKD Safety Population

Parameter	**Vadadustat N=1947**	**Darbepoetin Alfa N= 1955**	**Relative Risk (95% CI)**
Number of subjects with GI hemorrhage (Narrow FMQ), n (%)	124 (6.4%)	103 (5.3%)	
Subjects with RBC transfusion, n (%)	55 (44.4%)	51 (49.5%)	0.9 (0.68, 1.18)

Source: Applicant’s response to Information Request (IR)
Abbreviations: CI: confidence interval; FMQ: FDA Medical Query; GI: gastrointestinal; N: number of subjects; RBC: red blood cell

Table 16. Number and Proportion of Gastrointestinal Erosion (narrow) Events by Preferred Terms- INNO2VATE Trials, Pooled DD-CKD Safety Population

PT terms	Vadadustat N=1947		Darbepoetin N=1955	
	n	%	n	%
Diverticular perforation	4	0.21	1	0.05
Duodenal ulcer	11	0.56	4	0.20
Duodenal ulcer haemorrhage	2	0.10	3	0.15
Erosive duodenitis	1	0.05	0	0.00
Gastric haemorrhage	0	0.00	2	0.10
Gastric ulcer	11	0.56	4	0.20
Gastric ulcer haemorrhage	0	0.00	1	0.05
Gastric ulcer perforation	2	0.10	0	0.00
Gastritis erosive	13	0.67	6	0.31
Gastritis haemorrhagic	3	0.15	1	0.05
Gastrointestinal haemorrhage	43	2.21	46	2.35
Haematemesis	5	0.26	5	0.26
Haemorrhagic erosive gastritis	2	0.10	1	0.05
Helicobacter gastritis	2	0.10	2	0.10
Melaena	12	0.62	8	0.41
Peptic ulcer	5	0.26	0	0.00
Peptic ulcer haemorrhage	1	0.05	2	0.10
Upper gastrointestinal haemorrhage	7	0.36	17	0.87
Total	124	6.37	103	5.27

Source: DB7 Statistical Review
Abbreviations: n: number of subjects with an event; %: proportion of subjects with an event

The risk of GI erosion was also assessed in the pooled NDD-CKD population. The results showed a slightly increased risk of serious GI erosion, although the findings are unstable because of the small differences between treatment groups (3 patient difference for GI erosion; 4 patient difference for serious GI erosion).

Table 17. Risk of Gastrointestinal Erosion- Pooled NDD-CKD Safety Population

Endpoint	**Vadadustat N= 1739**				**Darbepoetin alfa N=1732**					
	n	%	PY	IR	n	%	PY	IR	IRD (95% CI)	HR (95% CI)
GI Erosion (Narrow FMQ)	68	3.9	3032	2.2	71	4.1	3096	2.3	-0.05 (-0.8, 0.7)	1 (0.71, 1.4)
Serious GI Erosion	39	2.2	3063	1.3	35	2.0	3136	1.1	0.16 (-0.4, 0.7)	1.15 (0.7, 1.8)

Endpoint	Vadadustat N= 1739				Darbepoetin alfa N=1732					
(Narrow FMQ)										

Note: Group terms were used for GI erosion, see Appendix 12.5 for further details.
Source: DB7 Statistical Review
Abbreviations: n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; HR: hazard ratio; 95% CI: 95% confidence interval; GI, gastrointestinal

Conclusion: An increase in GI erosions was observed with vadadustat compared to darbepoetin alfa in the DD-CKD population therefore this risk may be a class effect. Similar to the other HIF-PH inhibitor, a risk for gastric erosions, which includes a risk of GI hemorrhage resulting in a blood transfusion, will be a Warning in the vadadustat UPSI. Patients may be at an increased risk for gastrointestinal erosions, if they have a history of gastrointestinal erosion, peptic ulcer disease, use of concomitant medications that increase the risk of gastrointestinal erosion, and current tobacco smokers and alcohol drinkers. The long-term risk of gastric erosions will be assessed in a PMR.

5.2. Heart Failure leading to Hospitalization

Daprodustat, has a Warning in the label for risk of hospitalization for heart failure. Due to concerns that this may be a class effect, the clinical and statistical reviewers assessed the data from the INNO2VATE trials (CI-0016 and CI-0017) for this safety signal.

As stated in the finalized statistical review (See review in DARRTS dated February 23, 2024), "The risk of heart failure, using adjudicated data from the original submission, was not increased in the vadadustat arm compared to the darbepoetin arm (Table 18). The estimated IRD (95% CI) and HR (95% CI) of the adjudicated hospitalization from heart failure were -0.13 per 100 PY (-0.95 per 100 PY, 0.69 per 100 PY) and 0.97 (0.71, 1.31), respectively. Similar results were shown using the adverse events defined using MedDRA terms: the HRs (95% CI) of heart failure and serious events were 0.88 (0.72, 1.07) and 0.86 (0.69, 1.08), respectively." Heart failure events were identified using the cardiac failure MedDRA SMQ narrow.

Table 18. Risk of Heart Failure- INNO2VATE Trials, Pooled DD-CKD Safety Population -

Endpoint	Vadadustat N= 1947				Darbepoetin alfa N=1955					
	n	%	PY	IR	n	%	PY	IR	IRD (95% CI)	HR (95% CI)
Heart Failure (HF)	184	9.5	3063.7	6.0	212	10.8	3065.3	6.9	-0.92 (-2.19, 0.35)	0.88 (0.72, 1.07)
Serious HF	142	7.3	3093.6	4.6	168	8.6	3104.7	5.4	-0.83 (-1.94, 0.29)	0.86 (0.69, 1.08)

Endpoint	Vadadustat N= 1947				Darbepoetin alfa N=1955					
	n	%	PY	IR	n	%	PY	IR	IRD (95% CI)	HR (95% CI)
Hospitalization for HF (adjudicated)	84	4.3	3133.7	2.7	89	4.6	3164	2.8	-0.13 (-0.95, 0.69)	0.97 (0.72, 1.31)

Source: DB7 statistical review
Abbreviations: n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; HR: hazard ratio; 95% CI: 95% confidence interval Estimates of hospitalization from HF (adjudicated) were based on adjudicated data from the original submission.

The risk of heart failure was also assessed in the pooled NDD-CKD population. The results also did not show an increased risk of heart failure (Table 19).

Table 19. Risk of Heart Failure- Pooled NDD-CKD Safety Population

Endpoint	Vadadustat N= 1739				Darbepoetin alfa N=1732					
	n	%	PY	IR	n	%	PY	IR	IRD (95% CI)	HR (95% CI)
Heart Failure (HF)	197	11.3	2912	6.8	213	12.3	2956	7.2	-0.4 (-1.8, 0.9)	0.96 (0.8, 1.2)
Serious HF	157	9	2962	5.3	178	10.3	2991	6.0	-0.7 (-1.9, 0.6)	0.9 (0.7, 1.1)
Hospitalization for HF (adjudicated)	126	7.2	2987.3	4.2	130	7.5	3035.1	4.3	-0.1 (-1.1, 1_	1.0 (0.8, 1.3)

Source: DB7 statistical reviewer
Abbreviations: n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; HR: hazard ratio; 95% CI: 95% confidence interval Estimates of hospitalization from HF (adjudicated) were based on adjudicated data from the original submission.

Conclusion: Heart failure did not occur at a higher rate in the vadadustat group compared to the darbepoetin alfa group. The long-term risk of heart failure will be further assessed in a PMR.

6. Review of Safety of Studies CI-0036 and CI-0039

6.1. Safety Review Approach

The Applicant provided a safety update in the resubmission with a reporting period from February 24, 2021 to June 28, 2023. The safety update included two completed Akebia-sponsored clinical trials in patients with DD-CKD (Studies CI-0036 and CI-0039).

Study CI-0036 was a phase 3b, randomized, open-label, active controlled study of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in patients requiring hemodialysis, after conversion from ESA therapy in the US and Europe. See Section 12.1 of the review for details on the study design.

Study CI-0039 was a phase 3b, randomized, open-label, active controlled study evaluating the efficacy and safety of dose conversion from epoetin beta (Mircera®) to three times weekly (TIW) oral vadadustat for the maintenance treatment of anemia in patients requiring hemodialysis. See Section 12.2 of the review for details on the study design.

The review of safety for both clinical trials will be high-level and focus on deaths, SAEs, AEs leading to drug discontinuation, and AEs of special interest.

Additional statistical review assistance was provided by Dr. Joo-Yeon Lee, Dr. Jae Joon Song, and Dr. Clara Kim in the Division of Biometrics VII; and Dr. Sarabdeep Singh, and Dr. Lola Luo in the Division of Biometrics IX. Additional clinical analysis assistance was provided by Dr. Justin Penzenstadler in the Division of Metabolism and Endocrinology Products (DMEP). Clinical Decision Scientist (CDS) assistance was provided by Dr. Jinzhong Liu and Dr. Jizu Zhi.

Clinical reviewer comment: Studies CI-0036 and CI-0039 explore a different dosing regimen of vadadustat and support the safety review of vadadustat. An overview of protocols CI-0036 and CI-0039 are located in Appendix 12.1 and 12.2 in this review below, respectively. The objectives, design, efficacy, ethical, patient, drug, and safety assessment considerations of Studies CI-0036 and CI-0039 appear to be acceptable. The studies appear to be adequately designed to evaluate the safety of vadadustat compared to darbepoetin alfa or epoetin beta for the maintenance treatment of anemia in patients on hemodialysis after conversion from current ESA therapy.

6.2. Review of the Safety Database

6.2.1. Overall Exposure

Study CI-0036

A total of 319 patients were enrolled and randomized in the study. Two subjects were randomized but not treated because they failed screening. In total, 317 subjects were randomized, 105 (33.1%), were treated with vadadustat once daily (QD); 104 (32.8%) were treated with vadadustat three times per week (TIW), and 108 (34.1%) patients were treated with darbepoetin alfa . Of the patients randomized, 317 patients were included in the safety population. The median exposure to vadadustat was 50 weeks in the QD group and 43 weeks in the TIW group (range: <1 week to 54 weeks). The median exposure to darbepoetin alfa was 51 weeks (range: < 1 to 54 weeks). The table below summarizes the study drug exposure data of the safety population.

Table 20. Study CI-0036 Study Drug Exposure

Parameter	Vadadustat QD N=105	Vadadustat TIW N=104	Darbepoetin alfa N=108
Duration of treatment, weeks			
Mean (SD)	37.8 (17.6)	37 (17.3)	40.2 (17)
Median (Q1, Q3)	50 (24.4, 52.1)	42.9 (21.8, 52.1)	51.1 (29.1, 52.1)
Min, Max	2, 52.7	0.4, 53.7	0.1, 53.6
Total exposure (person years)	76	74	83
Patients treated, by duration, n (%)			
<12 weeks	16 (15.2)	13 (12.5)	14 (13.0)
>=12 to <26 weeks	14 (13.3)	20 (19.2)	9 (8.3)
>=26 to <50 weeks	22 (21.0)	26 (25.0)	24 (22.2)
>=50 to <100 weeks	53 (50.5)	45 (43.3)	61 (56.5)
>=100 weeks	0	0	0

Source: CDS reviewer, adex.xpt and adsl.xpt; Software: R
Duration is 52 week open label treatment period plus 4 week follow-up.
Abbreviations: N, number of patients in treatment arm; n, number of patients with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Study CI-0039

In total, 456 patients were randomized, there were 152 patients assigned to each treatment group (vadadustat 600 mg TIW, vadadustat 900 mg TIW, or epoetin beta, respectively). Of the patients randomized, 451 patients were included in the safety population. The median exposure to vadadustat was similar in the 600 mg and 900 mg groups, i.e., 51 weeks (range < 1 to 53 weeks), respectively. The median exposure in the epoetin beta group was 50 weeks (range < 1 to 64 weeks). The table below summarizes the study drug exposure data for the safety population.

Table 21. Study CI-0039 Study Drug Exposure

Parameter	Vadadustat 600 mg TIW N=151	Vadadustat 900 mg TIW N=150	Epoetin beta N=150
Duration of treatment, weeks			
Mean (SD)	39.3 (17.2)	38 (18.6)	42.4 (15.4)
Median (Q1, Q3)	51.3 (25.7, 52.1)	50.8 (24.2, 52.1)	50.1 (43.3, 51.1)
Min, Max	0.1, 53.1	0.1, 53.3	0.1, 64.4

Parameter	Vadadustat 600 mg TIW N=151	Vadadustat 900 mg TIW N=150	Epoetin beta N=150
Total exposure (person years)	114	109	122
Patients treated, by duration, n (%)			
<12 weeks	17 (11.3)	24 (16.0)	14 (9.3)
>=12 to <26 weeks	22 (14.6)	16 (10.7)	10 (6.7)
>=26 to <50 weeks	29 (19.2)	30 (20.0)	49 (32.7)
>=50 to <100 weeks	83 (55.0)	80 (53.3)	77 (51.3)
>=100 weeks	0	0	0

Source: CDS reviewer, adex.xpt and adsl.xpt; Software: R
Duration is 52 week open label treatment period plus 4 week follow-up.
Abbreviations: N, number of patients in treatment arm; n, number of patients with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

6.2.2. Relevant characteristics of the safety population:

Study CI-0036

The 3 treatment groups were balanced overall and for mean age, sex, race and ethnicity. Of the 319 patients, 136 (42.6%) were female. The median age was 61 years (range: 31-90 years). The majority of patients were White (206 [64.6%]) and from the U.S. The countries with the highest contribution of patients accounting for over 80% of the safety population were the US, Hungary, Czech Republic, and Poland. The table below summarizes the key baseline demographics of patients enrolled in Study CI-0036 (safety population).

Table 22. Study CI-0036 Baseline Demographic and Clinical Characteristics

Characteristic	Vadadustat QD N=105	Vadadustat TIW N=104	Darbepoetin alfa N=108
Sex, n (%)			
F	47 (44.8)	46 (44.2)	43 (39.8)
M	58 (55.2)	58 (55.8)	65 (60.2)
Age, years			
Mean (SD)	60.9 (13.4)	61.4 (12.4)	60.8 (12.8)
Median (min, max)	63 (31, 90)	60 (31, 84)	60 (30, 88)
Age group, years, n (%)			
< 65	59 (56.2)	63 (60.6)	69 (63.9)
>= 65	46 (43.8)	41 (39.4)	39 (36.1)
Age group >=75, years, n (%)			
>= 75	17 (16.2)	22 (21.2)	20 (18.5)

Characteristic	Vadadustat QD N=105	Vadadustat TIW N=104	Darbepoetin alfa N=108
Race, n (%)			
American Indian or Alaska Native	1 (1.0)	2 (1.9)	0
Asian	4 (3.8)	1 (1.0)	3 (2.8)
Black or African American	31 (29.5)	30 (28.8)	33 (30.6)
Native Hawaiian or Other Pacific Islander	0	2 (1.9)	1 (0.9)
Not Reported	1 (1.0)	3 (2.9)	0
Other	0	1 (1.0)	0
White	68 (64.8)	65 (62.5)	71 (65.7)
Ethnicity, n (%)			
Hispanic or Latino	23 (21.9)	34 (32.7)	26 (24.1)
Not Hispanic or Latino	82 (78.1)	70 (67.3)	82 (75.9)
Country of participation, n (%)			
CZE	8 (7.6)	11 (10.6)	7 (6.5)
HUN	8 (7.6)	8 (7.7)	17 (15.7)
POL	12 (11.4)	9 (8.7)	5 (4.6)
USA	75 (71.4)	75 (72.1)	77 (71.3)
Others	2 (1.9)	1 (1)	2 (1.9)
Is in USA, n (%)			
USA	75 (71.4)	75 (72.1)	77 (71.3)
Non-USA	30 (28.6)	29 (27.9)	31 (28.7)

Source: CDS reviewer, adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Study CI-0039

The 3 treatment groups overall were well balanced. The median age of patients was 62 years (range: 22 to 97 years). The majority of patients were male (57.5%), white (58.1%), and non-Hispanic or Latino (68.9%). The table below summarizes the key baseline demographics of patients enrolled in Study CI-0039 (safety population).

Table 23. Study CI-0039 Baseline Demographic and Clinical Characteristics

Characteristic	Vadadustat 600 mg TIW N=151	Vadadustat 900 mg TIW N=150	Epoetin beta N=150
Sex, n (%)			
F	68 (45.0)	60 (40.0)	64 (42.7)
M	83 (55.0)	90 (60.0)	86 (57.3)
Age, years			
Mean (SD)	59.4 (14.2)	61.9 (13.3)	61.9 (12.7)
Median (min, max)	61 (22, 90)	63.5 (28, 89)	62 (30, 97)
Age group, years, n (%)			

Characteristic	Vadadustat 600 mg TIW N=151	Vadadustat 900 mg TIW N=150	Epoetin beta N=150
<65 years	92 (60.9)	83 (55.3)	87 (58.0)
>=65 years	59 (39.1)	67 (44.7)	63 (42.0)
Age group >=75, years, n (%)			
>= 75	20 (13.2)	26 (17.3)	24 (16.0)
Race, n (%)			
American Indian or Alaska Native	5 (3.3)	3 (2.0)	4 (2.7)
Asian	3 (2.0)	2 (1.3)	3 (2.0)
Black or African American	55 (36.4)	58 (38.7)	52 (34.7)
Native Hawaiian or Other Pacific Islander	1 (0.7)	0	0
Other	1 (0.7)	1 (0.7)	0
White	86 (57.0)	86 (57.3)	91 (60.7)
Ethnicity, n (%)			
Hispanic or Latino	42 (27.8)	40 (26.7)	55 (36.7)
Not Hispanic or Latino	109 (72.2)	107 (71.3)	94 (62.7)
Not Reported	0	2 (1.3)	0
Unknown	0	1 (0.7)	1 (0.7)
Country of participation, n (%)			
USA	151 (100)	150 (100)	150 (100)
Is in USA, n (%)			
USA	151 (100)	150 (100)	150 (100)

Source: CDS reviewer, adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

6.2.3. Adequacy of the safety database:

The safety database of Studies CI-0036 and CI-0039 is adequate to support the safety analysis of vadadustat in the DD-CKD population. However, Studies CI-0036 and CI-0039 are not adequate to serve as the primary safety database for the DD-CKD population due to differences in the dosing regimen of vadadustat and small sample size. Therefore, the safety of vadadustat in the DD-CKD population is mainly derived from Studies CI-0016 and CI-0017. Studies CI-0036 and CI-0039 were reviewed to ensure there are no new safety concerns beyond the safety concerns found in CI-0016 and CI-0017.

In total, there were a total of 775 patients enrolled in studies CI-0036 and CI-0039. In these studies, 510 patients with DD-CKD were treated with vadadustat, and 265 patients were treated with a comparator drug , i.e., darbepoetin alfa or epoetin alfa.

6.3. Adequacy of Applicant's Clinical Safety Assessments

6.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues regarding the data integrity or quality with this submission.

6.3.2. Categorization of Adverse Events

In Studies CI-0036 and CI-0039 adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 for Study CI-0036 and version 25.1 for Study CI-0039.

6.4. Safety Results

6.4.1. Deaths

Study CI-0036

A higher proportion of patients in the vadadustat QD group (11.4%) and vadadustat TIW group (8.7%) had an AE resulting in death compared to the darbepoetin alfa group (6.5%). However, the difference in events rates was small, limiting conclusions. The majority of deaths were due to an infection and cardiovascular death, which is not unexpected in this very medically complex population. A list of AEs that led to death are listed in the table below.

Table 24. Study CI-0036 Deaths

Preferred Term	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Any AE leading to death	12 (11.4)	9 (8.7)	7 (6.5)	4.9 (-2.9, 13.3)	2.2 (-5.3, 10.0)
End stage renal disease	2 (1.9)	0	0	1.9 (-1.6, 6.7)	0.0 (-3.5, 3.6)
COVID-19 pneumonia	3 (2.9)	3 (2.9)	2 (1.9)	1.0 (-4.0, 6.5)	1.0 (-4.0, 6.5)
Failure to thrive	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Peritonitis bacterial	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Pneumonia	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Sepsis	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Sudden cardiac death	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Cardio-respiratory arrest	1 (1.0)	0	1 (0.9)	0.0 (-4.2, 4.4)	-0.9 (-5.1, 2.7)
Septic shock	1 (1.0)	1 (1.0)	1 (0.9)	0.0 (-4.2, 4.4)	0.0 (-4.2, 4.4)
Gastrointestinal hemorrhage	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Hypertensive crisis	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Traumatic hematoma	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Cardiac arrest	0	2 (1.9)	1 (0.9)	-0.9 (-5.1, 2.6)	1.0 (-3.3, 5.9)
COVID-19	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)
Hemorrhagic stroke	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)

Source: CDS reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs with an onset date on or after the start of open-label treatment.
Duration is 52-week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

Study CI-0039

A higher proportion of patients in the epoetin beta group (11.3%) had AEs resulting in death compared to the vadadustat 600 mg group (9.3%) and vadadustat 900 mg group (8%). However, the difference in events rates was small, limiting conclusions. The majority of deaths were related to cardiovascular related AEs. A list of AEs resulting in death are listed in the table below.

Table 25. Study CI-0039 Deaths

Preferred Term	Vadadustat 600 mg TIW N=151 n (%)	Vadadustat 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Any AE leading to death	14 (9.3)	12 (8.0)	17 (11.3)	-2.1 (-9.2, 5.0)	-3.3 (-10.4, 3.5)
Septic shock	2 (1.3)	1 (0.7)	0	1.3 (-1.2, 4.7)	0.7 (-1.8, 3.7)
Shock	2 (1.3)	0	0	1.3 (-1.2, 4.7)	0.0 (-2.5, 2.5)
Cardiogenic shock	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
COVID-19 pneumonia	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Failure to thrive	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Hip fracture	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Tachycardia	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Arteriovenous graft site infection	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Cardiac failure	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Road traffic accident	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Sepsis	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Acute respiratory failure	1 (0.7)	0	1 (0.7)	-0.0 (-3.1, 3.1)	-0.7 (-3.7, 1.8)
Atrial fibrillation	1 (0.7)	0	1 (0.7)	-0.0 (-3.1, 3.1)	-0.7 (-3.7, 1.8)
COVID-19	1 (0.7)	1 (0.7)	1 (0.7)	-0.0 (-3.1, 3.1)	-0.0 (-3.1, 3.1)
Myocardial infarction	1 (0.7)	0	1 (0.7)	-0.0 (-3.1, 3.1)	-0.7 (-3.7, 1.8)
Acute myocardial infarction	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Aortic stenosis	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Cardio-respiratory arrest	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Death	0	1 (0.7)	1 (0.7)	-0.7 (-3.7, 1.8)	-0.0 (-3.1, 3.1)
Enterococcal sepsis	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Cardiac arrest	1 (0.7)	3 (2.0)	8 (5.3)	-4.7 (-9.6, -1.0) *	-3.3 (-8.4, 1.1)

Source: CDS reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as AE that begins or worsens after treatment initiation.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

Conclusion: In study CI-0036, a higher proportion of patients in the vadadustat groups had AEs resulting in death, however in Study CI-0039, a higher proportion in the ESA group had AEs resulting in death. Proportion of deaths should be interpreted with caution given the small sample size of the study and low event rates. Given study results from CI-0016 and CI-0017

there will be a boxed warning for increased risk of death with vadadustat.

6.4.2. Serious Adverse Events (SAEs)

Study CI-0036

The rates of SAEs were similar across vadadustat QD (44.8%), vadadustat TIW (45.2%) and darbepoetin alfa (43.5%) treatment groups (Table 26). Table 26 below shows SAEs based on FDA Medical Queries (FMQs), which group related preferred terms into medical concepts. In the vadadustat groups, SAEs which occurred at >5% (based on preferred terms or FMQs) included COVID-19 pneumonia, acute myocardial infarction, myocardial ischemia, acute coronary syndrome, heart failure, viral infection, bacterial infection, hemorrhage, arterial thrombosis and venous thrombosis. A few of these events (e.g., myocardial infarction, myocardial ischemia, thrombosis) were reported at a higher rate with vadadustat TIW dosing compared to vadadustat QD dosing and darbepoietin alfa, but conclusions are limited by low event rates.

Table 26. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 1% of Patients in Any Arm, Safety Population Trial CI-0036

System Organ Class Preferred Term	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Any SAE	47 (44.8)	47 (45.2)	47 (43.5)	1.2 (-12.0, 14.5)	1.7 (-11.6, 14.9)
Blood and lymphatic system disorders (SOC)	4 (3.8)	7 (6.7)	5 (4.6)	-0.8 (-7.1, 5.4)	2.1 (-4.6, 9.2)
Blood loss anemia	1 (1.0)	2 (1.9)	0	1.0 (-2.5, 5.2)	1.9 (-1.6, 6.8)
Anemia	3 (2.9)	5 (4.8)	5 (4.6)	-1.8 (-7.9, 4.0)	0.2 (-6.3, 6.8)
Cardiac disorders (SOC)	10 (9.5)	14 (13.5)	8 (7.4)	2.1 (-5.7, 10.2)	6.1 (-2.3, 14.9)
Acute myocardial infarction	2 (1.9)	6 (5.8)	0	1.9 (-1.6, 6.7)	5.8 (2.2, 12.0) *
Cardiac failure	2 (1.9)	0	1 (0.9)	1.0 (-3.4, 5.9)	-0.9 (-5.1, 2.7)
Cardiac failure congestive	2 (1.9)	2 (1.9)	1 (0.9)	1.0 (-3.4, 5.9)	1.0 (-3.3, 5.9)
Atrial fibrillation	1 (1.0)	2 (1.9)	1 (0.9)	0.0 (-4.2, 4.4)	1.0 (-3.3, 5.9)
Cardiac arrest	1 (1.0)	2 (1.9)	1 (0.9)	0.0 (-4.2, 4.4)	1.0 (-3.3, 5.9)
Myocardial infarction	0	3 (2.9)	1 (0.9)	-0.9 (-5.1, 2.6)	2.0 (-2.5, 7.3)

System Organ Class Preferred Term	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Gastrointestinal disorders (SOC)	3 (2.9)	9 (8.7)	3 (2.8)	0.1 (-5.4, 5.6)	5.9 (-0.4, 13.2)
Gastrointestinal hemorrhage	0	3 (2.9)	0	0.0 (-3.5, 3.5)	2.9 (-0.6, 8.2)
Pancreatitis acute	0	2 (1.9)	0	0.0 (-3.5, 3.5)	1.9 (-1.6, 6.8)
Upper gastrointestinal hemorrhage	0	1 (1.0)	2 (1.9)	-1.9 (-6.5, 1.7)	-0.9 (-5.7, 3.6)
General disorders and administration site conditions (SOC)	4 (3.8)	1 (1.0)	1 (0.9)	2.9 (-1.7, 8.6)	0.0 (-4.2, 4.4)
Non-cardiac chest pain	3 (2.9)	1 (1.0)	0	2.9 (-0.6, 8.1)	1.0 (-2.5, 5.3)
Immune system disorders (SOC)	0	0	3 (2.8)	-2.8 (-7.9, 0.8)	-2.8 (-7.9, 0.8)
Kidney transplant rejection	0	0	2 (1.9)	-1.9 (-6.5, 1.7)	-1.9 (-6.5, 1.8)
Infections and infestations (SOC)	19 (18.1)	22 (21.2)	21 (19.4)	-1.3 (-12.0, 9.3)	1.7 (-9.2, 12.7)
COVID-19 pneumonia	7 (6.7)	8 (7.7)	4 (3.7)	3.0 (-3.4, 9.9)	4.0 (-2.5, 11.3)
Pneumonia	2 (1.9)	3 (2.9)	1 (0.9)	1.0 (-3.4, 5.9)	2.0 (-2.5, 7.3)
Cellulitis	2 (1.9)	2 (1.9)	2 (1.9)	0.1 (-4.8, 5.1)	0.1 (-4.8, 5.1)
Gangrene	1 (1.0)	1 (1.0)	2 (1.9)	-0.9 (-5.7, 3.5)	-0.9 (-5.7, 3.6)
Osteomyelitis	1 (1.0)	1 (1.0)	2 (1.9)	-0.9 (-5.7, 3.5)	-0.9 (-5.7, 3.6)
COVID-19	2 (1.9)	2 (1.9)	4 (3.7)	-1.8 (-7.5, 3.4)	-1.8 (-7.5, 3.5)
Sepsis	1 (1.0)	3 (2.9)	3 (2.8)	-1.8 (-7.0, 2.7)	0.1 (-5.4, 5.7)
Diverticulitis	0	1 (1.0)	2 (1.9)	-1.9 (-6.5, 1.7)	-0.9 (-5.7, 3.6)
Klebsiella sepsis	0	0	2 (1.9)	-1.9 (-6.5, 1.7)	-1.9 (-6.5, 1.8)
Injury, poisoning and procedural complications (SOC)	8 (7.6)	9 (8.7)	7 (6.5)	1.1 (-6.2, 8.7)	2.2 (-5.3, 10.0)
Arteriovenous fistula site complication	2 (1.9)	0	0	1.9 (-1.6, 6.7)	0.0 (-3.5, 3.6)
Arteriovenous fistula thrombosis	0	2 (1.9)	3 (2.8)	-2.8 (-7.9, 0.8)	-0.9 (-6.2, 4.3)
Investigations (SOC)	2 (1.9)	0	4 (3.7)	-1.8 (-7.5, 3.4)	-3.7 (-9.2, -0.1) *
Metabolism and nutrition disorders (SOC)	7 (6.7)	7 (6.7)	9 (8.3)	-1.7 (-9.3, 5.9)	-1.6 (-9.3, 6.0)
Hypoglycemia	1 (1.0)	2 (1.9)	1 (0.9)	0.0 (-4.2, 4.4)	1.0 (-3.3, 5.9)
Hypervolemia	2 (1.9)	4 (3.8)	4 (3.7)	-1.8 (-7.5, 3.4)	0.1 (-5.8, 6.3)
Hyperkalemia	1 (1.0)	0	3 (2.8)	-1.8 (-7.0, 2.7)	-2.8 (-7.9, 0.8)

System Organ Class Preferred Term	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Musculoskeletal and connective tissue disorders (SOC)	3 (2.9)	2 (1.9)	2 (1.9)	1.0 (-4.0, 6.5)	0.1 (-4.8, 5.1)
Back pain	0	2 (1.9)	0	0.0 (-3.5, 3.5)	1.9 (-1.6, 6.8)
Renal and urinary disorders (SOC)	3 (2.9)	1 (1.0)	0	2.9 (-0.6, 8.1)	1.0 (-2.5, 5.3)
End stage renal disease	2 (1.9)	0	0	1.9 (-1.6, 6.7)	0.0 (-3.5, 3.6)
Respiratory, thoracic and mediastinal disorders (SOC)	7 (6.7)	6 (5.8)	2 (1.9)	4.8 (-0.7, 11.5)	3.9 (-1.5, 10.4)
Acute respiratory failure	3 (2.9)	1 (1.0)	0	2.9 (-0.6, 8.1)	1.0 (-2.5, 5.3)
Acute pulmonary oedema	2 (1.9)	0	0	1.9 (-1.6, 6.7)	0.0 (-3.5, 3.6)
Dyspnea	2 (1.9)	0	0	1.9 (-1.6, 6.7)	0.0 (-3.5, 3.6)
Pulmonary oedema	0	2 (1.9)	1 (0.9)	-0.9 (-5.1, 2.6)	1.0 (-3.3, 5.9)
Vascular disorders (SOC)	6 (5.7)	6 (5.8)	1 (0.9)	4.8 (-0.0, 11.1)	4.8 (0.0, 11.2) *
Peripheral arterial occlusive disease	1 (1.0)	2 (1.9)	0	1.0 (-2.5, 5.2)	1.9 (-1.6, 6.8)
Hypertensive crisis	0	2 (1.9)	0	0.0 (-3.5, 3.5)	1.9 (-1.6, 6.8)

Source: CDS reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as Aes with an onset date on or after the start of open-label treatment.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 27. Patients With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CI-0036

System Organ Class FMQ (Narrow)	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)					
Thrombocytopenia	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Anemia	4 (3.8)	7 (6.7)	5 (4.6)	-0.8 (-7.1, 5.4)	2.1 (-4.6, 9.2)
Cardiac disorders (SOC)					
Heart Failure	7 (6.7)	5 (4.8)	2 (1.9)	4.8 (-0.7, 11.5)	3.0 (-2.3, 9.2)
Acute Coronary Syndrome	2 (1.9)	9 (8.7)	1 (0.9)	1.0 (-3.4, 5.9)	7.7 (2.5, 14.8) *
Myocardial Infarction	2 (1.9)	9 (8.7)	1 (0.9)	1.0 (-3.4, 5.9)	7.7 (2.5, 14.8) *
Systemic Hypertension	1 (1.0)	3 (2.9)	0	1.0 (-2.5, 5.2)	2.9 (-0.6, 8.2)
Myocardial Ischemia	2 (1.9)	9 (8.7)	2 (1.9)	0.1 (-4.8, 5.1)	6.8 (1.0, 14.0) *
Cardiac Conduction Disturbance	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Arrhythmia	1 (1.0)	2 (1.9)	2 (1.9)	-0.9 (-5.7, 3.5)	0.1 (-4.8, 5.1)
Endocrine disorders (SOC)					
Hyperglycemia	4 (3.8)	0	1 (0.9)	2.9 (-1.7, 8.6)	-0.9 (-5.1, 2.7)
Diabetic Ketoacidosis	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Hypoglycemia	1 (1.0)	2 (1.9)	1 (0.9)	0.0 (-4.2, 4.4)	1.0 (-3.3, 5.9)
Gastrointestinal disorders (SOC)					
Pancreatitis	0	2 (1.9)	0	0.0 (-3.5, 3.5)	1.9 (-1.6, 6.8)
General disorders and administration site conditions (SOC)					
Dizziness	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Fatigue	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)
Hepatobiliary disorders (SOC)					
Hepatic Injury	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Cholecystitis	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Immune system disorders (SOC)					
Hypersensitivity	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)

System Organ Class FMQ (Narrow)	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Infections and infestations (SOC)					
Viral Infection	9 (8.6)	11 (10.6)	8 (7.4)	1.2 (-6.5, 9.1)	3.2 (-4.8, 11.5)
Opportunistic Infection	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Pneumonia	3 (2.9)	3 (2.9)	3 (2.8)	0.1 (-5.4, 5.6)	0.1 (-5.4, 5.7)
Fungal Infection	1 (1.0)	0	1 (0.9)	0.0 (-4.2, 4.4)	-0.9 (-5.1, 2.7)
Purulent Material	0	2 (1.9)	0	0.0 (-3.5, 3.5)	1.9 (-1.6, 6.8)
Bacterial Infection	9 (8.6)	9 (8.7)	11 (10.2)	-1.6 (-9.9, 6.6)	-1.5 (-9.8, 6.8)
Musculoskeletal and connective tissue disorders (SOC)					
Fracture	4 (3.8)	4 (3.8)	2 (1.9)	2.0 (-3.2, 7.8)	2.0 (-3.1, 7.9)
Osteoporosis	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Arthritis	1 (1.0)	0	1 (0.9)	0.0 (-4.2, 4.4)	-0.9 (-5.1, 2.7)
Back Pain	0	2 (1.9)	0	0.0 (-3.5, 3.5)	1.9 (-1.6, 6.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)					
Malignancy	0	2 (1.9)	4 (3.7)	-3.7 (-9.2, -0.1) *	-1.8 (-7.5, 3.5)
Nervous system disorders (SOC)					
Seizure	2 (1.9)	0	0	1.9 (-1.6, 6.7)	0.0 (-3.5, 3.6)
Syncope	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)
Stroke and TIA	1 (1.0)	2 (1.9)	3 (2.8)	-1.8 (-7.0, 2.7)	-0.9 (-6.2, 4.3)
Renal and urinary disorders (SOC)					
Renal & Urinary Tract Infection	0	2 (1.9)	0	0.0 (-3.5, 3.5)	1.9 (-1.6, 6.8)
Reproductive system and breast disorders (SOC)					
Abnormal Uterine Bleeding	0	1 (1.0)	1 (0.9)	-0.9 (-5.1, 2.6)	0.0 (-4.2, 4.4)
Respiratory, thoracic and mediastinal disorders (SOC)					
Respiratory Failure	4 (3.8)	2 (1.9)	2 (1.9)	2.0 (-3.2, 7.8)	0.1 (-4.8, 5.1)
Dyspnea	2 (1.9)	0	0	1.9 (-1.6, 6.7)	0.0 (-3.5, 3.6)
Respiratory Depression	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)

System Organ Class FMQ (Narrow)	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Vascular disorders (SOC)					
Hemorrhage	5 (4.8)	8 (7.7)	5 (4.6)	0.1 (-6.3, 6.7)	3.1 (-3.8, 10.4)
Thrombosis	5 (4.8)	13 (12.5)	5 (4.6)	0.1 (-6.3, 6.7)	7.9 (0.4, 16.2) *
Thrombosis Arterial	4 (3.8)	13 (12.5)	5 (4.6)	-0.8 (-7.1, 5.4)	7.9 (0.4, 16.2) *
Thrombosis Venous	2 (1.9)	3 (2.9)	3 (2.8)	-0.9 (-6.2, 4.2)	0.1 (-5.4, 5.7)
Hypotension	0	1 (1.0)	1 (0.9)	-0.9 (-5.1, 2.6)	0.0 (-4.2, 4.4)

Source: CDS reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as Aes with an onset date on or after the start of open-label treatment.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

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The rates of SAEs were similar across vadadustat 600 mg TIW (45%), vadadustat 900 mg TIW (44%) and epoetin beta (44.7%) treatment groups (Table 28). Table 29 below shows SAEs based on FMQs. In the vadadustat groups, SAEs that were reported in >5% based on FMQs included bacterial infection, viral infection, respiratory failure, hemorrhage, arterial thrombosis, and thrombosis, but rates were generally similar between treatment groups and conclusions were limited by small numbers of events.

Table 28. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 1% of Patients in Any Arm, Safety Population Trial CI-0039

System Organ Class Preferred Term	Vadadust at 600 mg TIW N=151 n (%)	Vadadust at 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Any SAE	68 (45.0)	66 (44.0)	67 (44.7)	0.4 (-10.8, 11.5)	-0.7 (-11.9, 10.5)

System Organ Class Preferred Term	Vadadust at 600 mg TIW N=151 n (%)	Vadadust at 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)	5 (3.3)	1 (0.7)	2 (1.3)	2.0 (-1.8, 6.4)	-0.7 (-4.1, 2.5)
Blood loss anemia	3 (2.0)	1 (0.7)	0	2.0 (-0.5, 5.7)	0.7 (-1.8, 3.7)
Anemia	1 (0.7)	0	2 (1.3)	-0.7 (-4.1, 2.4)	-1.3 (-4.7, 1.2)
Cardiac disorders (SOC)	16 (10.6)	20 (13.3)	23 (15.3)	-4.7 (-12.6, 2.9)	-2.0 (-10.1, 6.1)
Cardiac failure congestive	5 (3.3)	2 (1.3)	1 (0.7)	2.6 (-0.7, 6.9)	0.7 (-2.5, 4.1)
Atrial fibrillation	3 (2.0)	3 (2.0)	3 (2.0)	-0.0 (-4.0, 3.9)	-0.0 (-4.0, 4.0)
Atrioventricular block complete	0	2 (1.3)	1 (0.7)	-0.7 (-3.7, 1.8)	0.7 (-2.5, 4.1)
Acute myocardial infarction	4 (2.6)	3 (2.0)	5 (3.3)	-0.7 (-5.3, 3.7)	-1.3 (-5.8, 2.8)
Coronary artery disease	0	0	2 (1.3)	-1.3 (-4.7, 1.2)	-1.3 (-4.7, 1.2)
Cardiac arrest	2 (1.3)	3 (2.0)	11 (7.3)	-6.0 (-11.5, -1.6) *	-5.3 (-10.9, -0.6) *
Gastrointestinal disorders (SOC)	7 (4.6)	13 (8.7)	8 (5.3)	-0.7 (-6.1, 4.6)	3.3 (-2.6, 9.6)
Impaired gastric emptying	2 (1.3)	1 (0.7)	1 (0.7)	0.7 (-2.5, 4.1)	-0.0 (-3.1, 3.1)
Constipation	0	2 (1.3)	0	0.0 (-2.5, 2.5)	1.3 (-1.2, 4.7)
Gastrointestinal hemorrhage	1 (0.7)	4 (2.7)	1 (0.7)	-0.0 (-3.1, 3.1)	2.0 (-1.3, 6.1)
General disorders and administration site conditions (SOC)	4 (2.6)	3 (2.0)	2 (1.3)	1.3 (-2.4, 5.5)	0.7 (-3.0, 4.5)
Catheter site thrombosis	0	2 (1.3)	0	0.0 (-2.5, 2.5)	1.3 (-1.2, 4.7)
Hepatobiliary disorders (SOC)	0	1 (0.7)	3 (2.0)	-2.0 (-5.7, 0.5)	-1.3 (-5.1, 1.9)
Cholecystitis acute	0	0	2 (1.3)	-1.3 (-4.7, 1.2)	-1.3 (-4.7, 1.2)
Infections and infestations (SOC)	30 (19.9)	27 (18.0)	30 (20.0)	-0.1 (-9.2, 9.0)	-2.0 (-11.0, 7.0)
Bacteremia	3 (2.0)	0	0	2.0 (-0.5, 5.7)	0.0 (-2.5, 2.5)
Osteomyelitis	4 (2.6)	0	1 (0.7)	2.0 (-1.3, 6.0)	-0.7 (-3.7, 1.8)
Septic shock	3 (2.0)	2 (1.3)	1 (0.7)	1.3 (-1.9, 5.1)	0.7 (-2.5, 4.1)
Pneumonia	4 (2.6)	7 (4.7)	2 (1.3)	1.3 (-2.4, 5.5)	3.3 (-0.7, 8.2)
Staphylococcal bacteremia	1 (0.7)	2 (1.3)	0	0.7 (-1.9, 3.7)	1.3 (-1.2, 4.7)
Sepsis	2 (1.3)	4 (2.7)	2 (1.3)	-0.0 (-3.6, 3.5)	1.3 (-2.4, 5.5)
Gangrene	3 (2.0)	0	3 (2.0)	-0.0 (-4.0, 3.9)	-2.0 (-5.7, 0.5)
Cellulitis	1 (0.7)	3 (2.0)	2 (1.3)	-0.7 (-4.1, 2.4)	0.7 (-3.0, 4.5)
Arteriovenous fistula site infection	0	1 (0.7)	2 (1.3)	-1.3 (-4.7, 1.2)	-0.7 (-4.1, 2.5)
Cellulitis staphylococcal	0	0	2 (1.3)	-1.3 (-4.7, 1.2)	-1.3 (-4.7, 1.2)
Urinary tract infection	0	1 (0.7)	2 (1.3)	-1.3 (-4.7, 1.2)	-0.7 (-4.1, 2.5)
Device related sepsis	0	0	3 (2.0)	-2.0 (-5.7, 0.5)	-2.0 (-5.7, 0.5)
COVID-19	3 (2.0)	5 (3.3)	6 (4.0)	-2.0 (-6.7, 2.2)	-0.7 (-5.6, 4.1)
COVID-19 pneumonia	1 (0.7)	4 (2.7)	8 (5.3)	-4.7 (-9.6, -1.0) *	-2.7 (-7.9, 2.0)

System Organ Class Preferred Term	Vadadust at 600 mg TIW N=151 n (%)	Vadadust at 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Injury, poisoning and procedural complications (SOC)	9 (6.0)	10 (6.7)	11 (7.3)	-1.4 (-7.5, 4.6)	-0.7 (-6.8, 5.4)
Arteriovenous fistula site complication	0	2 (1.3)	1 (0.7)	-0.7 (-3.7, 1.8)	0.7 (-2.5, 4.1)
Arteriovenous fistula thrombosis	1 (0.7)	3 (2.0)	2 (1.3)	-0.7 (-4.1, 2.4)	0.7 (-3.0, 4.5)
Arteriovenous graft thrombosis	1 (0.7)	3 (2.0)	5 (3.3)	-2.7 (-7.0, 0.7)	-1.3 (-5.8, 2.8)
Investigations (SOC)	1 (0.7)	3 (2.0)	1 (0.7)	-0.0 (-3.1, 3.1)	1.3 (-1.9, 5.1)
Aspartate aminotransferase increased	0	2 (1.3)	1 (0.7)	-0.7 (-3.7, 1.8)	0.7 (-2.5, 4.1)
Metabolism and nutrition disorders (SOC)	12 (7.9)	12 (8.0)	10 (6.7)	1.3 (-4.9, 7.6)	1.3 (-4.9, 7.6)
Hypervolemia	7 (4.6)	6 (4.0)	4 (2.7)	2.0 (-2.6, 6.9)	1.3 (-3.2, 6.1)
Failure to thrive	2 (1.3)	1 (0.7)	0	1.3 (-1.2, 4.7)	0.7 (-1.8, 3.7)
Hyperkalemia	4 (2.6)	4 (2.7)	5 (3.3)	-0.7 (-5.3, 3.7)	-0.7 (-5.2, 3.8)
Hypoglycemia	0	1 (0.7)	2 (1.3)	-1.3 (-4.7, 1.2)	-0.7 (-4.1, 2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	3 (2.0)	2 (1.3)	0	2.0 (-0.5, 5.7)	1.3 (-1.2, 4.7)
Colon cancer	2 (1.3)	0	0	1.3 (-1.2, 4.7)	0.0 (-2.5, 2.5)
Nervous system disorders (SOC)	8 (5.3)	5 (3.3)	8 (5.3)	-0.0 (-5.6, 5.5)	-2.0 (-7.3, 2.9)
Encephalopathy	2 (1.3)	0	1 (0.7)	0.7 (-2.5, 4.1)	-0.7 (-3.7, 1.8)
Syncope	0	0	2 (1.3)	-1.3 (-4.7, 1.2)	-1.3 (-4.7, 1.2)
Psychiatric disorders (SOC)	0	1 (0.7)	2 (1.3)	-1.3 (-4.7, 1.2)	-0.7 (-4.1, 2.5)
Mental status changes	0	1 (0.7)	2 (1.3)	-1.3 (-4.7, 1.2)	-0.7 (-4.1, 2.5)
Respiratory, thoracic and mediastinal disorders (SOC)	10 (6.6)	11 (7.3)	8 (5.3)	1.3 (-4.4, 7.1)	2.0 (-3.8, 8.0)
Acute respiratory distress syndrome	3 (2.0)	0	0	2.0 (-0.5, 5.7)	0.0 (-2.5, 2.5)
Pulmonary oedema	2 (1.3)	3 (2.0)	1 (0.7)	0.7 (-2.5, 4.1)	1.3 (-1.9, 5.1)
Acute respiratory failure	4 (2.6)	5 (3.3)	5 (3.3)	-0.7 (-5.3, 3.7)	-0.0 (-4.7, 4.7)
Skin and subcutaneous tissue disorders (SOC)	1 (0.7)	0	2 (1.3)	-0.7 (-4.1, 2.4)	-1.3 (-4.7, 1.2)
Diabetic foot	1 (0.7)	0	2 (1.3)	-0.7 (-4.1, 2.4)	-1.3 (-4.7, 1.2)
Vascular disorders (SOC)	10 (6.6)	8 (5.3)	9 (6.0)	0.6 (-5.2, 6.5)	-0.7 (-6.4, 5.0)
Shock	2 (1.3)	0	0	1.3 (-1.2, 4.7)	0.0 (-2.5, 2.5)
Hypertension	1 (0.7)	1 (0.7)	2 (1.3)	-0.7 (-4.1, 2.4)	-0.7 (-4.1, 2.5)
Hypotension	1 (0.7)	3 (2.0)	3 (2.0)	-1.3 (-5.1, 1.9)	-0.0 (-4.0, 4.0)

Source: CDS reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as AE that begins or worsens after treatment initiation.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 29. Patients With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CI-0039

System Organ Class FMQ (Narrow)	Vadadustat 600 mg TIW N=151 n (%)	Vadadustat 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)					
Anemia	4 (2.6)	1 (0.7)	2 (1.3)	1.3 (-2.4, 5.5)	-0.7 (-4.1, 2.5)
Cardiac disorders (SOC)					
Heart Failure	7 (4.6)	7 (4.7)	2 (1.3)	3.3 (-0.7, 8.1)	3.3 (-0.7, 8.2)
Tachycardia	1 (0.7)	0	1 (0.7)	-0.0 (-3.1, 3.1)	-0.7 (-3.7, 1.8)
Systemic Hypertension	3 (2.0)	2 (1.3)	3 (2.0)	-0.0 (-4.0, 3.9)	-0.7 (-4.5, 3.0)
Arrhythmia	4 (2.6)	5 (3.3)	5 (3.3)	-0.7 (-5.3, 3.7)	-0.0 (-4.7, 4.7)
Myocardial Infarction	5 (3.3)	4 (2.7)	6 (4.0)	-0.7 (-5.6, 4.0)	-1.3 (-6.1, 3.2)
Cardiac Conduction Disturbance	0	2 (1.3)	2 (1.3)	-1.3 (-4.7, 1.2)	-0.0 (-3.6, 3.6)
Acute Coronary Syndrome	5 (3.3)	4 (2.7)	7 (4.7)	-1.4 (-6.4, 3.5)	-2.0 (-7.0, 2.6)
Myocardial Ischemia	5 (3.3)	4 (2.7)	7 (4.7)	-1.4 (-6.4, 3.5)	-2.0 (-7.0, 2.6)
Endocrine disorders (SOC)					
Hypoglycemia	0	2 (1.3)	2 (1.3)	-1.3 (-4.7, 1.2)	-0.0 (-3.6, 3.6)
Hyperglycemia	1 (0.7)	0	3 (2.0)	-1.3 (-5.1, 1.9)	-2.0 (-5.7, 0.5)
Gastrointestinal disorders (SOC)					
Constipation	0	2 (1.3)	0	0.0 (-2.5, 2.5)	1.3 (-1.2, 4.7)
Pancreatitis	1 (0.7)	0	1 (0.7)	-0.0 (-3.1, 3.1)	-0.7 (-3.7, 1.8)
Diarrhea	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
General disorders and administration site conditions (SOC)					
Dizziness	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Fall	0	1 (0.7)	1 (0.7)	-0.7 (-3.7, 1.8)	-0.0 (-3.1, 3.1)
Hepatobiliary disorders (SOC)					
Hepatic Injury	0	3 (2.0)	1 (0.7)	-0.7 (-3.7, 1.8)	1.3 (-1.9, 5.1)
Cholecystitis	0	0	2 (1.3)	-1.3 (-4.7, 1.2)	-1.3 (-4.7, 1.2)
Infections and infestations (SOC)					
Pneumonia	5 (3.3)	7 (4.7)	3 (2.0)	1.3 (-2.8, 5.8)	2.7 (-1.7, 7.6)
Purulent Material	2 (1.3)	0	1 (0.7)	0.7 (-2.5, 4.1)	-0.7 (-3.7, 1.8)
Bacterial Infection	17 (11.3)	14 (9.3)	18 (12.0)	-0.7 (-8.2, 6.7)	-2.7 (-9.9, 4.5)
Viral Infection	7 (4.6)	12 (8.0)	15 (10.0)	-5.4 (-11.8, 0.6)	-2.0 (-8.8, 4.7)

System Organ Class FMQ (Narrow)	Vadadustat 600 mg TIW N=151 n (%)	Vadadustat 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Musculoskeletal and connective tissue disorders (SOC)					
Arthritis	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Back Pain	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Fracture	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Osteoporosis	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)					
Malignancy	2 (1.3)	2 (1.3)	0	1.3 (-1.2, 4.7)	1.3 (-1.2, 4.7)
Nervous system disorders (SOC)					
Paresthesia	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Seizure	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Syncope	0	0	2 (1.3)	-1.3 (-4.7, 1.2)	-1.3 (-4.7, 1.2)
Stroke and TIA	2 (1.3)	1 (0.7)	4 (2.7)	-1.3 (-5.5, 2.4)	-2.0 (-6.1, 1.3)
Renal and urinary disorders (SOC)					
Urinary Retention	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Renal & Urinary Tract Infection	2 (1.3)	1 (0.7)	2 (1.3)	-0.0 (-3.6, 3.5)	-0.7 (-4.1, 2.5)
Respiratory, thoracic and mediastinal disorders (SOC)					
Respiratory Failure	9 (6.0)	7 (4.7)	7 (4.7)	1.3 (-4.1, 6.9)	-0.0 (-5.3, 5.3)
Dyspnea	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Vascular disorders (SOC)					
Hemorrhage	9 (6.0)	8 (5.3)	6 (4.0)	2.0 (-3.3, 7.5)	1.3 (-3.8, 6.7)
Hypotension	1 (0.7)	3 (2.0)	3 (2.0)	-1.3 (-5.1, 1.9)	-0.0 (-4.0, 4.0)
Thrombosis Venous	2 (1.3)	6 (4.0)	7 (4.7)	-3.3 (-8.2, 0.6)	-0.7 (-5.8, 4.4)
Thrombosis	8 (5.3)	11 (7.3)	17 (11.3)	-6.0 (-12.8, 0.2)	-4.0 (-11.0, 2.7)
Thrombosis Arterial	8 (5.3)	8 (5.3)	17 (11.3)	-6.0 (-12.8, 0.2)	-6.0 (-12.7, 0.3)

Source: CDS reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as AE that begins or worsens after treatment initiation.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TIA, transient ischemic attack

Conclusion: Overall, SAEs occurred at similar rates in the vadadustat groups and ESA group in both trials. No new safety concerns were identified for the proposed vadadustat QD dosing regimen in these trials, but small numbers of events limit conclusions.

6.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study CI-0036

The rates of AEs leading to discontinuation were similar between vadadustat QD (2.9%), and darbepoetin alfa (2.8%) treatment groups (Table 30). The rate of AEs leading to discontinuation was higher in the vadadustat TIW group (10.6%) compared to the darbepoetin alfa group (2.8%) (Risk difference 7.8%; 95% CI = 1.2, 15.6), although there was not a specific AE driving this higher rate with TIW dosing. In the vadadustat groups, no AEs leading to discontinuation were reported in >5% of patients. Table 31 below shows AEs leading to discontinuation based on FMQs.

Table 30. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CI-0036

System Organ Class Preferred Term	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Any AE leading to Discontinuation	3 (2.9)	11 (10.6)	3 (2.8)	0.1 (-5.4, 5.6)	7.8 (1.2, 15.6) *
Blood and lymphatic system disorders (SOC)	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Anemia	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Cardiac disorders (SOC)	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Atrial fibrillation	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Gastrointestinal disorders (SOC)	2 (1.9)	5 (4.8)	0	1.9 (-1.6, 6.7)	4.8 (1.3, 10.8) *
Diarrhea	1 (1.0)	3 (2.9)	0	1.0 (-2.5, 5.2)	2.9 (-0.6, 8.2)
Nausea	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Abdominal pain	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Gastritis	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Melaena	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
General disorders and administration site conditions (SOC)	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Fatigue	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Infections and infestations (SOC)	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)
COVID-19	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	1 (1.0)	2 (1.9)	-1.9 (-6.5, 1.7)	-0.9 (-5.7, 3.6)
Liposarcoma	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Adenocarcinoma of appendix	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)
Invasive ductal breast carcinoma	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)

System Organ Class Preferred Term	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Nervous system disorders (SOC)	1 (1.0)	1 (1.0)	0	1.0 (-2.5, 5.2)	1.0 (-2.5, 5.3)
Headache	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Transient ischemic attack	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Vascular disorders (SOC)	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Peripheral vascular disorder	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)

Source: CDS reviewer; adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs with an onset date on or after the start of open-label treatment.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 31. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CI-0036

System Organ Class FMQ (Narrow)	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Blood and lymphatic system disorders (SOC)					
Anemia	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Cardiac disorders (SOC)					
Arrhythmia	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Gastrointestinal disorders (SOC)					
Diarrhea	1 (1.0)	3 (2.9)	0	1.0 (-2.5, 5.2)	2.9 (-0.6, 8.2)
Nausea	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Abdominal Pain	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
General disorders and administration site conditions (SOC)					
Fatigue	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Infections and infestations (SOC)					
Viral Infection	0	0	1 (0.9)	-0.9 (-5.1, 2.6)	-0.9 (-5.1, 2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)					
Malignancy	0	1 (1.0)	2 (1.9)	-1.9 (-6.5, 1.7)	-0.9 (-5.7, 3.6)
Nervous system disorders (SOC)					
Headache	1 (1.0)	0	0	1.0 (-2.5, 5.2)	0.0 (-3.5, 3.6)
Stroke and TIA	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)

System Organ Class FMQ (Narrow)	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin alfa N=108 n (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Vascular disorders (SOC)					
Hemorrhage	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Thrombosis	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)
Thrombosis Arterial	0	1 (1.0)	0	0.0 (-3.5, 3.5)	1.0 (-2.5, 5.3)

Source: CDS reviewer; adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs with an onset date on or after the start of open-label treatment.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Study CI-0039

The rates of AEs leading to discontinuation were higher among the vadadustat 600 mg group (6.6%) and the vadadustat 900 mg group (12.7%) compared to the epoetin beta group (1.3%) with a risk difference of 5.3% (95% CI = 1.0, 10.6) when comparing vadadustat 600 mg to epoetin beta; and a risk difference of 11.3% (95% CI = 6.1, 17.8) when comparing vadadustat 900 mg to epoetin beta, respectively (Table 32). In the vadadustat groups, no AEs leading to discontinuation were reported at >5% of patients. Table 33 below shows AEs leading to discontinuation based on FMQs. Other than diarrhea with the vadadustat 900 mg TIW dose, there were no specific AEs driving the higher discontinuation rates due to AEs in the vadadustat arms.

Table 32. Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CI-0039

System Organ Class Preferred Term	Vadadustat 600 mg TIW N=151 n (%)	Vadadustat 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Any AE leading to Discontinuation	10 (6.6)	19 (12.7)	2 (1.3)	5.3 (1.0, 10.6) *	11.3 (6.1, 17.8) *
Cardiac disorders (SOC)	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Myocardial infarction	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Eye disorders (SOC)	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Vision blurred	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)

System Organ Class Preferred Term	Vadadustat 600 mg TIW N=151 n (%)	Vadadustat 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Gastrointestinal disorders (SOC)	4 (2.6)	13 (8.7)	0	2.6 (0.1, 6.6) *	8.7 (5.1, 14.3) *
Nausea	2 (1.3)	2 (1.3)	0	1.3 (-1.2, 4.7)	1.3 (-1.2, 4.7)
Abdominal discomfort	1 (0.7)	2 (1.3)	0	0.7 (-1.9, 3.7)	1.3 (-1.2, 4.7)
Hemorrhoids	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Abdominal pain	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Diarrhea	0	5 (3.3)	0	0.0 (-2.5, 2.5)	3.3 (0.8, 7.6) *
Dyspepsia	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Gastroesophageal reflux disease	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Vomiting	0	2 (1.3)	0	0.0 (-2.5, 2.5)	1.3 (-1.2, 4.7)
General disorders and administration site conditions (SOC)	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Pain	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Fatigue	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Infections and infestations (SOC)	1 (0.7)	2 (1.3)	1 (0.7)	-0.0 (-3.1, 3.1)	0.7 (-2.5, 4.1)
COVID-19	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Arteriovenous graft site infection	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Cellulitis	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Sepsis	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Investigations (SOC)	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Weight increased	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Colon cancer	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Hepatic cancer metastatic	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Nervous system disorders (SOC)	2 (1.3)	3 (2.0)	0	1.3 (-1.2, 4.7)	2.0 (-0.5, 5.7)
Burning sensation	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Somnolence	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Dizziness	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Headache	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Hypoaesthesia	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Migraine	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Psychiatric disorders (SOC)	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Anxiety	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Vascular disorders (SOC)	0	2 (1.3)	0	0.0 (-2.5, 2.5)	1.3 (-1.2, 4.7)
Deep vein thrombosis	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Orthostatic hypotension	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Peripheral ischemia	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)

Source: CDS reviewer; adae.xpt; Software: R
Treatment-emergent adverse events defined as AE that begins or worsens after treatment initiation.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 33. Adverse Events Leading to Treatment Discontinuation by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial CI-0039

System Organ Class FMQ (Narrow)	Vadadustat 600 mg TIW N=151 n (%)	Vadadustat 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Cardiac disorders (SOC)					
Acute Coronary Syndrome	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Myocardial Infarction	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Myocardial Ischemia	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)
Gastrointestinal disorders (SOC)					
Nausea	2 (1.3)	2 (1.3)	0	1.3 (-1.2, 4.7)	1.3 (-1.2, 4.7)
Abdominal Pain	1 (0.7)	3 (2.0)	0	0.7 (-1.9, 3.7)	2.0 (-0.5, 5.7)
Diarrhea	0	5 (3.3)	0	0.0 (-2.5, 2.5)	3.3 (0.8, 7.6) *
Dyspepsia	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Vomiting	0	2 (1.3)	0	0.0 (-2.5, 2.5)	1.3 (-1.2, 4.7)
General disorders and administration site conditions (SOC)					
Dizziness	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Fatigue	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Infections and infestations (SOC)					
Viral Infection	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Bacterial Infection	0	2 (1.3)	1 (0.7)	-0.7 (-3.7, 1.8)	0.7 (-2.5, 4.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)					
Malignancy	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Nervous system disorders (SOC)					
Paresthesia	1 (0.7)	1 (0.7)	0	0.7 (-1.9, 3.7)	0.7 (-1.8, 3.7)
Somnolence	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Headache	0	2 (1.3)	0	0.0 (-2.5, 2.5)	1.3 (-1.2, 4.7)

System Organ Class FMQ (Narrow)	Vadadustat 600 mg TIW N=151 n (%)	Vadadustat 900 mg TIW N=150 n (%)	Epoetin beta N=150 n (%)	Vadadustat 600 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin beta Risk Difference (%) (95% CI)
Psychiatric disorders (SOC)					
Anxiety	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Study Agent Abuse Potential	1 (0.7)	0	0	0.7 (-1.9, 3.7)	0.0 (-2.5, 2.5)
Vascular disorders (SOC)					
Hypotension	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Thrombosis Venous	0	1 (0.7)	0	0.0 (-2.5, 2.5)	0.7 (-1.8, 3.7)
Thrombosis	0	1 (0.7)	1 (0.7)	-0.7 (-3.7, 1.8)	-0.0 (-3.1, 3.1)
Thrombosis Arterial	0	0	1 (0.7)	-0.7 (-3.7, 1.8)	-0.7 (-3.7, 1.8)

Source: CDS reviewer; adae.xpt; Software: R
Treatment-emergent adverse events defined as AE that begins or worsens after treatment initiation.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Conclusion: Overall, AEs leading to discontinuation were reported at low rates in Studies CI-0036 and CI-0039. However, at higher TIW doses, AEs leading to discontinuation were reported at higher rates in the vadadustat group compared to the darbepoetin alfa group or the epoetin beta group in Studies CI-0036 and CI-0039, respectively. No AEs leading to discontinuation were reported at > 5% in the vadadustat QD or TIW treatment group in either Study CI-0036 or CI-0039. GI AEs will be reported in the vadadustat product label based on analyses from the INNO2VATE trials.

6.4.4. DILI Screening

Refer to DHN DILI consult review in DARRTS and Section 4.1 of this review.

6.4.5. Adverse Events of Special Interest

6.3.5.1 Thrombosis

In Study CI-0036, there were 13/209 (6%) patients in the vadadustat QD and TIW groups compared to 11/108 (10%) patients in the darbepoetin alfa group that had device/shunt thrombotic events (Table 34). In Study CI-0039, there were 18/301 (6%) patients in the

vadadustat 600 mg and 900 mg groups compared to 12/150 (8%) patients in the epoetin beta group that had device/shunt thrombotic events (Table 35). The tables below show the incidence rates of thrombotic events reported in Studies CI-0036 and CI-0039, respectively. Thrombotic events included grouped PT terms as described in Section 12.3 of the review.

Table 34. Study CI-0036 Thrombosis Incidence Rate Difference

	Vadadustat QD N=105		Vadadustat TIW N=104		Darbepoetin Alfa N=108		Incidence Rate Difference (per 100 PY, 95% CI)	
	n (%)	PY	n (%)	PY	n (%)	PY	QD vs. Darb	TIW vs. Darb
Thrombosis*	11 (10.5%)	74.3	15 (14.4%)	74.7	13 (12%)	85.8	-0.3 (-12.4, 11.7)	4.9 (-8.2, 18.0)
DV/SH/OCC/MF/ST*	6 (5.7%)	76.1	10 (9.6%)	75.7	13 (12%)	85.6	-7.3 (-17.7, 3.1)	-2.0 (-13.6, 9.7)
Device/Shunt Thrombosis*	5 (4.8%)	76.2	8 (8%)	77.1	11 (10.2%)	86.5	-6.2 (-15.6, 3.3)	-2.4 (-12.8, 8.1)

Source: DB7 Statistical reviewer
*Thrombosis, DV/SH/OCC/MF/ST and Device/Shunt are FDA grouped terms. See Section 12.3 of the review for the list of preferred terms.
Abbreviations: Darb = darbepoetin; PY = Patients years; DV/SH/OCC/MF/ST = Device/shunt thrombosis/occlusion/malfunction stenosis, QD= once daily, TIW= three times a week

Table 35. Study CI-0039 Thrombosis Incidence Rate Difference

	Vadadustat 600 mg N=151		Vadadustat 900 mg N=150		Epoetin beta N=150		Incidence Rate Difference (per 100 PY, 95% CI)	
	n (%)	PY	n (%)	PY	N (%)	PY	600 mg vs. Epo	900 mg vs. Epo
Thrombosis*	14 (9.3%)	129.3	12 (8%)	123.2	19 (12.7%)	130.5	-3.7 (-12.4, 4.9)	-4.8 (-13.4, 3.7)
DV/SH/OCC/MF/ST*	8 (5.3%)	130.5	9 (6%)	124.5	13 (8.7%)	130.3	-3.8 (-10.7, 3.0)	-2.8 (-9.9, 4.4)
Device/Shunt* Thrombosis	9 (6%)	130.0	9 (6%)	124.6	12 (8%)	130.8	-2.3 (-9.1, 4.6)	-2.0 (-9.0, 5.1)

Source: DB7 Statistical reviewer
*Thrombosis, DV/SH/OCC/MF/ST and Device/Shunt are FDA grouped terms. See Section 12.3 of the review for the list of preferred terms.
Abbreviations: Epo= epoetin beta; PY = Patients years; DV/SH/OCC/MF/ST = Device/shunt thrombosis/occlusion/malfunction stenosis

Conclusion: Overall, the rates of thrombosis including VAT were lower in the vadadustat groups compared to the ESA groups. Results should be interpreted with caution given the small sample size and alternative dosing regimens. The risk of thrombosis will be described in the label in a boxed warning given increased risk identified in the pivotal trials (CI-0016 and CI-0017). See original NDA review for further details.

6.3.5.2 Heart Failure leading to Hospitalization

Heart failure (HF) leading to hospitalization was an adverse event of special interest as ESAs and daprodustat (another HIF-PH inhibitor) contain a warning for increased risk of congestive heart

failure (CHF), death, as well as, serious adverse cardiovascular reactions such as MI, stroke, venous TE, and thrombosis of vascular access.

In Study CI-0036, the incidence rate of HF was higher in the vadadustat arms (both QD and TIW) compared to the darbepoetin arm (Table 36). In Study CI-0039, the incidence rate of HF was higher in the vadadustat arms (both 600 mg and 900 mg) compared to the Epoetin beta arm (Table 37). The relatively small number of patients enrolled in Study CI-0036 and CI-0039 limits conclusions. Heart failure events were identified using the cardiac failure MedDRA SMQ narrow (similar approach used for Studies CI-0016 and CI-0017).

Table 36. Study CI-0036 Heart Failure Incidence Rate Difference

	Vadadustat QD N=105		**Vadadustat TIW N=104**		**Darbepoetin Alfa N=108**		**Incidence Rate Difference (per 100 PY, 95% CI)**	
	n (%)	PY	n (%)	PY	n (%)	PY	QD vs. Darb	TIW vs. Darb
Heart Failure	9 (8.6%)	77.9	7 (6.7%)	76.9	2 (1.9%)	88.8	9.3 (1.1,17.5)	6.9 (-0.6, 14.3)
Serious HF	7 (6.7%	78.2	5 (4.8%)	77.4	2 (1.9%)	88.8	6.7 (-0.6 14.0)	4.2 (-2.3, 10.7)

Source: Source: statistical review, using data adsl.xpt and adae.xpt.
Abbreviations: HF = Heart failure. Darb = darbepoetin alfa, QD= once daily, TIW= three times a week, PY= person-year

Table 37. Study CI-0039 Heart Failure Incidence Rate Difference

	Vadadustat 600 mg N=151		**Vadadustat 900 mg N=150**		**Epoetin beta N=150**		**Incidence Rate Difference (per 100 PY, 95% CI)**	
	n (%)	PY	n (%)	PY	n (%)	PY	QD vs. EPO	TIW vs. EPO
Heart Failure	9 (6%)	131.5	10 (6.7%)	124.7	5 (3.3%)	138	3.2 (-2.3,8.7)	4.4 (-1.5, 10.3)
Serious HF	7 (4.6%)	132.6	7 (4.7%)	126.2	2 (1.3%)	138.8	3.8 (-0.6, 8.2)	4.1 (-0.5, 8.7)

Source: statistical review, using data adsl.xpt and adae.xpt.
Abbreviations: HF = Heart failure. EPO= epoetin beta, PY= person-year, QD= once daily, TIW= three times a week

Conclusion: The rates of HF were higher in the vadadustat groups compared to the ESA groups in Studies CI-0036 and CI-0039. Results are difficult to interpret given the small sample size and alternative dosing regimens. The risk of HF leading to hospitalization was not observed in larger pivotal trials (studies CI-0016 and CI-0017) therefore, it is unlikely that heart failure is a risk related to vadadustat (See Section 5.2 for further details). More likely, events of heart failure in Studies CI-0036 and CI -0039 are due to comorbidities and underlying condition of CKD.

6.3.5.3 Gastric Erosion

Gastric erosion was an adverse event of special interest as daprodustat (another HIF-PH inhibitor) contains a warning for increased risk of gastric erosions.

Overall, GI erosions were rare in Studies CI-0036 and CI-0039. In Study CI-0036, the incidence rate of GI erosion was higher in the vadadustat TIW arm compared to the darbepoetin arm (Table 38). In Study CI-0039, the incidence rate of GI erosion was higher in the vadadustat arms (both 600 mg and 900 mg) compared to the epoetin beta arm (Table 39). The very low event rates limit conclusions. GI erosion was defined as a grouped medical query, see Section 12.3 for further details (this approach was also used for Studies CI-0016 and CI-0017).

Table 38. Study CI-0036 Gastrointestinal Erosion Incidence Rate Difference

	Vadadustat QD N=105		Vadadustat TIW N=104		Darbepoetin Alfa N=108		Incidence Rate Difference (per 100 PY, 95% CI)	
	n (%)	PY	n (%)	PY	n (%)	PY	QD vs. Darb	TIW vs. Darb
GI Erosion	4 (3.8%)	78.9	8 (7.7%)	77.6	5 (4.6%)	87.9	-0.02 (-7.7, 6.4)	4.8 (-4, 13.6)
Serious GI Erosion	1 (1.0%)	80.4	5 (4.8%)	77.9	2 (1.9%)	89.8	-1.0 (-4.9, 3.0)	4.2 (-2.2, 10.6)

Source: statistical review, using data adsl.xpt and adae.xpt.
Abbreviations: GI = gastrointestinal, Darb = darbepoetin alfa, QD= once daily, TIW= three times a week, PY= person-year
Note: GI erosion was a grouped term query, see Appendix for further details

Table 39. Study CI-0039 Gastrointestinal Erosion Incidence Rate Difference

	Vadadustat 600 mg N=151		Vadadustat 900 mg N=150		Epoetin Beta N=150		Incidence Rate Difference (per 100 PY, 95% CI)	
	n (%)	PY	n (%)	PY	n (%)	PY	QD vs. EPO	TIW vs. EPO
GI Erosion	5 (3.3%)	131.7	7 (4.7%)	126	2 (1.3%)	138.8	2.4 (-1.5, 6.2)	4.1 (-0.5, 8.7)
Serious GI Erosion	3 (2%)	132.5	5 (3.3%)	126.8	2 (1.3%)	138.8	0.8 (-2.4, 4.1)	2.5 (-1.5, 6.5)

Source: statistical review, using data adsl.xpt and adae.xpt.
Abbreviations: GI= gastrointestinal,. EPO= epoetin beta, PY= person-year
Note: GI erosion was a grouped term query, see Appendix for further details

Conclusion: An increased risk of gastric erosions among patients treated with vadadustat compared to those treated with darbepoetin alfa was identified in the INNO2VATE trials (see Section 5.1 for further details). The very low event rates of GI erosions in Studies CI-0036 and CI-0039 limit conclusions from these trials and do not meaningfully impact the conclusions from INNO2VATE. GI erosions will be listed as a Warning in the vadadustat USPI.

6.3.5.4 Seizure

Seizure is an adverse reaction for ESAs, therefore, this risk was further evaluated in Studies CI-0036 and CI-0039. Results are difficult to interpret due to the rarity of event (Table 40 and Table 41) and do not inform further on this risk with vadadustat.

Table 40. Study CI-0036 Seizures

FMQ (Narrow)	Vadadustat QD N=105 n (%)	Vadadustat TIW N=104 n (%)	Darbepoetin Alfa N=108	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
Seizure	2 (1.9%)	0 (0%)	1 (0.9%)	1.0 (-3.4, 5.9)	-0.9 (-5.1, 2.7)

Source: CDS reviewer
Treatment-emergent adverse events defined as AE that begins or worsens after treatment initiation.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; FMQ, FDA medical query; QD, once daily; TIW, three times a week

Table 41. Study CI-0039 Seizures

FMQ (Narrow)	Vadadustat 600 mg TIW N=151 n(%)	Vadadustat 900 mg TIW N=150 n(%)	Epoetin Beta N=150	Vadadustat 600 mg TIW vs Epoetin Beta Risk Difference (%) (95% CI)	Vadadustat 900 mg TIW vs Epoetin Beta Risk Difference (%) (95% CI)
Seizure	2 (1.3%)	1 (0.7%)	3 (2.0%)	-0.7 (-4.6, 2.9)	-1.3 (-5.1, 1.9)

Source: CDS review
Treatment-emergent adverse events defined as AE that begins or worsens after treatment initiation.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; TIW, three times a week; FMQ, FDA medical query

Conclusion: Seizures are a risk with ESAs. While seizures were not listed as a deficiency in the CRL for vadadustat, it was noted that this risk should be studied in future clinical trials. Studies CI-0036 and CI-0039 had too few events of seizures to further inform this risk. Given the rate of seizures in the vadadustat clinical development program (see original NDA review for further details) is similar to that with ESAs, this risk will be described in a Warning in the vadadustat USPI.

6.3.5.5 Rhabdomyolysis

No adverse events of rhabdomyolysis were reported in Studies CI-0036 or CI-0039. Elevated creatine phosphokinase (CPK) >5x ULN were observed in only vadadustat arms.

Table 42. CPK Levels- Study CI-0036

Laboratory Parameter	Vadadustat QD N=105 n/Nw (%)	Vadadustat TIW N=104 n/Nw (%)	Darbepoetin alfa N=108 n/Nw (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
CPK, high (U/L)					
Level 1 (>3X ULN)	1/100 (1.0)	1/100 (1.0)	0/105 (0)	1.0 (-2.6, 5.5)	1.0 (-2.6, 5.5)
Level 2 (>5X ULN)	0/100 (0)	1/100 (1.0)	0/105 (0)	0.0 (-3.5, 3.7)	1.0 (-2.6, 5.5)
Level 3 (>10X ULN)	0/100 (0)	1/100 (1.0)	0/105 (0)	0.0 (-3.5, 3.7)	1.0 (-2.6, 5.5)

Source: CDS reviewer, adlbco.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data; ULN, upper limit of normal

Table 43. CPK Levels- Study CI-0039

Laboratory Parameter	Vadadustat QD N=105 n/Nw (%)	Vadadustat TIW N=104 n/Nw (%)	Darbepoetin alfa N=108 n/Nw (%)	Vadadustat QD vs Darbepoetin alfa Risk Difference (%) (95% CI)	Vadadustat TIW vs Darbepoetin alfa Risk Difference (%) (95% CI)
CPK, high (U/L)					
Level 1 (>3X ULN)	7/144 (4.9)	3/146 (2.1)	6/142 (4.2)	0.6 (-4.7, 6.0)	-2.2 (-7.1, 2.2)
Level 2 (>5X ULN)	4/144 (2.8)	1/146 (0.7)	0/142 (0)	2.8 (0.1, 6.9) *	0.7 (-2.0, 3.8)
Level 3 (>10X ULN)	0/144 (0)	1/146 (0.7)	0/142 (0)	0.0 (-2.6, 2.6)	0.7 (-2.0, 3.8)

Source: CDS reviewer, adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 52 week open label treatment period plus 4 week follow-up.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; Nw, number of patients with data; ULN, upper limit of normal

As shown in Table 42 (Study CI-0036) and Table 43 (Study CI-0039) there appears to be an imbalance of cases of elevated CPK > 5 x upper limit of normal (ULN), i.e., 6 cases among vadadustat treated subjects and 0 cases among darbepoetin alfa or epoetin beta treated subjects, which may signal an increased risk for rhabdomyolysis among patients exposed to vadadustat (see below for unique patient ID numbers and brief case narratives for cases identified) (based on Applicant's response dated March 12, 2024 to IR sent March 11, 2024).

Subject Narratives

1. Subject [redacted] (b) (6) (CI-0036) is a 39-year-old female who was randomized to vadadustat 600 mg TIW on [redacted] (b) (6) Concomitant medications included

atorvastatin, azithromycin, calcitriol, clonidine, labetalol, losartan, nifedipine, ondansetron and sevelamer carbonate. The subject had a medical history of diabetes, hypercholesterolemia, and muscle spasms. The subject had elevated CPK levels (554 U/L) at the screening visit (Day -21) and at Baseline (Day 1) (305 U/L), which normalized to 162 U/L on (b) (6) (Day 85). The subject stopped vadadustat on (b) (6) (b) (6) (Day 299) and received epoetin beta on (b) (6) and (b) (6) On (b) (6) (Day 349), the subject received a flu vaccine and her CPK reached 2825 U/L (50 days post last dose of vadadustat); based on ESA rescue stopping criteria, the subject was withdrawn from the study on this day and no further CPK measurements are available. No myopathy or rhabdomyolysis was reported as an AE by the investigator for this subject during the study.

2. Subject CI-0039- (b) (6) is a 66-year-old female who was randomized to vadadustat 600 mg TIW on (b) (6). Concomitant medications included ferric citrate, IV iron sucrose, epinephrine and lisinopril. Screening visit (Day -40) and Baseline (Day 1) CPKs were elevated at 468 U/L and 458 U/L, respectively. On (b) (6) (Day 87), elevated CPK (807 U/L) was reported as an AE by the investigator. The event was considered mild and not related to vadadustat and vadadustat treatment was continued. CPK levels remained elevated at Day 183 and Day 366, 860 U/L and 526 U/L, respectively. No myopathy or rhabdomyolysis was reported as an adverse event by the investigator for this subject during the study.

3. Subject CI-0039- (b) (6) is a 49 year old male who was randomized to vadadustat 600 mg TIW on (b) (6). Concomitant medications included iron sucrose, allopurinol, amlodipine, and epoetin beta. Screening visit (Day -24) and Baseline (Day 1) CPKs were elevated at 505 U/L and 302 U/L, respectively. The investigator reported that the subject had experienced elevated CPK since (b) (6) prior to starting dialysis and before the subject's participation in the study. Vadadustat treatment was interrupted based on Hb assessment on (b) (6) (Day 171) and reinstated on (b) (6) (Day 248). On (b) (6) (Day 183), while the subject had been off vadadustat for two weeks, the subject's CPK increased to 1446 U/L. The investigator attributed the CPK elevation to the subject's muscular physique, weightlifting, and iron sucrose which was administered between (b) (6) (Day 101) – (b) (6) (Day 122) and from (b) (6) (Day 171) – (b) (6) (Day 234). No myopathy or rhabdomyolysis was reported as an adverse event by the investigator for this subject during the study.

4. Subject CI-0039- (b) (6) is a 49-year-old male who was randomized to vadadustat 600 mg on (b) (6). Concomitant medications include atorvastatin, iron sucrose, nifedipine, carvedilol. This subject has a history of elevated CPK. Screening visit (Day -22) and Baseline (Day1) CPKs were elevated at 932 U/L and 1407 U/L, respectively. CPK levels were 757 U/L and 1072 U/L on Day 85 and Day 183, respectively. Atorvastatin was discontinued on Day 212. No changes were made to the vadadustat dose. The subject

completed the study on Day 363 and the CPK level was 1186 U/L. No myopathy or rhabdomyolysis was reported as an adverse event by the investigator for this subject.

5. Subject CI-0039-(b) (6) is a 35-year-old female who was randomized to vadadustat 600 mg TIW on (b) (6). Concomitant medications included lisinopril, hydrocodone, prednisone and iron sucrose. The subject has past medical history of generalized chronic pain, muscle cramps and hypertension. CPK was elevated at 372 U/L at the screening visit (Day -37). At Baseline (Day 1) and throughout the study, the CPK levels were normal except at the last study visit on (b) (6), Day 363 when CPK of 871 U/L was reported. At a subsequent unscheduled visit on (b) (6) (Day 377), CPK was 121 U/L. No myopathy or rhabdomyolysis was reported as an adverse event by the investigator for this subject.

6. Subject CI-0039 (b) (6) is an 89 year old male who was randomized to vadadustat 900 mg TIW on (b) (6). Screening visit (Day -28) and Baseline (Day 3) CPKs were 41 U/L and 58 U/L, respectively. Concomitant medications included iron sucrose, atorvastatin 80 mg and amlodipine. The subject has a history of coronary heart disease, hyperlipidemia and hypertension. Vadadustat was increased to 1200 mg TIW on Day 38, decreased to 900 mg TIW on Day 190 and further reduced to 600 mg TIW on Day 213. On (b) (6) (Day 218) CPK was 2717 U/L. Vadadustat and atorvastatin were held on (b) (6) (Day 220) and (b) (6) (Day 225), respectively. CPK levels remained elevated from July 21, 2022 (Day 220) (CPK 3165 U/L at the time) to (b) (6) (Day 232) (CPK 217 U/L at the time), before returning to normal on (b) (6) (Day 241) (CPK 68 U/L at the time) and remaining normal on August 18, 2022 (Day 248) (CPK 66 U/L at the time]. The event was considered resolved and vadadustat was restarted on (b) (6) (Day 250) at 600 mg TIW without subsequent incidences of CPK elevations. Atorvastatin was never restarted. No myopathy or rhabdomyolysis was reported as an adverse event by the investigator for this subject.

Clinical reviewer comment: While not listed as a deficiency in the CRL, the CRL stated that numerically, a higher number of patients had rhabdomyolysis in the vadadustat arm compared to the darbepoetin alfa arm. Elevations of CPK are not uncommon in patients with CKD. Both studies (CI-0036 and CI-0039) randomized twice as many subjects to vadadustat and more cases of elevated CPK were reported in the vadadustat groups. In 5 of the 6 vadadustat cases, the CPKs measured at Screening or Baseline were abnormally elevated and either resolved while taking vadadustat or continued to be abnormally elevated while on vadadustat. The sixth case (CI-0039-(b) (6)) had elevated CPK while receiving vadadustat and atorvastatin after 218 days of treatment. Following interruption of atorvastatin and vadadustat, the CPK returned to normal. Vadadustat was restarted at the prior dose (600 mg TIW) and atorvastatin was permanently discontinued without recurrence of elevated CPK. This sixth case appears to be consistent with atorvastatin-induced myopathy. No subject discontinued vadadustat for elevated CPK and all were asymptomatic. Based on available data from Studies CI-0036 and CI-

0039, there does not appear to be a clear association of rhabdomyolysis and vadadustat, this is consistent with the findings from Studies CI-0016 and CI-0017. As stated in the original NDA review, "There was no significant difference in CPK elevation observed between treatment arms. Overall, the occurrence and severity of rhabdomyolysis in the DD-CKD population is balanced between treatment arms, is considered relatively rare and, after review of the individual narratives, may be due to the presence of clinical risk factors."

7 Japanese Post-marketing Safety Database Review

Vadadustat, under the trade name VAFSEO™, was launched in Japan on August 26, 2020 for the treatment of anemia in patients with DD-CKD and NDD-CKD. A summary of the Japanese postmarketing database and reported hepatic events is discussed in Section 4.1 of this review. This section of the review focuses on the general safety assessment. Below are key points from the DEPI-1 (OSE) review, see finalized review in DARRTS on March 4, 2024.

MTPC estimates that more than (b) (4) CKD patients have been exposed to vadadustat as of the data lock date of June 28, 2023.

EPPV

The vadadustat EPPV was conducted for 6 months from August 26, 2020 to February 25, 2021, with over 800 hospitals and 3,000 clinics participating. Approximately 4,000 patients with CKD took part in the EPPV. Data from this reporting period were previously submitted in the initial NDA. The Applicant states no new safety signals were identified from the EPPV. The Applicant reported that no safety measures were taken during the survey period. The Agency did not identify any new safety concerns.

Postmarketing Spontaneous Reports and PSURs

During the reporting period from launch in Japan to June 28, 2023, a total of 4,159 AEs/ADRs in 2,793 unique patients were received by MTPC. Of the 4,159 AEs/ADRs, 1,070 were classified as serious adverse events (SAEs). Of the 1,070 SAEs, 201 were assessed as related to vadadustat by the reporter and 306 resulted in a fatal outcome. There have been five Japan PSURs since approval of vadadustat in Japan. The Applicant states that no new safety signals or changes in the safety profile of vadadustat were identified based on these data, and no new safety measures were considered necessary at the time of reporting. There were 3,089 non-serious AEs/ADRs reported during the period. The Agency did not identify any new safety concerns.

Post-marketing Surveillance (PMS) Observational Study – VIOLET

See Section 4.1 for baseline characteristic data and exposure. Among the 1,847 patients included in the safety analysis, AEs/ADRs were reported in 202 patients (10.9%), of which 63 (3.4%) were classified as SAEs. A total of ten AEs/ADRs resulting in death were reported (0.54%) (Table 44). Of the total 1,847 patients enrolled in the VIOLET Study, 162 patients discontinued treatment with vadadustat due to AEs/ADRs. The most frequently reported MedDRA system

organ class (SOC) associated with treatment discontinuation was Gastrointestinal Disorders (n=37; 2.0%), followed by Cardiac Disorders (n=22; 1.2%), Metabolism and Nutrition Disorders (n=20; 1.1%), Infections and Infestations (n=19; 1.0%), Skin and Subcutaneous Tissue Disorders (n=16; 0.9%), Nervous System Disorders (n=13; 0.7%), and Hepatobiliary Disorders (n=8; 0.4%). In addition, 94 patients discontinued vadadustat treatment due to "hospital transfer." See review by DEPI-1 for further details on specific adverse event terms that led to treatment discontinuation.

Table 44. VIOLET Study Adverse Events Resulting in Death

	Overall (n=1,847)	Dialysis-dependent (n=614)
Number (%) of patients with a fatal outcome	10 (0.54%)	7 (1.14%)
Infections and infestations (SOC)		
Pneumonia	1	1
Hepatic cyst infection	1	1
Blood and lymphatic system disorders (SOC)		
Atypical hemolytic uremic syndrome	1	1
Cardiac disorders (SOC)		
Arrhythmia	1	1
Cardiac failure congestive	1	0
Vascular disorders (SOC)		
Circulatory collapse	1	1
Renal and urinary disorders (SOC)		
Chronic kidney disease	1	0
General disorders and administration site conditions (SOC)		
Death	1	1
Sudden death	2	1

Source: Vadadustat Japan VIOLET Study Interim Results. June 28, 2023. Attachment 1-10

Clinical reviewer comment: The Japanese post-marketing database did not reveal any new safety risks. However, as stated in the DEPI-1 review, there are several limitations with this database including missing patient level data and data quality issues.

8 Advisory Committee Meeting and Other External Consultations

An advisory committee (AC) meeting was not convened to discuss this application. No issues were identified that would have benefitted from a public discussion with external experts.

9 Labeling Recommendations

9.3 Prescription Drug Labeling

Table 45 Summary of Significant Labeling Changes

Section	Revision Summary	Rationale for Change
Highlights of Prescribing Information		
Boxed Warning	Title and contents revised	To be consistent with other class labeling (Jesduvroq)
1 Indications and Usage	Revised indication to state for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least three months. Added limitations of use for "not been shown to improve quality of life, fatigue, or patient well-being".	To be consistent with other class labeling (Jesduvroq and ESAs) FDA revised the indication statement to state patients should be on dialysis for at least 3 months due to the concern that there was an increased risk of MACE in the NDD population and only a small number of patients (<10%) initiated dialysis within a few months before starting vadadustat in the DD-CKD population. Therefore, the risk of MACE has not been sufficiently studied in patients recently initiating dialysis. In addition, recent literature has shown mortality rate in patients on dialysis is high within the first few months of initiating

		dialysis (Heaf et al. BMC Nephrology 2022).
2 Dosage and Administration	Revised monitoring recommendation duration for ALT, AST, and bilirubin from (b) (4) to 6 months. Added subsection 2.2 "Important Dosing Information"	To cover the timeframe in which liver test abnormalities were seen in trials. To place important dosing instructions in one subsection.
3 Dosage Forms and Strengths	No significant changes.	
4 Contraindications	Added Contraindication for uncontrolled hypertension	To be consistent with other class labeling (Jesduvroq and ESAs)
5 Warnings and Precautions	5.1 "Increased Risk of Death…."Added instructions to use the lowest dose sufficient to reduce the need for RBC transfusions. 5.3 "Hypertension" revised to include data from clinical trials on the rate of hypertension and to add mitigating strategies. 5.4 "Seizures" revised to remove (b) (4) (b) (4) (b) (4) added the rates of the risk. 5.5 Added a W&P for "Gastrointestinal Erosion" 5.6 Added a W&P for "Serious Adverse Reactions in Patients with Anemia Due to CKD and Not On Dialysis"	To be consistent with other class labeling. Warnings were revised to report events per PY using time in risk set. To be consistent with the W&P guidance on what information to include. To be consistent with the W&P guidance on what information to include. To describe the risk as experienced in the clinical trials. To describe the risk seen in the non-indicated population.

	5.7 Added a W&P for "Malignancy"	To describe the possible risks associated with increased HIF-1 levels and c/w JESDUVROQ and ESA labeling.
6 Adverse Reactions	Revised to describe the basis of the safety evaluation and to describe the pooling technique used. Added exposure data, treatment discontinuations, and most common ARs. Revised the common AR table to replace (b) (4) (b) (4) with "adverse reactions". Revised adverse reactions with FMQs (FDA MedDRA Queries). Defined grouped terms (FMQs) that included non-synonyms. From Table 2 Adjudicated Thromboembolic Events removed (b) (4) (b) (4)	To be consistent with the Adverse Reactions guidance. MedDRA terms are not clinically meaningful. To avoid splitting and capture terms together that are likely to be the same medical concept. To be c/w Adverse Reactions labeling guidance. (b) (4)
7 Drug Interactions	Revised drug interaction table to organize by the drug being affected rather than the drug class. Added implications of interactions. Added text describing interactions with statins	To organize the information and be consistent with the Drug Interactions guidance. Differential effects with different levels of renal dysfunction.

8 Use in Specific Populations	8.1 Pregnancy, 8.2 Lactation revised to be c/w PLLR guidance and animal data description revised to be c/w other class labelings. Deleted 8.6 (b) (4) (b) (4)	Per PLLR guidance and per Jesduvroq labeling. Per 21CFR201.57: Additional subsections. Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment). Additional subsections should not be created if there are no clinically relevant differences in response, safety, or recommendations for use of the drug in that subpopulation compared to the indicated population.
10 Overdosage	Removed description of (b) (4) Added "there is no specific antidote".	To Applicant: Per 21 CFR 201.57(c)(3)(ii), this section should not include information about an unapproved dosage (e.g., dosage greater than the maximum recommended dosage in Dosage and Administration section) not associated with an overdosage because this information may imply or suggest an unapproved dosage regimen.
11 Description	Added appearance of drug and solubility in water.	Per 21 CFR 201.57(c)(12).
12 Clinical Pharmacology	12.1 Revised MoA to specify the HIF hydroxylases that are affected.	To be c/w Jesduvroq.

	12.2 Pharmacodynamics—Qualified dosages outside the approved range. Revised text for Cardiac Electrophysiology. Summarized the specific populations without clinically significant PK changes or studies.	Per Clinical Pharmacology Section of Labeling Guidance. Per Clinical Pharmacology Section of Labeling Guidance.
13 Non-Clinical Toxicology	Removed (b) (4) Added text stating that vadadustat was not carcinogenic. Added the margin based on the maximum recommended human dose.	Per usual labeling practices and to increase applicability of findings to the recommended dosage.
14 Clinical Studies	Reorganized the section to remove proposed (b) (4) (b) (4) and use 14.1 to describe the studies in "Treatment of Anemia Due to CKD in Adult Patients on Dialysis". Removed (b) (4) (b) (4)	Information duplicative with subsection 14.2. (b) (4)

	Added table (b) (4) which describes the MACE results in the U.S. region in patients treated to Hb target of 10-11 g/dL.	Describes the US population.
15 References	n/a	
16 How Supplied/Storage and Handling	Added the tablet descriptions (tablet shape/color and tablet markings). Revised the storage statement to reflect the USP controlled room temperature.	To provide useful information and to be c/w carton/container labeling.
17 Patient Counseling Information	Updated to include description of newly revised/added W&P.	This section should include a description of the clinically relevant risks for the product.
Patient Labeling (Medication Guide)	Revised to be consistent with changes to the USPI.	Consistency with USPI.

10 Risk Evaluation and Mitigation Strategies (REMS)

Based on the available data, a risk evaluation and mitigation strategy is not necessary to ensure the benefits of vadadustat in the DD-CKD population outweigh the risks.

11 Postmarketing Requirements and Commitments

PMR 1: Conduct an observational study to characterize the long-term safety (up to 5 years follow up) of VAFSEO in adults with dialysis dependent chronic kidney disease treated with the approved dosing regimen of VAFSEO in the United States. Specific safety outcomes of interest include: thrombotic vascular events including vascular access thrombosis; hospitalization for heart failure; and serious gastrointestinal bleeds. The study population should include adults previously treated with erythropoiesis-stimulating agents (ESAs) and adults naïve to ESAs. The effect of baseline and maximum achieved hemoglobin on the specified safety outcomes should be evaluated.

PMR 2: Conduct an observational study (up to 5 years follow up) to assess the risk for malignancy (hematological and non-hematological) in adults with dialysis dependent chronic kidney disease with anemia treated with VAFSEO versus an erythropoiesis-stimulating agent comparator arm. The study should include an assessment of primary malignancies among adults with no cancer history (including assessment by type and location), and the impact of VAFSEO on progression-free survival, and overall survival in adults with prior cancers.

PMR 3: Conduct a worldwide descriptive study to collect prospective and retrospective data on women exposed to VAFSEO during pregnancy to assess the risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

PREA PMR: Conduct a trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of VAFSEO for the treatment of anemia associated with chronic kidney disease in children and adolescents aged 3 months to under 17 years requiring dialysis. Submit datasets at the time of the final clinical study report submission.

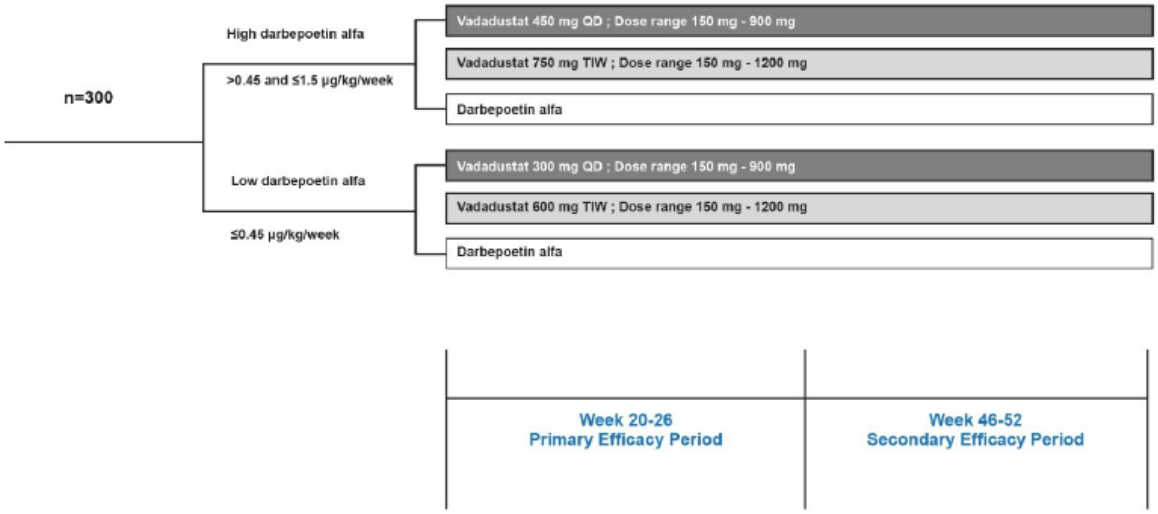
12 Appendices

12.1 Study AKB-6548-CI-0036 [MO2DIFY]

Study CI-0036 (Protocol #404-201-00012), was a phase 3b, randomized, open-label, active-controlled study of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in patients on hemodialysis, after conversion from ESA therapy. Following a Screening period of up to 8 weeks (56 days), patients were randomized 1:1:1 to vadadustat administered QD, vadadustat administered TIW, or darbepoetin alfa administered according to each country's approved labeling (Figure 3). Treatment groups were based on initial darbepoetin alfa dosing and patient weight and were grouped into darbepoetin low dose or high dose. Patients were converted from a low darbepoetin alfa dose group (≤ 0.45 µg/kg/week) to vadadustat 300 mg QD or vadadustat 600 mg administered TIW. Patients were converted from a high darbepoetin alfa dose group (> 0.45 and ≤ 1.5 µg/kg/week) to vadadustat 450 mg QD or

vadadustat 750 mg TIW. The goal of dosing was to maintain Hb levels 10.0 g/dL - 11.0 g/dL in the US and 10.0 g/dL - 12.0 g/dL in the EU. Study drug was permanently discontinued if ESA or red blood cell transfusion rescue treatment was required. Study drug was also discontinued for serum ALT or aspartate aminotransferase (AST) > 3 x ULN or serum TB > 2 x ULN. Additional discontinuation criteria for hepatoxicity were incorporated into the study.

Figure 3. Study CI-0036 Schema



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

Source: Applicant's CSR

Key enrollment criteria were as follows:

- Age ≥ 18 years.
- Receiving chronic, outpatient TIW hemodialysis for end-stage renal disease for at least 12 weeks prior to Screening.
- Hemodialysis single-pool Kt/Vurea ≥ 1.2 using the measurement within 8 weeks prior to or during Screening.
- Use of any approved ESA for at least the 8 weeks prior to Screening Visit 2.
- Two Hb values, at least 4 days apart, measured by the central laboratory during Screening within the following prespecified ranges.
    - a) Hb values between 8.0 and 11.0 g/dL (inclusive) in the US.
    - b) Hb values between 9.0 and 12.0 g/dL (inclusive) in Europe.
- Serum ferritin ≥ 100 ng/mL and transferrin saturation (TSAT) ≥ 20% during Screening.
- Folate and vitamin B12 measurements ≥ lower limit of normal during Screening.

Key exclusion criteria were as follows:

- Active bleeding or recent blood loss within 8 weeks prior to randomization.
- Patients requiring red blood cell transfusion within 8 weeks prior to randomization.
- Hemodialysis anticipated to be discontinued during the trial.

- Investigator decision that the patient is likely to need rescue therapy (e.g., ESA administration or RBC transfusion) immediately after enrollment in the trial.
- History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis, or fibrosis of the liver).
- Serum AST, ALT, or total bilirubin > 1.5 x ULN during Screening.
- Uncontrolled hypertension as determined by the investigator that would contraindicate the use of an ESA.
- 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.
- History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Patients with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded.
- History of a new or recurrent episode of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening.

The primary efficacy endpoints of the trial included efficacy parameters for change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive). Key secondary efficacy endpoints of the trial included efficacy parameters for change in Hb value between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 46 to 52). Treatment response that required dosing interruption was defined as any Hb increase > 1.0 g/dL within any 2-week interval or > 2.0 g/dL within any 4-week interval post Baseline after Day 1 of therapy.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Patients were monitored clinically, including complete blood counts, every 2 weeks up to week 20 and then approximately every 4 weeks from week 20 to 52.

12.1.1 Schedule of Events

Table 46. Study CI-0036 Schedule of Events

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

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

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

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

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

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

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

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

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

[f] Subjects may be retested.

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

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

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

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

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

[l] The biomarkers include, but are not limited to hepcidin and VEGF.

[m] Additional (optional) blood samples will be collected for PGx and future biospecimen research for consenting subjects only. Exploratory PGx and FBR plasma samples will be taken at Baseline, Weeks 26 and 52, and ET.

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

12.1.2 Protocol Synopsis

Protocol 404-201-00012

1 Protocol Summary

1.1 Synopsis

Name of Sponsor:

Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)

Name of Investigational Medicinal Product:

Vadadustat

Protocol No.:

404-201-00012

IND No.:

102,465

EudraCT No.:

2019-004851-36

Protocol Title:

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

Clinical Phase:

3b

Treatment/Indication:

Anemia of chronic kidney disease (CKD)

Objectives and Endpoints:

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

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

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

Other efficacy endpoints of the trial include the following:

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

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

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

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

Exploratory endpoints of the trial include biomarkers (including, but not limited to hepcidin and vascular endothelial growth factor [VEGF]).

Trial Design:

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

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

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

Randomization will be stratified with respect to:

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

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

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

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

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

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

Trial Population:

An estimated 300 subjects with approximately:

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

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

Inclusion Criteria:

Subjects are required to meet the following inclusion criteria:

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

Exclusion Criteria:

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

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

6) Anemia due to a cause other than CKD (eg, sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia).
7) Subjects meeting cut-off of the following equivalent mean weekly doses calculated over 8 weeks prior to Screening Visit 2:
   a) Methoxy polyethylene glycol-epoetin beta > 50 µg/week.
   b) Darbepoetin alfa > 100 µg/week.
   c) Epoetin analogues > 23000 IU/week.
8) Active bleeding or recent blood loss within 8 weeks prior to randomization.
9) Red blood cell transfusion within 8 weeks prior to randomization.
10) Anticipated to discontinue hemodialysis during the trial.
11) Judged by the investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the trial.
12) History of chronic liver disease (eg, chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis, or fibrosis of the liver).
13) Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin > 1.5 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded.
14) Current uncontrolled hypertension as determined by the investigator that would contraindicate the use of an ESA.
15) Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening.
16) History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Subjects with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded.
17) History of a new or recurrent episode of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening.
18) History of hemosiderosis or hemochromatosis.
19) History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded).
20) Scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months.
21) History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded).
22) Known hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients.

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

Retesting/Rescreening

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

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

Screening is limited to 3 attempts (initial Screening and 2 additional rescreening attempts). A new informed consent is required to be signed prior to every rescreening.

Trial Sites:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dose Adjustment

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

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

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

Guideline for Dose Adjustment	
Status of Hb Levels	**Dose Adjustment[a]**
Hb levels are to be maintained in the following target ranges: US only: 10.0 to 11.0 g/dL, inclusive. Europe only: 10.0 to 12.0 g/dL, inclusive.	A dose increase or decrease is required to achieve and maintain Hb levels within the target range. Dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for darbepoetin alfa approximately 25%)
Subject has a decline in Hb ≥ 0.5 g/dL from Baseline/Day 1 in the first 2-week period (the initial period from Baseline/Day 1 to Week 2 following conversion from prior ESA) and if Hb is < 10.0 g/dL.	A subject's dose may be increased by 1 dose level.
A rapid rise in Hb is observed (defined as follows): > 1.0 g/dL in any 2-week period or > 2.0 g/dL in any 4-week period.	Reduce or interrupt the dose.[b]
Hb levels are in the following setting: US only: Hb > 11.0 g/dL. Europe only: > 12.0 g/dL.	Reduce or interrupt the dose. After Hb falls below 11.0 g/dL (US) or 12.0 g/dL (Europe), restart IMP and consider restarting at a lower dose.

[a]In general, do not increase the dose more frequently than once every 4 weeks. A one-time dose increase after 2 weeks is allowed on only one occasion. Dose adjustment should be based on the investigator's clinical discretion.
[b]See Section 7.3.1 (Treatment Interruption).

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

Trial Assessments:

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

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

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

Biomarker Assessments: Samples for biomarker analysis, including, but not limited to hepcidin, and VEGF, will be drawn.

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

Other Assessments: optional pharmacogenomics (PGx) and future biospecimen research (FBR).

Statistical Methods:

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

Primary Efficacy Endpoint Analysis

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

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

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

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

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

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

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

Trial Duration:

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

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

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

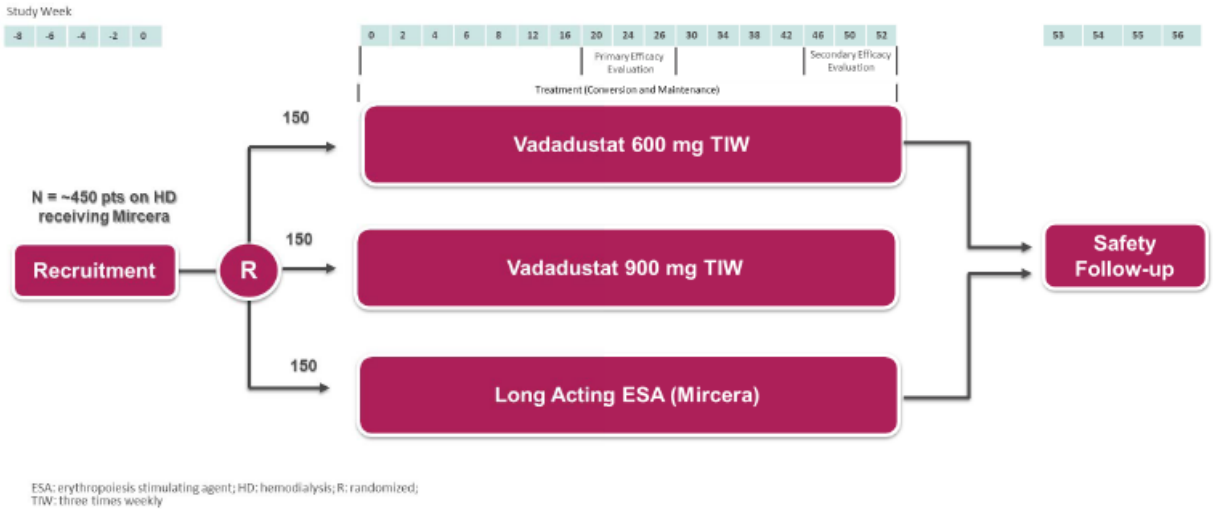
Subject Completion: A subject will be considered as having completed the trial after completion of their final trial visit (ET or Week 52/EOT). Safety Follow-up Visit data summarization and analysis will be performed separately.

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

12.2 Study AKB-6548-CI-0039 [FO2CUS]

Study CI-0039 was a multi-center, randomized, open-label, active-controlled study of the efficacy and safety of conversion from long-acting ESA (Mircera or Epoetin beta) to vadadustat TIW for the maintenance treatment of anemia in hemodialysis patients. Following the Screening Period of up to 8 weeks (56 days), patients were randomized 1:1:1 to vadadustat 600 mg administered TIW , vadadustat 900 mg administered TIW, or epoetin beta as standard of care according to the dialysis center's protocol (minimum vadadustat dose 300 mg TIW – maximum 1200 mg TIW) (Figure 4). The goal of dosing was to maintain Hb levels 10.0 g/dL - 11.0 g/dL. Study drug was permanently discontinued if ESA or red blood cell transfusion treatment was required rescue**.** Study drug was also discontinued for serum ALT or AST > 3 x ULN or serum TB > 2 x ULN. Additional discontinuation criteria for hepatoxicity were incorporated into the study.

Figure 4: Study Schema CI-0039



Source: Applicant's CSR

Key enrollment criteria were as follows.

- Age ≥ 18 years.
- Receiving chronic, outpatient TIW hemodialysis for end-stage renal disease for at least 12 weeks prior to Screening.
- Receiving epoetin beta therapy
- Mean Hb ≥ 8.5 and ≤ 11.0 g/dL determined by the average of 2 Hb values measured by the central laboratory at least 4 days apart.
- Serum ferritin ≥ 100 ng/mL and TSAT ≥ 20% during Screening.
- Serum folate and vitamin B12 measurements at or above the lower limit of normal during Screening.

Key exclusion criteria were as follows.

- Clinically meaningful bleeding event in opinion of investigator within 8 weeks prior to Baseline.
- RBC transfusion within 8 weeks prior to enrollment.
- History of chronic liver disease.
- Serum AST, ALT or TB >2 x ULN.
- Uncontrolled hypertension.
- 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 New York Heart Association Class IV, or stroke within 12 weeks prior to or during Screening.
- History of new, active or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer.

The primary efficacy endpoint of the trial included mean change in Hb between Baseline and the primary evaluation period from Weeks 20 to 26. The secondary efficacy endpoint was mean change in Hb between Baseline and the secondary evaluation period from Weeks 46 to 52. Treatment response that required dosing interruption was defined as any Hb increase > 1.0 g/dL within any 2-week interval or > 2.0 g/dL within any 4-week interval post Baseline after Day 1 of therapy.

AEs will be coded using MedDRA. Patients were monitored for clinically, including complete blood counts, every 2 weeks up to week 20 and then approximately every 4 weeks from week 20 to 52.

12.2.1 Schedule of Events

Table 47. Study CI-0039 Schedule of Events

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
KDQOL-36[e]			X					X				X							X	
FACT-An Score[e]			X					X				X							X	
PGI-S[e]			X					X				X							X	
PGI-C[e]								X				X							X	
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]																				
Biomarkers[m]			X		X			X				X							X	
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)																		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
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; FACT-An: Functional Assessment of Cancer Therapy-Anemia; Hb: hemoglobin; HDL: high density lipoprotein; I/E: inclusion/exclusion; KDQOL-36: Kidney Disease Quality of Life-36; LDH: lactate dehydrogenase; LDL: low density lipoprotein; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; 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; VEGF: vascular endothelial growth factor.

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. KDQOL-36, FACT-An, PGI-S, and PGI-C must be completed within the first 2 hours of dialysis.

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.

m. The biomarkers include, but are not limited to VEGF and hepcidin.

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

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

12.2.2 Protocol 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_{trs}) The PD endpoints include the following: • EPO • Reticulocyte count • Markers of iron metabolism (including iron, ferritin, total iron binding capacity [TIBC]).
Exploratory Endpoints	• Biomarkers (including, but not limited to vascular endothelial growth factor [VEGF] and hepcidin)
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).

12.3 Additional Safety Analysis Studies CI-0036 and CI-0039

FDA Grouped Terms

The below includes a list of FDA grouped terms. These grouped terms were similar to the ones used for the approved HIF-PH inhibitor (daprodustat).

FDA Thrombosis adverse group term = “Cerebral infarction“ “Embolic cerebral infarction” “Ischemic stroke“ “Cerebellar infarction” “Lacunar stroke“ “Embolic stroke” “Brain stem stroke“ “Lacunar infarction” “Thrombosis in device“ “Arteriovenous fistula thrombosis” “Arteriovenous graft thrombosis“ “Vascular access site thrombosis” “Vascular graft thrombosis“ “Graft thrombosis” “Shunt thrombosis“ “Acute myocardial infarction” “Myocardial infarction“ “Deep vein thrombosis” “Thrombosis“ “Atrial thrombosis“ “Peripheral artery thrombosis” “Subclavian vein thrombosis“ “Brachiocephalic vein thrombosis” “Subclavian artery thrombosis“ “Vena cava thrombosis” “Thrombophlebitis superficial“ “Arterial thrombosis” “Thrombophlebitis“ “Jugular vein thrombosis” “Venous thrombosis“ “Pelvic venous thrombosis” “Venous thrombosis limb“ “Cardiac ventricular thrombosis” “Intracardiac thrombus”

FDA Device/shunt thrombosis/occlusion/malfunction stenosis adverse event terms = “Thrombosis in device” “Arteriovenous fistula thrombosis”

"Arteriovenous graft thrombosis" "Vascular access site thrombosis" "Vascular graft thrombosis" "Medical device site thrombosis" "Device occlusion" "Arteriovenous fistula occlusion" "Vascular access site occlusion" "Vascular access complication" "Vascular access malfunction" "Arteriovenous graft site stenosis" "Shunt occlusion" "Shunt malfunction" "Vascular graft stenosis" "Anastomotic stenosis" "Vascular access site complication" "Vascular graft occlusion"

FDA Device/Shunt Thrombosis adverse event terms = "Thrombosis in device" "Arteriovenous fistula thrombosis" "Arteriovenous graft thrombosis" "Vascular access site thrombosis" "Vascular graft thrombosis" "Graft thrombosis" "Shunt thrombosis" "Medical device site thrombosis" "Device related thrombosis" "Injection site thrombosis"

FDA narrow (N) gastrointestinal bleeding adverse event terms = High level term (AEHLT) in ("Duodenal ulcers and perforation", "Gastric ulcers and perforation", "Gastrointestinal ulcers and perforation, site unspecified", Esophageal ulcers and perforation", "Peptic ulcers and perforation")
OR Preferred term (AEDECOD) in ("Hematemesis", "Gastrointestinal hemorrhage", "Upper gastrointestinal hemorrhage", "Helicobacter duodenitis", "Helicobacter gastritis", "Melaena", "Erosive esophagitis", "Gastric hemorrhage", "Gastritis hemorrhagic")

FDA Heart failure term = Narrow SMQ scope "Cardiac failure"

12.4 Financial Disclosure

A review of the financial disclosures was completed with the original submission for vadadustat for the INNO2VATE trials (See Clinical Review final signature March 29, 2022) for the current proposed vadadustat indication in dialysis dependent CKD. For the current review of studies CI-0036 and CI-0039 no financial disclosure information was submitted. Studies CI-0036 and CI-0039 only provided supportive safety data for the vadadustat proposed indication and therefore no financial disclosure information was required from the Applicant.

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/s/

ANDREW DMYTRIJUK
03/27/2024 10:38:23 AM

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03/27/2024 10:46:47 AM

ANN T FARRELL
03/27/2024 10:54:37 AM

HYLTON V JOFFE
03/27/2024 11:00:14 AM
This review serves as the decisional memorandum on the application. I concur with approval.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NDA SUPPLEMENT

NDA/BLA #:	215192
Supplement #:	S-046
Drug Name:	Vadadustat (Vafseo®) tablets 150 mg, 300 mg, 450 mg
Indication(s):	Treatment of anemia associated with chronic kidney disease in adults on dialysis
Applicant:	Akebia Therapeutics Inc.
Date(s):	Stamp date: September 27, 2023 PDUFA due date: March 27, 2024 Review completion date: February 23, 2024
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Joo-Yeon Lee, PhD
Concurring Reviewers:	Clara Kim, PhD, Supervisory Mathematical Statistician Mark Levenson, PhD, Division Director
Medical Division:	Division of Nonmalignant Hematology
Clinical Team:	Andrew Dmytrijuk, MD Carrie Diamond, MD, Clinical Team Leader
Project Manager:	Carleveva Thompson

Keywords: gastrointestinal erosion, heart failure, thrombosis, vascular access thrombosis, Cox proportional hazards model, incidence rate difference

1. BACKGROUND

On March 29, 2021, the Applicant (Akebia Therapeutics Inc.) submitted a new drug application (NDA) seeking approval of vadadustat for the treatment of anemia associated with chronic kidney disease (CKD) in both non-dialysis-dependent (NDD-CKD) and dialysis-dependent (DD-CKD) patients. The Office of Cardiology, Hematology, Endocrinology and Nephrology issued a complete response letter (CRL) because the review team determined that the benefits of vadadustat did not outweigh the risk in both, NDD-CKD and DD-CKD, populations on March 29, 2022. The main safety concerns were as follows:

- NDD-CKD population: non-inferiority of vadadustat compared to the comparator, darbepoetin alfa, regarding the primary safety endpoint of adjudicated major adverse cardiac events (MACE) ─ a composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke ─ was not established.
- DD-CKD population: identified a concerning signal of adjudicated thromboembolic (TE) events among vadadustat subjects compared to darbepoetin alfa subjects.
- Both populations: identified a clinically significant risk of drug-induced liver injury (DILI).

A Type A meeting took place on July 13, 2022, to discuss the concerns raised in the CRL and a potential path forward for approval of vadadustat in the DD-CKD adult population. Note that the Applicant is seeking approval of vadadustat in the DD-CKD population only. The Applicant claim that the safety concerns raised in the DD-CKD population could be resolved through drug labeling. On October 24, 2022, the Applicant submitted a formal dispute resolution request, and the Office of New Drugs issued an appeal denied letter (ADL) on May 26, 2023. In the ADL, the FDA acknowledged that the issue of TE can be handled through labeling, but additional information, such as the post-market experience from Japan, will be required to make the final decision on whether the risk of DILI can also be managed through labeling. An end of dispute Type A meeting took place on July 17, 2023, to discuss and reach an agreement on the (1) Japanese post-marketing safety data that will be submitted to address the DILI deficiency in the CRL; 2) proposed data cutoff date and content of the safety update report; and 3) structure and content of the planned NDA resubmission.

The Applicant resubmitted the NDA to seek the approval of vadadustat (300 mg once daily) for the treatment in *dialysis-dependent patients* with anemia associated with chronic kidney disease. This resubmission included data from two new clinical trials (AKB-6548-CI-0036 and AKB-6548-CI-0039). However, because of the differences in trial design, such as dose (600 mg and 900 mg) and dosing regimen (three times per week, or TIW), and small trial sample sizes, the data from INNO$_2$VATE program (AKB-6548-CI-0016 and AKB-6548-CI-0017) submitted in the original submission were used as the primary source of data for the analysis of additional safety outcomes (see section 2.3). Therefore, this review summarizes the results from the analyses of the new safety outcomes of interest from studies in INNO$_2$VATE program. Review of data from two newly submitted clinical trials are in the Appendix. Refer to the final integrated review[1] for the details of the trial design and analysis methods of the INNO$_2$VATE program.

[1] Integrated review: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80653285

2. STATISTICAL METHOD

2.1 Overview of INNO$_2$VATE program

INNO$_2$VATE program included two clinical trials: AKB-6548-CI-0016 and AKB-6548-CI-0017. Both AKB-6548-CI-0016 and AKB-6548-CI-0017 were similar in design, a phase 3b, randomized, open-label, active-controlled trial. In both trials, vadadustat was compared to darbepoetin alfa. INNO$_2$VATE was designed to rule out a risk margin of 1.25 with 80% power and 2.5% one-sided type I error rate for the primary safety endpoint, MACE based on pooled data of the two trials. MACE was defined as a composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke. The trial designs are summarized in Table 1.

Table 1: Overview of Trial Design: INNO$_2$VATE Program.

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned / Randomized	Number of Sites and Countries
INNO2VATE – CONVERSION AKB-6548-CI-0017 (NCT02892149)	Adult subjects with DD-CKD (received dialysis for at least 12 weeks prior to screening) and anemia associated with CKD (baseline Hb 8-11 g/dL in the United States and 9-12 g/dL outside the United States) on maintenance ESA therapy, with no evidence of other causes of anemia and no recent exposure to RBC transfusions	Control type: Active control (with darbepoetin alfa) Randomization: Ratio of 1:1, with stratification by geographic region, heart failure class and baseline Hb Blinding: Open-label, Sponsor-blinded Biomarkers: Mean hemoglobin value	Drug: Vadadustat (oral tablet) vs. Darbepoetin alfa (injectable solution for IV or SC administration) Dosage: Vadadustat 300 mg daily (dose adjustment depending on serial Hb values) vs. Darbepoetin alfa administered as per USPI Number treated: 3537 treated (1768 on vadadustat vs. 1769 on darbepoetin alfa) Duration: Minimum of 36 weeks	Primary: Mean change in Hb from baseline to the primary evaluation period Risk of MACE and its components Secondary: Mean change in Hb from baseline to the secondary evaluation period Risk of thromboembolic events	3300 / 3537	275 / 18
INNO2VATE – CORRECTION / CONVERSION, AKB-6548-CI-0016 (NCT02865850)	Adult subjects with DD-CKD (started dialysis within 16 weeks of screening) and anemia associated with CKD (baseline Hb 8-11 g/dL), with no evidence of other causes of anemia, no recent exposure to RBC transfusions and no evidence of ESA resistance	Control type: Active control (with darbepoetin alfa) Randomization: Ratio of 1:1, with stratification by geographic region, heart failure class and baseline Hb Blinding: Open-label, Sponsor-blinded Biomarkers: Mean hemoglobin value	Drug: Vadadustat (oral tablet) vs. Darbepoetin alfa (injectable solution for IV or SC administration) Dosage: Vadadustat 300 mg daily (dose adjustment depending on serial Hb values) vs. Darbepoetin alfa administered as per USPI Number treated: 365 treated (179 on vadadustat vs. 186 on darbepoetin alfa) Duration: Minimum of 36 weeks	Primary: Mean change in Hb from baseline to the primary evaluation period Risk of MACE and its components Secondary: Mean change in Hb from baseline to the secondary evaluation period Risk of thromboembolic events	300 / 369	83 / 10

Source: Integrated review of original submission, pages 45-46.

In addition to the primary endpoint, MACE, the key secondary endpoints included MACE2 (a composite of MACE, hospitalization for heart failure (HF), and TE excluding vascular access thrombosis (VAT)), cardiovascular (CV) MACE (a composite of CV death, non-fatal MI, and non-fatal stroke), CV death and all-cause mortality.

Other secondary endpoints were individual components of MACE, TE events, MACE+, defined as a composite of MACE and TE. All primary and secondary endpoints were independently adjudicated by the Endpoint Adjudication Committee (EAC) once they were reported by the investigator.

All analyses were conducted on the data from the two trials in $INNO_2VATE$. The pre-specified primary analysis was a study-stratified Cox proportional hazards model to analyze the time to first event of MACE. The pre-specified covariates adjusted in the model were baseline hemoglobin level, age (<65 versus ≥65 years), sex, race, history of CV disease, diabetes status, region, and New York Heart Association class (NYHAC). On-study analysis, which followed subjects until the date of last contact or date of event, whichever came first, was used as the primary analysis. To take the difference in duration of drug exposure into consideration, on-treatment (OT) +7 analysis, which followed subjects until the date of last contact, date of event, or 7 days after the last dose, whichever came first was used as a post-hoc sensitivity analysis.

2.2 Data

The adverse events (adae.xpt) from the $INNO_2VATE$ program were reported by verbatim term, then coded and categorized by Medical Dictionary for Regulatory Activities (MedDRA). Subject-level analysis data (adsl.xpt) were used to analyze the safety outcomes of interest.

2.3 Endpoints

The reviewer analyzed gastrointestinal erosion (GE), HF and rhabdomyolysis as the main safety events of interest per discussion with the clinical team. In addition, thrombosis, which were adjudicated and analyzed using the adjudicated cases during the original review cycle, was re-analyzed based on adverse event categorized by MedDRA. The list of preferred terms (AEDECOD), lowest coded level terms (AELLT), highest coded level terms (AEHLT) and standard medical query (SMQ) terms used to define each outcome is summarized in Table 2. FDA clinical team decided on the terms to define each outcome. The Applicant used different terms for GE and thrombosis from the FDA. The Applicant's definition is presented in Appendix A. Note that the outcomes were not adjudicated unless mentioned.

Table 2: FDA's List of MedDRA Terms to Define Endpoints.

Endpoint	Definition
Thrombosis	cerebral infarction, embolic cerebral infarction, ischaemic stroke, cerebellar infarction, lacunar stroke, embolic stroke, brain stem stroke, lacunar infarction, thrombosis in device, arteriovenous fistula thrombosis, arteriovenous graft thrombosis, vascular access site thrombosis, vascular graft thrombosis, graft thrombosis, shunt thrombosis, acute myocardial infarction, myocardial infarction, deep vein thrombosis, thrombosis, atrial thrombosis, peripheral artery thrombosis, subclavian vein thrombosis, brachiocephalic vein thrombosis, subclavian artery thrombosis, vena cava thrombosis, thrombophlebitis superficial, arterial thrombosis, thrombophlebitis, jugular vein thrombosis, venous thrombosis, pelvic venous thrombosis, venous thrombosis limb, cardiac ventricular thrombosis, intracardiac thrombus
Thrombosis A: Device/Shunt thrombosis/ occlusion/	thrombosis in device, arteriovenous fistula thrombosis, arteriovenous graft thrombosis, vascular access site thrombosis, vascular graft thrombosis, medical device site thrombosis, device occlusion, arteriovenous fistula occlusion, vascular access site occlusion, vascular access complication, vascular access malfunction, arteriovenous graft

malfunction stenosis		site stenosis, shunt occlusion, shunt malfunction, vascular graft stenosis, anastomotic stenosis, vascular access site complication, vascular graft occlusion
Thrombosis B: Device/Shunt thrombosis		thrombosis in device, arteriovenous fistula thrombosis, arteriovenous graft thrombosis, vascular access site thrombosis, vascular graft thrombosis, graft thrombosis, shunt thrombosis, medical device site thrombosis, device related thrombosis, injection site thrombosis
gastrointestinal erosion	Narrow	duodenal ulcers and perforation, gastric ulcers and perforation, gastrointestinal ulcers and perforation, site unspecified, esophageal ulcers and perforation, peptic ulcers and perforation by high level term (AEHLT) OR haematemesis, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, helicobacter duodenitis, helicobacter gastritis, melaena, gastric haemorrhage, gastritis haemorrhagic by preferred term (AEDECOD)
	Broad	GI ulceration, GI perforation, GI hemorrhage by SMQ
Heart Failure		cardiac failure (SMQ, narrow scope)
Rhabdomyolysis		blood creatine phosphokinase abnormal, blood creatine phosphokinase abnormal NOS, blood creatine phosphokinase increased, blood creatine phosphokinase MM increased, blood myoglobin increased, CPK increase, CPK increased, creatine kinase high, creatine kinase increased, creatine phosphokinase increased, creatine phosphokinase serum inc, muscle dissolution, muscle necrosis, myoglobin blood increased, myoglobin urine increased, myoglobinuria, myoglobin urine present, myonecrosis, phosphokinase creatine serum increased, plasma creatine phosphokinase abnormal, plasma creatine phosphokinase increased, rhabdomyolysis, serum creatine phosphokinase abnormal, serum creatine phosphokinase increased, urine myoglobin increased, creatine phosphokinase serum increased, muscle enzyme increased, CPK-MM increased, myoglobinaemia, myoglobinemia, myoglobin blood present, creatine phosphokinase abnormal, muscle enzyme abnormal by low level terms (AELLT)

2.4 Analysis Methods

This resubmission did not include a statistical analysis plan (SAP) with pre-specified analyses. However, at the end of dispute Type A meeting, the FDA requested the Applicant to estimate hazard ratios (HR) (using the pre-specified Cox proportional hazards model used in the original submission) and to calculate incidence rate differences (IRD), for the new safety outcomes of interest. Therefore, the reviewer analyzed the time-to-first event using the study-stratified Cox proportional hazards model including the same covariates used in the original submission model.

The incidence rate (IR) and IRD were calculated without adjusting for covariates. The IR was defined as the number of subjects with an event divided by person-years (time at-risk). Person-years were defined as the time from the first dose to the first onset of an event for those who had an event and the end of follow-up for those who did not have an event. To preserve randomization and to account for the differences in the two studies, the Mantel-Haenszel estimate for the IRD with the normal approximation for the confidence interval was used. The primary analysis was on-study. Note that because the $INNO_2VATE$ program was not designed to statistically test hypotheses that rule out a risk of the new safety outcomes of interest, all analyses should be considered descriptive.

3. RESULTS

The analysis results are of the safety outcomes using the FDA's definition.
A total of 3923 subjects were randomized, of which 3902 subjects received at least one dose of study drug, which comprised of safety population. Of 3902 subjects, 1947 subjects received vadadustat and 1955 subjects received darbepoetin.

Gastrointestinal Erosion

Table 3 summarizes the results from the analyses of gastrointestinal erosion events.
Narrowly defined gastrointestinal erosion events occurred more frequently in the vadadustat arm than the darbepoetin arm (4.0 per 100 PY versus 3.28 per 100 PY). The estimated IRD (95% CI) and HR (95% CI) were 0.72 per 100 PY (-0.23 per 100 PY, 1.67 per 100 PY) and 1.23 (0.94, 1.59), respectively. This risk was mainly driven by gastrointestinal hemorrhage, gastritis erosive, melaena in both arms (Table 4). A larger proportion of subjects in the vadadustat arm had serious gastrointestinal erosion events compared to those in the darbepoetin arm (2.12 per 100 PY versus 2.04 per 100 PY). However, for the broadly defined gastrointestinal erosion events, the risk in the vadadustat arm compared to the darbepoetin arm was not increased (HR, 0.98; 95% CI, 0.81, 1.19).

Table 3: Risk of Gastrointestinal Erosion.

Endpoint	Vada dustat N= 1947				Darbe poetin N= 1955				IRD	HR
	n	%	PY	IR	n	%	PY	IR	(95% CI)	(95% CI)
Gastrointestinal Erosion (GI, broad)	203	10.43	3006.1	6.75	210	10.74	3043.4	6.9	-0.15 (-1.47, 1.17)	0.98 (0.81, 1.19)
Gastrointestinal Erosion (narrow)	124	6.37	3099.36	4	103	5.27	3144.46	3.28	0.72 (-0.23, 1.67)	1.23 (0.94, 1.59)
Serious GI (broad)	108	5.55	3109.2	3.47	127	6.5	3125.8	4.06	-0.59 (-1.55, 0.37)	0.86 (0.67, 1.12)
Serious GI (narrow)	67	3.44	3154.02	2.12	65	3.32	3181.37	2.04	0.08 (-0.63, 0.79)	1.05 (0.75, 1.48)

n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; HR: hazard ratio; 95% CI: 95% confidence interval
Source: reviewer's analysis using data adsl.xpt and adae.xpt.

Table 4: Number and Proportion of Gastrointestinal Erosion (narrow) Events by Preferred Terms.

PT terms	Vadadustat N=1947		Darbepoetin N=1955	
	n	%	n	%
Diverticular perforation	4	0.21	1	0.05
Duodenal ulcer	11	0.56	4	0.20
Duodenal ulcer haemorrhage	2	0.10	3	0.15
Erosive duodenitis	1	0.05	0	0.00
Gastric haemorrhage	0	0.00	2	0.10
Gastric ulcer	11	0.56	4	0.20
Gastric ulcer haemorrhage	0	0.00	1	0.05
Gastric ulcer perforation	2	0.10	0	0.00
Gastritis erosive	13	0.67	6	0.31
Gastritis haemorrhagic	3	0.15	1	0.05
Gastrointestinal haemorrhage	43	2.21	46	2.35
Haematemesis	5	0.26	5	0.26
Haemorrhagic erosive gastritis	2	0.10	1	0.05
Helicobacter gastritis	2	0.10	2	0.10
Melaena	12	0.62	8	0.41
Peptic ulcer	5	0.26	0	0.00
Peptic ulcer haemorrhage	1	0.05	2	0.10
Upper gastrointestinal haemorrhage	7	0.36	17	0.87
Total	124	6.37	103	5.27

n: number of subjects with an event; %: proportion of subjects with an event
Source: reviewer's analysis using data adsl.xpt and adae.xpt.

Heart failure

The risk of heart failure, using adjudicated data from the original submission, was not increased in the vadadustat arm compared to the darbepoetin arm (Table 5). The estimated IRD (95% CI) and HR (95% CI) of the adjudicated hospitalization from heart failure were -0.13 per 100 PY (-0.95 per 100 PY, 0.69 per 100 PY) and 0.97 (0.71, 1.31), respectively. Similar results were shown using the adverse events defined using MedDRA terms: the HRs (95% CI) of heart failure and serious events were 0.88 (0.72, 1.07) and 0.86 (0.69, 1.08), respectively.

Table 5: Risk of Heart Failure.

Endpoint	Vada dustat N= 1947				Darbe poetin N= 1955				IRD	HR
	n	%	PY	IR	n	%	PY	IR	(95% CI)	(95% CI)
Heart Failure (HF)	184	9.45	3063.7	6.01	212	10.84	3065.3	6.92	-0.92 (-2.19, 0.35)	0.88 (0.72, 1.07)
Serious HF	142	7.29	3093.6	4.59	168	8.59	3104.7	5.41	-0.83 (-1.94, 0.29)	0.86 (0.69, 1.08)
Hospitalization from HF (adjudicated)	84	4.31	3133.7	2.68	89	4.55	3164	2.81	-0.13 (-0.95, 0.69)	0.97 (0.72, 1.31)

n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; HR: hazard ratio; 95% CI: 95% confidence interval
Estimates of hospitalization from HF (adjudicated) were based on adjudicated data from the original submission.
Source: reviewer's table using data adsl.xpt and adae.xpt.

Thrombosis

Table 6 summarizes the results from the analysis of thrombosis events. The analysis results of the adjudicated data showed that a greater proportion of subjects in the vadadustat arm experienced a thromboembolic event compared to those in the darbepoetin arm: 169 (5.58 per 100 PY) versus 148 (4.79 per 100 PY). The estimated IRD (95% CI) and HR (95% CI) were 0.79 per 100 PY (-0.35 per 100 PY, 1.93 per 100 PY) and 1.20 (0.96, 1.50). When using the adverse event data based on the FDA's definition, the HR (95% CI) was reduced to 1.0 (0.86, 1.18). However, the risk of narrowly defined thrombosis (thrombosis A or thrombosis B) was higher in the vadadustat arm compared to the darbepoetin arm: the estimated HRs (95% CI) were 1.14 (0.95, 1.37) for thrombosis A and 1.17 (0.94, 1.44) for thrombosis B.

Table 6: The Risk of Thrombosis.

Endpoint	Vada dustat N= 1947				Darbe poetin N= 1955				IRD (95% CI)	HR (95% CI)
	n	%	PY	IR	n	%	PY	IR		
Thrombosis	306	15.72	2913.8	10.50	312	15.96	2952.7	10.57	-0.07 (-1.73, 1.60)	1 (0.86, 1.18)
Thrombosis A	241	12.38	2944.6	8.18	215	11.00	2986.8	7.20	0.99 (-0.42, 2.40)	1.14 (0.95, 1.37)
Thrombosis B	185	9.50	3006.4	6.15	161	8.24	3047.3	5.28	0.87 (-0.33, 2.08)	1.17 (0.94, 1.44)
Thromboembolic Event (adjudicated)	169	8.68	3027.9	5.58	148	7.57	3090.7	4.79	0.79 (-0.35, 1.93)	1.2 (0.96, 1.50)

n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; HR: hazard ratio; 95% CI: 95% confidence interval
Thrombosis A: Device/Shunt thrombosis/occlusion/malfunction stenosis; Thrombosis B: Device/Shunt thrombosis
Thromboembolic event (adjudicated) was based on adjudicated data in the original submission.
Source: reviewer's table using datasets adsl.xpt and adae.xpt.

Rhabdomyolysis

A small number of subjects (11 subjects (0.34 per 100 PY) in the vadadustat arm and 11 subjects (0.34 per 100 PY) in the darbepoetin arm) experienced a rhabdomyolysis event. The estimated IRD (95% CI) and HR (95% CI) were 0.0 per 100 PY (-0.28 per 100 PY, 0.28 per 100 PY) and 0.95 (0.41, 2.21).

4. SUMMARY AND CONCLUSIONS

The Applicant resubmitted the NDA to seek approval of vadadustat for the treatment in *dialysis-dependent patients* with anemia associated with chronic kidney disease. Data from the $INNO_2VATE$ program (AKB-6548-CI-0016 and AKB-6548-CI-0017) submitted in the original submission were used as the primary source of data.

The safety outcomes of interest in this resubmission included gastrointestinal erosion, heart failure and rhabdomyolysis. Thrombosis events, which were analyzed using adjudicated events in the original submission, were re-analyzed using adverse events defined using MedDRA. Trial-stratified Cox proportional hazards model including the covariates that were pre-specified in the original submission was used to analyze the safety outcomes of interest. The Mantel-Haenszel

estimate of the incidence rate difference was also calculated taking study variability into consideration.

Narrowly defined gastrointestinal erosion events occurred more frequently in the vadadustat arm than in the darbepoetin arm (4.0 per 100 PY versus 3.28 per 100 PY). The estimated IRD (95% CI) and HR (95% CI) were 0.72 per 100 PY (-0.23 per 100 PY, 1.67 per 100 PY) and 1.23 (0.94, 1.59), respectively. The risk of narrowly defined thrombosis events such as device/shunt thrombosis, occlusion, malfunction and stenosis (thrombosis A) and the events of device / shunt thrombosis (thrombosis B) was higher in the vadadustat arm compared to the darbepoetin arm: the estimated HR (95% CI) was 1.14 (0.95, 1.37) for thrombosis A and 1.17 (0.94, 1.44) for thrombosis B. However, the risk of heart failure and rhabdomyolysis was not increased in the vadadustat arm: the estimated HR (95% CI) was 0.97 (0.71, 1.31) for heart failure (adjudicated) and 0.95 (0.41, 2.21) for rhabdomyolysis.

Because there is no pre-specified statistical analysis plan, and no adjudication for the new safety outcomes of interest, results are descriptive. However, we recommend including the risk of gastrointestinal erosion and thromboembolic events in section 5 (warnings and precautions) and section 6 (adverse reactions) of the label.

APPENDIX A: Applicant's Definition of Endpoints Using MedDRA Terms

Endpoint		Definition
Thrombosis		Thrombosis in device, Arteriovenous fistula thrombosis, Arteriovenous graft thrombosis, Vascular access site thrombosis, Vascular graft thrombosis, Graft thrombosis, Shunt thrombosis, Deep vein thrombosis, Thrombosis, Atrial thrombosis, Peripheral artery thrombosis, Subclavian vein thrombosis, Brachiocephalic vein thrombosis, Subclavian artery thrombosis, Vena cava thrombosis, Thrombophlebitis superficial, Arterial thrombosis, Thrombophlebitis, Jugular vein thrombosis, Venous thrombosis, Pelvic venous thrombosis, Venous thrombosis limb, Cardiac ventricular thrombosis, Intracardiac thrombus, Arteriovenous fistula thrombosis, Arteriovenous graft thrombosis, Vascular access site thrombosis, Vascular graft thrombosis, Arteriovenous fistula occlusion, Vascular access site occlusion, Shunt occlusion, Vascular graft occlusion, Arteriovenous fistula thrombosis, Arteriovenous graft thrombosis, Vascular access site thrombosis, Vascular graft thrombosis, Graft thrombosis, Shunt thrombosis
Gastrointestinal erosion	Narrow	Duodenal ulcers and perforation, Gastric ulcers and perforation, Gastrointestinal ulcers and perforation, site unspecified, Esophageal ulcers and perforation, Peptic ulcers and perforation by high level term (AEHLT) and excluded the records if preferred terms belonged to (abdominal abscess, anal abscess, colonic abscess, perineal abscess, perirectal abscess, peritoneal abscess, peritonitis, peritonitis bacterial, pneumoperitoneum, retroperitoneal abscess, diverticular perforation) OR Hematemesis, Gastrointestinal hemorrhage, Upper gastrointestinal hemorrhage, Helicobacter duodenitis, Helicobacter gastritis, Melaena, Erosive oesophagitis, Gastric haemorrhage, Gastritis haemorrhagic, Haematemesis, Haemorrhagic erosive gastritis, Oesophageal ulcer, Oesophagitis ulcerative, Ulcer, Upper gastrointestinal haemorrhage by preferred term (AEDECOD)
	Broad	GI ulceration, GI perforation, GI hemorrhage by SMQ but excluded the records if preferred terms belonged to (abdominal abscess, anal abscess, colonic abscess, perineal abscess, perirectal abscess, peritoneal abscess, peritonitis, peritonitis bacterial, pneumoperitoneum, retroperitoneal abscess, diverticular perforation)
Heart Failure		Same as FDA's definition
Rhabdomyolysis		Same as FDA's definition

APPENDIX B: Analysis of Data from AKB-6548-CI-0036 and AKB-6548-CI-0039

Overview of Trial Design

AKB-6548-CI-0036: The trial was designed as a phase 3b, randomized, open-label, active-controlled study of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in hemodialysis subjects, after conversion from erythropoietin stimulating agents (ESA) therapy. Following a screening period of up to 8 weeks (56 days), subjects were randomized 1:1:1 to vadadustat QD (once daily), vadadustat TIW (three times per week), or darbepoetin alfa, stratified with respect to region (United States or Europe), mean weekly darbepoetin alfa dose (or ESA equivalent) calculated over a period of 8 weeks prior to screening visit 2 (low darbepoetin alfa dose group (≤0.45 μg/kg/week) or high darbepoetin alfa dose group (>0.45 and ≤1.5 μg/kg/week)).

Following screening and randomization, there were 2 periods during the study:

- Conversion and maintenance treatment period (weeks 0 to 52): conversion to investigational drug for maintaining hemoglobin (Hb) (weeks 0 to 20), primary efficacy evaluation (weeks 20 to 26), and secondary efficacy evaluation (weeks 46 to 52).
- Safety follow-up period: post-treatment safety follow-up visit (end of treatment + 4 weeks).

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

A total of 319 subjects were enrolled and randomized. Of the subjects randomized, 105, 104, and 108 subjects were treated with vadadustat QD, vadadustat TIW or darbepoetin alfa and 51.4%, 47.2%, and 62.0% of the subjects completed the study.

AKB-6548-CI-0039: The trial was designed as 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 the screening period of up to 8 weeks (56 days), subjects who met all eligibility criteria were randomized 1:1:1 to vadadustat 600 mg TIW, vadadustat 900 mg TIW, or to remain on Mircera. Randomization was stratified by dialysis organization (b) (4) (b) (4) Following randomization, there were 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), a primary efficacy evaluation period (weeks 20 to 26) and a secondary efficacy evaluation period (weeks 46 to 52).

- Safety follow-up period: post-treatment safety follow-up visit (end of treatment +4 weeks)

The primary objective of the trial was to demonstrate the efficacy and safety of vadadustat administered three times weekly (TIW) compared to long-acting ESA, Mircera, for the maintenance treatment of anemia in hemodialysis subjects.

A total of 456 subjects were randomized and 152 subjects were assigned to each treatment group. However, 5 subjects were randomized but not treated because they were considered screen failures (vadadustat 600 mg: 2, vadadustat 900 mg: 2, Mircera:2). Therefore, the safety population included a total of 451 subjects.

Statistical Methods

The endpoints analyzed in the $INNO_2VATE$ program were analyzed. Because of the small sample size and lack of NYHA class covariate collected, the reviewer calculated the incidence

rates and incidence rate differences with normal approximation confidence intervals only. Both vadadustat arms were compared to the comparator group (darbepoetin or mircera) separately

Results:

Table 7 and Table 8 are the results from the analysis of data from trials AKB-6548-CI-0036 and AKB-6548-CI-0039. In AKB-6548-CI-0036, the incidence rate of heart failure was higher in the vadadustat arms (both QD and TIW) compared to the darbepoetin arm. The incidence rates of thrombosis and gastrointestinal erosion were higher in the vadadustat TIW arm compared to darbepoetin.

In AKB-6548-CI-0039, the incidence rate of gastrointestinal erosion (both narrow and broad) was higher in the vadadustat arms (both 600 mg and 900 mg) compared to the Mircera arm in addition to the heart failure. For rhabdomyolysis, no subject had the event in AKB-6548-CI-0036 and a total of 3 subjects (vadadustat 600 mg: 2, vadadustat 900 mg: 1) had an event.

Table 7: Incidence Rate Difference of Safety Outcomes of Interest (AKB-6548-CI-0036).

Endpoint	Vadadusat QD N=105				Vadadustat TIW N=104				Darbepoetin N=108				IRD (95% CI) Vadadustat QD vs. Darbepoetin	IRD (95% CI) Vadadustat TIW vs. Darbepoetin
	n	%	PY	IR	n	%	PY	IR	n	%	PY	IR		
Thrombosis	11	10.48	74.26	14.81	15	14.42	74.7	20.08	13	12.04	85.82	15.15	-0.33 (-12. 35, 11.68)	4.93 (-8.15, 18.01)
Thrombosis A	6	5.71	76.1	7.88	10	9.62	75.67	13.21	13	12.04	85.59	15.19	-7.3 (-17.69, 3.09)	-1.97 (-13.60, 9.66)
Thrombosis B	5	4.76	76.23	6.56	8	7.69	77.14	10.37	11	10.19	86.47	12.72	-6.16 (-15.63, 3.30)	-2.35 (-12.75, 8.05)
Heart failure (HF)	9	8.57	77.94	11.55	7	6.73	76.91	9.1	2	1.85	88.75	2.25	9.29 (1.13, 17.46)	6.85 (-0.58, 14.28)
Serious HF	7	6.67	78.18	8.95	5	4.81	77.45	6.46	2	1.85	88.75	2.25	6.7 (-0.63, 14.03)	4.2 (-2.26, 10.67)
Gastrointestinal erosion (narrow)	4	3.81	78.84	5.07	8	7.69	76.44	10.47	5	4.63	87.93	5.69	-0.61 (-7.65, 6.42)	4.78 (-4.02, 13.58)
Gastointetinal erosion (broad)	6	5.71	78.70	7.62	9	8.65	76.43	11.78	8	7.41	87.62	9.13	-1.51 (-10.30, 7.28)	2.65 (-7.32, 12.61)
Serious GE (narrow)	1	0.95	80.36	5.07	5	4.81	77.92	6.42	2	1.85	89.75	2.23	-0.98 (-4.92, 2.95)	4.19 (-2.23, 10.60)
Serious GE (broad)	3	2.86	79.61	3.77	6	5.77	77.91	7.7	3	2.78	89.62	3.35	0.42 (-5.28, 6.12)	4.35 (-2.88, 11.59)

n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; 95% CI: 95% confidence interval
Source: reviewer's table using data adsl.xpt and adae.xpt.

Table 8: Incidence Rate Difference of Safety Outcomes of Interest (AKB-6548-CI-0039).

Endpoint	Vadadustat 600 mg N=151				Vadadustat 900 mg N=150				Mircera N=150				IRD (95% CI) Vadadustat 600 mg vs. Mircera	IRD (95% CI) Vadadustat 900 mg vs. Mircera
	n	%	PY	IR	n	%	PY	IR	n	%	PY	IR		
Thrombosis	14	9.27	129.28	10.83	12	8	123.15	9.74	19	12.67	130.54	14.55	-3.73 (-12.39, 4.94)	-4.81 (-13.37, 3.75)
Thrombosis A	8	5.3	130.51	6.13	9	6	124.51	7.23	13	8.67	130.33	9.97	-3.84 (-10.73, 3.04)	-2.75 (-9.94, 4.44)
Thrombosis B	9	5.96	129.95	6.93	9	6	124.61	7.22	12	8	130.75	9.18	-2.25 (-9.14, 4.64)	-1.96 (-8.97, 5.06)
Heart failure (HF)	9	5.96	131.52	6.84	10	6.67	124.74	8.02	5	3.33	138.01	3.62	3.22 (-2.26, 8.70)	4.39 (-1.50, 10.29)
Serious HF	7	4.64	132.55	5.28	7	4.67	126.16	5.55	2	1.33	138.83	1.44	3.84 (-0.55, 8.23)	4.11 (-0.46, 8.68)
Gastrointestinal erosion (narrow)	5	3.31	131.66	3.80	7	4.67	125.99	5.56	2	1.33	138.84	1.44	2.36 (-1.52, 6.24)	4.12 (-0.46, 8.69)
Gastointetinal erosion (broad)	8	5.3	129.88	6.16	11	7.33	124.1	8.86	4	2.67	138.57	2.89	3.27 (-1.85, 8.39)	5.98 (0.02, 11.93)
Serious GE (narrow)	3	1.99	132.45	2.27	5	3.33	126.79	3.94	2	1.33	138.84	1.44	0.82 (-2.42, 4.07)	2.5 (-1.49, 6.49)
Serious GE (broad)	4	2.65	131.88	3.03	8	5.33	125.39	6.38	3	2	138.73	2.16	0.87 (-2.98, 4.72)	4.22 (-0.84, 9.27)

n: number of subjects with an event; %: proportion of subjects with an event; PY: 100 person-year; IR: incidence rate per 100 PY; IRD: incidence rate difference per 100 PY; 95% confidence interval

Source: reviewer's table using data adsl.xpt and adae.xpt.

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/s/

JOO YEON LEE
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02/23/2024 03:50:31 PM

MARK S LEVENSON
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Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215192
Priority or standard	Standard
Submit date(s)	3/29/2021
Received date(s)	3/29/2021
PDUFA goal date	3/29/2022
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	1/15/2022
Established/proper name	Vadadustat
(Proposed) proprietary name	VAFSEO
Pharmacologic class	Hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) inhibitor
Code name	AKB-6548
Applicant	Akebia Therapeutics, Inc.
Dosage form(s)/formulation(s)	Vadadustat Tablets 150 mg, 300 mg, and 450 mg
Dosing regimen	Starting dose is 300 mg daily, with hemoglobin-dependent dose adjustment based upon a dose adjustment algorithm and a dose range of 150 to 600 mg daily
Applicant proposed indication(s)/ population(s)	Treatment of anemia associated with chronic kidney disease in adult patients not on dialysis and on dialysis
Proposed SNOMED indication	707323002 Anemia co-occurrent and due to chronic kidney disease (disorder)
Regulatory action	Complete response
Approved dosage (if applicable)	Not applicable
Approved indication(s)/ population(s) (if applicable)	Not applicable
Approved SNOMED term for indication (if applicable)	Not applicable

[To complete this integrated review, please see detailed instructions in the Integrated Review Template How-to Guide.]

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Glossary

ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AST	aspartate aminotransferase
ATE	arterial thromboembolism
AUC	area under the concentration-time curve
AV	arteriovenous
CBC	complete blood count
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
CSR	clinical study report
CV	cardiovascular
CVA	cerebrovascular accident
CYP	cytochrome P450 isoenzyme
DBP	diastolic blood pressure
DD	dialysis dependent
DDI	drug-drug interaction
DILI	drug-induced liver injury
DVT	deep vein thrombosis
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EPO	erythropoietin
EOS	end of study
EOT	end of treatment
E-R	exposure-response
ESA	erythropoietin stimulating agents
FAS	full analysis set
FDA	Food and Drug Administration
FDQ	financial disclosure questionnaire
GCP	good clinical practice
GD	gestation day
GI	gastrointestinal
GLP	good laboratory practice
Hb	hemoglobin
HD	hemodialysis
HF	heart failure
HIF-PH	hypoxia inducible factor-prolyl hydroxylase
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration

IIV	inter-individual variability
IND	investigational new drug
IPD	important protocol deviation
iPSP	initial pediatric study plan
IV	intravenous
LS	least squares
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed model repeated measure
NDA	new drug application
NDD	non-dialysis-dependent
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
PE	pulmonary embolism
PHD	prolyl hydroxylase domain-containing proteins
PD	pharmacodynamic
PI	Prescribing Information
PK	pharmacokinetic
PND	post-natal day
PO	by mouth
PopPK	population pharmacokinetics
PP	per protocol
PT	preferred term
PY	person year
QD	once daily
R_{ac}	accumulation index
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of mean
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
TE	thromboembolic
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
T_{max}	time to maximum concentration
TSAT	transferrin saturation
ULN	upper limit of normal
UGT	uridine diphosphate glucuronosyltransferase
U.S.	United States
VAT	vascular access thrombosis
VS	vital signs

VTE	venous thromboembolism
WBC	white blood cell

I. Executive Summary

1. Summary of Regulatory Action

On March 29, 2021, Akebia Therapeutics submitted NDA 215192 to the FDA asking for approval of vadadustat for the treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis and not on dialysis.

Vadadustat is an inhibitor of hypoxia inducible factor-prolyl hydroxylase (HIF-PH), and if approved, would be the first-in-class therapy for this indication. Vadadustat would provide the convenience of an oral route of administration compared to the intravenous route of administration for erythropoietin stimulating agents (ESAs), which are the main therapies (together with iron supplementation) for treating anemia associated with CKD.

Hematologic response and reduction in RBC transfusions have been used to establish efficacy for traditional approval for drugs intended to treat anemia of CKD. The Applicant has established non-inferiority of vadadustat to darbepoetin alfa (an approved ESA), based on hemoglobin (Hb) response in both the non-dialysis dependent (NDD) and dialysis-dependent (DD) CKD populations, even after accounting for differences in rescue therapy use between treatment arms. However, there was a higher rate of ESA rescue therapy in both the NDD CKD and DD CKD populations and a higher rate of red blood cell (RBC) transfusion rescue in the DD CKD trials with vadadustat compared to darbepoietin alfa, which introduces uncertainty in the efficacy conclusions of vadadustat in the treatment of anemia of CKD. In addition, the higher rate of RBC transfusion rescue raises concerns because one of the goals of treating anemia is to reduce the need for transfusion as it helps limit alloreactivity, a critical risk factor for renal allograft rejection.

Significant safety concerns with vadadustat include hepatotoxicity and increased risks compared to darbepoietin alfa for major adverse cardiac events in the NDD population, and thromboembolic events, including vascular-access thrombosis in the DD population.

The clinical team, statistical team, and deputy division director conclude that the overall benefit/risk is unfavorable as described in the Benefit-Risk Framework below, and the office director, who is the signatory authority, concurs. For detailed information supporting the basis for this Complete Response action, refer to the detailed sections included in this Interdisciplinary Assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Chronic kidney disease (CKD) is a progressive condition that results in decreased kidney function due to irreversible kidney damage. • The prevalence of CKD in the U.S. adult population is ~15%, with an estimated 17.2 million having advanced CKD. • Patients with CKD may be on dialysis or not on dialysis, and those with advanced CKD are commonly awaiting kidney transplant as a definitive therapy for their disease. Patients who are on dialysis have frequent but vital vascular access procedures and healthcare interactions. • Anemia is a common, early and progressive complication of CKD, affecting ~90% of patients with advanced CKD, regardless of dialysis status. • Anemia in CKD is caused by decreases in production of erythropoetin (EPO) due to progressive loss of EPO-producing cells in the diseased kidney, iron deficiency from inadequate intake or absorption, and chronic inflammation. • CKD is associated with increased risk of cardiovascular disease, morbidity due to symptomatic anemia, and mortality due to cardiac disease, stroke, and renal-associated causes.	CKD is a prevalent and serious disease with significant morbidiy and mortality. It is associated with increased risk of cardiovascular disease, anemia and anemia-related signs and symptoms. Untreated anemia of CKD may lead to a variety of signs and symptoms, including fatigue, dyspnea, tachycardia, myocardial ischemia and decreases in cognitive function and mental acuity, resulting in significant morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Several erythropoiesis stimulating agents (ESAs) – Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta) and Retacrit (epoetin alfa-epbx) – are injectable therapies approved for the treatment of anemia in patients with CKD, on dialysis and not on dialysis. • Red blood cell (RBC) transfusions are used mainly for acute and life-threating anemia, and are associated with risk of transmission of infection, alloimmunization, iron overload, and allergic reactions. • All ESA labels contain a boxed warning for increased risk of cardiovascular mortality and morbidity associated with targeting a higher hemoglobin (Hb) value, compared to a lower Hb value. • There is no identified trial-based Hb target value, ESA dose, or dosing strategy that does not increase these risks. • The general dosing recommendations for ESAs is to use the lowest dose sufficient to reduce the need for RBC transfusions, while targeting a Hb value less than 11 g/dL. • There are no approved oral treatments for patients with anemia of CKD.	ESAs are considered the current standard therapy for the treatment of anemia in patients with CKD, while RBC transfusions are mainly considered in acute scenarios. ESAs are associated with cardiovascular mortality and morbidity when higher Hb values (>11 g/dL) are targeted, compared to lower Hb values. RBC transfusions are associated with foreign antigen exposure that may result in alloimmunization, thus RBC transfusions may impact a patient's eligibility for a kidney transplant. There is an unmet need for safer and orally available therapies for patients with anemia of CKD that will allow patients to avoid the need for transfusion and its potential impact on transplant eligibility.

Benefit	• Four appropriately designed and powered, phase 3, randomized, actively controlled, open-label, clinical trials were conducted; two trials in subjects with NDD CKD and two trials in subjects with DD CKD. • Hematologic response and reduction in RBC transfusions have been used to establish efficacy for traditional approval for drugs intended to treat anemia of CKD. • The primary efficacy analysis of the change in mean Hb between baseline and the primary efficacy period (weeks 24 to 36) showed that vadadustat was non-inferior to darbepoetin alfa (an approved ESA) in raising and maintaining the Hb in subjects with NDD-CKD and in subjects with DD-CKD. • The key secondary efficacy analysis of the change in mean Hb between baseline and the secondary efficacy period (weeks 40 to 52) showed that vadadustat was non-inferior to darbepoetin alfa in raising and maintaining the Hb in subjects with NDD-CKD and in subjects with DD-CKD. • There was no appreciable difference in the rate of RBC transfusion rescue between vadadustat and darbepoetin alfa in the NDD-CKD population. There was a higher rate of ESA rescue therapy in patients with NDD-CKD on vadadustat compared to patients on darbepoetin alfa, but the non-inferiority conclusion on Hb response remained robust to sensitivity analyses that treated Hb values as missing within four weeks after rescue therapy (see Sections II.6.2.1.3, II.6.2.2.3, II.6.2.3 and II.6.3.1). • In the DD-CKD population, there was a higher rate of ESA rescue therapy in patients on vadadustat compared to patients on darbepoetin alfa, as well as a higher rate of RBC transfusions with vadadustat compared to darbepoetin alfa. The non-inferiority conclusion on Hb response remained robust to sensitivity analyses that treated Hb values as missing within four weeks after rescue therapy (see Sections II.6.2.4.3, II.6.2.5.3, II.6.2.6 and II.6.3.1). • See Table 3 for a trial-based comparative qualitative summary of important benefits.	Vadadustat demonstrated non-inferiority to darbepoetin alfa in raising and maintaining Hb up to a treatment period of at least 52 weeks in subjects with NDD-CKD and in subjects with DD-CKD. This conclusion on the Hb response remained robust after accounting for a higher rate of rescue therapy with vadadustat compared to darbepoetin alfa. In the NDD-CKD population, the non-inferiority on Hb response was not associated with an appreciable increase in the rate of RBC transfusions, but was associated with an increased rate of ESA rescue therapy with vadadustat, compared to darbepoetin alfa. Even though results of the senstivity analysis for rescue therapy were consistent with the primary analysis results, the imbalance in ESA rescue rates between treatment arms introduces uncertainty in the efficacy conclusions of vadadustat in the treatment of anemia of CKD in the NDD-CKD population. Despite the non-inferiority findings on Hb response in the DD-CKD population, there was a higher rate of rescue ESA therapy and RBC transfusions with vadadustat, compared to darbepoetin alfa. Even though results of the senstivity analysis for rescue therapy were consistent with the primary analysis results, the imbalance in ESA and RBC transfusion rescue rates between treatment arms introduces uncertainty in the efficacy conclusions of vadadustat in the treatment of anemia of CKD in the DD-CKD population. Other important benefits of avoidance of RBC transfusions are limiting alloreactivity, a critical risk factor for renal allograft rejection in patients who undergo renal transplantation, and avoidance of other transfusion-related risks, such as infection and allergic reactions. Any future trials should assess the occurrence of ESA and RBC transfusion rescue therapies, as key secondary efficacy endpoints. The trials did not establish any other clinical benefits with vadadustat.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		As an oral therapy, vadadustat would offer convenience compared to the intravenous route of ESAs, especially in the NDD-CKD population. The convenience of an oral drug in the DD-CKD population is less clear, particularly for the majority of DD patients in the US who receive hemodialysis, rather than peritoneal dialysis, and who are administered ESA at the time of hemodialysis.

Risk and Risk Management	• The safety database for vadadustat was adequate to evaluate the safety profile for the proposed dosing regimen and intended patient populations. • Major adverse cardiac events (MACE) and thromboembolism were key safety endpoints, based on the safety profile of ESAs, given their similarities to the HIF-PH inhibitor drug-class in mechanism of action, with the initial hypothesis of a decrease in MACE risk, compared to ESAs. • For the NDD-CKD population, the pre-specified adjusted primary safety analysis, based on adjudicated MACE (non-fatal myocardial infarction, non-fatal stroke and all-cause mortality), showed an estimated hazard ratio (HR) for time-to-first-event of 1.17 (95% CI: 1.01, 1.36). Because the upper bound of the 95% CI exceeds the pre-specified risk margin of 1.25, vadadustat did not demonstrate non-inferiority compared to darbepoetin alfa for MACE. In addition, the 95% CI for MACE excluded the value of no effect. Sensitivity analyses examining other cardiovascular (CV) outcomes, the impact of differential duration of drug exposure and the impact of geographical location showed similar unfavorable risk for vadadustat. In the US NDD-CKD population, the estimated hazard ratio for adjudicated MACE was 1.06 (95% CI, 0.87, 1.29), with a HR of 1.49 (95% CI 0.97, 2.30) for non-fatal MI. • For the DD-CKD population, the analysis of the adjudicated data for thromboembolic (TE) events showed an estimated HR of 1.20 (95% CI: 0.96, 1.50). This increased risk of adjudicated TE was more apparent in the US DD-CKD population, with an estimated HR of 1.46 (95% CI: 1.13, 1.89). More than 80% of the adjudicated TE events were due to vascular access thrombosis. The estimated HR of adjudicated vascular access thrombosis was 1.28 (95% CI: 1.00, 1.63). Sensitivity analyses using the Agency's definition of access-related TE events, examining the impact of differential duration of drug exposure, and the impact of geographical location showed similar unfavorable risk for vadadustat. • Given the identification of one probable Hy's Law case, at least seven cases of probable drug-induced liver injury (DILI) in Temple's Corollary and a higher incidence of cases detected in the higher alanine aminotransferase (ALT) categories in the vadadustat arm, compared to the darbepoetin alfa arm, there is a clinically significant hepatocellular injury risk with the use of vadadustat in patients with CKD. These findings were confirmed by	In subjects with NDD-CKD, vadadustat did not demonstrate non-inferiority compared to darbepoetin alfa for the primary safety endpoint, adjudicated MACE, with the 95% CI excluding the value of no effect and the HR showing an increase risk of MACE with vadadustat. In subjects with DD-CKD, vadadustat demonstrated a concerning signal for TE compared to darbepoetin alfa, with the majority of events caused by vascular access thrombosis, impacting vital vascular access in subjects on chronic dialysis for CKD. In patients with CKD, the use of vadadustat is associated with a clinically significant hepatocellular injury risk. Vadadustat had a comparable risk of seizures but an increased risk of gastrointestinal adverse reactions, compared to darbepoetin alfa. These findings could be adequately mitigated with labeling when vadadustat can be approved. Any future trials of vadadustat should include rhabomyolysis as an adverse event of interest and further assess this safety signal.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	both an Applicant-driven independent unblinded hepatology assessment and an FDA DILI team assessment. • Other risks with vadadustat included a risk for seizures comparable to that of darbepoetin alfa and a higher risk for GI-acid related disease and GI symptoms. • Rhabdomyolysis is a rare event and was reported at a numerically higher incidence with vadadustat compared to darbepoetin alfa in both the NDD-CKD (10 vs. 4) and DD-CKD populations (5 vs. 3). Vadadustat has a drug-drug interaction potential with some statins but the role that this may have played in the development of rhabdomyolysis is unclear. • See Table 3 for a trial-based comparative qualitative summary of important risks	

Table 3. Effects Table

Outcomes[1]	NDD-CKD Population				DD-CKD Population			
	Trial 0014		Trial 0015		Trial 0016		Trial 0017	
	VAD	DARB	VAD	DARB	VAD	DARB	VAD	DARB
Benefits								
Absolute difference in change in Hb (g/dL) between treatment arm – baseline to weeks 24-36 – LS mean (95% CI)[2]	0.1 (0, 0.2)		0 (-0.1, 0.1)		-0.3 (-0.5, -0.1)		-0.2 (-0.2, -0.1)	
Absolute difference in change in Hb (g/dL) between treatment arm – baseline to weeks 40-52 – LS mean (95% CI)[2]	0 (-0.1, 0.1)		0 (-0.1, 0.1)		-0.1 (-0.3, 0.2)		-0.2 (-0.3, -0.1)	
Rate of ESA rescue for worsening anemia – n/N (%)[2]	88/879 (10.0)	59/872 (6.8)	95/862 (11.0)	44/863 (5.1)	40/181 (22.3)	10/188 (5.4)	620/1777 (35.1)	249/1777 (14.1)
Rate of RBC transfusion rescue for worsening anemia – n/N (%)[2]	77/879 (8.8)	79/872 (9.1)	59/862 (6.9)	56/863 (6.5)	13/181 (7.3)	8/188 (4.3)	132/1777 (7.5)	112/1777 (6.3)
Risks								
Time-to-first MACE – HR (95% CI)[3]	1.17 (1.01, 1.36)				0.96 (0.83, 1.11)			
Time-to-first TE – HR (95% CI)[3]	0.89 (0.56, 1.42)				1.20 (0.96, 1.50)			
Description of hepatotoxicity signal with vadadustat[3]	One probable Hy's Law case, at least seven cases of probable DILI in Temple's Corollary, and higher incidence of cases detected in the higher ALT categories in the vadadustat arm. Darbepoetin alfa, the glycosylated form of human erythropoietin, does not have a DILI risk.							
Exposure-adjusted RR (AD) of seizures[3]	1.07 (0.04 / 100 pt-yrs)				1.29 (0.37 / 100 pt-yrs)			
Exposure-adjusted RR (AD) of GI acid-related disease[3]	1.20 (1.35 / 100 pt-yrs)				1.52 (3.51 / 100 pt-yrs)			
Exposure-adjusted RR (AD) of any GI symptoms[3]	1.39 (7.88 / 100 pt-yrs)				1.34 (7.13 / 100 pt-yrs)			

Source: Clinical and Statistical Teams Review

[1] Outcomes measuring improvement in how subjects feel, reduced treatment burden and increased satisfaction were not measured, thus are not included in the effects table.

[2] Efficacy results obtained from individual trials due to difference in study design. Efficacy-related results obtained from analyses conducted on the randomized population. Definitions of important efficacy endpoints can be found in section II.6.2.

[3] Safety results obtained from pooled database of safety population, due to smaller numbers in the individual trials. Safety terms coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.

Abbreviations: NDD, non-dialysis dependent; CKD, chronic kidney disease; DD, dialysis-dependent; VAD, vadadustat arm; DARB, darbepoetin alfa arm; Hb, hemoglobin; LS, least squares; CI, confidence interval; ESA, erythropoietin stimulating agent; RBC, red blood cell; N, number of subjects; n, number of subjects within specific category; HR, hazard ratio; MACE, major adverse cardiovascular events; TE, thromboembolism; DILI, drug-induced liver injury; ALT, alanine aminotransferase; RR, relative risk; AD, absolute difference; GI, gastrointestinal.

2.2. Conclusions Regarding Benefit-Risk

Chronic kidney disease (CKD) is a progressive and irreversible condition that affects many U.S. adults. Patients with CKD may become dialysis-dependent, and those with advanced CKD are commonly awaiting kidney transplant as definitive therapy. Importantly, exposure to foreign antigens, such as that occurring during a RBC transfusion, may result in alloimmunization, which may impact the patient's eligibility for a kidney transplant.

The anemia of CKD is a prevalent and impactful condition in the U.S. adult population, with significant morbidity and mortality. The main approved treatment, erythropoietin stimulating agents (ESAs), are effective at improving the anemia but are administered intravenously and are associated with significant cardiovascular and thrombotic adverse reactions, especially when higher hemoglobin values are targeted. Currently, there is no approved oral therapy besides iron supplementation for the treatment of anemia of CKD. There is an unmet need for safer and orally available therapies for anemia of CKD that will allow patients to avoid the need for RBC transfusions and its potential impact on transplant eligibility.

The efficacy and safety of vadadustat, an oral HIF-PH inhibitor that gradually increases the production of erythropoietin, was evaluated in four randomized, open-label trials that used darbepoetin alfa (an approved ESA) as the active comparator.Vadadustat demonstrated non-inferiority to darbepoetin alfa in raising and maintaining hemoglobin, up to a treatment period of at least 52 weeks, in subjects with CKD and anemia who were not dialysis dependent (NDD) and those who were dialysis-dependent (DD). There was a higher rate of ESA rescue therapy use with vadadustat compared to darbepoetin alfa in both the NDD-CKD and DD-CKD populations, and a higher rate of RBC transfusions with vadadustat compared to darbepoetin alfa in the DD-CKD population. Although the finding of non-inferiority on Hb was is met after sensitivity analyses that accounted for these differences in rescue therapy, the higher rate of rescue therapies with vadadustat, compared to darbepoetin alfa, in the NDD-CKD and DD-CKD populations introduces uncertainty in the efficacy conclusions of vadadustat in the treatment of anemia of CKD.

Other important benefits of avoidance of RBC transfusions are limiting alloreactivity, a critical risk factor for renal allograft rejection in patients who undergo renal transplantation, and avoidance of other transfusion-related risks, such as infection and allergic reactions. Furthermore, as an oral therapy, vadadustat would offer convenience compared to the intravenous route of ESAs, especially in the NDD-CKD population. The convenience of an oral drug in the DD-CKD population is less clear, particularly for the majority of DD-CKD patients in the US, who receive hemodialysis rather than peritoneal dialysis and who are administered ESA at the time of hemodialysis. The trials established no other benefits of vadadustat in the NDD-CKD or DD-CKD populations.

The clinical trials identified several major safety concerns with vadadustat. In the NDD-CKD population, vadadustat did not demonstrate non-inferiority for the primary safety endpoint of adjudicated MACE compared to darbepoetin alfa. In the DD-CKD population, vadadustat demonstrated a concerning signal for TE compared to darbepoetin alfa with the majority of events caused by vascular access thrombosis, which could impact the ability of subjects to maintain life-saving dialysis. The use of vadadustat was also associated with a clinically

significant hepatocellular injury risk in patients with CKD as evident by the occurrence of one Hy's Law case and at least seven cases of probable drug-induced liver injury.

With real-world use, the convenience of an oral drug may result in less-frequent hemoglobin monitoring for patients not seeking regular medical follow-up, such as those with CKD not on dialysis, leading to a potentially higher risk of adverse reaction occurrence compared to the already unfavorable safety profile seen in the clinical trials where patients were more closely monitored. Furthermore, approval of vadadustat may result in wider prescribing practices of the drug (e.g., in patients with anemia and decreased creatinine clearance who do not presently receive ESAs). Some of these patients, particularly the elderly, would be at greater risk of MACE, thus increasing the number of exposed at-risk patients leading to an increase of known associated adverse reactions.

Given the seriousness of the adverse reactions identified with the use of vadadustat in this patient population, demonstration of the effectiveness of any proposed strategy to sufficiently decrease the risks identified would be crucial to a favorable benefit-risk assessment. Overall, we could not identify a risk mitigation strategy or a post-marketing approach that will allow for the safe administration of vadadustat at the proposed dosing regimen to ensure that the benefits of vadadustat outweigh its risks. Regarding the risk of MACE in the NDD-CKD population and TE, including vascular access thrombosis, in the DD-CKD population, we could not identify a sub-population of patients where the benefit-risk evaluation would be favorable.

In conclusion, the increased risk of MACE and thromboembolic events relative to ESAs, which themselves carry an increased risk for these events, and the risk of severe hepatotoxity with vadadustat outweighs the benefits on hemoglobin levels and the oral route of administration. In addition, the increased rates of ESA and RBC transfusion rescue with vadadustat, compared to darbepoetin alfa, introduces uncertainty in the efficacy conclusions of vadadustat in the treatment of anemia of CKD and transfusion-related risks, including alloreactivity (see summary in Table 2 and Table 3). As a result of our benefit-risk assessment and based on the currently available data, we recommend against the approval of vadadustat for the treatment of anemia associated with CKD in adults. New trials would be needed with a dosing regimen that has a more favorable benefit/risk assessment.

II. Interdisciplinary Assessment

3. Introduction

The Applicant, Akebia Therapeutics Inc., seeks approval of vadadustat, under the 505(b)(1) regulatory pathway, for the treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis. Vadadustat is the second submission of an NDA for a new molecular entity of its drug class (inhibitors of hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) enzymes), of which none have been yet approved. Vadadustat mimics the physiological effects of hypoxia inside the cell, leading to increased production of erythropoietin (EPO) and improved oxygen-carrying capacity through increased production of red blood cells (RBCs) and elevation of hemoglobin (Hb). The starting dose of vadadustat oral tablets is 300 mg

daily, with Hb-dependent dose adjustment based upon a dose adjustment algorithm to allow for strict adherence to target Hb range, with a dose range of 150 mg to 600 mg daily.

Chronic kidney disease (CKD) is defined as the presence of kidney damage or a decreased level of kidney function for a period of at least three months, with or without glomerular filtration rate impairment. The prevalence of CKD in the United States adult population is estimated at 15%, with an estimated 17.2 million having stage 3-5 CKD. Anemia, defined as a decreased number of RBCs, is a common complication of CKD that develops early in the course of the disease and worsens as CKD progresses, occurring in approximately 90% of patients with Stages 4 and 5 CKD, regardless of dialysis status. The mechanism of anemia in CKD is multifactorial but is mainly caused by a decrease in production of EPO due to progressive loss of EPO-producing cells in the diseased kidney, iron deficiency from inadequate intake or absorption, and chronic inflammation. It is important to evaluate patients with anemia of CKD to rule out other reversible causes such as iron, vitamin B12, and folate deficiencies. Of note, two commonly used surrogate endpoints for anemia of CKD are Hb response and reduction in the need for RBC transfusions. In addition, anemia in patients with CKD is associated with increased risk of cardiovascular disease, infections, morbidity due to symptomatic anemia and increased risk of hospitalization, and mortality due to cardiac disease, stroke, and renal-associated causes.

Available treatments for anemia due to CKD include RBC transfusions, androgen (off-label use), and erythropoietin stimulating agents (ESA), with ESAs considered to be the current standard of care for treatment of anemia due to CKD. ESAs are recombinant proteins and include Epogen / Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta), and Retacrit (epoetin alfa-epbx). All ESAs are approved for the treatment of anemia to reduce the need for RBC transfusions in patients with dialysis-dependent (DD) CKD and patients with non-dialysis dependent (NDD) CKD. All ESA labels contain a boxed warning for increased risk of cardiovascular mortality and morbidity associated with targeting higher Hb value compared to lower Hb value (see Section II.7.2 for a detailed discussion of the safety profile of ESAs). It is important to note that there is no identified trial-based Hb target value, ESA dose or dosing strategy that does not increase these risks. However, the general dosing recommendation is to use the lowest ESA dose sufficient to reduce the need for RBC transfusions, while targeting a Hb value less than 11 g/dL. Table 4 summarizes the year of approval, route, and frequency of administration of all approved ESAs. RBC transfusions are mainly used in scenarios of acute and/or life-threatening anemia. RBC transfusions are associated with risk of transmission of infection, alloimmunization, iron overload, and allergic reactions. There are no approved oral treatments for patients with anemia associated with CKD.

The schedule of administration of inhibitors of HIF-PH is close to being continuous because HIF-PH inhibitors are administered daily. In contrast, ESAs are given intermittently (weekly, every other week or monthly). The maximum levels of endogenous erythropoietin generated by daily administration of inhibitors of HIF-PH are lower compared to the peak levels of exogenous erythropoietin generated by intravenous intermittent pulses of ESAs. This has led to the assumption that the toxicity profile of the inhibitors of HIF-PH would be more favorable (less toxic) than that of the ESAs.

Three different inhibitors of the HIF-PH class are being developed to treat the anemia of CKD: roxadustat, the first in class, vadadustat, and daprodustat. Roxadustat was given a complete response due to an excess risk of major adverse cardiac events (MACE) and thrombotic events (see section II.7.2 for details). This suggests that the hypothesis that the HIF-HP as a class would

be less toxic than the ESAs may not be true of all the members of the class of inhibitors of HIF-PH.

Table 4. Approved Therapies for Anemia Due to Chronic Kidney Disease

Product Name	Year of Approval	Route and Frequency of Administration
EPOGEN / PROCRIT (epoetin alfa) (Janssen Pharmaceuticals 2018)	1989	Intravenous or subcutaneous injection. Starting dose in adults: 50 – 100 Units/kg three times per week, regardless of dialysis status. Monitoring of Hb response and dose adjustment as per guidelines in USPI.
ARANESP (darbepoetin alfa) (Amgen Inc. 2019)	2001	Intravenous or subcutaneous injection. Starting dose in adults with NDD-CKD: 0.75 µg/kg every 4 weeks. Starting dose in adults with DD-CKD: 0.45 µg/kg every week or 0.75 µg/kg every 2 weeks. Monitoring of Hb response and dose adjustment as per guidelines in USPI.
MIRCERA (methoxy polyethylene glycol-epoetin beta) (Vifor (International) Inc. 2018)	2007	Intravenous or subcutaneous injection. Starting dose in adults: 0.6 mcg/kg once every two weeks, regardless of dialysis status. Monitoring of Hb response and dose adjustment as per guidelines in USPI.
RETACRIT (epoetin alfa-epbx) (Pfizer 2020)	2018	Intravenous or subcutaneous injection. Starting dose in adults: 50 – 100 Units/kg three times per week, regardless of dialysis status. Monitoring of Hb response and dose adjustment as per guidelines in USPI.

Source: clinical reviewer
Abbreviations: DD-CKD, dialysis dependent chronic kidney disease; NDD-CKD, non-dialysis dependent chronic kidney disease; USPI, United States Prescribing Information

The Applicant submitted an investigational new drug (IND) application for vadadustat to the FDA on July 21, 2009. Multiple meetings took place throughout the phases of drug development to provide tailored guidance to the Applicant and to ensure regulatory alignment with the Applicant (see Section III.12 for complete regulatory history). The Applicant completed eighteen phase 1 studies in healthy volunteers, ten phase 2 trials in subjects with CKD (see Sections III.17.1 and III.17.2 for details) and eight phase 3 trials in subjects with CKD. Of the eight phase 3 trials, four trials were conducted in Japan (see Section III.17.3 for details) and four trials were conducted globally (see Sections II.3.2 and II.6.2 for details), the latter trials being used to support the benefit-risk assessment of vadadustat. The following is a list of key regulatory points of consensus reached throughout the interactions with the Applicant:

- The conduct of two adequate and well-controlled phase 3 trials for each population mentioned in the proposed indication (i.e., subjects with dialysis-dependent (DD) CKD and subjects with non-dialysis dependent (NDD) CKD).
- The use of an active comparator in all phase 3 trial.
- The use of the following stratification criteria: 1) Geographic region (i.e., United States versus Europe versus Rest of World), 2) New York Heart Association (NYHA) heart failure Class 0 / I versus II / III, and 3) Baseline Hb thresholds, based on the trial population.
- The use of a target range of Hb for the U.S. sites of 10.0 to 11.0 g/dL (versus a target range of Hb for sites outside the United States of 10.0 to 12.0 g/dL), with U.S. subjects accounting for more than 30% of the total phase 3 trial population.
- The use of a starting dose of 300 mg daily, with a dose adjustment approach to remain within the target range of Hb and a dose range of 150 to 600 mg daily.

- The use of a primary efficacy endpoint of the mean change in Hb between baseline and the primary evaluation period (i.e., weeks 24 to 36). The key secondary efficacy endpoint is the mean change in Hb between baseline and the secondary evaluation period (i.e., weeks 40 to 52). The non-inferiority margin is -0.75 g/dL (i.e., the lower bound of 2 sided 95% CI) for the treatment comparison for the primary and secondary efficacy endpoints. The basis for -0.75 g/dL for the non-inferiority margin is discussed in section II.6.2.
- The use of a primary safety endpoint is time to first adjudicated major adverse cardiovascular event (MACE) defined as death, non-fatal myocardial infarction (MI), and non-fatal stroke. The non-inferiority margin is 1.25 (i.e., the upper bound of 2 sided 95% CI for the hazard ratio [HR]) for the primary safety endpoint.

3.1. Review Issue List

The review team identified six key review issues that had a significant impact on the overall determination of approvability of vadadustat. All key review issues were risk issues, with no benefit issues identified during the NDA review process. In depth analyses of the risk issues can be found in section II.7.7.

- Benefit Issue 1: Impact of Rescue Therapy Use on the Non-Inferiority Efficacy Conclusion of Vadadustat
  Benefit Issue 2: Impact of US vs. Non-US Darbepoetin Alfa on the Efficacy Results
- Risk Issue 1: Failure to demonstrate non-inferiority of MACE in the NDD-CKD population
- Risk Issue 2: Increased risk of thromboembolic events in the DD-CKD population
- Risk Issue 3: Hepatotoxicity in the NDD-CKD population and the DD-CKD population:
- Risk Issue 4: Increased risk of seizures in the DD-CKD population
- Risk Issue 5: Increased risk of gastrointestinal adverse reactions in the CKD population

3.2. Approach to the Review

The early phase studies in healthy volunteers, summarized in Section III.14.2, allowed the determination of bioavailability, bioequivalence, food-effect, pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of several drug formulations and dosing approaches, in addition to providing preliminary safety and tolerability data. Analysis of this portion of the drug development plan will be addressed by the clinical pharmacology team. The early phase trials in subjects with CKD, summarized in Section III.14.2, provided additional PK, PD, safety, tolerability, and preliminary efficacy data, in both the NDD-CKD population and the DD-CKD population, which guided dose and dose regimen selection for the four larger phase 3 trials. Analysis of this portion of the drug development plan will be addressed by the clinical pharmacology team. Table 5 provides an overview of the clinical trials conducted to support the benefit-risk assessment of vadadustat. Overall, these trials were identical in study design and statistical analysis method but had different eligibility criteria. Analysis of efficacy outcomes of the individual phase 3 trials provided the basis of the benefit assessment in the two target populations (see section II.6 for more details). Analysis of this portion of the drug development plan will be addressed by the efficacy statistical team and the clinical team. However, analysis of

safety outcomes of the pooled data from the PRO$_2$TECT program (i.e., trial 0014 and trial 0015) provided the basis of the risk assessment in the NDD-CKD population, while analysis of safety outcomes of the pooled data from the INNO$_2$VATE program (i.e., trial 0016 and trial 0017) provided the basis of the risk assessment in the DD-CKD population (see section II.7 for more details). Analysis of this portion of the drug development plan will be addressed by the safety statistical team and the clinical team.

Table 5. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations for Vadadustat

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned / Randomized	Number of Sites and Countries
PRO2TECT – CORRECTION / AKB-6548-CI-0014 (NCT02648347)	Adult subjects with NDD-CKD and anemia associated with CKD (baseline Hb <10.0 g/dL), with no evidence of other causes of anemia and no recent exposure to ESAs or RBC transfusions	Control type: Active control (with darbepoetin alfa) Randomization: Ratio of 1:1, with stratification by geographic region, heart failure class and baseline Hb Blinding: Open-label, Sponsor-blinded Biomarkers: Mean hemoglobin value	Drug: Vadadustat (oral tablet) vs. Darbepoetin alfa (injectable solution for IV or SC administration) Dosage: Vadadustat 300 mg daily (dose adjustment depending on serial Hb values) vs. Darbepoetin alfa administered as per USPI Number treated: 1748 (878 on vadadustat vs. 870 on darbepoetin alfa) Duration: Minimum of 36 weeks	Primary: Mean change in Hb from Baseline to the primary evaluation period Risk of MACE and its components Secondary: Mean change in Hb from Baseline to the secondary evaluation period Risk of thromboembolic events	1850 / 1751	274 / 15

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned / Randomized	Number of Sites and Countries
PRO2TECT – CONVERSION / AKB-6548-CI-0015 (NCT02680574)	Adult subjects with NDD-CKD and anemia associated with CKD (baseline Hb 8-11 g/dL in the United States and 9-12 g/dL outside the United States) on maintenance ESA therapy, with no evidence of other causes of anemia and no recent exposure to RBC transfusions	Control type: Active control (with darbepoetin alfa) Randomization: Ratio of 1:1, with stratification by geographic region, heart failure class and baseline Hb Blinding: Open-label, Sponsor-blinded Biomarkers: Mean hemoglobin value	Drug: Vadadustat (oral tablet) vs. Darbepoetin alfa (injectable solution for IV or SC administration) Dosage: Vadadustat 300 mg daily (dose adjustment depending on serial Hb values) vs. Darbepoetin alfa administered as per USPI Number treated: 1723 treated (861 on vadadustat vs. 862 on darbepoetin alfa) Duration: Minimum of 36 weeks	Primary: Mean change in Hb from Baseline to the primary evaluation period Risk of MACE and its components Secondary: Mean change in Hb from Baseline to the secondary evaluation period Risk of thromboembolic events	1850 / 1725	328 / 26

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned / Randomized	Number of Sites and Countries
INNO2VATE – CORRECTION / CONVERSION, AKB-6548-CI-0016 (NCT02865850)	Adult subjects with DD-CKD (started dialysis within 16 weeks of screening) and anemia associated with CKD (baseline Hb 8-11 g/dL), with no evidence of other causes of anemia, no recent exposure to RBC transfusions and no evidence of ESA resistance	Control type: Active control (with darbepoetin alfa) Randomization: Ratio of 1:1, with stratification by geographic region, heart failure class and baseline Hb Blinding: Open-label, Sponsor-blinded Biomarkers: Mean hemoglobin value	Drug: Vadadustat (oral tablet) vs. Darbepoetin alfa (injectable solution for IV or SC administration) Dosage: Vadadustat 300 mg daily (dose adjustment depending on serial Hb values) vs. Darbepoetin alfa administered as per USPI Number treated: 365 treated (179 on vadadustat vs. 186 on darbepoetin alfa) Duration: Minimum of 36 weeks	Primary: Mean change in Hb from baseline to the primary evaluation period Risk of MACE and its components Secondary: Mean change in Hb from baseline to the secondary evaluation period Risk of thromboembolic events	300 / 369	83 / 10

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned / Randomized	Number of Sites and Countries
INNO2VATE – CONVERSION AKB-6548-CI-0017 (NCT02892149)	Adult subjects with DD-CKD (received dialysis for at least 12 weeks prior to screening) and anemia associated with CKD (baseline Hb 8-11 g/dL in the United States and 9-12 g/dL outside the United States) on maintenance ESA therapy, with no evidence of other causes of anemia and no recent exposure to RBC transfusions	Control type: Active control (with darbepoetin alfa) Randomization: Ratio of 1:1, with stratification by geographic region, heart failure class and baseline Hb Blinding: Open-label, Sponsor-blinded Biomarkers: Mean hemoglobin value	Drug: Vadadustat (oral tablet) vs. Darbepoetin alfa (injectable solution for IV or SC administration) Dosage: Vadadustat 300 mg daily (dose adjustment depending on serial Hb values) vs. Darbepoetin alfa administered as per USPI Number treated: 3537 treated (1768 on vadadustat vs. 1769 on darbepoetin alfa) Duration: Minimum of 36 weeks	Primary: Mean change in Hb from baseline to the primary evaluation period Risk of MACE and its components Secondary: Mean change in Hb from baseline to the secondary evaluation period Risk of thromboembolic events	3300 / 3537	275 / 18

Source: Clinical reviewer
Abbreviations: CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythrocyte stimulating agent; Hb, hemoglobin; IV, intravenous; MACE, major adverse cardiovascular events; NCT, national clinical trial; NDD, non-dialysis dependent; RBC, red blood cell; SC, subcutaneous; USPI, United States prescribing information.

4. Patient Experience Data

Table 6. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 7. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHDi).
Mechanism of action	Inhibitor of prolyl hydroxylase domain-containing proteins (PHD) that regulate stability of hypoxia-inducible factor alpha (HIFα), mimicking a cellular state of hypoxia and initiating a HIF-dependent pathway of increased erythropoiesis.
Active moieties	Vadadustat
QT prolongation	A thorough QT (TQT) study demonstrated that vadadustat was not associated with any potential to cause QTc interval prolongation (i.e., >10 msec) after single doses of 600 mg and 1200 mg. A single-dose of 1200 mg adequately covers the worst-case clinical exposures.
	General Information
Bioanalysis	Validated LC-MS/MS methods were used to determine the concentrations of vadadustat and its metabolites in human plasma and urine. The methods are validated as per the criteria outlined in the Bioanalytical Method Validation Guidance.
Healthy subjects versus patients	Vadadustat clearance decreased with decreasing estimated glomerular filtration rate (eGFR) in NDD-CKD patients and exposures in dialysis patients were approximately 2-fold higher compared to healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	Parameter — Mean ± SD (300 mg) — Mean ± SD (600 mg) AUC — 365.5 ± 230.3 µg/mL — 730.9 ± 460.8 µg/mL C_{max} — 20.6 ± 9.8 µg/mL — 41.2 ± 19.7 µg/mL
Range of effective dosage(s) or exposure	Pivotal clinical trials had a vadadustat starting dose of 300 mg QD with the opportunity to up-or down-titrate the dose to 150 or 600 mg QD to reach and maintain the Hb in the target range (10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL ex-US).
Maximally tolerated dosage or exposure	A maximum tolerated dose was not identified for vadadustat. A maximum single dose of 1200 mg was studied in healthy subjects in Study CI-0001 and a multiple dose of 900 mg daily for 10 days was studied in DD-CKD subjects in Study CI-0034.
Dosage proportionality	Vadadustat AUC and C_{max} increased proportionally after single doses from 80 mg to 1200 mg (0.27 to 4 times the approved recommended starting dosage).
Accumulation	No significant accumulation is observed at steady state with once daily dosing
Time to achieve steady-state	Vadadustat is expected to reach steady state by day 3 following once daily dosing.

Characteristic	Drug Information
Bridge between to-be-marketed and clinical trial formulations	To-be-marketed tablets (Formulation F1; 450 mg) were found to be bioequivalent to the phase 3 tablets (Formulation E2; 3 x 150 mg). Office of Study Integrity and Surveillance determined that the inspections for the clinical and analytical sites are not warranted at this time because the past inspections were within the surveillance interval and the final classification was No Action Indicated.
Absorption	
Bioavailability	The absolute bioavailability of vadadustat after oral dosing was not determined.
T_{max}	The median time to peak plasma concentrations of vadadustat is approximately 2 to 3 hours.
Food effect (fed/fasted) Geometric least square mean and 90% CI	450 mg to-be-marketed tablet (Formulation F1) taken with a high-fat breakfast (Study CI-0028) $AUC_{0-\infty}$, GMR (90% CIs): 94.3 (90.3 – 98.5%) C_{max}, GMR (90% CIs): 73.1 (67.9 – 78.6%) T_{max}, median: 2 h (fasted), 3.5 h (fed) Clinical studies of vadadustat were carried out by administering the drug without regard to meals. Therefore, vadadustat can be administered with or without food.
Distribution	
Volume of distribution	The mean apparent volume of distribution (Vd/F) is 11.6 L in subjects with CKD.
Plasma protein binding	Protein binding of vadadustat ≥99.5%
Drug as substrate of transporters	Vadadustat, in vitro, is a substrate of BCRP, OATP1B1, and OAT1/3.

Characteristic	Drug Information
	Elimination
Mass balance results	Following administration of 650 mg of [^{14}C]-vadadustat in capsule form, 58.9% of the dose was recovered in urine and 26.9% was recovered in feces. Unchanged vadadustat represented about 9% of the administered dose in feces and <1% in urine (Study CI-0008).
Clearance	The mean apparent clearance (CL/F) is 1.68 L/h in healthy subjects; 0.80 L/h in patients with NDD-CKD; and 0.79 L/h in patients on chronic hemodialysis.
Half-life	The mean terminal half-life in healthy subjects is 4.8 hours; 7.9 hours in patients with NDD-CKD; and 9.2 hours in patients on chronic hemodialysis.
Metabolic pathway(s)	Vadadustat is primarily metabolized via glucuronidation by UDP-glucuronosyltransferase (UGT) enzymes.
	Intrinsic Factors and Specific Populations
Body weight	Increasing body weight is associated with decreasing AUC of vadadustat. The change in AUC with body weight is modest and not clinically significant.
Age	The effect of age on the PK of vadadustat was evaluated by population pharmacokinetic (popPK) analysis. Age was not found to be a statistically significant covariate.
Renal impairment	Vadadustat clearance decreased with decreasing estimated glomerular filtration rate (eGFR) in NDD-CKD patients and exposures in dialysis patients were approximately 2-fold higher compared to healthy subjects. In patients with Stage 5 dialysis-dependent (DD) CKD, no significant differences in pharmacokinetics (Cmax, AUC or mean half-life) were observed when vadadustat was administered 4 hours before dialysis or 2 hours after dialysis. The target population with renal impairment, both NDD-CKD and DD-CKD was studied in the pivotal trials. Therefore, dose-adjustments for renal impairment are not warranted.
Hepatic impairment	The LS-mean-ratios for Cmax and AUC values for those with moderate (Child Pugh B) hepatic impairment compared to healthy individuals were 1.02 and 1.06, respectively, after a single 450 mg dose. These data indicated that moderate hepatic impairment did not appear to significantly affect systemic exposure to vadadustat. The impact of severe hepatic impairment on vadadustat exposures is unknown.

Characteristic	Drug Information
	Drug Interaction Liability (drug as perpetrator)
Inhibition/induction of metabolism	In vitro, vadadustat is not an inhibitor of major CYP isoforms and UGT isoforms nor inducer of CYP1A2, CYP2B6, and CYP3A4.
Inhibition/induction of transporter systems	In vitro, vadadustat is an inhibitor of P-gp, BCRP, OATP1B1, OAT1, OAT3. **In vivo evaluation:** • Exposure to furosemide, an OAT1/3 substrate increased about 2-fold upon co-administration with vadadustat. • Co-administration of vadadustat with adefovir, an OAT1 probe substrate, did not alter the PK of adefovir. • Co-administration of vadadustat and pravastatin (OATP1B1 probe substrate) did not alter the PK of pravastatin. • When vadadustat is co-administered with digoxin (P-gp substrate), digoxin AUC was unchanged, but its Cmax decreased by 35%. • Co-administration of vadadustat with the BCRP substrate sulfasalazine resulted in an approximate 4.5-fold increase in sulfasalazine exposure but minimal impact on the exposure to mesalamine (5-amino salicylic acid [5-ASA]). • Co-administration of vadadustat with rosuvastatin (BCRP and OATP1B1 substrate) increased rosuvastatin exposures 2- to 3-fold. • Co-administration of vadadustat with atorvastatin weakly (<1.5-fold) increased the systemic exposure to atorvastatin. Exposures to simvastatin and its active metabolite (beta-hydroxy acid) were weakly to moderately increased when co-administered with vadadustat.

5.1. Nonclinical Assessment of Potential Effectiveness

Summary

Vadadustat is a small molecule inhibitor of prolyl hydroxylase domain-containing proteins (PHD), which are a family of oxygen-sensitive enzymes that regulate stability of hypoxia-inducible factor alpha (HIFα).

Under normoxic conditions, PHDs actively hydroxylate the alpha subunit of HIF proteins which lead to its targeting and degradation by intracellular proteasomal enzymes. Hypoxic conditions inhibit PHD enzymatic activity, leading to cellular accumulation of HIFα and its translocation to the nucleus, which in association with HIFβ initiates transcription that increases expression of a plethora of genes including some associated with erythropoiesis, most notably erythropoietin.

By inhibiting HIF-PHD enzymes directly, vadadustat mimics a cellular state of hypoxia and initiates a HIF1-dependent pathway of increased erythropoiesis mediated predominately by increased expression of erythropoietin, providing a therapeutic rationale for its use in treating anemia.

Vadadustat was not studied in any animal model of anemia. Vadadustat increased key measures of erythropoiesis in pharmacology studies conducted in normoxic, non-anemic mice and rats. Increased erythropoiesis was also evident in the general toxicity studies conducted in rodents and dogs. Erythropoietin, a key intermediary in the mechanism of action, was increased in response to vadadustat, as was red cell and reticulocyte count, hematocrit, hemoglobin, and total iron binding capacity. Effective modeled exposures for increasing Hb and hematocrit by ~15% in normoxic rodents and dogs ranged from 108 to 242 µg.h/ml; for comparison, exposure from the clinical dose of 600 mg ranges from 416 to 625 µg.h/ml area under the concentration-time curve (AUC), depending on patient population.

Background and Key Findings

Primary In Vitro Pharmacology

Vadadustat is not isoform specific, inhibiting three isoforms of human recombinant PH domain enzymes with half maximal inhibitory concentration (IC_{50}) values at nanomolar potencies. Inhibition of the three PHD hydroxylases, which have partly overlapped expression profiles, would stabilize cellular HIFα proteins in a manner similar to a low oxygen environment. Although activity against the Factor-inhibiting Hypoxia Inducible Factor (FIH), a related HIFα hydroxylase, was not evaluated, inhibition of the PHD hydroxylases stabilized and increased cellular levels of HIF1α as assessed by in vitro studies. Rodent and dog isoforms of HIF-PHD were not tested but pharmacological activity was clearly demonstrated in these species, validating their use for toxicological evaluation.

Vadadustat metabolites (vadadustat-o-glucuronide and B-504) had 100 to 200-fold lower inhibitory potency for PHD enzymes relative to vadadustat and are unlikely to contribute to pharmacodynamic activity at clinical exposure.

Vadadustat increased cellular levels and nuclear translocation of HIF1α in cultured human vascular endothelial cells under normoxic conditions. Stabilization of HIF2α was also observed

but required a longer duration of exposure (24hr). The cellular expression profile of HIF proteins and their susceptibility to hydroxylation by PHD enzymes is known to differ (Harnoss et al. 2015), likely accounting for the different time course of HIF stabilization observed in this in vitro study.

Vadadustat stimulated EPO secretion (half maximal effective concentration 9.97 µM) but not vascular endothelial growth factor in Hep3B cells under normoxic conditions.

In a CEREP panel, vadadustat showed no remarkable off-target activities.

Table 8. IC50 and Pic50 of Vadadustat Against Human Recombinant PHD1, PHD2, and PHD3 by TR-FRET Assay

		IC_{50} value (nM)	pIC_{50} value
PHD1 (n=3)	Mean ± SEM	15.41 ± 0.91	7.81 ± 0.03
	Geometric Mean (95% CI)	15.36 (11.96, 19.73)	7.81 (7.71, 7.92)
PHD2 (n=3)	Mean ± SEM	11.91 ± 1.00	7.93 ± 0.04
	Geometric Mean (95% CI)	11.83 (8.20, 17.07)	7.93 (7.77, 8.09)
PHD3 (n=3)	Mean ± SEM	7.63 ± 0.10	8.12 ± 0.01
	Geometric Mean (95% CI)	7.63 (7.21, 8.07)	8.12 (8.09, 8.14)

CI: confidence interval; IC_{50}: half-maximal inhibitory concentration; PHD1: proly-4-hydroxylase domain 1; PHD2: prolyl-4-hydroxylase domain 2; PHD3: prolyl-4-hydroxylase domain 3; pIC_{50}: IC_{50} in log units; SEM: standard error of the mean; TR-FRET: time-resolved fluorescence resonance energy transfer
The IC_{50} values represent the concentration of vadadustat that reduces PHD enzyme activity to half-maximal activity.

Source: NDA 215192

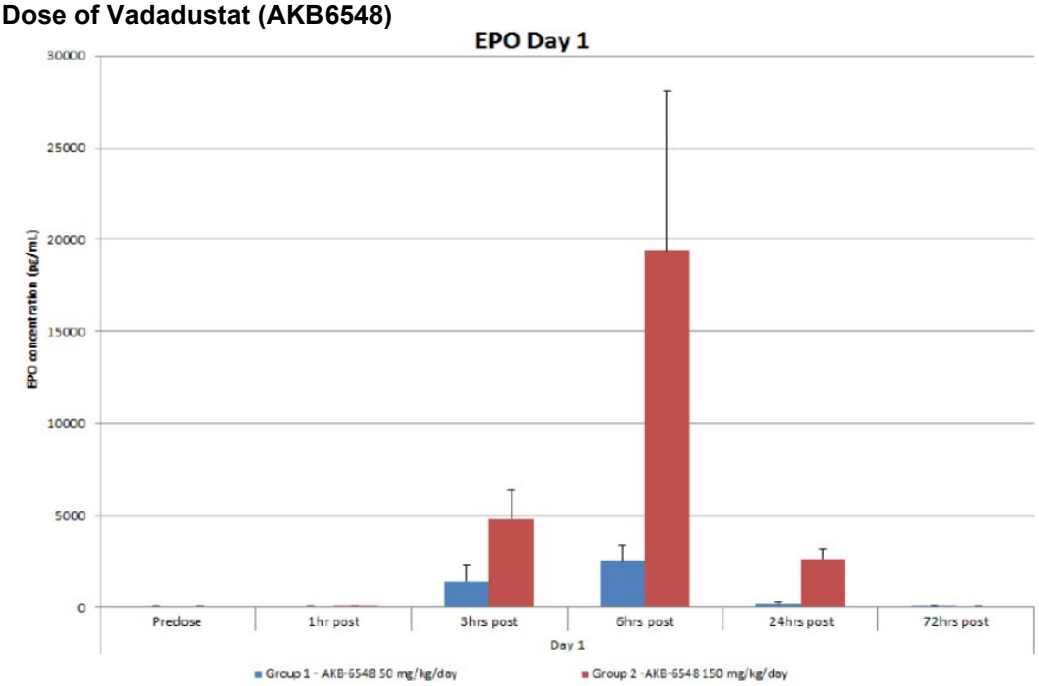
Primary In Vivo Pharmacology:

Vadadustat was evaluated in exploratory studies of healthy, normoxic mice and rats but not in any animal model of anemia. These studies provide a demonstration of the intended pharmacology of increased erythropoiesis downstream of HIF-PHD inhibition; however, they do not capture potential differences in the pharmacology within the context of anemia. For example, the quantitative effect of vadadustat on erythropoietin levels or total iron binding capacity may differ under conditions where anemia and cellular hypoxia are present. Further, these studies are not capable of identifying exposures to vadadustat that would correct anemias of different etiologies (e.g., renal disease versus iron deficiencies).

Vadadustat increased serum erythropoietin in a dose- and time-dependent manner in both Sprague-Dawley rats and Swiss mice under normoxic conditions. In Sprague-Dawley rats, a single dose effectively increased serum EPO at 50 and 150 mg/kg with peak levels occurring 6 hours post-dose followed by a decline to baseline by 24 to 72 hours post-dose (Figure 1). In Swiss mice, a 4-day regimen of vadadustat resulted in a 7-fold increase in serum EPO at a dose of 270 mg/kg/day but not at 90 mg/kg/day and lower doses, when measured 24 hours following the last dose (Figure 2).

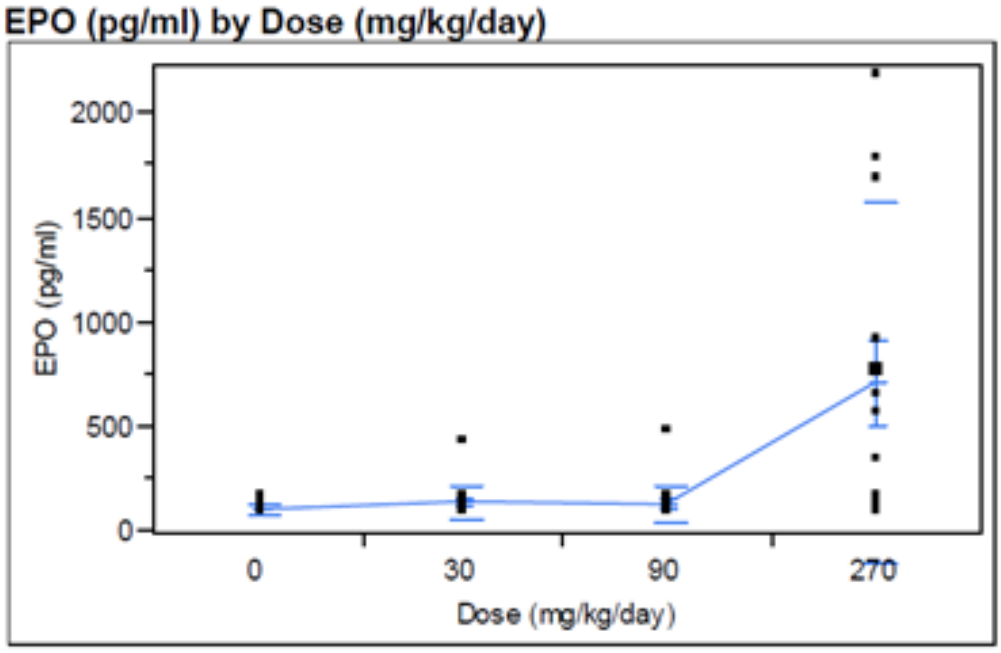
The ability of vadadustat to increase serum EPO was found to decline after repeated dosing in normoxic rats (see Section III.13.1). While still higher than control, the fold increase declined nearly 80% by dosing day 1.

Figure 1. Change in Serum Erythropoietin in Sprague Dawley Rats in Response to a Single Oral Dose of Vadadustat (AKB6548)



Source: Excerpted from Applicant submission, Study 6401491
Data are mean ± SE.
Abbreviations: AKB-6548, vadadustat; EPO, erythropoietin

Figure 2. Dose Response of Change In Serum Erythropoietin in Swiss Mice Following Four Daily Oral Doses of Vadadustat, Measured 24 hrs Following Last Dose



Source: Excerpted from Applicant Submission, Study SW07-302
Data are individual EPO values per animal.
Abbreviations: EPO, erythropoietin

Vadadustat increased clinically relevant markers of erythropoiesis in Swiss mice and Sprague Dawley rats, including increases in reticulocytes, hemoglobin, and hematocrit values. The rise in

hemoglobin (Hb) and hematocrit levels was sustained upon repeat dosing of vadadustat in both rats and mice over 7 to 14 days of dosing (Table 9; refer to Section III.13.1).

Table 9. Vadadustat-Induced Changes in Reticulocyte, Hemoglobin and Hematocrit

Species	Treatment	Dose, mg/kg QD	Day 7 or Day 8			Day 14		
			Retic	Hb	HCT	Retic	Hb	HCT
Mouse	7 days, PO	200	+27%	+14%	+13%			
Rat	8 days, PO	150	+43%	+33%	+44%			
Rat (male only)	14 days, PO	30					+6%	
		90	+150%	+14%	+19%	+125%	+34%	+36%

Source: obtained from sponsor's submission, studies SW08-0102, SW08-0146, and 6901491
Data are in comparison with control
Abbreviations: Hb, hemoglobin, HCT, hematocrit; PO, by mouth; QD, once per day; Retic, reticulocyte count

Additionally, the rat 14-day study (Study 6901491) showed increases in total iron binding capacity and unsaturated iron binding capacity with 90 mg/kg/day vadadustat administered orally. However, the findings in total iron binding capacity and unsaturated iron binding capacity were variable and lack a consistent pattern in the 4-week and 3-month toxicology studies in rats where dose dependent decreased serum iron levels were observed.

Table 10. Vadadustat-Induced Changes in TIBC and UIBC

Species	Treatment	Dose, mg/kg QD	Day 7 or 8		Day 14	
			TIBC	UIBC	TIBC	UIBC
Rat	14 days, PO	30	+9.6%	+26.4%	+7.6%	-1.3%
		90	+25.7%	+92.4%	+22.8%	-11.4%

Source: obtained from sponsor's submission, study 6901491
Data are in comparison with control
Abbreviations: PO, by mouth; QD, once per day; TIBC, total iron binding capacity; Treatment, vadadustat; UIBC, unsaturated iron binding capacity

Established Pharmacological Classification

The Applicant proposes and we concur with an established pharmacological classification of hypoxia-inducible factor prolyl hydroxylase (HIF-PHD) inhibitor. The designation of 'HIF' identifies the family of prolyl hydroxylase domain-containing enzymes that interact with the oxygen dependent degradation domain (ODD) of proteins as found in HIF and distinguishes them from the family of collagen-prolyl 4 hydroxylases (C-P4H) that harbor collagen-binding domains (Selvaraju et al. 2014). Vadadustat was demonstrated to inhibit the three commonly recognized HIF-PHD enzymes PHD1, PHD2, and PHD3. While the pharmacological intent of vadadustat is to stimulate erythropoiesis, an established pharmacological classification of 'erythropoiesis stimulating agent', or ESA, is not recommended, as this designation is closely associated with erythropoietin protein products. In addition, HIF-PHD enzymes regulate transcriptional expression of over 150 genes (Selvaraju et al. 2014), which includes erythropoietin, further separating the pharmacological classification of HIF-PHD inhibitors from the currently approved ESA therapeutics.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Applicant's Proposed Dosing Regimen

Dose Initiation

The recommended starting dose is 300 mg once daily.

Dose Titration for All Patients With CKD

Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently.

When initiating or adjusting therapy, monitor hemoglobin levels every two weeks until stable, then monitor at least monthly.

Dose adjustment should be done in increments of 150 mg within the range of 150 mg to 600 mg to achieve or maintain Hb levels within 10 to 11 g/dL. When adjusting the dose, consider the patient's clinical condition, Hb variability, Hb rate of increase and rate of decline, and vadadustat responsiveness. A single Hb excursion may not require a dosing change.

- If the Hb rises rapidly (e.g., more than 1 g/dL in any 2-week period or more than 2 g/dL in 4 weeks), interrupt or reduce the dose.
- If the Hb level exceeds 11 g/dL, interrupt the dose of vadadustat until Hb is less than or equal to 11 g/dL then resume with dose that is 150 mg less than the dose prior to interruption.

Selection of Dosing Regimen for the Phase 3 Trials

The vadadustat starting dose for the phase 3 studies was 300 mg once daily (QD). The dosing algorithm was developed to maintain Hb levels within the target ranges of 10 to 11 g/dL or 10 to 12 g/dL (depending on region), based on results of simulations performed using non-linear mixed effect modeling. Vadadustat doses were titrated from 300 mg to between 150 to 600 mg once daily to maintain Hb within the target range. Vadadustat's apparent terminal half-life was approximately 4 to 5 hours in healthy subjects, 7 to 8 hours in non-dialysis patients, and 9 to 10 hours in dialysis patients with no substantial accumulation (R_{ac} <1.5) for doses up to 600 mg once daily. The vadadustat once daily oral dosing regimen with the above mentioned dose levels was intended to provide sufficient exposures for a favorable Hb response. Subjects were up- or down-titrated in 150 mg increments to achieve and/or maintain target Hb levels. The titration dose was chosen to avoid rapid fluctuations in Hb concentrations. Efficacy and safety findings from the phase 3 studies are discussed in sections II.6.2.6 and II.7.6.

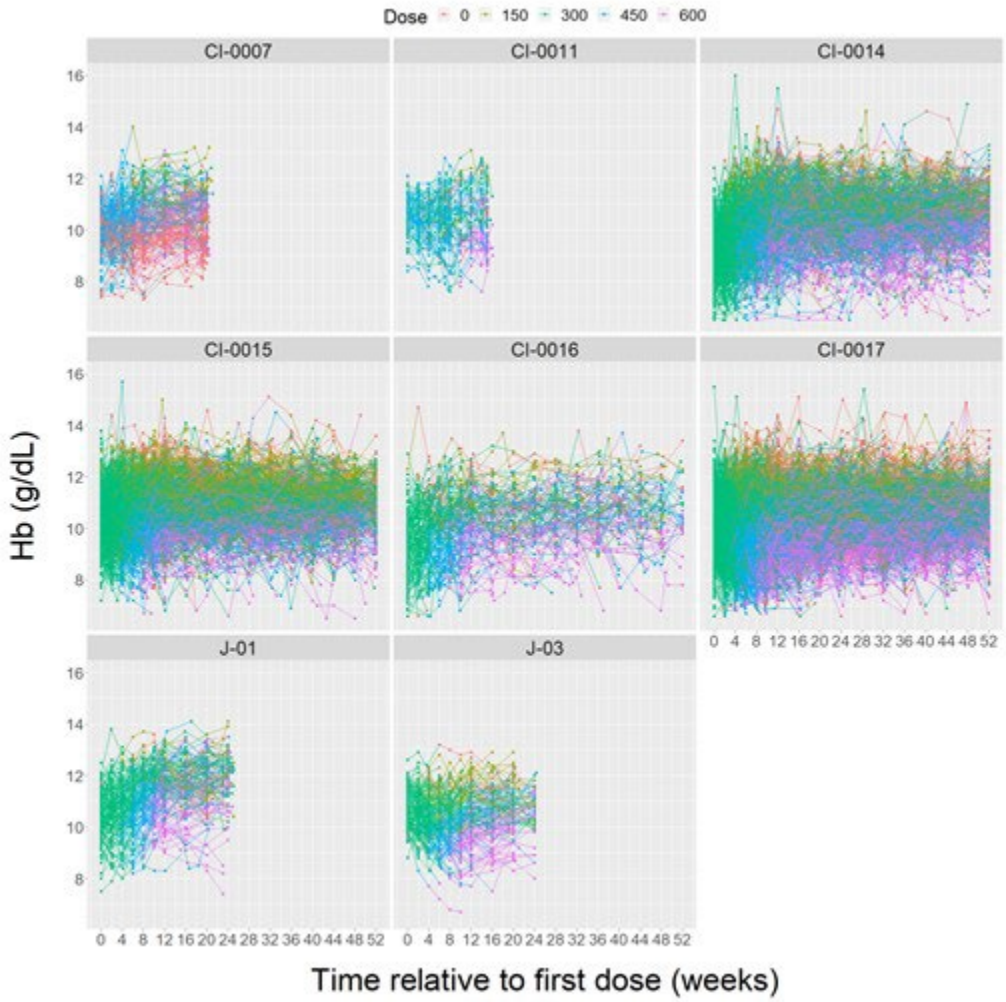
An integrated PK/PD model was developed to quantify the relationship between vadadustat exposure (i.e., AUC) and Hb response using data from two phase 2 studies (CI-0007 and CI-0011), two phase 3 studies (J-01 and J-03), and four global phase 3 studies (CI-0014, CI-0015, CI-0016, and CI-0017). The PD component employed a RBC life span model based on the mechanism of action of vadadustat, which adequately described the time courses of EPO, reticulocyte count, and Hb response. Using the developed model and the proposed dosing

algorithm, simulations were performed to evaluate the Hb PD effects of different starting doses to support the phase 3 dosing. Results of the simulations indicated that the proposed dosing algorithm appeared to maintain Hb levels of 10.0 to 11.0 g/dL in the United States and 10.0 to 12.0 g/dL Ex-United States while minimizing excessive rises, which supported the proposed starting dose of 300 mg once daily and dose titration algorithm for the registrational Phase 3 trials.

Dose-Response

As the Hb target window is small and dosing titration is guided by Hb response, delineating a meaningful dose-response relationship is challenging. As demonstrated in Figure 3, subjects received dosages from 150 mg to 600 mg (0 mg indicates dosing interruption) and could have overlapping Hb response over time (regardless of study regions). Furthermore, subjects receiving 600 mg may be "slow responders" or "non-responders." As such, their Hb response overall may trend towards the lower bound of the observed longitudinal Hb data.

Figure 3. Individual Hb Concentration-Time Profiles by Studies

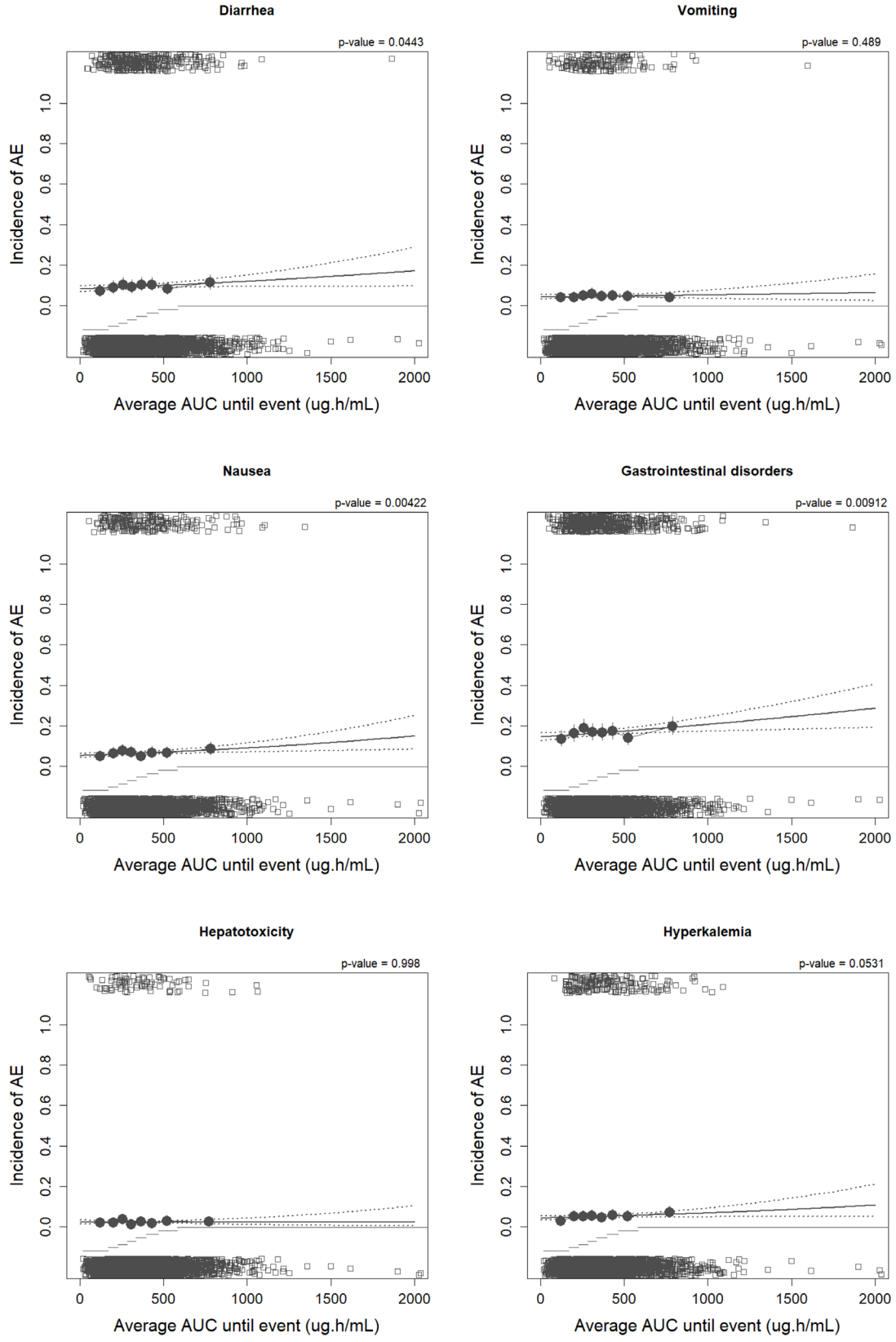


Source: Applicant's PK/PD Analysis Report, Figure 5-1
Solid lines represent individual Hb time profiles colored following dose level administered. Dots are observation after the first vadadustat administration
Abbreviation: Hb, hemoglobin

Exposure-Response for Safety

Exposure-response (E-R) analyses were conducted for safety events of interest, including diarrhea, nausea, vomiting, hepatotoxicity, and hyperkalemia. Individual posterior predictions from the finalized population pharmacokinetic (popPK) model were utilized to derive time-averaged daily AUC of vadadustat up to the event of interest. Logistic regressions (Figure 4) demonstrated flat or close-to-flat E-R relationships across the vadadustat exposure range, with GI-related event having the largest increase in incidence (model-predicted 15.3% and 18.1% at the 10^{th} and 90^{th} percentiles of vadadustat exposure distribution) compared to other safety endpoints of interest. Same methodologies were performed for MACE and non-fatal MI and non-significant E-R relationships were observed across the vadadustat exposure range. (Figure 5). Time-to-event analyses were also conducted and demonstrated that there was no significant E-R relationship between vadadustat exposure and safety endpoints of interest (data not shown). Refer to section III.14.3 Pharmacometric Review for more information.

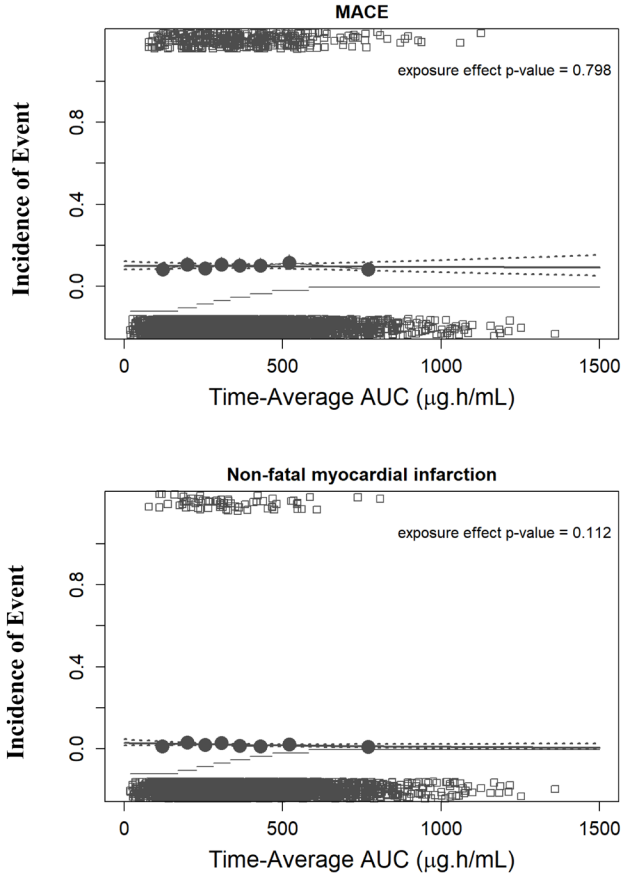
Figure 4. Incidence of Safety Endpoints Versus Exposure (Safety Incidence Grouped by Exposure Quantiles)



Source: Applicant's PK/PD Analysis Report, Figure 5-16

Abbreviations: AE, adverse event; AUC, area under the concentration time curve; open squares represent subjects with event (top of each panel) and with no event (bottom of each panel); solid dots represent incidence within each exposure quantile (eight quantiles total); solid line represents fitted logistic regression (Aithal et al.); dashed lines represent 95% confidence interval; horizontal lines represent the width of each exposure quantile

Figure 5. Incidence of MACE and Non-Fatal Myocardial Infarction Versus Exposure (Safety Incidence Grouped by Exposure Quantiles)



Source: Clinical Information Amendment 1.11.3 (submitted in SN 0021 on September 28, 2021, by the Applicant), Figure 13
Abbreviations: AUC, area under the concentration time curve, MACE, major adverse cardiac event; open squares represent subjects with event (top of each panel) and with no event (bottom of each panel); solid dots represent incidence within each exposure quantile (eight quantiles total); solid line represents fitted logistic regression {logit[P(event)] * exposure * slope + intercept}; dashed lines represent 95% confidence interval; horizontal lines represent the width of each exposure quantile

In summary, the Applicant's proposed starting dose of 300 mg once daily, with a dose titration range of 150 mg to 600 mg in increments of 150 mg no more frequently than once every 4 weeks appears acceptable.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial AKB-6548-CI-0014

6.2.1.1. Design, Trial 0014

Title

Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction of Anemia in Subjects With NDD-CKD (PRO_2TECT - CORRECTION)

Overview and Objectives

Trial 0014 was a multi-center, multi-national, randomized, open-label, sponsor-blinded, active-controlled trial of the efficacy and safety of vadadustat versus darbepoetin alfa for the correction of anemia and maintenance of Hb in subjects with NDD-CKD.

The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the correction and maintenance of Hb in subjects with anemia secondary to NDD-CKD.

Trial Design

Eligible subjects were randomized at the baseline visit, in a 1:1 ratio, between receiving vadadustat or darbepoetin alfa. Subjects living in the U.S. received U.S.-approved darbepoetin alfa, while subjects living outside the U.S received non-U.S.-approved darbepoetin alfa. Enrolled subjects were also stratified by the following factors:

- Geographic region (United States versus Europe versus Rest of World)
- New York Heart Association (NYHA) heart failure Class 0 or I versus II or III
- Study entry Hb (<9.5 versus ≥9.5 g/dL), based on the most recent central laboratory Hb measurement prior to the baseline/randomization visit

Following randomization, the trial consisted of five periods:

- Screening period (up to eight weeks)
- Correction period (Weeks 0-23): period on study medication for the correction of Hb
- Maintenance period (Weeks 24-52): period on study medication during which efficacy will be assessed
- Primary evaluation period (Weeks 24-36), during which expected peak hemoglobin response can be assessed
- Secondary evaluation period (Weeks 40-52), during which evidence of a sustained hemoglobin response can be assessed
- Long-term treatment period (Weeks 53-end of treatment [EOT])
- Follow-up period (EOT +4 weeks): subjects who discontinued study drug were followed to end of study (EOS) to assess major adverse cardiac events (MACE).

Hemoglobin was monitored using a point of care device and was assessed with a complete blood count (CBC) through the local or central laboratory. Hemoglobin measurements used to decide on study eligibility and to calculate all efficacy endpoints were obtained using a central laboratory, while hemoglobin measurements used to decide on the need for dose adjustment could be obtained using any one of the three methods listed. Baseline Hb was used to determine study eligibility and was defined as the average of 2 Hb values measured by the central laboratory during the screening period, at least 4 days apart.

The need for dose adjustment was determined according to a treatment-specific dose adjustment algorithm (section III.15), which depended on the dialysis-dependence status (since patients could progress to needing dialysis during the trial) and the geographic location of the patient. In addition, subjects randomized to receive darbepoetin alfa were allowed to have dose adjustment based on the available prescribing information and local standard of care guidelines. The frequency of Hb assessment was every 2 weeks from weeks 0 to 12, every 4 weeks from weeks 12 to 52 and at least every 12 weeks thereafter with every 4-week frequency recommended by the Applicant. More frequent Hb assessments were indicated if modification of dosing or an unscheduled visit occurred due to clinical reasons.

The aim of the dosing strategy was to increase and maintain Hb levels of 10.0 g/dL to 11.0 g/dL in the United States and 10.0 g/dL to 12.0 g/dL outside of the United States throughout the trial. The difference in target Hb levels between the two geographic regions was based on the Agency's previous observation of greater risks for MACE when ESAs were used to target Hb levels greater than 11 g/dL. The use of ESA or RBC transfusion for rescue was allowed, up to the discretion of the investigator, but specific guidelines were provided in the trial protocol. The use of ESA rescue was discouraged if subjects were not experiencing worsening symptoms of anemia and had a Hb < 9.0 g/dL. Concomitant administration of RBC transfusion and study drug was allowed but concomitant administration of ESA rescue and study drug was not allowed. Additional important aspects of trial design and important protocol amendments can be found in section III.15.There were three committees involved in conducting the trial:

- Executive Steering Committee (ESC): oversaw the study and provided expert input to assure a high scientific standard. Members of the committee were blinded to the randomization and were recognized academic leaders, including those from the field of nephrology and cardiology. Details of the roles and responsibilities of the ESC were described in the ESC charter.
- Independent Data Monitoring Committee (IDMC): reviewed and discussed study safety data in an unblinded fashion during regularly scheduled meetings. The IDMC was composed of at least one nephrologist, one cardiologist, and one biostatistician. Written records of their meetings and decisions were submitted by the Applicant and reviewed. Details of the roles and responsibilities of the IDMC were described in the IDMC charter.
- Endpoint Adjudication Committee (EAC): independently adjudicated the primary safety endpoints of interest (i.e., all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, thromboembolic events, and hospitalization for heart failure) in a blinded fashion. Members of the committee were independent experts, selected prior to commencement of the trial, with experience and training in adjudication of the primary safety endpoints of interest. Details of the roles and responsibilities of the EAC were described in the EAC charter.

Key Eligibility Criteria

Inclusion criteria:

- At least 18 years of age
- Diagnosis of CKD with an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation during screening and not expected to start dialysis within 6 months of screening
- Mean Hb <10.0 g/dL at screening as determined by the average of two Hb values measured by the central laboratory during screening
- Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during screening
- Folate and vitamin B12 measurements ≥ lower limit of normal during screening
- Understood the procedures and requirements of the study and provided written informed consent and authorization for protected health information disclosure

Exclusion criteria:

- Presented with anemia due to a cause other than CKD or with active bleeding or recent blood loss.
- Subjects with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia.
- RBC transfusion within 8 weeks prior to randomization.
- Receiving any ESA (e.g., recombinant human EPO, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta) within 8 weeks prior to randomization.
- Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin >2.0 × upper limit of normal (ULN) during screening. Subjects with a history of Gilbert's syndrome were not excluded.
- Uncontrolled hypertension (confirmed diastolic blood pressure [DBP] >110 mmHg or systolic blood pressure [SBP] >180 mmHg) during screening.
- Severe heart failure (HF) during screening (NYHA Class IV).
- Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction [MI]), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for HF, or stroke within 12 weeks prior to or during screening.
- History of active malignancy within two years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ.
- History of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 12 weeks prior to randomization.
- History of hemosiderosis or hemochromatosis.
- History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list were not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis were not excluded).
- Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever was longer), prior to the screening visit.

- Previous participation in this study, or previous participation in a study with an HIF prolyl-hydroxylase inhibitor other than vadadustat.
- Females who were pregnant or breast-feeding. Women of childbearing potential who were unable or unwilling to use an acceptable method of contraception.
- Non-vasectomized male subjects who were unable or unwilling to use an acceptable method of contraception.
- Any other reason that in the opinion of the investigator would make the subject not suitable for participation in the study.
- Hypersensitivity to darbepoetin alfa or vadadustat, or to any of their excipients.

Study Endpoints:

Primary efficacy endpoint:

- Mean change in Hb between baseline (mean pre-treatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36).

Key secondary efficacy endpoints:

- Mean change in Hb value between baseline (mean pre-treatment Hb) and the secondary evaluation period (Weeks 40-52)

Other secondary efficacy endpoints:

- Proportion of subjects with Hb values within the geography-specific target range during the primary evaluation period (Weeks 24-36)
- Proportion of subjects with Hb values within the geography-specific target range during the secondary evaluation period (Weeks 40-52)
- Proportion of time with Hb values within the target range during the primary evaluation period (Weeks 24-36)
- Proportion of time with Hb values within the target range during the secondary evaluation period (Weeks 40-52)
- Proportion of subjects with Hb increase of >1.0 g/dL from baseline to week 52
- Time to achieve Hb increase of >1.0 g/dL from baseline (censored at week 52)
- Mean change in Hb between baseline (mean pre-treatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36) stratified by pre-baseline ESA exposure
- Progression of CKD
- Proportion of subjects receiving intravenous (IV) iron therapy from baseline to Week 52
- Mean monthly dose of IV elemental iron administered from baseline to Week 52 in subjects who have received IV iron
- ESA rescue
- Dose adjustments from baseline to Week 52
- Proportion of subjects receiving RBC transfusion(s) from baseline to Week 52

Safety endpoints:

- MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke
- Individual components of MACE:
  - All-cause mortality
  - Non-fatal MI

  - Non-fatal stroke

- Thromboembolic (TE) events: arterial thromboembolism (ATE), DVT, PE, or vascular access thrombosis (VAT)
- Hospitalization for HF
- Expanded MACE, defined as all-cause mortality, non-fatal MI, non-fatal stroke, hospitalization for HF, or TE event
- Fatal/non-fatal MI
- Fatal/non-fatal stroke
- Sudden death
- Cardiovascular (CV) death
- Non-CV death
- Hospitalization
- Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
- Hb <8.0 g/dL or <9.0 g/dL
- Hb increase >1.0 g/dL within any two-week interval or >2.0 g/dL within any four-week interval
- Adverse events (AEs) and SAEs
- Vital signs and clinical laboratory values
- Adrenal function assessment (via an adrenocorticotropic hormone [ACTH] stimulation test) in a subset of 200 subjects in the European Union – 100 subjects per arm, across the 2 NDD-CKD trials (due to findings in the non-clinical program discussed in section 7.1)
- Assessment of adrenal disorders as an AE of special interest, using a MedDRA high-level group term of adrenal gland disorders and MedDRA high-level term adrenal cortex tests

To ensure the ability to evaluate primary efficacy and safety endpoints, study completion was achieved when:

- ~631 MACE events were reached in both trial 0014 and 0015, representing the NDD-CKD trial population, and
- All enrolled subjects completed at least 36 weeks on trial (i.e., visit 13)

6.2.1.2. Statistical Analysis Plan, Trial 0014

Definitions of the Analysis Populations

The analysis populations were defined as follows:

- Randomized population: All subjects randomized. Analyses for this population were based on subjects' randomized treatment.
- Full analysis set (FAS) population: All subjects in the randomized population who received at least one dose of study drug and had at least one post-dose Hb level. Analyses for this population were based on subjects' randomized treatment.
- Safety population: All subjects in the randomized population who received at least one dose of study drug. Analysis for this population were based on the actual treatment received. Subjects who received in error some vadadustat and some darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received drug.
- Per Protocol (PP) population: All randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least one Hb assessment during the

primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviations affecting the primary endpoint analyses (i.e., prior to Week 36). Analyses for this population were based on actual treatment received, as described for the safety population.

Efficacy analyses utilized the randomized, FAS, and PP populations while safety analyses (including analyses of MACE) utilized the safety population. The randomized population was used for major efficacy analyses.

Analysis for the Primary Efficacy Endpoint

According to the Applicant's SAP and CSR, the primary efficacy endpoint is the change in average Hb between baseline and the primary efficacy period (Weeks 24 to 36). The primary analysis model used ANCOVA with multiple imputation. In particular, missing data were imputed based on information of the group to which the subject was randomized. The primary analysis model contains treatment group, baseline Hb level, and the two stratification factors (region and NYHA CHF class) as predictor variables. The randomization stratification factor of entry Hb level was not included in the model because of the inclusion of baseline Hb. The single master seed was used to generate all the multiple imputations runs for each trial. The noninferiority of vadadustat to darbepoetin alfa was to be demonstrated if the lower bound of the 95% confidence interval for the difference in estimated change from baseline in the two groups (vadadustat minus darbepoetin alfa) exceeded the pre-specified noninferiority margin of -0.75. This ensures a type I error rate of 0.05 control based on a 1-sided alpha of 0.025 for the primary analysis. We recommended the -0.75 noninferiority margin, which has been used in other applications for treatments of anemia due to chronic kidney disease and is based on preserving at least 50% treatment effect of an ESA in the conversion studies.

Analyses for the Key Secondary Efficacy Endpoint

According to the Applicant's SAP and CSR, the key secondary efficacy endpoint was change in average Hb value between baseline and the secondary efficacy period (Weeks 40 to 52). Evaluation of the key secondary efficacy endpoint employed the same approach described for the primary endpoint assessing Weeks 40 to 52 instead of Weeks 24 to 36. The power for this endpoint for a noninferiority margin of -0.75 g/dL is expected to be close to the power of the primary endpoint, which is 90%. Similar to the primary endpoint, the Agency recommended the -0.75 non-inferiority margin, which has been used in other applications for treatment of anemia due to chronic kidney disease and is based on preserving at least 50% treatment effect of an ESA in the conversion studies.

Multiple Testing Approach

The key secondary efficacy endpoint was analyzed formally only if the primary analysis met the prespecified non-inferiority margin. The formal testing procedure for the key secondary efficacy endpoint would be stopped if the analysis failed to confirm non-inferiority of the primary efficacy endpoint using a 1-sided significance level of 2.5%.

Method for Handling of Missing Data

Standard multiple imputations via imputation of missing values based on the group to which the subject was randomized, was used for all analyses for the primary and secondary efficacy outcomes to handle missing data.

6.2.1.3. Results of Analyses, Trial 0014

This section summarizes subjects' baseline demographics and clinical characteristics, disposition data, and major efficacy results for the correction of anemia in subjects with NDD-CKD from trial 0014.

Baseline Demographics and Clinical Characteristics

Baseline demographics of the randomized population data are summarized by treatment group in Table 11. Subjects' demographic characteristics were generally similar between treatment groups.

Table 11. Baseline Demographic, Randomized Population, Trial 0017

Characteristics	Vadadustat N=879	Darbepoetin Alfa N=872	Total N=1751
Age[1] (Years)			
n	879	872	1751
Mean (SD)	65.2 (14.3)	64.9 (13.7)	65.0 (14.0)
Age category, n (%)			
<65 years	398 (45.3)	374 (42.9)	772 (44.1)
≥65 years	481 (54.7)	498 (57.1)	979 (55.9)
Sex, n (%)			
Male	404 (46.0)	366 (42.0)	770 (44.0)
Female	475 (54.0)	506 (58.0)	981 (56.0)
Ethnicity, n (%)			
Hispanic or Latino	306 (34.8)	310 (35.6)	616 (35.2)
Not Hispanic or Latino	566 (64.4)	554 (63.5)	1120 (64.0)
Not reported	2 (0.2)	5 (0.6)	7 (0.4)
Unknown	5 (0.6)	3 (0.3)	8 (0.5)
Race, n (%)			
American Indian or Alaska Native	22 (2.5)	23 (2.6)	45 (2.6)
Asian	48 (5.5)	37 (4.2)	85 (4.9)
Black or African American	188 (21.4)	172 (19.7)	360 (20.6)
Native Hawaiian or Pacific Islander	6 (0.7)	6 (0.7)	12 (0.7)
White	546 (62.1)	571 (65.5)	1117 (63.8)
Not Reported	5 (0.6)	6 (0.7)	11 (0.6)
Other	58 (6.6)	48 (5.5)	106 (6.1)
Multiple	6 (0.7)	9 (1.0)	15 (0.9)

Characteristics	Vadadustat N=879	Darbepoetin Alfa N=872	Total N=1751
Country, n (%)			
Argentina	25 (2.8)	26 (3.0)	51 (2.9)
Australia	10 (1.1)	8 (0.9)	18 (1.0)
Brazil	62 (7.1)	58 (6.7)	120 (6.9)
Bulgaria	41 (4.7)	42 (4.8)	83 (4.7)
Hungary	7 (0.8)	8 (0.9)	15 (0.9)
Israel	2 (0.2)	2 (0.2)	4 (0.2)
Italy	7 (0.8)	9 (1.0)	16 (0.9)
Mexico	45 (5.1)	46 (5.3)	91 (5.2)
Republic of Korea	6 (0.7)	10 (1.1)	16 (0.9)
Russian Federation	7 (0.8)	10 (1.1)	17 (1.0)
South Africa	52 (5.9)	51 (5.8)	103 (5.9)
Spain	5 (0.6)	5 (0.6)	10 (0.6)
Ukraine	67 (7.6)	64 (7.3)	131 (7.5)
United Kingdom	11 (1.3)	4 (0.5)	15 (0.9)
United States	532 (60.5)	529 (60.7)	1061 (60.6)
Height (cm)			
n	857	859	1716
Mean (SD)	164.6 (10.5)	164.4 (10.2)	164.49 (10.3)
Weight (kg)			
n	872	867	1739
Mean (SD)	80.7 (21.8)	81.1 (22.1)	80.86 (21.9)
BMI (kg/m^2)			
n	855	857	1712
Mean (SD)	29.7 (7.2)	29.8 (7.2)	29.74 (7.2)

Source: Study 0014 Clinical Study Report Table 11 (p. 67)
[1] Reported age on the case report forms. 2 Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2
Abbreviations: BMI, body mass index; N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Subjects' baseline clinical characteristics of the randomized population are summarized by treatment group in Table 12.

Table 12. Baseline Clinical Characteristics, Randomized Population, Trial 0014

Characteristics	Vadadustat N=879	Darbepoetin Alfa N=872	Total N=1751
Randomization stratification factors, n (%)			
Region of enrollment[1]			
United States	532 (60.5)	529 (60.7)	1061 (60.6)
Europe	71 (8.1)	68 (7.8)	139 (7.9)
Rest of World	276 (31.4)	275 (31.5)	551 (31.5)
New York Heart Association HF Class			
Class 0 (no HF) or I	762 (86.7)	754 (86.5)	1516 (86.6)
Class II or III	117 (13.3)	118 (13.5)	235 (13.4)
Central lab baseline Hb category			
<9.5 g/dL	564 (64.2)	563 (64.6)	1127 (64.4)
≥9.5 g/dL	315 (35.8)	309 (35.4)	624 (35.6)
IV iron, ESA & transfusion history, n (%)			
IV iron use prior to first dose of study drug			
Yes	163 (18.6)	162 (18.6)	325 (18.6)
No	713 (81.4)	707 (81.4)	1420 (81.4)
Missing	3	3	6
ESA use prior to first dose of study drug			

Characteristics	Vadadustat N=879	Darbepoetin Alfa N=872	Total N=1751
Yes	93 (10.6)	79 (9.1)	172 (9.8)
No	784 (89.4)	792 (90.9)	1576 (90.2)
Missing	2	1	3
Received a transfusion within 8 weeks of screening period prior to randomization through to the first dose of study drug			
Yes	0 (0)	2 (0.2)	2 (0.1)
No	878 (100.0)	870 (99.8)	1748 (99.9)
Missing	1	0	1
Baseline iron use, n (%)			
0 - subjects not receiving any iron	483 (54.9)	467 (53.6)	950 (54.3)
I - subjects receiving oral iron only	362 (41.2)	372 (42.7)	734 (41.9)
II - subjects receiving IV iron only	22 (2.5)	20 (2.3)	42 (2.4)
III - subjects receiving IV and oral iron	12 (1.4)	13 (1.5)	25 (1.4)
Baseline IV iron dose (mg/week)			
n	15	14	29
Mean (SD)	341 (351)	2187 (6573)	1232 (4583)
Baseline oral iron dose (mg/week)			
n	360	367	727
Mean (SD)	2547 (2056)	2743 (2044)	2646 (2051)
Diabetes mellitus, n (%)			
Yes	581 (66.1)	599 (68.7)	1180 (67.4)
No	298 (33.9)	273 (31.3)	571 (32.6)
History of cardiovascular disease[2], n (%)			
Yes	406 (46.2)	412 (47.2)	818 (46.7)
No	473 (53.8)	460 (52.8)	933 (53.3)
History of retinal disorder, n (%)			
Yes	183 (20.8)	199 (22.8)	382 (21.8)
No	696 (79.2)	673 (77.2)	1369 (78.2)
Baseline systolic blood pressure (mmHg)			
n	878	872	1750
Mean (SD)	139 (19)	139 (18)	139 (18)
Baseline diastolic blood pressure (mmHg)			
n	878	872	1750
Mean (SD)	74 (12)	73 (13)	74 (12)
Baseline heart rate (beats/min)			
n	878	872	1750
Mean (SD)	71 (12)	72 (11)	72 (11)

Source: Study 0014 Clinical Study Report Table 12 (p. 68)
Note: The percentage is calculated based on the number of subjects with non-missing data.
[1] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
[2] Cardiovascular (CV) disease included coronary artery disease, myocardial infarction, stroke, and HF.
Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HF, heart failure; IV, intravenous; N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Disposition, Trial 0014

Subject disposition information for trial 0014 is summarized in Table 13 and Table 14.

A total of 4708 subjects were screened for entry into trial 0014. Of these, 2957 subjects failed screening and 1751 subjects were enrolled and randomized into the study. The majority of subjects who failed screening did not meet one or more inclusion/exclusion criteria, with no specific pattern detected upon analysis. Of the subjects randomized, 1748 were included in the safety population, and 1723 subjects were included in the FAS population. Overall, a lower

percentage of each treatment group qualified for the per protocol population, with a much lower percentage (65.8% versus 80.2%) in the vadadustat treatment group than the control group administered darbepoetin alfa. Slightly lower proportions of subjects in the vadadustat (76.2%) as compared to darbepoetin alfa (80.6%) treatment groups completed the study, with death being the main reason for discontinuation from study in both treatment groups, with a higher incidence of death in the vadadustat treatment group (19.8% versus 15.7%). The number of subjects discontinuing study drug treatment (but continuing to be followed in the trial) was higher in the vadadustat treatment group (411 [46.8%]) compared with the darbepoetin alfa treatment group (355 [40.7%]). The primary reasons for discontinuation of study drug in the vadadustat treatment group were unacceptable toxicity, drug intolerability or AE (13.4%), and subject no longer wants to receive study drug (14.5%). The primary reasons for discontinuation of study drug in the darbepoetin alfa treatment group were unacceptable toxicity, drug intolerability or AE (12.3%), and subject no longer wants to receive study drug (11.1%).

Table 13. Subject Screening and Randomization, Trial 0014

Disposition	Value
No. subjects screened	4708
No. subjects not randomized	2957
No. screening failures	2957/4708 (62.8%)
No. subjects randomized	1751

Source: Study 0014 Clinical Study Report Figure 2 (p. 61)

Table 14. Subject Disposition, Trial 0014

Disposition Category	Vadadustat N=879 n (%)	Darbepoetin Alfa N=872 n (%)	Relative Risk	Risk Difference (%)
Subjects randomized	879 (100)	872 (100)	NA	NA
FAS population	865 (98.4)	858 (98.4)	NA	NA
Per protocol population	578 (65.8)	699 (80.2)	NA	NA
Safety population	878 (99.9)	870 (99.7)	NA	NA
Completed study drug	467 (53.1)	517 (59.3)	0.90	-6.2
Discontinued study drug	411 (46.8)	355 (40.7)	1.15	6.2
Death	40 (4.6)	42 (4.8)	0.94	-0.3
Dialysis or transplant	41 (4.7)	42 (4.8)	0.97	-0.2
Adverse event[1]	118 (13.4)	107 (12.3)	1.09	1.1
Rapid Increase in Hb	1 (0.1)	1 (0.1)	1.00	0
Lack of efficacy	16 (1.8)	6 (0.7)	2.64	1.1
Decision to switch to ESA	5 (0.6)	2 (0.2)	2.48	0.3
Investigator's decision[2]	31 (3.5)	26 (3.0)	1.18	0.5
Lack of compliance	2 (0.2)	2 (0.2)	1.00	0
Lost to follow-up	19 (2.2)	15 (1.7)	1.26	0.4
Global termination[3]/Sponsor decision	11 (1.3)	13 (1.5)	0.84	-0.2
Patient wishes[4]	127 (14.5)	97 (11.1)	1.30	3.3
Completed study	670 (76.2)	703 (80.6)	0.99	-1.2
Discontinued study	208 (23.7)	158 (18.1)	1.05	1.2
Death	174 (19.8)	137 (15.7)	1.04	0.7
Lost to follow-up	18 (2.1)	21 (2.4)	0.85	-0.4
Dialysis or transplant	2 (0.2)	3 (0.3)	0.68	-0.1
Subject wishes	14 (1.6)	6 (0.7)	2.30	0.9
Adverse event	0 (0)	0 (0)	0	0

Source: SDTM datasets; Software: JMP

Note: Percentages were calculated based on all randomized subjects.

1, Discontinuation due to adverse events included discontinuation of study drug due to unacceptable toxicity, drug tolerability and adverse events.

2, The investigator's decision to discontinue study drug was not due to occurrence of an adverse event. Further details were not provided by the Applicant.
3, When the target number of MACE was reached, global study termination was initiated, resulting in discontinuation of study drug and conducting end-of-study visits in all on-study subjects, regardless of their current study period status.
4, Patient wishes, as a reason for discontinuation of study drug, were not due to occurrence of an adverse event. In the majority of cases, discontinuation of study drug was associated with practical inconveniences of being enrolled on study, due to social external circumstances or not specified.
Abbreviation: ESA, erythropoiesis-stimulating agent; FAS, full analysis set; Hb, hemoglobin; N, number of subjects; n, number of subjects with at least one event

Analysis for the Primary Efficacy Endpoint, Trial 0014

The primary efficacy endpoint for this study was the change in average Hb between baseline and the primary efficacy period (Weeks 24 to 36).

The primary efficacy endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's primary efficacy results demonstrated a least squares (LS) mean (standard error of mean [SEM]) change from baseline to the average Hb over Weeks 24 to 36 of 1.4 (0.1) in both the vadadustat and darbepoetin alfa treatment groups. The LS mean (and SEM) treatment difference was 0.1 (0.1) g/dL with a 95% CI of (-0.04, 0.2). The non-inferiority of vadadustat to darbepoetin alfa was demonstrated for the randomized population because the lower bound of the 95% CI (0) was above the pre-specified non-inferiority margin of -0.75 g/dL. It is important to note that the change from baseline to the average Hb over the primary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa. The Applicant's analyses results are shown in Table 15.

Table 15. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population, Trial 0014

Visit Statistics	Vadadustat N=879	Darbepoetin Alfa N=872	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	879	872	
Mean (SD)	9.1 (0.8)	9.1 (0.8)	
Weeks 24 to 36 (observed)			
n	755	767	
Mean (SD)	10.4 (1.0)	10.4 (1.0)	
Weeks 24 to 36 (observed + imputed)			
n	879	872	
Mean (SD)	10.4 (1.0)	10.4 (1.0)	
Change from baseline			
n	879	872	
Mean (SD)	1.3 (1.0)	1.2 (1.1)	
Least squares mean (SEM)	1.4 (0.1)	1.4 (0.1)	0.1 (0.1)
95% CI	(1.3, 1.5)	(1.3, 1.5)	(0, 0.2)

Source: Study 0014 Clinical Study Report Table 19 (p. 81), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

The Applicant also performed a sensitivity analysis using mixed model repeated measure (MMRM) with missing at random assumption. MMRM results are not shown but they also demonstrated non-inferiority of vadadustat to darbepoetin alfa for the primary endpoint.

Analysis for the Key Secondary Efficacy Endpoint, Trial 0014

The key secondary efficacy endpoint for this study was the change in average Hb between baseline and the secondary efficacy period (Weeks 40 to 52).

The key secondary endpoint was analyzed using ANCOVA with multiple imputations based on the randomized population. The Applicant's efficacy results demonstrated a LS mean (and SEM) change from baseline to the average over Weeks 40 to 52 of 1.5 (0.1) g/dL in both the vadadustat and darbepoetin alfa treatment groups. The LS mean (and SEM) difference between treatment groups was 0.04 (0.05) g/dL with a 95% CI of (-0.1, 0.1). Since the lower bound of the 95% CI (-0.1) was above the prespecified non-inferiority margin of -0.75 g/dL, non-inferiority of vadadustat to darbepoetin alfa was demonstrated. The change from baseline to the average Hb over the secondary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa. The analyses results are shown in Table 16.

Table 16. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Randomized Population, Trial 0014

Visit Statistics	Vadadustat N=879	Darbepoetin Alfa N=872	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	879	872	
Mean (SD)	9.1 (0.8)	9.1 (0.8)	
Weeks 40 to 52 (observed)			
N	638	641	
Mean (SD)	10.5 (1.0)	10.5 (1.0)	
Weeks 40 to 52 (observed + imputed)			
n	879	872	
Mean (SD)	10.5 (1.1)	10.5 (1.0)	
Change from baseline			
n	879	872	
Mean (SD)	1.4 (1.1)	1.3 (1.1)	
Least squares mean (SEM)	1.5 (0.1)	1.5 (0.1)	0 (0.1)
95% CI	(1.4, 1.6)	(1.4, 1.6)	(-0.1, 0.1)

Source: Study 0014 Clinical Study Report Table 22 (p. 85), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean.

Similar to the primary endpoint, the Applicant performed a sensitivity analysis using MMRM assuming data missing at random. The non-inferiority of vadadustat to darbepoetin alfa was also demonstrated for the randomized population for the key secondary endpoint analysis using MMRM (results not shown in this review).

The FDA statistical review team has confirmed the Applicant's primary and key secondary efficacy endpoint results and agreed that Trial 0014 demonstrated the non-inferiority of vadadustat to darbepoetin alfa. In addition, Applicant's conducted analyses of selected important secondary efficacy endpoints were summarized in section III.16.3.1.

Important Secondary Efficacy Endpoints, Trial 0014

Patients in the trial were allowed to receive RBC transfusions or ESA as rescue therapy. As pre-specified secondary endpoints, the Applicant analyzed the following rescue-based endpoints,

whose analysis is essential to determine if there is any impact of rescue therapy on the non-inferiority conclusions:

- Proportion of subjects that received ESA rescue medications, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received ESA rescue medications, using the broad-on-treatment rescue therapy definition, where any exposure to ESA rescue is counted for any reason, as long it is not started after permanent study treatment discontinuation
- Proportion of subjects that received RBC transfusion, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received RBC transfusion, using the broad-on-treatment rescue therapy definition, where any exposure to RBC transfusion is counted for any reason, as long it is not started after permanent study treatment discontinuation

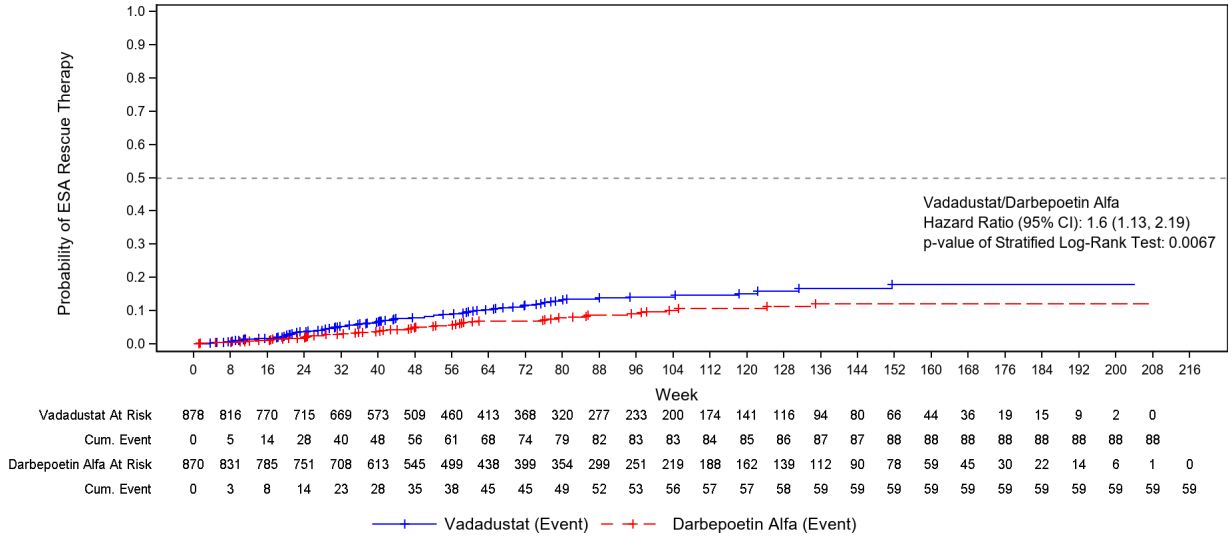
Proportion of Subjects That Received ESA Rescue Medications, Narrow Rescue Therapy

Table 17. Time to ESA Rescue Therapy - Narrow Rescue Therapy (Randomized Population), Trial 0014

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
Subjects with ESA rescue therapy, n (%)	88 (10.0)	59 (6.8)
Subjects censored, n (%)	791 (90.0)	813 (93.2)
Cumulative incidence (95% CI)		
24 Weeks	0.04 (0.02, 0.05)	0.02 (0.01, 0.03)
36 Weeks	0.06 (0.04, 0.08)	0.03 (0.02, 0.05)
40 Weeks	0.06 (0.05, 0.08)	0.04 (0.03, 0.05)
52 Weeks	0.08 (0.06, 0.10)	0.05 (0.04, 0.07)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.01	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.6 (1.13, 2.19)	

Source: Applicant's analysis in response to submitted information request

Figure 6. Kaplan-Meier Curve of Time to ESA Rescue Therapy- Narrow Rescue Therapy (Randomized Population), Trial 0014



Source: Applicant's analysis in response to submitted information request

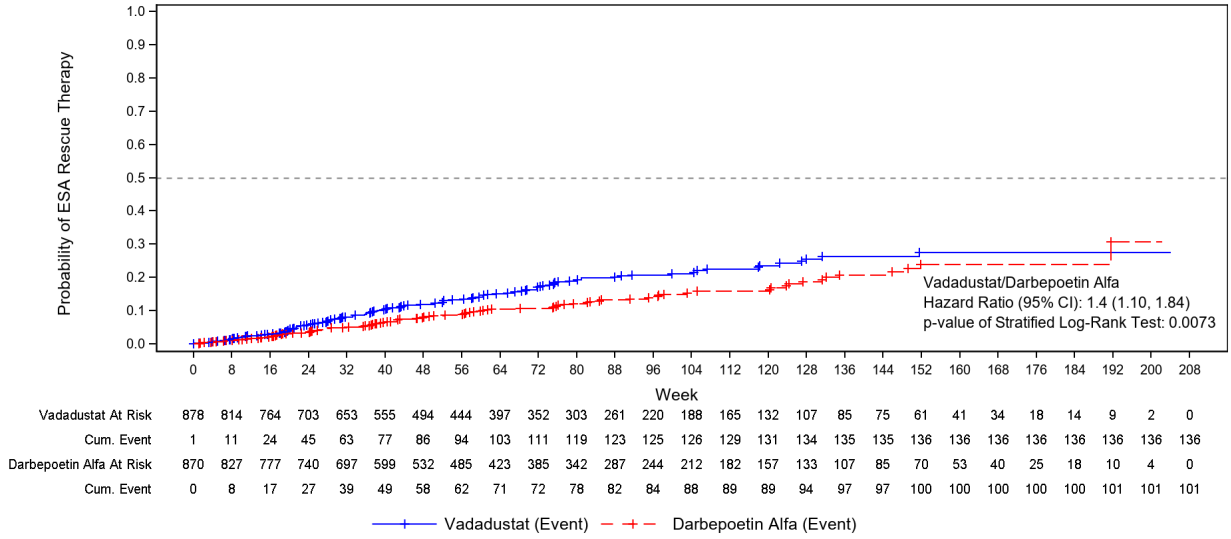
Proportion of Subjects That Received ESA Rescue Medications, Broad-on-Treatment Rescue Therapy

Table 18. Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0014

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
Subjects with ESA rescue therapy, n (%)	136 (15.5)	101 (11.6)
Subjects censored, n (%)	742 (84.5)	769 (88.4)
Cumulative incidence (95% CI)		
24 Weeks	0.06 (0.04, 0.08)	0.03 (0.02, 0.05)
36 Weeks	0.09 (0.07, 0.11)	0.05 (0.04, 0.07)
40 Weeks	0.10 (0.08, 0.13)	0.06 (0.05, 0.08)
52 Weeks	0.13 (0.10, 0.15)	0.08 (0.07, 0.11)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.01	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.4 (1.10, 1.84)	

Source: Applicant's analysis in response to submitted information request

Figure 7. Kaplan-Meier Curve of Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0014



Source: Applicant's analysis in response to submitted information request

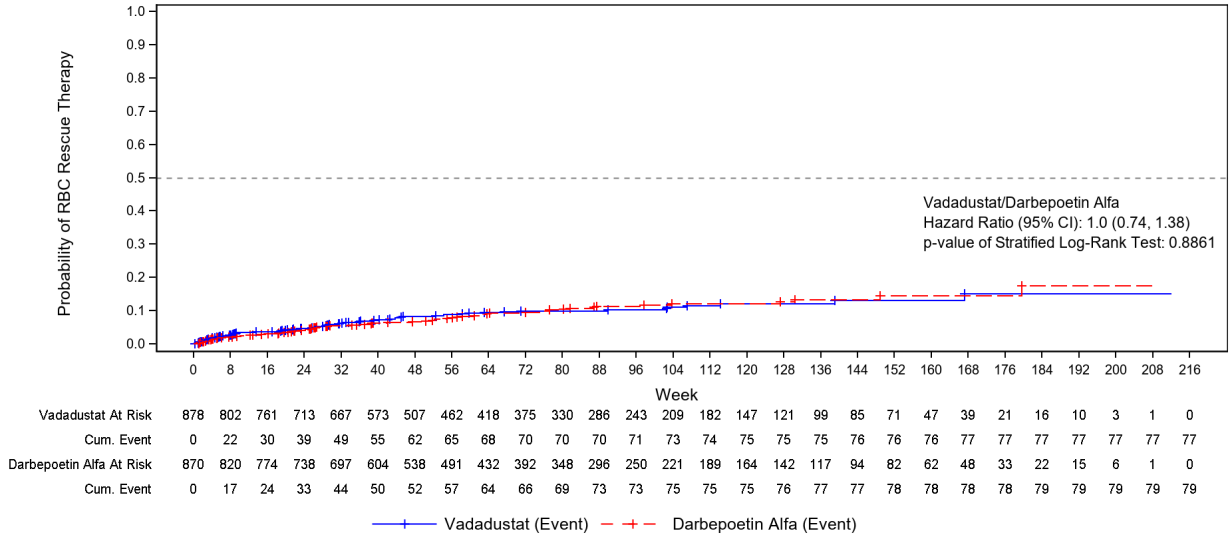
Proportion of Subjects That Received RBC Transfusion, Narrow Rescue Therapy

Table 19. Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0014

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
Subjects with RBC transfusion, n (%)	77 (8.8)	79 (9.1)
Subjects censored, n (%)	801 (91.2)	791 (90.9)
Cumulative incidence (95% CI)		
24 Weeks	0.05 (0.03, 0.06)	0.04 (0.03, 0.06)
36 Weeks	0.07 (0.05, 0.09)	0.06 (0.04, 0.08)
40 Weeks	0.07 (0.05, 0.09)	0.06 (0.05, 0.08)
52 Weeks	0.08 (0.06, 0.10)	0.07 (0.05, 0.09)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.89	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.0 (0.74, 1.38)	

Source: Applicant's analysis in response to submitted information request

Figure 8. Kaplan-Meier Curve of Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0014



Source: Applicant's analysis in response to submitted information request

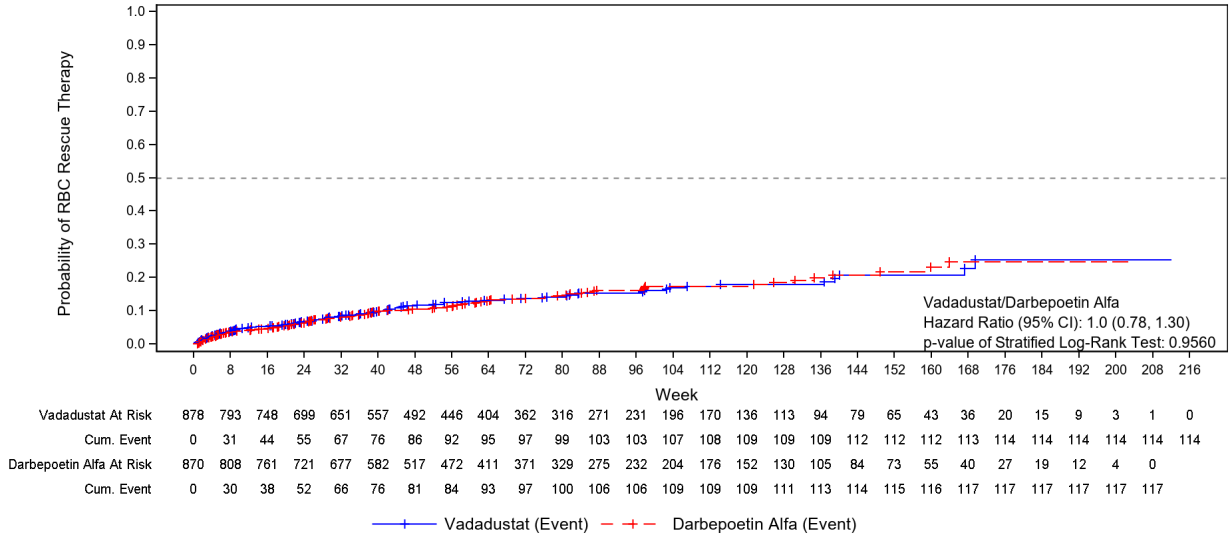
Proportion of Subjects That Received RBC Transfusion, Broad-on-Treatment Rescue Therapy

Table 20. Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0014

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
Subjects with RBC transfusion, n (%)	114 (13.0)	117 (13.4)
Subjects censored, n (%)	764 (87.0)	753 (86.6)
Cumulative incidence (95% CI)		
24 Weeks	0.07 (0.05, 0.09)	0.06 (0.05, 0.08)
36 Weeks	0.09 (0.07, 0.11)	0.09 (0.07, 0.11)
40 Weeks	0.10 (0.08, 0.12)	0.20 (0.08, 0.12)
52 Weeks	0.12 (0.10, 0.1433)	0.11 (0.09, 0.13)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.96	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.0 (0.78, 1.30)	

Source: Applicant's analysis in response to submitted information request

Figure 9. Kaplan-Meier Curve of Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0014



Source: Applicant's analysis in response to submitted information request

Considering rescue use therapy, more patients in the vadadustat arm received ESA rescues than those in the darbepoetin alfa arm and they took rescue significantly earlier, which was more apparent when the narrow definition of ESA rescue was used. However, in terms of RBC transfusions rescue (using either narrow or broad definitions) both treatment arms had similar proportions of patients who received this type of rescue throughout the study. The Applicant conducted sensitivity analyses for both the primary and key secondary efficacy endpoints to further examine the impact of rescue use, according to the narrow definition, by setting all per-visit hemoglobin values to missing within four weeks after administration rescue therapy and results are consistent with the final analysis results (see section III.16.3.1).

Subgroup Analyses for the Primary Endpoint, Trial 0014

The Applicant conducted subgroup analyses for various demographic and clinical characteristics groups and their results are presented in section III.16.2.1. The statistical reviewer confirmed their findings. Overall, the treatment effect of vadadustat compared to darbepoetin alfa appeared consistent across all prespecified subgroups, except for regional subgroups. In particular, the US had a significantly larger Hb mean change from baseline of vadadustat than ROW (excluding Europe) to Week 24 to 36 compared with darbepoetin (LSM: 0.2 versus -0.2). Although the sample size is much smaller in ROW than that in US, the two CIs for the mean change from baseline between the two treatment groups separated. The Applicant used US-approved darbepoetin alfa (a deemed biologic since March 2020) at the US sites and non-US approved darbepoetin alfa at the non-US sites. Therefore, the review team assessed the performance of US-approved and non-US-approved darbepoetin alfa, and the impact, if any, on the conclusion of non-inferiority between vadadustat and darbepoetin alfa (see section II.6.3.2 and III.16.2.5). Note that the sample sizes for some subgroups were small and thus the ability to identify trends from the subgroup analysis results is limited. In addition, conducting multiple subgroup analyses without any multiplicity adjustment could result in spurious findings due to chance, even if the observed result for one subgroup is seemingly very different from the other subgroups.

6.2.2. Trial AKB-6548-CI-0015

6.2.2.1. Design, Trial 0015

Title

Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects With NDD-CKD (PRO_2TECT - CONVERSION)

Overview and Objectives

Trial 0015 was a multi-center, multi-national, randomized, open-label, sponsor-blinded, active-controlled trial of the efficacy and safety of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia after conversion from current ESA therapy in subjects with NDD-CKD.

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

Trial Design

Eligible subjects discontinued their ESA before the 2nd screening visit, which occurred at a minimum of 4 days from the baseline visit. Randomization took place at the baseline visit, in a 1:1 ratio, where subjects were randomized between receiving vadadustat or darbepoetin alfa. Subjects living in the U.S. received U.S.-approved darbepoetin alfa, while subjects living outside the U.S received non-U.S.-approved darbepoetin alfa. Enrolled subjects were also stratified by the following factors:

- Geographic region (United States versus Europe versus Rest of World)
- NYHA heart failure Class 0 or I versus II or III
- Study entry Hb (<10 versus ≥10 g/dL), based on the most recent central laboratory Hb measurement prior to the baseline/randomization visit

Following randomization, the trial consisted of five periods:

- Screening period (up to eight weeks)
- Conversion period (Weeks 0-23): period for converting to study medication, while maintaining Hb
- Maintenance period (Weeks 24-52): period on study medication during which efficacy will be assessed:
- Primary evaluation period (Weeks 24-36)
- Secondary evaluation period (Weeks 40-52)
- Long-term treatment period (Weeks 53-EOT)
- Follow-up period (EOT +4 weeks): subjects who discontinued study drug were followed to EOS to assess MACE.

Hemoglobin was monitored using a point of care device and was assessed with a CBC through the local or central laboratory. Hemoglobin measurements used to decide on study eligibility and to calculate all efficacy endpoints were obtained using a central laboratory, while hemoglobin

measurements used to decide on the need for dose adjustment could be obtained using any one of the three methods listed. Baseline Hb was used to determine study eligibility and was defined as the average of 2 Hb values measured by the central laboratory during the screening period, at least 4 days apart.

The need for dose adjustment was determined according to a treatment-specific dose adjustment algorithm (section III.15), which depended on the dialysis-dependence status (since patients could progress to dialysis during the trial) and the geographic location of the patient. In addition, subjects randomized to receive darbepoetin alfa were allowed to have dose adjustment based on the available prescribing information and local standard of care guidelines. The frequency of Hb assessment was every 2 weeks from weeks 0 to 12, every 4 weeks from weeks 12 to 52, and at least every 12 weeks thereafter with every 4-week frequency recommended by the Applicant. More frequent Hb assessments were indicated if modification of dosing or an unscheduled visit occurred due to clinical reasons.

The aim of the dosing strategy was to increase and maintain Hb levels of 10.0 g/dL to 11.0 g/dL in the United States and 10.0 g/dL to 12.0 g/dL outside of the United States throughout the trial. The difference in target Hb levels between the two geographic regions was based on the Agency's previous observation of greater risks for MACE when ESAs were used to target Hb levels greater than 11 g/dL. The use of ESA or RBC transfusion for rescue was allowed, up to the discretion of the investigator, but specific guidelines were provided in the trial protocol. The use of ESA rescue was discouraged if subjects were not experiencing worsening symptoms of anemia and had a Hb < 9.0 g/dL. Concomitant administration of RBC transfusion and study drug was allowed but concomitant administration of ESA rescue and study drug was not allowed. Additional important aspects of trial design and important protocol amendments can be found in section III.15.

There were three committees involved in conducting the trial:

- Executive Steering Committee: Oversaw the study and provided expert input to assure a high scientific standard. Members of the committee were blinded to the randomization and were recognized academic leaders, including those from the field of nephrology and cardiology. Details of the roles and responsibilities of the ESC were described in the ESC charter.
- Independent Data Monitoring Committee: Reviewed and discussed study safety data in an unblinded fashion during regularly scheduled meetings. The IDMC was composed of at least one nephrologist, one cardiologist and one biostatistician. Written records of their meetings and decisions were submitted by the Applicant and reviewed. Details of the roles and responsibilities of the IDMC were described in the IDMC charter.
- Endpoint Adjudication Committee: Independently adjudicated the primary safety endpoints of interest (i.e., all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, thromboembolic events, and hospitalization for heart failure) in a blinded fashion. Members of the committee were independent experts, selected prior to commencement of the trial, with experience and training in adjudication of the primary safety endpoints of interest. Details of the roles and responsibilities of the EAC were described in the EAC charter.

Key Eligibility Criteria

Inclusion criteria:

- At least 18 years of age
- Diagnosis of CKD with an eGFR ≤60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation during screening and not expected to start dialysis within 6 months of screening
- Currently maintained on ESA therapy, with a dose received within six weeks prior to or during screening
- Mean screening Hb level between 8.0 and 11.0 g/dL (inclusive) in the United States and between 9.0 and 12.0 g/dL (inclusive) outside of the United States, as determined by the average of 2 Hb values measured by the central laboratory during screening
- Serum ferritin ≥100 ng/mL and TSAT ≥20% during screening
- Folate and vitamin B12 measurements ≥ lower limit of normal during screening
- Understood the procedures and requirements of the study and provided written informed consent and authorization for protected health information disclosure

Exclusion criteria:

- Presented with anemia due to a cause other than CKD or with active bleeding or recent blood loss.
- Subjects with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia.
- RBC transfusion within eight weeks prior to randomization.
- AST, ALT, or total bilirubin >2.0 × ULN during screening. Subjects with a history of Gilbert's syndrome were not excluded.
- Uncontrolled hypertension (confirmed DBP >110 mmHg or SBP >180 mmHg) during screening.
- Severe HF during screening (NYHA Class IV).
- Acute coronary syndrome (hospitalization for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for HF, or stroke within 12 weeks prior to or during screening.
- History of active malignancy within 2 years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ.
- History of DVT or PE within 12 weeks prior to randomization.
- History of hemosiderosis or hemochromatosis.
- History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list were not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis were not excluded).
- Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever was longer), prior to the screening visit.
- Previous participation in this study, or previous participation in a study with an HIF-PH inhibitor other than vadadustat.

- Females who were pregnant or breast-feeding. Women of childbearing potential who were unable or unwilling to use an acceptable method of contraception.
- Non-vasectomized male subjects who were unable or unwilling to use an acceptable method of contraception.
- Any other reason that in the opinion of the investigator would make the subject not suitable for participation in the study.
- Hypersensitivity to darbepoetin alfa or vadadustat, or to any of their excipients.

Study Endpoints:

Primary efficacy endpoint:

- Mean change in Hb levels between baseline (mean pre-treatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36).

Key secondary efficacy endpoints:

- Mean change in Hb value between baseline (mean pre-treatment Hb) and the secondary evaluation period (Weeks 40-52)

Other secondary efficacy endpoints:

- Proportion of subjects with Hb values within the geography-specific target range during the primary evaluation period (Weeks 24-36)
- Proportion of subjects with Hb values within the geography-specific target range during the secondary evaluation period (Weeks 40-52)
- Proportion of time with Hb values within the target range during the primary evaluation period (Weeks 24-36)
- Proportion of time with Hb values within the target range during the secondary evaluation period (Weeks 40-52)
- Proportion of subjects with Hb increase of >1.0 g/dL from baseline to week 52
- Time to achieve Hb increase of >1.0 g/dL from baseline (censored at week 52)
- Mean change in Hb levels between baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36) stratified by pre-baseline ESA exposure
- Progression of CKD
- Proportion of subjects receiving IV iron therapy from baseline to Week 52
- Mean monthly dose of IV elemental iron administered from baseline to Week 52 in subjects who have received IV iron
- ESA rescue
- Dose adjustments from baseline to Week 52
- Proportion of subjects receiving RBC transfusion(s) from baseline to Week 52

Safety endpoints:

- MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke
- Individual components of MACE:
  - All-cause mortality
  - Non-fatal MI
  - Non-fatal stroke
- TE events: ATE, DVT, PE, or VAT

- Hospitalization for HF
- Expanded MACE, defined as all-cause mortality, non-fatal MI, non-fatal stroke, hospitalization for HF, or TE event
- Fatal/non-fatal MI
- Fatal/non-fatal stroke
- Sudden death
- CV death
- Non-CV death
- Hospitalization
- Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
- Hb <8.0 g/dL
- Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
- AEs and SAEs
- Vital signs and clinical laboratory values
- Adrenal function assessment (via an adrenocorticotropic hormone stimulation test) in a subset of 200 subjects in the European Union – 100 subjects per each arm, across the 2 NDD-CKD trials (due to findings in the non-clinical program discussed in section 7.1)
- Assessment of adrenal disorders as an AE of special interest, using a MedDRA high-level group term of adrenal gland disorders and MedDRA high-level term adrenal cortex tests

To ensure the ability to evaluate primary efficacy and safety endpoints, study completion was achieved when:

- 631 MACE events were reached in both trials 0014 and 0015, representing the NDD-CKD trial population, and
- All enrolled subjects completed at least 36 weeks on trial (i.e., visit 13)

6.2.2.2. Statistical Analysis Plan, Trial 0015

Definitions of the Analysis Populations

The analysis populations were defined as follows:

- Randomized population: all subjects randomized. Analyses for this population were based on subjects' randomized treatment.
- Full analysis set (FAS) population: all subjects in the randomized population who received at least 1 dose of study drug and had at least 1 post-dose Hb. Analyses for this population were based on subjects' randomized treatment.
- Safety population: all subjects in the randomized population who received at least 1 dose of study drug. Analysis for this population were based on the actual treatment received. Subjects who received in error some vadadustat and some darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received drug.
- PP population: all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least 1 Hb assessment during the primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviations affecting the primary endpoint analyses (i.e., prior to Week 36). Analyses for this

population were based on actual treatment received, as described for the Safety population.

Efficacy analyses utilized the randomized, FAS, and PP populations while safety analyses (including analyses of MACE) utilized the safety population. The randomized population was used for major efficacy analyses.

Analysis for the Primary Efficacy Endpoint

According to the Applicant's SAP and CSR, the primary efficacy endpoint is the change in average Hb value between baseline and the primary efficacy period (Weeks 24 to 36). The primary analysis model used ANCOVA with multiple imputation. Missing data were imputed based on information of the group to which the subject was randomized. The primary analysis model contains treatment group, baseline Hb level, and the 2 stratification factors (region and NYHA CHF class) as predictor variables. The randomization stratification factor of entry Hb level was not included in the model because of the inclusion of baseline Hb. The single master seed was used to generate all the multiple imputations run for each trial. The non-inferiority of vadadustat to darbepoetin alfa was to be demonstrated if the lower bound of the 95% confidence interval for the difference in estimated change from baseline in the 2 groups (vadadustat minus darbepoetin alfa) exceeded the noninferiority margin of -0.75. This ensures a type I error rate of 0.05 control based on 1-sided alpha of 0.025 for the primary analysis.

Analyses for the Key Secondary Efficacy Endpoint

According to the Applicant's SAP and CSR, the key secondary efficacy endpoint was change in average Hb value between baseline and the secondary efficacy period (Weeks 40 to 52). Evaluation of the key secondary efficacy endpoint employed the same approach described for the primary endpoint assessing Weeks 40 to 52 instead of Weeks 24 to 36. The power for this endpoint for a noninferiority margin of -0.75 g/dL is expected to be close to the power of the primary endpoint, which is 90%. Similar to the primary endpoint, the Agency recommended the -0.75 non-inferiority margin, which has been used in other applications for treatment of anemia due to chronic kidney disease and is based on preserving at least 50% treatment effect of an ESA in the conversion studies.

Multiple Testing Approach

The key secondary efficacy endpoint was analyzed formally only if the primary analysis met the prespecified non-inferiority margin. The formal testing procedure for the key secondary efficacy endpoint would be stopped if the analysis failed to confirm non-inferiority of the primary efficacy endpoint using a 1-sided significance level of 2.5%.

Method for Handling of Missing Data

Standard multiple imputation of missing values based on the group to which the subject was randomized was used for all analyses for the primary and secondary efficacy outcomes to handle missing data.

6.2.2.3. Results of Analyses, Trial 0015

This section summarizes subjects' baseline demographics and clinical characteristics, disposition data, and major efficacy results for vadadustat for the maintenance treatment of anemia in subjects with NDD-CKD from Trial 0015.

Baseline Demographics and Clinical Characteristics, Trial 0015

Baseline demographics of the randomized population data are summarized by treatment group in Table 21. Subjects' demographic characteristics were generally balanced between treatment groups.

Table 21. Baseline Demographic, Randomized Population, Trial 0015

Characteristics	Vadadustat N=862	Darbepoetin Alfa N=863	Total N=1725
Age[1] (Years)			
n	862	863	1725
Mean (SD)	67.3 (13.1)	66.5 (13.5)	66.9 (13.3)
Age category, n (%)			
<65 years	313 (36.3)	338 (39.2)	651 (37.7)
≥65 years	549 (63.7)	525 (60.8)	1074 (62.3)
Sex, n (%)			
Male	468 (54.3)	488 (56.5)	956 (55.4)
Female	394 (45.7)	375 (43.5)	769 (44.6)
Ethnicity, n (%)			
Hispanic or Latino	255 (29.6)	255 (29.5)	510 (29.6)
Not Hispanic or Latino	584 (67.7)	591 (68.5)	1175 (68.1)
Not reported	8 (0.9)	5 (0.6)	13 (0.8)
Unknown	15 (1.7)	12 (1.4)	27 (1.6)
Race, n (%)			
American Indian or Alaska Native	32 (3.7)	26 (3.0)	58 (3.4)
Asian	62 (7.2)	55 (6.4)	117 (6.8)
Black or African American	93 (10.8)	131 (15.2)	224 (13.0)
Native Hawaiian or Pacific Islander	3 (0.3)	0 (0)	3 (0.2)
White	631 (73.2)	603 (69.9)	1234 (71.5)
Not reported	15 (1.7)	13 (1.5)	28 (1.6)
Other	25 (2.9)	32 (3.7)	57 (3.3)
Multiple	1 (0.1)	3 (0.3)	4 (0.2)
Country, n (%)			
Argentina	55 (6.4)	42 (4.9)	97 (5.6)
Australia	15 (1.7)	16 (1.9)	31 (1.8)
Austria	3 (0.3)	3 (0.3)	6 (0.3)
Brazil	40 (4.6)	46 (5.3)	86 (5.0)
Bulgaria	48 (5.6)	48 (5.6)	96 (5.6)
Chile	4 (0.5)	7 (0.8)	11 (0.6)
Colombia	9 (1.0)	11 (1.3)	20 (1.2)
Czech Republic	3(0.3)	1 (0.1)	4 (0.2)
France	11 (1.3)	11 (1.3)	22 (1.3)
Germany	10 (1.2)	13 (1.5)	23 (1.3)
Hungary	32 (3.7)	32 (3.7)	64 (3.7)
Israel	7 (0.8)	1 (0.1)	8 (0.5)
Italy	11 (1.3)	8 (0.9)	19 (1.1)
Malaysia	10 (1.2)	16 (1.9)	26 (1.5)
Mexico	58 (6.7)	61 (7.1)	119 (6.9)
Republic of Korea	22 (2.6)	19 (2.2)	41 (2.4)

Characteristics	Vadadustat N=862	Darbepoetin Alfa N=863	Total N=1725
Romania	30 (3.5)	32 (3.7)	62 (3.6)
Russian Federation	17 (2.0)	12 (1.4)	29 (1.7)
Serbia	32 (3.7)	26 (3.0)	58 (3.4)
Slovak Republic	9 (1.0)	4 (0.5)	13 (0.8)
South Africa	20 (2.3)	14 (1.6)	34 (2.0)
Spain	16 (1.9)	22 (2.5)	38 (2.2)
Turkey	9 (1.0)	12 (1.4)	21 (1.2)
Ukraine	50 (5.8)	62 (7.2)	112 (6.5)
United Kingdom	11 (1.3)	9 (1.0)	20 (1.2)
United States	330 (38.3)	335 (38.8)	665 (38.6)
Height (cm)			
n	844	846	1690
Mean (SD)	164.7 (10.6)	164.5 (10.4)	164.6 (10.5)
Weight (kg)			
n	853	856	1709
Mean (SD)	79.3 (21.1)	80.2 (21.1)	79.7 (21.1)
BMI (kg/m^2)			
n	843	844	1687
Mean (SD)	29.1 (7.1)	29.6 (7.3)	29.4 (7.2)

Source: Study 0015 Clinical Study Report Table 12 (p.75)
[1] Reported age on the case report forms.
[2] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
Abbreviations: BMI, body mass index; N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Subjects' baseline clinical characteristics of the randomized population are summarized by treatment group in Table 22.

Table 22. Baseline Clinical Characteristics, Randomized Population, Trial 0015

Characteristics	Vadadustat N=862	Darbepoetin Alfa N=863	Total N=1725
Randomization stratification factors, n (%)			
Region of enrollment[1]			
United States	330 (38.3)	335 (38.8)	665 (38.6)
Europe	225 (26.1)	221 (25.6)	446 (25.9)
Rest of World	307 (35.6)	307 (35.6)	614 (35.6)
New York Heart Association HF Class			
Class 0 (no HF) or I	735 (85.3)	739 (85.6)	1474 (85.4)
Class II or III	127 (14.7)	124 (14.4)	251 (14.6)
Central lab baseline Hb category			
<10 g/dL	273 (31.7)	279 (32.3)	552 (32.0)
≥10 g/dL	589 (68.3)	584 (67.7)	1173 (68.0)
IV iron, ESA & transfusion history, n (%)			
IV iron use prior to first dose of study drug			
Yes	248 (28.8)	249 (28.9)	497 (28.9)
No	613 (71.2)	612 (71.1)	1225 (71.1)
Missing	1	2	3
Received a transfusion within 8 weeks of screening period prior to randomization through to the first dose of study drug			
Yes	1 (0.1)	4 (0.5)	5 (0.3)
No	861 (99.9)	859 (99.5)	1720 (99.7)
Baseline ESA use[2]			
N	833	843	1676
Epoetin, n (%)	510 (61.2)	523 (62.0)	1033 (61.6)
Darbepoetin Alfa, n (%)	262 (31.5)	273 (32.4)	535 (31.9)

Characteristics	Vadadustat N=862	Darbepoetin Alfa N=863	Total N=1725
Methoxy polyethylene glycol-epoetin β, n (%)	61 (7.3)	47 (5.6)	108 (6.4)
Baseline ESA dose – Mean (SD), U/kg/week	105 (143.2)	105 (221.7)	105 (186.8)
Baseline ESA dose category			
N	824	836	1660
≤90 U/kg/week	551 (66.9)	559 (66.9)	1110 (66.9)
>90 and <300 U/kg/week	221 (26.8)	238 (28.5)	459 (27.7)
≥300 U/kg/week	52 (6.3)	39 (4.7)	91 (5.5)
Baseline iron use, n (%)			
0 - subjects not receiving any iron	418 (48.5)	459 (53.2)	877 (50.8)
I - subjects receiving oral iron only	378 (43.9)	332 (38.5)	710 (41.2)
II - subjects receiving IV iron only	43 (5.0)	49 (5.7)	92 (5.3)
III - subjects receiving IV and oral iron	23 (2.7)	23 (2.7)	46 (2.7)
Baseline IV iron dose (mg/week)			
n	61	62	123
Mean (SD)	297 (423)	217 (245)	257 (346)
Baseline oral iron dose (mg/week)			
n	371	327	698
Mean (SD)	2090 (1807)	2244 (2507)	2162 (2163)
Diabetes mellitus, n (%)			
Yes	517 (60.0)	518 (60.0)	1035 (60.0)
No	345 (40.0)	345 (40.0)	690 (40.0)
History of cardiovascular disease[3], n (%)			
Yes	375 (43.5)	402 (46.6)	777 (45.0)
No	487 (56.5)	461 (53.4)	948 (55.0)
History of retinal disorder, n (%)			
Yes	177 (20.5)	169 (19.6)	346 (20.1)
No	685 (79.5)	694 (80.4)	1379 (79.9)
Baseline systolic blood pressure (mmHg)			
n	862	863	1725
Mean (SD)	137 (18)	136 (18)	137 (18)
Baseline diastolic blood pressure (mmHg)			
n	862	863	1725
Mean (SD)	73 (11)	74 (11)	74 (11)
Baseline heart rate (beats/min)			
n	862	863	1725
Mean (SD)	71 (10)	71 (11)	71 (10)

Source: Study 0015 Clinical Study Report Table 13 (p. 77)
[1] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
[2] ESA doses were converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin alfa to IV epoetin was 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin was 1:220; subcutaneous epoetin to IV epoetin was 1:1.25.
[3] Cardiovascular (CV) disease included coronary artery disease, myocardial infarction, stroke, and HF.
Abbreviations: ESA, erythropoiesis-stimulating agents; HF, heart failure; Hb, hemoglobin; IV, intravenous; MI, myocardial infarction; N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Disposition, Trial 0015

Subject disposition information for trial 0015 is summarized in Table 23 and Table 24.

A total of 2961 subjects were screened for entry into Trial 0015. Of these, 1236 subjects failed screening and 1725 were enrolled and randomized into the study. The majority of subjects who failed screening did not meet one or more inclusion/exclusion criteria, with no specific pattern detected upon analysis. Of the subjects randomized, 1723 subjects were included in the safety population and 1710 (99.2%) subjects were included in the FAS population. Overall, a lower percentage of each treatment group qualified for the per protocol population, with a much lower

percentage (69.6% versus 85.4%) in the vadadustat treatment group than the control group of darbepoetin alfa.

Similar proportions of subjects in the vadadustat and darbepoetin alfa treatment groups completed the study, with death being the main reason for discontinuation from study in both treatment groups, with similar contribution. The number of subjects discontinuing study drug treatment (but continuing to be followed in the trial) was higher in the vadadustat treatment group (338 [39.2%]) compared with the darbepoetin alfa treatment group [279 (32.3%)]. The primary reasons for discontinuation of study drug in the vadadustat treatment group were unacceptable toxicity, drug intolerability or AE (12.2%]) and subject no longer wants to receive study drug (10.6%). The primary reasons for discontinuation of study drug in the darbepoetin alfa treatment group was subject no longer wanted to receive study drug (9.0%) and unacceptable toxicity, drug intolerability, and AE (7.8%).

Table 23. Subject Screening and Randomization, Trial 0015

Disposition	Value
No. subjects screened	2961
No. subjects not randomized	1236
No. screening failures	1236/2961 (41.7%)
No. subjects randomized	1725

Source: Study 0015 Clinical Study Report Figure 2 (p. 68)

Table 24. Subject Disposition, Trial 0015

Disposition Category	Vadadustat N=862 n (%)	Darbepoetin Alfa N=863 n (%)	Relative Risk	Risk Difference (%)
Subjects randomized	862 (100)	863 (100)	NA	NA
FAS population	852 (98.8)	858 (99.4)	NA	NA
Per protocol population	600 (69.6)	737 (85.4)	NA	NA
Safety population	861 (99.9)	862 (99.9)	NA	NA
Completed study drug	524 (60.8)	584 (67.7)	0.90	-6.9
Discontinued study drug	338 (39.2)	279 (32.3)	1.21	6.9
Death	32 (3.7)	42 (4.9)	0.76	-1.2
Dialysis or transplant	46 (5.3)	48 (5.6)	0.96	-0.2
Adverse event[1]	105 (12.2)	67 (7.8)	1.57	4.4
Rapid increase in Hb	0 (0)	0 (0)	-	0
Lack of efficacy	12 (1.4)	0 (0)	-	1.4
Decision to switch to ESA	0 (0)	0 (0)	-	0
Investigator's decision[2]	43 (5.0)	30 (3.5)	1.43	1.5
Lack of compliance	0 (0)	0 (0)	-	0
Lost to follow-up	5 (0.6)	4 (0.5)	1.25	0.1
Global termination[3] /Sponsor decision	3 (0.4)	9 (1.0)	0.33	-0.7
Patient wishes[4]	91 (10.6)	78 (9.0)	1.17	1.5
Completed study	703 (81.6)	710 (82.3)	0.99	-0.7

Disposition Category	Vadadustat N=862 n (%)	Darbepoetin Alfa N=863 n (%)	Relative Risk	Risk Difference (%)
Discontinued study	158 (18.3)	152 (17.6)	1.04	0.7
Death	137 (15.9)	137 (15.9)	1.00	0.0
Lost to follow-up	4 (0.5)	6 (0.7)	0.67	-0.2
Dialysis or transplant	4 (0.5)	1 (0.1)	4.00	0.4
Patient wishes	9 (1.0)	6 (0.7)	1.50	0.3
Adverse event	4 (0.5)	2 (0.2)	2.00	0.2

Source: SDTM datasets; Software: JMP
Note: Percentages were calculated based on all randomized subjects.
1, Discontinuation due to adverse events included discontinuation of study drug due unacceptable toxicity, drug tolerability and adverse events.
2, The investigator's decision to discontinue study drug was not due to occurrence of an adverse event. Further details were not provided by the Applicant.
3, When the target number of MACE was reached, global study termination was initiated, resulting in discontinuation of study drug and conducting end-of-study visits in all on-study subjects, regardless of their current study period status.
4, Patient wishes, as a reason for discontinuation of study drug, were not due to occurrence of an adverse event. In the majority of cases, discontinuation of study drug was associated with practical inconveniences of being enrolled on study, due to social external circumstances or not specified.
Abbreviation: ESA, erythropoiesis-stimulating agents; FAS, full analysis set; Hb, hemoglobin; N, number of subjects; n, number of subjects with at least one event

Analysis of the Primary Efficacy Endpoint, Trial 0015

The primary efficacy endpoint for this study was the change in average Hb values between baseline and the primary efficacy period (Weeks 24 to 36).

The primary efficacy endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's primary efficacy results demonstrated a LS mean (SEM) change from baseline to the average Hb over Weeks 24 to 36 of 0.4 (0) g/dL in both the vadadustat and darbepoetin alfa treatment groups. The LS mean (and SEM) treatment difference was 0 (0) g/dL with a 95% CI of (-0.1, 0.1). The magnitude of change from baseline was lower in trial 0015, compared to trial 0014, because subjects enrolled in trial 0015 were treated with ESA prior to enrollment, while subjects in trial 0014 were not on stable treatment. The non-inferiority of vadadustat to darbepoetin alfa was demonstrated for the randomized population because the lower bound of the 95% CI (-0.1) was above the prespecified non-inferiority margin of -0.75 g/dL. It is important to note that the change from baseline to the average Hb over the primary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa. The Applicant's analyses results are shown in Table 25.

Table 25. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputation), Randomized Population, Trial 0015

Visit Statistics	Vadadustat N=862	Darbepoetin Alfa N=863	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	862	863	
Mean (SD)	10.4 (0.9)	10.4 (0.9)	
Weeks 24 to 36 (observed)			
n	779	804	
Mean (SD)	10.8 (1.0)	10.8 (1.0)	
Weeks 24 to 36 (observed + imputed)			
n	862	863	
Mean (SD)	10.8 (1.0)	10.8 (1.0)	

Visit Statistics	Vadadustat N=862	Darbepoetin Alfa N=863	Treatment Comparison Vadadustat – Darbepoetin Alfa
Change from baseline			
n	862	863	
Mean (SD)	0.4 (1.0)	0.4 (1.0)	
Least squares mean (SEM)	0.4 (0)	0.4 (0)	0 (0)
95% CI	(0.3, 0.5)	(0.4, 0.5)	(-0.1, 0.1)

Source: Study 0015 Clinical Study Report Table 21 (p. 91), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

The Applicant also performed a sensitivity analysis using MMRM with missing at random (MAR) assumption. MMRM results are not shown but they also demonstrated non-inferiority of vadadustat to darbepoetin alfa for the primary endpoint.

Analysis for the Key Secondary Efficacy Endpoint, Trial 0015

The key secondary efficacy endpoint for this study was the change in average Hb between baseline and the secondary efficacy period (Weeks 40 to 52).

The key secondary endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's efficacy results demonstrated a LS mean (and SEM) change from baseline to the average over Weeks 40 to 52 of 0.4 (0.0) in both the vadadustat and darbepoetin alfa treatment groups. The LS mean (and SEM) difference between treatment groups was 0 (0.1) g/dL with a 95% CI of (-0.1, 0.1). Since the lower bound of the 95% CI (-0.1) was above the prespecified non-inferiority margin of -0.75 g/dL, non-inferiority of vadadustat to darbepoetin alfa was demonstrated. The change from baseline to the average Hb over the secondary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa. The analyses results are shown in Table 26.

Table 26. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Randomized Population, Trial 0015

Visit Statistics	Vadadustat N=862	Darbepoetin Alfa N=863	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	862	863	
Mean (SD)	10.4 (0.9)	10.4 (0.9)	
Weeks 40 to 52 (observed)			
N	649	673	
Mean (SD)	10.8 (1.0)	10.8 (1.0)	
Weeks 40 to 52 (observed + imputed)			
n	862	863	
Mean (SD)	10.8 (1.0)	10.8 (1.1)	
Change from baseline			
n	862	863	
Mean (SD)	0.4 (1.0)	0.4 (1.1)	
Least squares mean (SEM)	0.4 (0)	0.4 (0)	0 (0.1)
95% CI	(0.4, 0.5)	(0.4, 0.5)	(-0.1, 0.1)

Source: Study 0015 Clinical Study Report Table 24 (p. 96), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Similar to the primary endpoint, the Applicant performed a sensitivity analysis using MMRM assuming data missing at random (MAR). The non-inferiority of vadadustat to darbepoetin alfa was also demonstrated for the randomized population for the key secondary endpoint analysis using MMRM (results not shown in this review).

The FDA statistical review team has confirmed the sponsor's primary and key secondary efficacy endpoint results and agreed that trial 0015 demonstrated the non-inferiority of vadadustat to darbepoetin alfa. The Applicant's conducted analyses of selected important secondary efficacy endpoints are summarized in section III.16.3.2.

Important Secondary Efficacy Endpoints, Trial 0015

Patients in the trial were allowed to receive RBC transfusions or ESA as rescue therapy. As pre-specified secondary endpoints, the Applicant analyzed the following rescue-based endpoints, whose analysis is essential to determine if there is any impact of rescue therapy on the non-inferiority conclusions:

- Proportion of subjects that received ESA rescue medications, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received ESA rescue medications, using the broad-on-treatment rescue therapy definition, where any exposure to ESA rescue is counted for any reason, as long it is not started after permanent study treatment discontinuation
- Proportion of subjects that received RBC transfusion, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received RBC transfusion, using the broad-on-treatment rescue therapy definition, where any exposure to RBC transfusion is counted for any reason, as long it is not started after permanent study treatment discontinuation

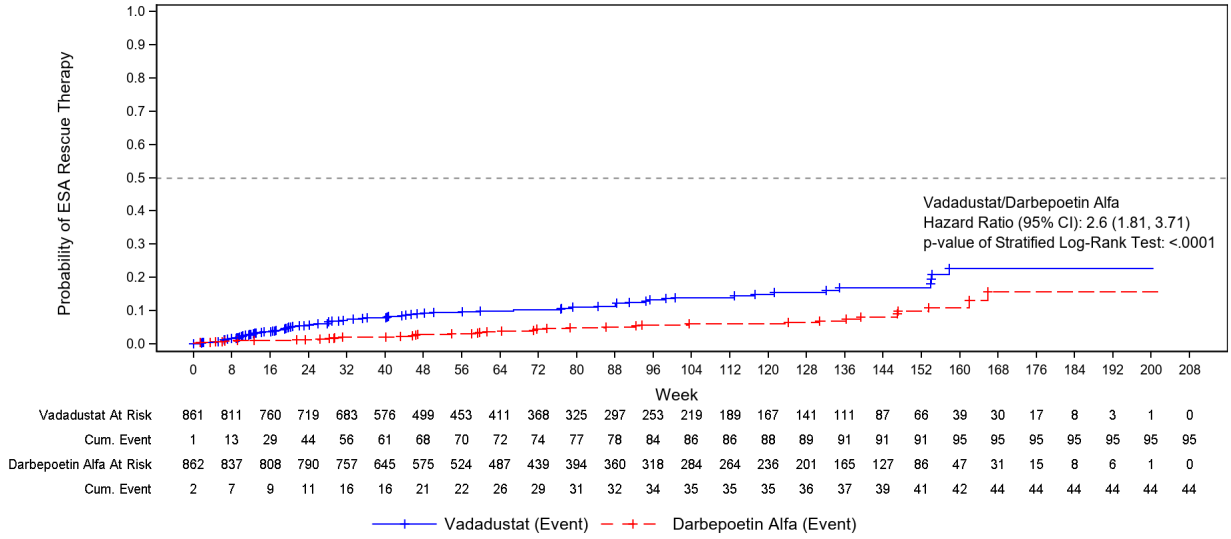
Proportion of Subjects That Received ESA Rescue Medications, Narrow Rescue Therapy

Table 27. Time to ESA Rescue Therapy - Narrow Rescue Therapy (Randomized Population), Trial 0015

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
Subjects with ESA rescue therapy, n (%)	95 (11.0)	44 (5.1)
Subjects censored, n (%)	766 (89.0)	818 (94.9)
Cumulative incidence (95% CI)		
24 Weeks	0.06 (0.04, 0.07)	0.01 (0.01, 0.02)
36 Weeks	0.08 (0.06, 0.10)	0.02 (0.01, 0.03)
40 Weeks	0.08 (0.06, 0.10)	0.02 (0.01, 0.03)
52 Weeks	0.09 (0.07, 0.12)	0.03 (0.02, 0.04)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	<0.0001	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	2.6 (1.81, 3.71)	

Source: Applicant's analysis in response to submitted information request

Figure 10. Kaplan-Meier Curve of Time to ESA Rescue Therapy- Narrow Rescue Therapy (Randomized Population), Trial 0015



Source: Applicant's analysis in response to submitted information request

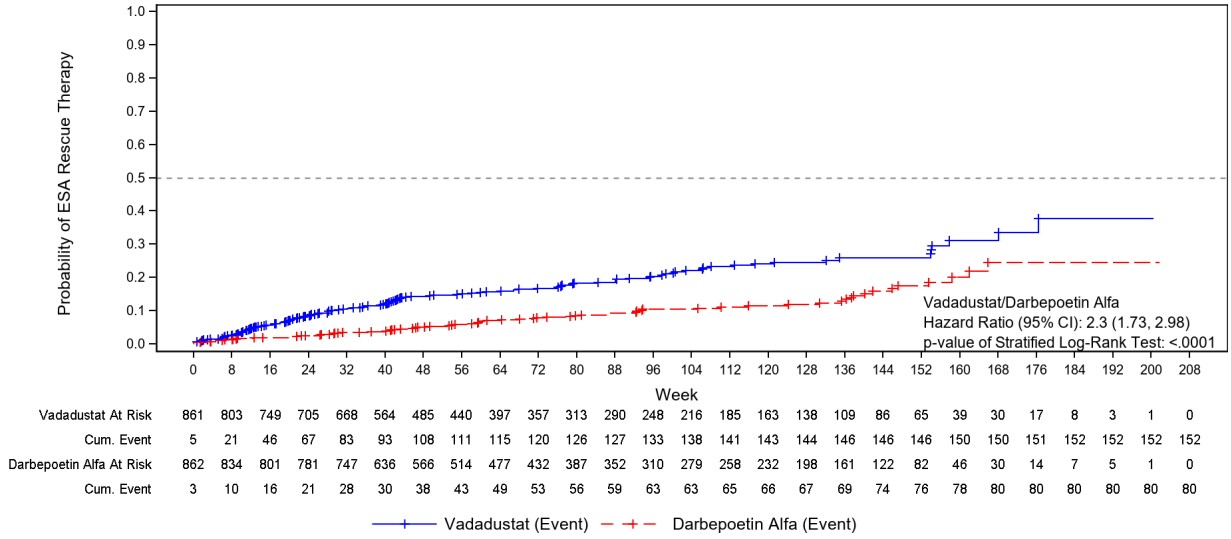
Proportion of Subjects That Received ESA Rescue Medications, Broad-on-Treatment Rescue Therapy

Table 28. Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0015

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
Subjects with ESA rescue therapy, n (%)	152 (17.7)	80 (9.3)
Subjects censored, n (%)	709 (82.3)	782 (90.7)
Cumulative incidence (95% CI)		
24 Weeks	0.08 (0.07, 0.10)	0.03 (0.02, 0.04)
36 Weeks	0.11 (0.09, 0.13)	0.04 (0.02, 0.05)
40 Weeks	0.12 (0.10, 0.14)	0.04 (0.03, 0.05)
52 Weeks	0.15 (0.12, 0.17)	0.05 (0.04, 0.07)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	<0.0001	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	2.3 (1.73, 2.98)	

Source: Applicant's analysis in response to submitted information request

Figure 11. Kaplan-Meier Curve of Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0015



Source: Applicant's analysis in response to submitted information request

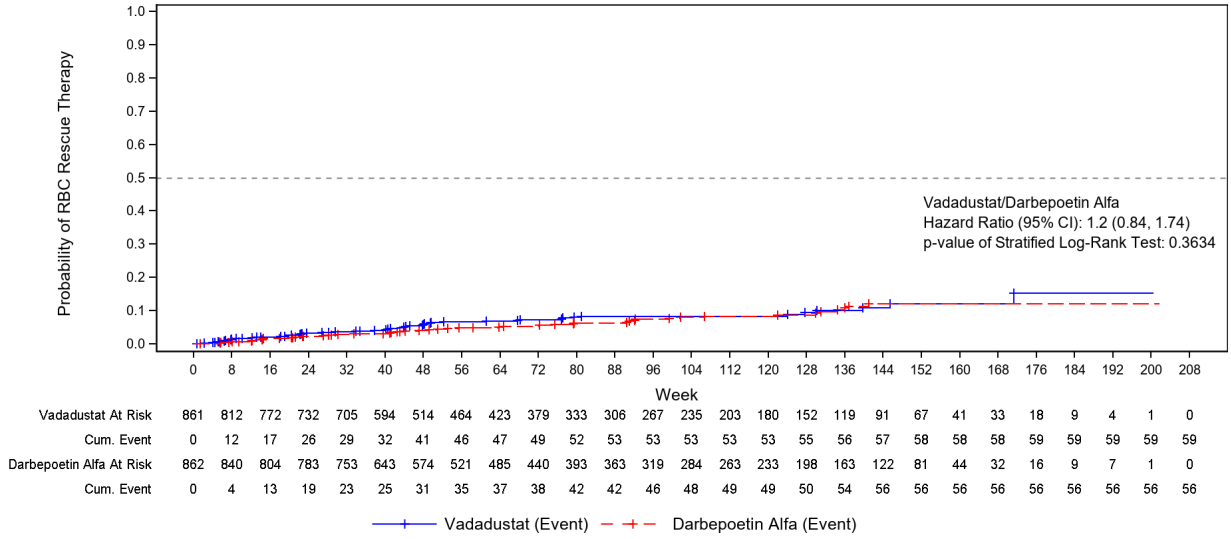
Proportion of Subjects That Received RBC Transfusion, Narrow Rescue Therapy

Table 29. Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0015

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
Subjects with RBC transfusion, n (%)	59 (6.9)	56 (6.5)
Subjects censored, n (%)	802 (93.1)	806 (93.5)
Cumulative incidence (95% CI)		
24 Weeks	0.03 (0.02, 0.05)	0.02 (0.01, 0.04)
36 Weeks	0.04 (0.03, 0.06)	0.03 (0.02, 0.04)
40 Weeks	0.04 (0.03, 0.06)	0.03 (0.02, 0.05)
52 Weeks	0.06 (0.05, 0.09)	0.04 (0.03, 0.06)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.36	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.2 (0.84, 1.74)	

Source: Applicant's analysis in response to submitted information request

Figure 12. Kaplan-Meier Curve of Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0015



Source: Applicant's analysis in response to submitted information request

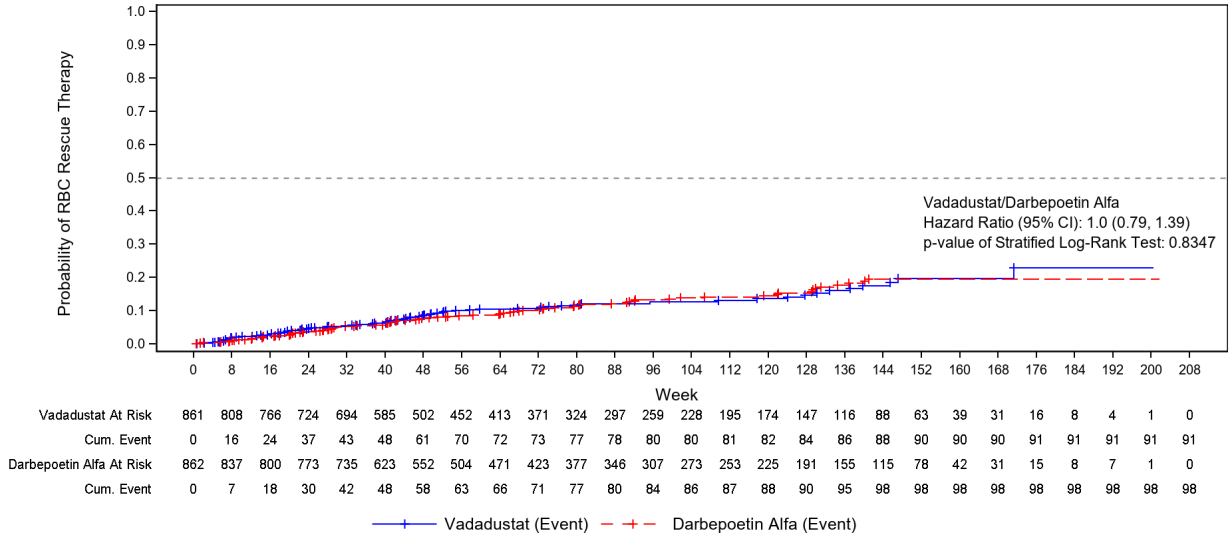
Proportion of Subjects That Received RBC Transfusion, Broad-on-Treatment Rescue Therapy

Table 30. Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0015

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
Subjects with RBC transfusion, n (%)	91 (10.6)	98 (11.4)
Subjects censored, n (%)	770 (89.4)	764 (88.6)
Cumulative incidence (95% CI)		
24 Weeks	0.05 (0.03, 0.06)	0.04 (0.03, 0.05)
36 Weeks	0.06 (0.044, 0.08)	0.05 (0.04, 0.07)
40 Weeks	0.06 (0.05, 0.08)	0.06 (0.05, 0.08)
52 Weeks	0.09 (0.07, 0.12)	0.08 (0.06, 0.10)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.83	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.0 (0.79, 1.39)	

Source: Applicant's analysis in response to submitted information request

Figure 13. Kaplan-Meier Curve of Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0015



Source: Applicant's analysis in response to submitted information request

Similar to Study 0014, more patients in the vadadustat arm received ESA rescue therapies than patients in the darbepoetin alfa arm and they took the therapies significantly earlier, which was more apparent when the narrow definition of ESA rescue was used. However, when considering RBC transfusions, patients in the vadadustat arm received RBC transfusion rescue at a similar rate compared to patients in the darbepoetin alfa arm. The Applicant also conducted sensitivity analyses for both the primary and key secondary efficacy endpoints to further examine the impact of rescue use, according to the narrow definition, by setting all per-visit hemoglobin values to missing within four weeks after administration rescue therapy and results are consistent with the final analysis results (see III.16.3.1).

Subgroup Analyses for the Primary Endpoint, Trial 0015

The Applicant conducted subgroup analyses for various demographic and clinical characteristics groups and their results are presented in section III.16.2.2. The statistical reviewer confirmed their findings. Overall, the treatment effect of vadadustat compared to darbepoetin alfa appeared consistent across all prespecified subgroups, including regional subgroup analyses (see III.16.2.5). As noted previously, the Applicant used US-approved darbepoetin alfa at the US sites and non-US approved darbepoetin alfa at the non-US sites. Therefore, the review team assessed the performance of US-approved and non-US-approved darbepoetin alfa, and the impact, if any, on the conclusion of non-inferiority between vadadustat and darbepoetin alfa (see section II.6.3.2 and III.16.2.5). Note that the sample sizes for some subgroups were small and thus the ability to identify trends from the subgroup analysis results is limited. In addition, conducting multiple subgroup analyses without any multiplicity adjustment could result in spurious findings due to chance, even if the observed result for one subgroup is seemingly very different from the other subgroups.

6.2.3. Results of Analyses for the NDD Trials, Trials AKB-6548-CI-0014 and AKB-6548-CI-0015

This section gives a side-by-side comparison between trials 0014 and 0015, in relation to subjects' baseline demographics and clinical characteristics, patient disposition, and primary analysis results for the primary and the key secondary efficacy endpoints to support the efficacy of oral vadadustat in subjects with NDD-CKD.

Baseline Demographics and Clinical Characteristics

Baseline demographics of the randomized population for trials 0014 and 0015 are summarized by treatment group in Table 31.

Table 31. Baseline Demographics, Randomized Population, Trials 0014 and 0015

	Trial 0014		Trial 0015	
Characteristics	**Vadadustat N=879**	**Darbepoetin Alfa N=872**	**Vadadustat N=862**	**Darbepoetin Alfa N=863**
Age[1] (Years)				
n	879	872	862	863
Mean (SD)	65.2 (14.3)	64.9 (13.7)	67.3 (13.1)	66.5 (13.5)
Age category, n (%)				
<65 years	398 (45.3)	374 (42.9)	313 (36.3)	338 (39.2)
≥65 years	481 (54.7)	498 (57.1)	549 (63.7)	525 (60.8)
Sex, n (%)				
Male	404 (46.0)	366 (42.0)	394 (45.7)	375 (43.5)
Female	475 (54.0)	506 (58.0)	468 (54.3)	488 (56.5)
Ethnicity, n (%)				
Hispanic or Latino	306 (34.8)	310 (35.6)	255 (29.6)	255 (29.5)
Not Hispanic or Latino	566 (64.4)	554 (63.5)	584 (67.7)	591 (68.5)
Not reported	2 (0.2)	5 (0.6)	8 (0.9)	5 (0.6)
Unknown	5 (0.6)	3 (0.3)	15 (1.7)	12 (1.4)
Race, n (%)				
American Indian or Alaska Native	22 (2.5)	23 (2.6)	32 (3.7)	26 (3.0)
Asian	48 (5.5)	37 (4.2)	62 (7.2)	55 (6.4)
Black or African American	188 (21.4)	172 (19.7)	93 (10.8)	131 (15.2)
Native Hawaiian or Pacific Islander	6 (0.7)	6 (0.7)	3 (0.3)	0 (0)
White	546 (62.1)	571 (65.5)	631 (73.2)	603 (69.9)
Not Reported	5 (0.6)	6 (0.7)	15 (1.7)	13 (1.5)
Other	58 (6.6)	48 (5.5)	25 (2.9)	32 (3.7)
Multiple	6 (0.7)	9 (1.0)	1 (0.1)	3 (0.3)
Country, n (%)				
Argentina	25 (2.8)	26 (3.0)	55 (6.4)	42 (4.9)
Australia	10 (1.1)	8 (0.9)	15 (1.7)	16 (1.9)
Austria	--	--	3 (0.3)	3 (0.3)
Brazil	62 (7.1)	58 (6.7)	40 (4.6)	46 (5.3)
Bulgaria	41 (4.7)	42 (4.8)	48 (5.6)	48 (5.6)
Chile	--	--	4 (0.5)	7 (0.8)
Colombia	--	--	9 (1.0)	11 (1.3)
Czech Republic	--	--	3 (0.3)	1 (0.1)
France	--	--	11 (1.3)	11 (1.3)
Germany	--	--	10 (1.2)	13 (1.5)
Hungary	7 (0.8)	8 (0.9)	32 (3.7)	32 (3.7)

Characteristics	Trial 0014 Vadadustat N=879	Trial 0014 Darbepoetin Alfa N=872	Trial 0015 Vadadustat N=862	Trial 0015 Darbepoetin Alfa N=863
Israel	2 (0.2)	2 (0.2)	7 (0.8)	1 (0.1)
Italy	7 (0.8)	9 (1.0)	11 (1.3)	8 (0.9)
Malaysia	--	--	10 (1.2)	16 (1.9)
Mexico	45 (5.1)	46 (5.3)	58 (6.7)	61 (7.1)
Republic of Korea	6 (0.7)	10 (1.1)	22 (2.6)	19 (2.2)
Romania	--	--	30 (3.5)	32 (3.7)
Russian Federation	7 (0.8)	10 (1.1)	17 (2.0)	12 (1.4)
Serbia	--	--	32 (3.7)	26 (3.0)
Slovak Republic	--	--	9 (1.0)	4 (0.5)
South Africa	52 (5.9)	51 (5.8)	20 (2.3)	14 (1.6)
Spain	5 (0.6)	5 (0.6)	16 (1.9)	22 (2.5)
Turkey	--	--	9 (1.0)	12 (1.4)
Ukraine	67 (7.6)	64 (7.3)	50 (5.8)	62 (7.2)
United Kingdom	11 (1.3)	4 (0.5)	11 (1.3)	9 (1.0)
United States	532 (60.5)	529 (60.7)	330 (38.3)	335 (38.8)
Height (cm)				
n	857	859	844	846
Mean (SD)	164.6 (10.5)	164.4 (10.2)	164.7 (10.6)	164.5 (10.4)
Weight (kg)				
n	872	867	853	856
Mean (SD)	80.7 (21.8)	81.1 (22.1)	79.3 (21.1)	80.2 (21.1)
BMI (kg/m^2)				
n	855	857	843	844
Mean (SD)	29.7 (7.2)	29.8 (7.2)	29.1 (7.1)	29.6 (7.3)

Source: Study 0014 Clinical Study Report Table 11 (p. 67); Study 0015 Clinical Study Report Table 12 (p.75)
[1] Reported age on the case report forms.
Abbreviations: BMI, body mass index; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; --: not applicable

Baseline clinical characteristics of the randomized population for trials 0014 and 0015 are summarized by treatment group in Table 32.

Table 32. Baseline Clinical Characteristics, Randomized Population, Trials 0014 and 0015

Characteristics	Trial 0014 Vadadustat N=879	Trial 0014 Darbepoetin Alfa N=872	Trial 0015 Vadadustat N=862	Trial 0015 Darbepoetin Alfa N=863
Randomization stratification factors, n (%)				
Region of enrollment[1]				
United States	532 (60.5)	529 (60.7)	330 (38.3)	335 (38.8)
Europe	71 (8.1)	68 (7.8)	225 (26.1)	221 (25.6)
Rest of World	276 (31.4)	275 (31.5)	307 (35.6)	307 (35.6)
New York Heart Association HF Class				
Class 0 (no HF) or I	762 (86.7)	754 (86.5)	735 (85.3)	739 (85.6)
Class II or III	117 (13.3)	118 (13.5)	127 (14.7)	124 (14.4)
Central lab baseline Hb category				
<9.5 g/dL for 0014 / <10 g/dL for 0015	564 (64.2)	563 (64.6)	273 (31.7)	279 (32.3)
≥9.5 g/dL for 0014 / ≥10 g/dL for 0015	315 (35.8)	309 (35.4)	589 (68.3)	584 (67.7)
IV iron, ESA & transfusion history, n (%)				
IV iron use prior to first dose of study drug				

Characteristics	Trial 0014 Vadadustat N=879	Trial 0014 Darbepoetin Alfa N=872	Trial 0015 Vadadustat N=862	Trial 0015 Darbepoetin Alfa N=863
Yes	163 (18.6)	162 (18.6)	248 (28.8)	249 (28.9)
No	713 (81.4)	707 (81.4)	613 (71.2)	612 (71.1)
Missing	3	3	1 (0.1)	2 (0.2)
ESA use prior to first dose of study drug[2]				
Yes	93 (10.6)	79 (9.1)	--	--
No	784 (89.4)	792 (90.9)	--	--
Missing	2	1	--	--
Received a transfusion within 8 weeks of screening period prior to randomization through to the first dose of study drug				
Yes	0 (0)	2 (0.2)	1 (0.1)	4 (0.5)
No	878 (100.0)	870 (99.8)	861 (99.9)	859 (99.5)
Missing	1	0	--	--
Baseline ESA use[3], n (%)				
n	--	--	833	843
Epoetin	--	--	510 (61.2)	523 (62.0)
Darbepoetin Alfa	--	--	262 (31.5)	273 (32.4)
Methoxy polyethylene glycol-epoetin β	--	--	61 (7.3)	47 (5.6)
Baseline ESA dose (U/kg/week), n (%)				
n	--	--	824	836
Mean (SD)	--	--	105 (143)	105 (222)
≤90 U/kg/week	--	--	551 (67)	559 (67)
>90 and <300 U/kg/week	--	--	221 (27)	238 (29)
≥300 U/kg/week	--	--	52 (6)	39 (5)
Baseline iron use, n (%)				
0 - subjects not receiving any iron	483 (54.9)	467 (53.6)	418 (48.5)	459 (53.2)
I - subjects receiving oral iron only	362 (41.2)	372 (42.7)	378 (43.9)	332 (38.5)
II - subjects receiving IV iron only	22 (2.5)	20 (2.3)	43 (5.0)	49 (5.7)
III - subjects receiving IV and oral iron	12 (1.4)	13 (1.5)	23 (2.7)	23 (2.7)
Baseline IV iron dose (mg/week)				
n	15	14	61	62
Mean (SD)	341 (351)	2187 (6573)	297 (423)	217 (245)
Baseline oral iron dose (mg/week)				
n	360	367	371	327
Mean (SD)	2547 (2056)	2743 (2044)	2090 (1807)	2244 (2507)
Diabetes mellitus, n (%)				
Yes	581 (66.1)	599 (68.7)	517 (60.0)	518 (60.0)
No	298 (33.9)	273 (31.3)	345 (40.0)	345 (40.0)
History of cardiovascular disease[4], n (%)				
Yes	406 (46.2)	412 (47.2)	375 (43.5)	402 (46.6)
No	473 (53.8)	460 (52.8)	487 (56.5)	461 (53.4)
History of retinal disorder, n (%)				
Yes	183 (20.8)	199 (22.8)	177 (20.5)	169 (19.6)
No	696 (79.2)	673 (77.2)	685 (79.5)	694 (80.4)
Baseline systolic blood pressure (mmHg)				
n	878	872	862	863
Mean (SD)	139 (19)	139 (18)	137 (18)	136.4 (18)
Baseline diastolic blood pressure (mmHg)				
n	878	872	862	863
Mean (SD)	74 (12)	73 (13)	73 (11)	74 (11)

Characteristics	Trial 0014 Vadadustat N=879	Trial 0014 Darbepoetin Alfa N=872	Trial 0015 Vadadustat N=862	Trial 0015 Darbepoetin Alfa N=863
Baseline heart rate (beats/min)				
n	878	872	862	863
Mean (SD)	71.3 (11.5)	71.9 (11.4)	70.9 (10.3)	71.1 (10.5)

Source: Study 0014 Clinical Study Report Table 12 (p. 68); Study 0015 Clinical Study Report Table 13 (p. 77)
Note: The percentage is calculated based on the number of subjects with non-missing data.
1, Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
2, For trial 0014, subjects were not eligible if they were on prior stable ESA therapy but some subjects had history of previous exposure to ESA. For trial 0015, all subjects had to be on stable ESA therapy prior to enrollment as part of satisfying their eligibility criteria.
3, ESA doses were converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin alfa to IV epoetin was 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin was 1:220; subcutaneous epoetin to IV epoetin was 1:1.25.
4, Cardiovascular (CV) disease included coronary artery disease, myocardial infarction, stroke, and HF.
Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HF, heart failure; IV, intravenous; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; --: not applicable

Disposition, Trials 0014 and 0015

Patient disposition information for trials 0014 and 0015 is summarized in Table 33 and Table 34.

Table 33. Subject Screening and Randomization, Trials 0014 and 0015

Disposition	Trial 0014	Trial 0015
No. subjects screened	4708	2961
No. subjects not randomized	2957	1236
No. screening failures	2957/4708 (62.8%)	1236/2961 (41.7%)
No. subjects randomized	1751	1725

Source: Study 0014 Clinical Study Report Figure 2 (p. 61); Study 0015 Clinical Study Report Figure 2 (p. 68)

Table 34. Subject Disposition, Randomized Population, Trials 0014 and 0015

Disposition Category	Trial 0014 Vadadustat N=879 n (%)	Trial 0014 Darbepoetin Alfa N=872 n (%)	Trial 0015 Vadadustat N=862 n (%)	Trial 0015 Darbepoetin Alfa N=863 n (%)
Subjects randomized	879 (100)	872 (100)	862 (100)	863 (100)
FAS population	865 (98.4)	858 (98.4)	852 (98.8)	858 (99.4)
Per protocol population	578 (65.8)	699 (80.2)	600 (69.6)	737 (85.4)
Safety population	878 (99.9)	870 (99.7)	861 (99.9)	862 (99.9)
Completed study drug	467 (53.1)	517 (59.3)	524 (60.8)	584 (67.7)
Discontinued study drug	411 (46.8)	355 (40.7)	337 (39.1)	278 (32.2)
Death	40 (4.6)	42 (4.8)	32 (3.7)	42 (4.9)
Dialysis or transplant	41 (4.7)	42 (4.8)	46 (5.3)	48 (5.6)
Adverse event[1]	118 (13.4)	107 (12.3)	105 (12.2)	67 (7.8)
Rapid increase in Hb	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Lack of efficacy	16 (1.8)	6 (0.7)	12 (1.4)	0 (0)
Decision to switch to ESA	5 (0.6)	2 (0.2)	0 (0)	0 (0)
Investigator's decision[2]	31 (3.5)	26 (3.0)	43 (5.0)	30 (3.5)
Lack of compliance	2 (0.2)	2 (0.2)	0 (0)	0 (0)
Lost to follow-up	19 (2.2)	15 (1.7)	5 (0.6)	4 (0.5)
Global termination[3]/Sponsor decision	11 (1.3)	13 (1.5)	3 (0.4)	9 (1.0)
Patient wishes[4]	127 (14.5)	97 (11.1)	91 (10.6)	78 (9.0)
Completed study	670 (76.2)	703 (80.6)	703 (81.6)	710 (82.3)
Discontinued study	208 (23.7)	158 (18.1)	158 (18.3)	152 (17.6)
Death	174 (19.8)	137 (15.7)	137 (15.9)	137 (15.9)
Lost to follow-up	18 (2.1)	21 (2.4)	4 (0.5)	6 (0.7)

	Trial 0014		Trial 0015	
Disposition Category	Vadadustat N=879 n (%)	Darbepoetin Alfa N=872 n (%)	Vadadustat N=862 n (%)	Darbepoetin Alfa N=863 n (%)
Dialysis or transplant	2 (0.2)	3 (0.3)	4 (0.5)	1 (0.1)
Patient wishes	14 (1.6)	6 (0.7)	9 (1.0)	6 (0.7)
Adverse event	0 (0)	0 (0)	4 (0.5)	2 (0.2)

Source: SDTM datasets; Software: JMP
Note: Percentages were calculated based on all randomized subjects.
1, Discontinuation due to adverse events included discontinuation of study drug due unacceptable toxicity, drug tolerability and adverse events.
2, The investigator's decision to discontinue study drug was not due to occurrence of an adverse event. Further details were not provided by the Applicant.
3, When the target number of MACE was reached, global study termination was initiated, resulting in discontinuation of study drug and conducting end-of-study visits in all on-study subjects, regardless of their current study period status.
4, Patient wishes, as a reason for discontinuation of study drug, were not due to occurrence of an adverse event. In the majority of cases, discontinuation of study drug was associated with practical inconveniences of being enrolled on study, due to social external circumstances or not specified.
Abbreviation: ESA, erythropoiesis-stimulating agent; FAS, full analysis set; Hb, hemoglobin; N, number of subjects; n, number of subjects with at least one event

Analysis of the Primary Efficacy Endpoint, Trials 0014 and 0015

According to the Applicant's statistical analysis plans (SAPs) and clinical study reports (CSRs), the primary efficacy endpoint for these studies was the change in average Hb between baseline and the primary efficacy period (Weeks 24 to 36).

The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA) with multiple imputation based on the randomized population. The Applicant's primary efficacy results were confirmed by the statistical review team. The lower bound of the 95% CIs were both above the prespecified non-inferiority margin of -0.75 g/dL for both trials, therefore the non-inferiority of vadadustat to darbepoetin alfa was demonstrated (Table 35). Detailed efficacy analysis results for the primary efficacy endpoint for different patient populations for Trials 0014 and 0015 can be found in sections II.6.2.1.3 and II.6.2.2.3, respectively.

Table 35. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population, Trials 0014 and 0015

	Trial 0014			Trial 0015		
Visit Statistics	Vadadustat N=879	Darbepoetin Alfa N=872	Treatment Comparison Vadadustat – Darbepoetin Alfa	Vadadustat N=862	Darbepoetin Alfa N=863	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline						
n	879	872		862	863	
Mean (SD)	9.1 (0.8)	9.1 (0.8)		10.4 (0.9)	10.4 (0.9)	
Weeks 24 to 36 (observed)						
n	755	767		779	804	
Mean (SD)	10.4 (1.0)	10.4 (1.0)		10.8 (1.0)	10.8 (1.0)	
Weeks 24 to 36 (observed + imputed)						
n	879	872		862	863	
Mean (SD)	10.4 (1.0)	10.4 (1.0)		10.8 (1.0)	10.8 (1.0)	
Change from baseline						
n	879	872		862	863	
Mean (SD)	1.3 (1.0)	1.2 (1.1)		0.4 (1.0)	0.4 (1.0)	
Least squares mean (SEM)	1.4 (0.1)	1.4 (0.1)	0.1 (0.1)	0.4 (0)	0.42 (0)	0. (0)
95% CI	(1.3, 1.5)	(1.3, 1.5)	(0, 0.2)	(0.3, 0.5)	(0.4, 0.5)	(-0.1, 0.1)

Source: Study 0014 Clinical Study Report Table 19 (p. 81); Study 0015 Clinical Study Report Table 21 (p. 91); Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Analysis of the Key Secondary Efficacy Endpoint, Trials 0014 and 0015

According to the Applicant's SAPs and CSRs, the key secondary efficacy endpoint for both studies was the change in average Hb between baseline and the secondary efficacy period (Weeks 40 to 52).

The key secondary endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's key secondary efficacy endpoint results were confirmed by the statistical review team. The lower bound of the 95% CIs were both above the prespecified non-inferiority margin of -0.75 g/dL for both trials, therefore the non-inferiority of vadadustat to darbepoetin alfa was demonstrated (Table 36). More detailed efficacy analysis results for the key secondary efficacy endpoint for different patient populations for Trials 0014 and 0015 can be found in sections II.6.2.1.3 and II.6.2.2.3, respectively.

Table 36. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Randomized Population, Trials 0014 and 0015

	Trial 0014			Trial 0015		
Visit Statistics	Vadadustat N=879	Darbepoetin Alfa N=872	Treatment Comparison Vadadustat – Darbepoetin Alfa	Vadadustat N=862	Darbepoetin Alfa N=863	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline						
n	879	872		862	863	
Mean (SD)	9.1 (0.8)	9.1 (0.8)		10.4 (0.9)	10.4 (0.9)	
Weeks 40 to 52 (observed)						
n	638	641		649	673	
Mean (SD)	10.5 (1.0)	10.5 (1.0)		10.8 (1.0)	10.8 (1.0)	
Weeks 40 to 52 (observed + imputed)						
n	879	872		862	863	
Mean (SD)	10.5 (1.1)	10.5 (1.0)		10.8 (1.0)	10.8 (1.1)	
Change from baseline						
n	879	872		862	863	
Mean (SD)	1.4 (1.1)	1.3 (1.1)		0.4 (1.0)	0.4 (1.1)	
Least squares mean (SEM)	1.5 (0.1)	1.5 (0.1)	0.04 (0.05)	0.43 (0.04)	0.44 (0.04)	0.0 (0.1)
95% CI	(1.4, 1.6)	(1.4, 1.6)	(-0.1, 0.1)	(0.4, 0.5)	(0.4, 0.5)	(-0.1, 0.1)

Source: Study 0014 Clinical Study Report Table 22 (p. 85); Study 0015 Clinical Study Report Table 24 (p. 96); Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Summary:

After conducting a thorough evaluation of the data from the vadadustat PRO$_2$TECT program, we concluded that the enrolled patient population is appropriately reflective of the patient population with NDD-CKD associated anemia. In addition, the two treatment arms were balanced in relation to baseline demographic and clinical characteristics, with appropriate representation across ages, genders, and races/ethnicities.

Based on results of the primary and key secondary efficacy analysis, evaluating hemoglobin response at the primary efficacy period (i.e., weeks 24 to 36) and the secondary efficacy period (i.e., weeks 40 to 52) respectively, the non-inferiority of vadadustat, compared to darbepoetin alfa, was established in the NDD-CKD population. Although there was a higher rate of ESA rescue therapy in patients with NDD-CKD on vadadustat compared to patients treated with on-study darbepoetin alfa, sensitivity analyses that set Hb values within 4 weeks after rescue therapy as missing yielded efficacy results consistent with that of the primary efficacy analysis (see Section II.6.3.1). Other pre-specified subgroup sensitivity analyses showed results consistent with the primary efficacy analysis, and are thus supportive of the efficacy of vadadustat across the different subgroups.

There were no efficacy endpoints that directly measured how patients feel, function, or survive (e.g., patient-reported outcomes). Hematologic response and reduction in RBC transfusions have been used for traditional approval for drugs intended to treat anemia of CKD. Trials 0014 and 0015 showed that vadadustat is non-inferior to darbepoetin alfa on hematologic response. The trials were not designed to show non-inferiority or superiority of vadadustat to darbepoetin alfa on RBC transfusions, but the RBC transfusion data across the two trials did not show an appreciable difference in RBC transfusion burden between vadadustat and darbepoetin alfa (narrow RBC transfusion rescue HR 1.0 in trial 0014 and 1.2 in trial 0015; broad RBC transfusion rescue HR 1.0 in trial 0014 and 1.0 in trial 0015). The HR of 1.2 for narrow RBC transfusion rescue in trial 0015 was based on a difference between treatment arms of only 3 events, limiting conclusions. We conclude that the Applicant has established substantial evidence of effectiveness of vadadustat in the treatment of patients with NDD-CKD associated anemia. Vadadustat's oral route of administration offers a convenience benefit over parenteral ESAs in this patient population.

6.2.4. Trial AKB-6548-CI-0016

6.2.4.1. Design, Trial 0016

Title

Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction or Maintenance Treatment of Anemia in Subjects with Incident DD-CKD (INNO$_2$VATE – Correction/Conversion)

Overview and Objectives

Trial 0016 was a multi-center, multi-national, randomized, open-label, sponsor-blinded, active-controlled trial of the efficacy and safety of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia after correction of Hb or conversion from current ESA in adult

subjects with incident dialysis (defined as initiation of chronic maintenance peritoneal or hemodialysis within 16 weeks prior to Screening).

The primary objective of this trial was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia after the correction of Hb or conversion from current ESA therapy, in subjects who have recently initiated dialysis treatment for DD-CKD.

Trial Design

Eligible subjects discontinued their ESA before the 2nd screening visit, which occurred at a minimum of 4 days from the baseline visit. Randomization took place at the baseline visit, in a 1:1 ratio, where subjects were randomized between receiving vadadustat or darbepoetin alfa. Subjects living in the U.S. received U.S.-approved darbepoetin alfa, while subjects living outside the U.S received non-U.S.-approved darbepoetin alfa. Enrolled subjects were also stratified by the following factors:

- Geographic region (United States versus Europe versus Rest of World)
- New York Heart Association (NYHA) heart failure Class 0 or I versus II or III
- Study entry Hb (<9.5 versus ≥9.5 g/dL), based on the most recent central laboratory Hb measurement prior to the baseline/randomization visit

Following randomization, the trial consisted of five periods:

- Screening period (up to eight weeks)
- Correction/Conversion period (Weeks 0-23): period for converting to study medication, while maintaining Hb
- Maintenance period (Weeks 24-52): period on study medication during which efficacy will be assessed:
  - Primary evaluation period (Weeks 24-36)
  - Secondary evaluation period (Weeks 40-52)
- Long-term treatment period (Weeks 53- EOT)
- Follow-up period (EOT +4 weeks): subjects who discontinued study drug were followed to EOS to assess MACE.

Hemoglobin was monitored using a point of care device and was assessed with a CBC through the local or central laboratory. Hemoglobin measurements used to decide on study eligibility and to calculate all efficacy endpoints were obtained using a central laboratory, while hemoglobin measurements used to decide on the need for dose adjustment could be obtained using any one of the three methods listed. Baseline Hb was used to determine study eligibility and was defined as the average of 2 Hb values measured by the central laboratory during the screening period, at least 4 days apart.

The need for dose adjustment was determined according to a treatment-specific dose adjustment algorithm (section III.15), which depended on the geographic location of the patient. In addition, subjects randomized to receive darbepoetin alfa were allowed to have dose adjustment based on the available prescribing information and local standard of care guidelines. The frequency of Hb assessment was every 2 weeks from weeks 0 to 12, every 4 weeks from weeks 12 to 52 and at least every 12 weeks thereafter with every 4-week frequency recommended by the Applicant.

More frequent Hb assessments were indicated if modification of dosing or an unscheduled visit occurred due to clinical reasons.

The aim of the dosing strategy was to increase and maintain Hb levels of 10.0 g/dL to 11.0 g/dL in the United States and 10.0 g/dL to 12.0 g/dL outside of the United States throughout the trial. The difference in target Hb levels between the two geographic regions was based on the Agency's previous observation of greater risks for MACE when ESAs were used to target Hb levels greater than 11 g/dL. The use of ESA or RBC transfusion for rescue was allowed, up to the discretion of the investigator, but specific guidelines were provided in the trial protocol. The use of ESA rescue was discouraged if subjects were not experiencing worsening symptoms of anemia and had a Hb < 9.0 g/dL. Concomitant administration of RBC transfusion and study drug was allowed but concomitant administration of ESA rescue and study drug was not allowed. Additional important aspects of trial design and important protocol amendments can be found in section III.15.

There were three committees involved in conducting the trial:

- Executive Steering Committee: oversaw the study and provided expert input to assure a high scientific standard. Member of the committee were blinded to the randomization and were recognized academic leaders, including those from the field of nephrology and cardiology. Details of the roles and responsibilities of the ESC were described in the ESC charter.
- Independent Data Monitoring Committee: reviewed and discussed study safety data in an unblinded fashion during regularly scheduled meetings. The IDMC was composed of at least one nephrologist, one cardiologist and one biostatistician. Written records of their meetings and decisions were submitted by the Applicant and reviewed. Details of the roles and responsibilities of the IDMC were described in the IDMC charter.
- Endpoint Adjudication Committee: independently adjudicated the primary safety endpoints of interest (i.e., all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, thromboembolic events, and hospitalization for heart failure) in a blinded fashion. Members of the committee were independent experts, selected prior to commencement of the trial, with experience and training in adjudication of the primary safety endpoints of interest. Details of the roles and responsibilities of the EAC were described in the EAC charter.

Key Eligibility Criteria

Inclusion criteria:

- At least 18 years of age
- Initiated chronic maintenance dialysis (either peritoneal or hemodialysis) for end-stage kidney disease within 16 weeks prior to Screening
- Mean Screening Hb between 8.0 and 11.0 g/dL (inclusive), as determined by the average of two Hb values measured by the central laboratory during Screening
- Serum ferritin ≥100 ng/mL and TSAT ≥20% during Screening
- Folate and vitamin B12 measurements ≥ lower limit of normal during Screening
- Understood the procedures and requirements of the study and provided written informed consent and authorization for protected health information disclosure

Exclusion criteria:

- Presented with anemia due to a cause other than CKD or with active bleeding or recent blood loss.
- Subjects with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia.
- RBC transfusion within eight weeks prior to randomization.
- Anticipated to recover adequate kidney function to no longer require dialysis.
- AST, ALT, or total bilirubin >2.0 × ULN during Screening. Subjects with a history of Gilbert's syndrome were not excluded.
- Uncontrolled hypertension (confirmed DBP >110 mmHg or SBP >180 mmHg) during Screening.
- Severe HF during Screening (NYHA Class IV).
- Acute coronary syndrome (hospitalization for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for HF, or stroke within 12 weeks prior to or during Screening.
- History of active malignancy within two years prior to or during Screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ.
- History of DVT or PE within 12 weeks prior to randomization.
- History of hemosiderosis or hemochromatosis.
- History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list were not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis were not excluded).
- Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever was longer), prior to the Screening visit.
- Previous participation in this study, or previous participation in a study with an HIF prolyl-hydroxylase inhibitor other than vadadustat.
- Females who were pregnant or breast-feeding. Women of childbearing potential who were unable or unwilling to use an acceptable method of contraception.
- Non-vasectomized male subjects who were unable or unwilling to use an acceptable method of contraception.
- Any other reason that in the opinion of the investigator would make the subject not suitable for participation in the study.
- Hypersensitivity to darbepoetin alfa or vadadustat, or to any of their excipients.
- Subjects meeting the criteria of ESA resistance within 8 weeks prior to or during Screening defined as follows:
  - Epoetin >7700 units/dose three times per week or >23,000 units per week
  - Darbepoetin alfa:>100 mcg/week
  - Methoxy polyethylene glycol-epoetin beta: >100 mcg every other week or >200 mcg/month

Study Endpoints:

Primary efficacy endpoint:

- Mean change in Hb between baseline (mean pre-treatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36).

Key secondary efficacy endpoints:

- Mean change in Hb value between baseline (mean pre-treatment Hb) and the secondary evaluation period (Weeks 40-52)

Other secondary efficacy endpoints:

- Proportion of subjects with Hb values within the geography-specific target range during the primary evaluation period (Weeks 24-36)
- Proportion of subjects with Hb values within the geography-specific target range during the secondary evaluation period (Weeks 40-52)
- Proportion of time with Hb values within the target range during the primary evaluation period (Weeks 24-36)
- Proportion of time with Hb values within the target range during the secondary evaluation period (Weeks 40-52)
- Proportion of subjects with Hb increase of >1.0 g/dL from baseline to week 52
- Time to achieve Hb increase of >1.0 g/dL from baseline (censored at week 52)
- Mean change in Hb between baseline (mean pre-treatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36) stratified by pre-baseline ESA exposure
- Proportion of subjects receiving IV iron therapy from baseline to Week 52
- Mean monthly dose of IV elemental iron administered from baseline to Week 52 in subjects who have received IV iron
- ESA rescue
- Dose adjustments from baseline to Week 52
- Proportion of subjects receiving RBC transfusion(s) from baseline to Week 52

Safety endpoints:

- MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke
- Individual components of MACE:
  - All-cause mortality
  - Non-fatal MI
  - Non-fatal stroke
- TE events: ATE, DVT, PE, or VAT
- Hospitalization for HF
- Expanded MACE, defined as all-cause mortality, non-fatal MI, non-fatal stroke, hospitalization for HF, or TE event
- Fatal/non-fatal MI
- Fatal/non-fatal stroke
- Sudden death
- CV death
- Non-CV death
- Hospitalization

- Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/Dl
- Hb <8.0 g/dL
- Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
- AEs and SAEs
- Vital signs and clinical laboratory values
- Assessment of adrenal disorders as an AE of special interest, using a MedDRA high-level group term of adrenal gland disorders and MedDRA high-level term adrenal cortex tests

To ensure the ability to evaluate primary efficacy and safety endpoints, study completion was achieved when:

- 631 MACE events were reached in both trials 0016 and 0017, representing the DD-CKD trial population, and
- All enrolled subjects completed at least 36 weeks on trial (i.e., visit 13)

6.2.4.2. Statistical Analysis Plan, Trial 0016

Definitions of the Analysis Populations

The analysis populations were defined as follows:

- Randomized population: all subjects randomized. Analyses for this population were based on subjects' randomized treatment.
- Full analysis set (FAS) population: all subjects in the randomized population who received at least one dose of study drug and had at least one post-dose Hb. Analyses for this population were based on subjects' randomized treatment.
- Safety population: all subjects in the randomized population who received at least one dose of study drug. Analysis for this population were based on the actual treatment received. Subjects who received in error some vadadustat and some darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received drug.
- PP population: all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least one Hb assessment during the primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviations affecting the primary endpoint analyses (i.e., prior to Week 36). Analyses for this population were based on actual treatment received, as described for the Safety population.

Efficacy analyses utilized the randomized, FAS, and PP populations while safety analyses (including analyses of MACE) utilized the Safety population. The randomized population was used for major efficacy analyses.

Analysis for the Primary Efficacy Endpoint

According to the Applicant's SAP and CSR, the primary efficacy endpoint is the change in average Hb between baseline and the primary efficacy period (Weeks 24 to 36). The primary analysis model used ANCOVA with multiple imputation. Missing data were imputed based on information of the group to which the subject was randomized. The primary analysis model contains treatment group, baseline Hb level, and the two stratification factors (region and NYHA CHF class) as predictor variables. The randomization stratification factor of entry Hb level was

not included in the model because of the inclusion of baseline Hb. The noninferiority of vadadustat to darbepoetin alfa was to be demonstrated if the lower bound of the 95% confidence interval for the difference in estimated change from baseline in the 2 groups (vadadustat minus darbepoetin alfa) exceeded the noninferiority margin of -0.75. This ensures a type I error rate of 0.05 control based on 1-sided alpha of 0.025 for the primary analysis.

Analyses for the Key Secondary Efficacy Endpoint

According to the Applicant's SAP and CSR, the key secondary efficacy endpoint was change in average Hb value between baseline and the secondary efficacy period (Weeks 40 to 52). Evaluation of the key secondary efficacy endpoint employed the same approach described for the primary endpoint assessing Weeks 40 to 52 instead of Weeks 24 to 36. The power for this endpoint for a noninferiority margin of -0.75 g/dL is expected to be close to the power of the primary endpoint, which is 90%. Similar to the primary endpoint, the Agency recommended the -0.75 non-inferiority margin, which has been used in other applications for treatment of anemia due to chronic kidney disease and is based on preserving at least 50% treatment effect of an ESA in the conversion studies.

Multiple Testing Approach

The key secondary efficacy endpoint was analyzed formally only if the primary analysis met the prespecified non-inferiority margin. The formal testing procedure for the key secondary efficacy endpoint would be stopped if the analysis failed to confirm non-inferiority of the primary efficacy endpoint using a 1-sided significance level of 2.5%.

Method for Handling of Missing Data

Standard multiple imputation of missing values based on the group to which the subject was randomized was used for all analyses for the primary and secondary efficacy outcomes to handle missing data.

6.2.4.3. Results of Analyses, Trial 0016

This section summarizes subjects' baseline demographics and clinical characteristics, disposition data, and major efficacy results for the correction or maintenance treatment of anemia in subjects with incident DD-CKD from trial 0016.

Baseline Demographics and Clinical Characteristics, Trial 0016

Baseline demographics of the randomized population data are summarized by treatment group in Table 37. Subjects' demographic characteristics were generally similar between treatment groups.

Table 37. Baseline Demographic, Randomized Population, Trial 0016

Characteristics	Vadadustat N=181	Darbepoetin Alfa N=188	Total N=369
Age[1] (Years)			
n	181	188	369
Mean (SD)	56.5 (14.8)	55.6 (14.6)	56.0 (14.7)

Characteristics	Vadadustat N=181	Darbepoetin Alfa N=188	Total N=369
Age category, n (%)			
<65 years	122 (67.4)	137 (72.9)	259 (70.2)
≥65 years	59 (32.6)	51 (27.1)	110 (29.8)
Sex, n (%)			
Male	107 (59.1)	113 (60.1)	220 (59.6)
Female	74 (40.9)	75 (39.9)	149 (40.4)
Ethnicity, n (%)			
Hispanic or Latino	71 (39.2)	66 (35.1)	137 (37.1)
Not Hispanic or Latino	104 (57.5)	118 (62.8)	222 (60.2)
Not reported	5 (2.8)	3 (1.6)	8 (2.2)
Unknown	1 (0.6)	1 (0.5)	2 (0.5)
Race, n (%)			
American Indian or Alaska Native	1 (0.6)	0	1 (0.3)
Asian	12 (6.6)	8 (4.3)	20 (5.4)
Black or African American	38 (21.0)	35 (18.6)	73 (19.8)
Native Hawaiian or Pacific Islander	0	0	0
White	129 (71.3)	143 (76.1)	272 (73.7)
Not reported	0	1 (0.5)	1 (0.3)
Other	0	1 (0.5)	1 (0.3)
Multiple	1 (0.6)	0	1 (0.3)
Country, n (%)			
Argentina	3 (1.7)	5 (2.7)	8 (2.2)
Brazil	18 (9.9)	20 (10.6)	38 (10.3)
Germany	0	0	0
Italy	6 (3.3)	1 (0.5)	7 (1.9)
Mexico	1 (0.6)	0	1 (0.3)
Poland	11 (6.1)	9 (4.8)	20 (5.4)
Portugal	9 (5.0)	6 (3.2)	15 (4.1)
Republic of Korea	6 (3.3)	3 (1.6)	9 (2.4)
Russian Federation	4 (2.2)	6 (3.2)	10 (2.7)
Ukraine	26 (14.4)	36 (19.1)	62 (16.8)
United States	97 (53.6)	102 (54.3)	199 (53.9)
Height (cm)			
n	178	184	362
Mean (SD)	167.6 (10.7)	166.9 (9.0)	167.25 (9.8)
Weight (kg)			
n	177	184	361
Mean (SD)	77.9 (20.6)	77.6 (19.7)	77.7 (20.1)
BMI (kg/m^2)			
n	174	181	355
Mean (SD)	27.6 (6.1)	27.5 (6.0)	27.6 (6.0)

Source: Study 0016 Clinical Study Report Table 11 (p. 64)
[1] Reported age on the case report forms.
[2] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
Abbreviations: N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Subjects' baseline clinical characteristics of the randomized population are summarized by treatment group in Table 38.

Table 38. Baseline Clinical Characteristics, Randomized Population, Trial 0016

Characteristics	Vadadustat N=181	Darbepoetin Alfa N=188	Total N=369
Randomization stratification factors, n (%)			
Region of enrollment[1]			
United States	97 (53.6)	102 (54.3)	199 (53.9)
Europe	26 (14.4)	16 (8.5)	42 (11.4)
Rest of World	58 (32.0)	70 (37.2)	128 (34.7)
New York Heart Association HF Class			
Class 0 (no HF) or I	162 (89.5)	162 (86.2)	324 (87.8)
Class II or III	19 (10.5)	26 (13.8)	45 (12.2)
Central lab baseline Hb category			
<9.5 g/dL	94 (51.9)	99 (52.7)	193 (52.3)
≥9.5 g/dL	87 (48.1)	89 (47.3)	176 (47.7)
IV iron, ESA & transfusion history, n (%)			
IV iron use prior to first dose of study drug			
Yes	119 (65.7)	140 (74.5)	259 (70.2)
No	62 (34.3)	48 (25.5)	110 (29.8)
Received a transfusion within 8 weeks of screening period prior to randomization through to the first dose of study drug			
Yes	6 (3.3)	9 (4.8)	15 (4.1)
No	175 (96.7)	179 (95.2)	354 (95.9)
Baseline ESA use			
N	92	85	177
Epoetin, n (%)	54 (58.7)	44 (51.8)	98 (55.4)
Darbepoetin Alfa, n (%)	18 (19.6)	21 (24.7)	39 (22.0)
Methoxy polyethylene glycol-epoetin β, n (%)	20 (21.7)	20 (23.5)	40 (22.6)
Baseline ESA dose – Mean (SD), U/kg/week	155 (113)	148 (115)	151 (114)
Baseline ESA dose category			
N	90	83	173
≤90 U/kg/week, n (%)	36 (40.0)	30 (36.1)	66 (38.2)
>90 and <300 U/kg/week, n (%)	45 (50.0)	47 (56.6)	92 (53.2)
≥300 U/kg/week, n (%)	9 (10.0)	6 (7.2)	15 (8.7)
Baseline iron use[2], n (%)			
0 - subjects not receiving any iron	52 (28.7)	56 (29.8)	108 (29.3)
I - subjects receiving oral iron only	19 (10.5)	9 (4.8)	28 (7.6)
II - subjects receiving IV iron only	92 (50.8)	110 (58.5)	202 (54.7)
III - subjects receiving IV and oral iron	18 (9.9)	13 (6.9)	31 (8.4)
Baseline IV iron dose (mg/week)			
n	68	75	143
Mean (SD)	567 (3380)	403 (1018)	481 (2437)
Baseline oral iron dose (mg/week)			
n	29	20	49
Mean (SD)	3767 (7607)	2197 (1813)	3126 (5972)
Diabetes mellitus, n (%)			
Yes	105 (58.0)	96 (51.1)	201 (54.5)
No	76 (42.0)	92 (48.9)	168 (45.5)
History of cardiovascular disease[3], n (%)			
Yes	69 (38.1)	73 (38.8)	142 (38.5)
No	112 (61.9)	115 (61.2)	227 (61.5)
History of retinal disorder, n (%)			
Yes	37 (20.4)	35 (18.6)	72 (19.5)
No	144 (79.6)	153 (81.4)	297 (80.5)

Characteristics	Vadadustat N=181	Darbepoetin Alfa N=188	Total N=369
Years since chronic dialysis initiated[4]			
n	179	186	365
Mean (SD)	0.14 (0.09)	0.15 (0.29)	0.15 (0.21)
Baseline systolic blood pressure (mmHg)			
n	181	188	369
Mean (SD)	143 (22)	143 (20)	143 (21)
Baseline diastolic blood pressure (mmHg)			
n	181	188	369
Mean (SD)	77 (13)	79 (13)	78 (13)
Baseline heart rate (beats/min)			
n	181	188	369
Mean (SD)	76 (11)	75 (10)	76 (11)

Source: Study 0016 Clinical Study Report Table 12 (p. 65)
Note: The percentage is calculated based on the number of subjects with non-missing data.
[1] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
[2] ESA doses were converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin alfa to IV epoetin was 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin was 1:220; subcutaneous epoetin to IV epoetin was 1:1.25.
[3] Cardiovascular (CV) disease included coronary artery disease, myocardial infarction, stroke, and HF.
[4] The handling of the partial date of chronic dialysis initiated: If day was missing, day was set to 15th of the month. If month was missing, month and day were set to Jul 1. If year was missing, date was missing. Years since chronic dialysis initiated was calculated based on date of chronic dialysis initiated and date of Screening 1.
Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HF, heart failure; IV, intravenous; N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Disposition, Trial 0016

Subject disposition information for Trial 0016 is summarized in Table 39 and Table 40.

A total of 677 subjects were screened for entry into Trial 0016. Of these, 308 subjects failed screening and 369 subjects were enrolled and randomized in the study. The majority of subjects who failed screening did not meet one or more inclusion/exclusion criteria, with no specific pattern detected upon analysis. Of subjects randomized, 365 subjects were included in the Safety population and 364 subjects were included in the FAS population. Overall, a lower percentage of each treatment group qualified for the per protocol population, with a much lower percentage (59.1% versus 75.5%) in the vadadustat treatment group than the control group of darbepoetin alfa.

Similar proportions of subjects in the vadadustat and darbepoetin alfa treatment groups completed the study, with death being the main reason for discontinuation from study in both treatment groups, with similar contribution. The total number of discontinuations of study drug treatment (but continuing to be followed in the trial) was higher (60 [33.2%]) in the vadadustat treatment group compared with the darbepoetin alfa treatment group (49 [26.1%]). The primary reasons for discontinuation of study drug in the vadadustat treatment group were patient no longer wants to receive study drug (11.6%), unacceptable toxicity, drug intolerability or AE (8.8%), and investigator's decision (6.1%). The primary reasons for discontinuation of study drug in the darbepoetin alfa treatment group were patient no longer wants to receive study drug (6.9%), patient receiving a kidney transplant (6.9%) and death (5.9%).

Table 39. Subjects Screening and Randomization, Trial 0016

Disposition	Value
No. subjects screened	677
No. subjects not randomized	308
No. screening failures	308/677 (45.5%)

No. subjects randomized	369

Source: Study 0016 Clinical Study Report Figure 2 (p. 58)

Table 40. Subject Disposition, Trial 0016

Disposition Category	Vadadustat N=181 n (%)	Darbepoetin Alfa N=188 n (%)	Relative Risk	Risk Difference (%)
Subjects randomized	181 (100)	188 (100)	NA	NA
ITT/mITT population	178 (98.3)	186 (98.9)	NA	NA
Per protocol population	107 (59.1)	142 (75.5)	NA	NA
Safety population	179 (98.9)	186 (98.9)	NA	NA
Completed study drug	121 (66.9)	139 (73.9)	0.90	-7.
Discontinued study drug	60 (33.2)	49 (26.1)	1.27	7.1
Death	1 (0.6)	11 (5.9)	0.09	-5.3
Kidney transplant	7 (3.9)	13 (6.9)	0.56	-3.1
Adverse event[1]	16 (8.8)	6 (3.2)	2.77	5.7
Lack of efficacy	1 (0.6)	0 (0)	-	0.6
Decision to switch to ESA	0 (0)	0 (0)	-	0
Investigator's decision[2]	11 (6.1)	3 (1.6)	3.81	4.5
Lack of compliance	0 (0)	0 (0)	-	0
Lost to follow-up	1 (0.6)	1 (0.5)	1.04	0
Global termination[3] /Sponsor decision	0 (0)	0 (0)	-	0
Patient wishes[4]	21 (11.6)	13 (6.9)	1.68	4.7
Completed study	159 (87.9)	163 (86.7)	1.01	1.1
Discontinued study	20 (11.1)	23 (12.2)	0.90	-1.2
Death	15 (8.3)	19 (10.1)	0.82	-1.8
Lost to follow-up	3 (1.7)	2 (1.1)	1.56	0.6
Kidney transplant	0 (0)	1 (0.5)	0	-0.5
Patient wishes	2 (1.1)	1 (0.5)	2.08	0.6
Adverse event	0 (0)	0 (0)	-	0
Lack of efficacy	0 (0)	0 (0)	-	0

Source: SDTM datasets; Software: JMP
Note: Percentages were calculated based on all randomized subjects.
1, Discontinuation due to adverse events included discontinuation of study drug due unacceptable toxicity, drug tolerability and adverse events.
2, The investigator's decision to discontinue study drug was not due to occurrence of an adverse event. Further details were not provided by the Applicant.
3, When the target number of MACE was reached, global study termination was initiated, resulting in discontinuation of study drug and conducting end-of-study visits in all on-study subjects, regardless of their current study period status.
4, Patient wishes, as a reason for discontinuation of study drug, were not due to occurrence of an adverse event. In the majority of cases, discontinuation of study drug was associated with practical inconveniences of being enrolled on study, due to social external circumstances or not specified.
Abbreviation: ESA, erythropoiesis-stimulating agent; FAS, full analysis set; ITT, intent to treat; mITT, modified intent to treat; N, number of subjects; n, number of subjects with at least one event

Analysis for the Primary Efficacy Endpoint, Trial 0016

The primary efficacy endpoint for this study was the change in average Hb levels between baseline and the primary efficacy period (Weeks 24 to 36).

The primary efficacy endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's primary efficacy results demonstrated a LS mean (and SEM) change from baseline to the average Hb over Weeks 24 to 36 of 1.3 (0.1) and 1.6 (0.1) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (and SEM) treatment difference was -0.3 (0.1) g/dL with a 95% CI of (-0.5, -0.1). The magnitude of the within group change from baseline was comparable to that seen in trial 0014 in the NDD-CKD population despite about one-half of patients in trial 0016 being treated with ESA prior to enrollment. It is important to note that the change from baseline to the average Hb over

the primary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa.

Although the lower bound of the 95% CI (-0.5) was above the prespecified non-inferiority margin of -0.75 g/dL, the upper bound of the 95% CI was less than 0. However, since the magnitude of difference between the upper bound and zero is very small (i.e., 0.1 g/dL) and this finding was not observed in the analysis of the key secondary efficacy endpoint, the clinical significance of this finding is limited. Therefore, the review team determined this is not a concern. The Applicant's analyses results are shown in Table 41.

Table 41. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population, Trial 0016

Visit Statistics	Vadadustat N=181	Darbepoetin Alfa N=188	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	181	188	
Mean (SD)	9.4 (1.1)	9.2 (1.1)	
Weeks 24 to 36 (observed)			
n	157	171	
Mean (SD)	10.4 (1.1)	10.7 (0.9)	
Weeks 24 to 36 (observed + imputed)			
n	181	188	
Mean (SD)	10.4 (1.1)	10.6 (0.9)	
Change from baseline			
n	181	188	
Mean (SD)	1.0 (1.3)	1.4 (1.4)	
Least squares mean (SEM)	1.3 (0.1)	1.6 (0.1)	-0.3 (0.1)
95% CI	(1.1, 1.5)	(1.4, 1.8)	(-0.5, -0.1)

Source: Study 0016 Clinical Study Report Table 19 (p. 78), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

The Applicant also performed a sensitivity analysis using MMRM with missing at random (MAR) assumption. MMRM results are not shown but they also showed non-inferiority of vadadustat to darbepoetin alfa for the primary endpoint.

Analysis for the Key Secondary Efficacy Endpoint, Trial 0016

The key secondary efficacy endpoint for this study was the change in average Hb values between baseline and the secondary efficacy period (Weeks 40 to 52).

The key secondary endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's efficacy results demonstrated a LS mean (and SEM) change from baseline to the average over Weeks 40 to 52 of 1.4 (0.1) and 1.5 (0.1) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (and SEM) difference between treatment groups was -0.1 (0.1) g/dL with a 95% CI of (-0.3, 0.2). Since the lower bound of the 95% CI (-0.3) was above the prespecified non-inferiority margin of -0.75 g/dL, the non-inferiority of vadadustat to darbepoetin alfa was demonstrated. It is important to note that there was higher use of rescue therapy with vadadustat. The impact of rescue therapy on the non-inferiority conclusion is discussed below and in section II.6.3.1. The analyses results are shown in Table 42.

Table 42. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Randomized Population, Trial 0016

Visit Statistics	Vadadustat N=181	Darbepoetin Alfa N=188	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	181	188	
Mean (SD)	9.4 (1.1)	9.2 (1.1)	
Weeks 40 to 52 (observed)			
n	133	145	
Mean (SD)	10.5 (1.1)	10.6 (1.1)	
Weeks 40 to 52 (observed + imputed)			
n	181	188	
Mean (SD)	10.5 (1.2)	10.6 (1.1)	
Change from baseline			
n	181	188	
Mean (SD)	1.2 (1.4)	1.4 (1.6)	
Least squares mean (SEM)	1.4 (0.1)	1.5 (0.1)	-0.1 (0.1)
95% CI	(1.2, 1.7)	(1.2, 1.8)	(-0.3, 0.2)

Source: Study 0016 Clinical Study Report Table 22 (p. 82), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Similar to the primary endpoint, the Applicant performed a sensitivity analysis using MMRM assuming data missing at random (MAR). The non-inferiority of vadadustat to darbepoetin alfa was also demonstrated for the randomized population for the key secondary endpoint analysis using MMRM (results not shown in this review).

The FDA statistical review team has confirmed the sponsor's primary and key secondary efficacy endpoint results and agreed that trial 0016 demonstrated the non-inferiority of vadadustat to darbepoetin alfa. The change from baseline to the average Hb over the secondary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa. The Applicant's conducted analyses of selected important secondary efficacy endpoints are summarized in section III.16.3.3.

Important Secondary Efficacy Endpoints

Patients in the trial were allowed to receive RBC transfusions or ESA as a rescue therapy. As pre-specified secondary endpoints, the Applicant analyzed the following rescue-based endpoints, whose analysis is essential to determine if there is any impact of rescue therapy on the non-inferiority conclusions:

- Proportion of subjects that received ESA rescue medications, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received ESA rescue medications, using the broad-on-treatment rescue therapy definition, where any exposure to ESA rescue is counted for any reason, as long it is not started after permanent study treatment discontinuation

- Proportion of subjects that received RBC transfusion, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received RBC transfusion, using the broad-on-treatment rescue therapy definition, where any exposure to RBC transfusion is counted for any reason, as long it is not started after permanent study treatment discontinuation

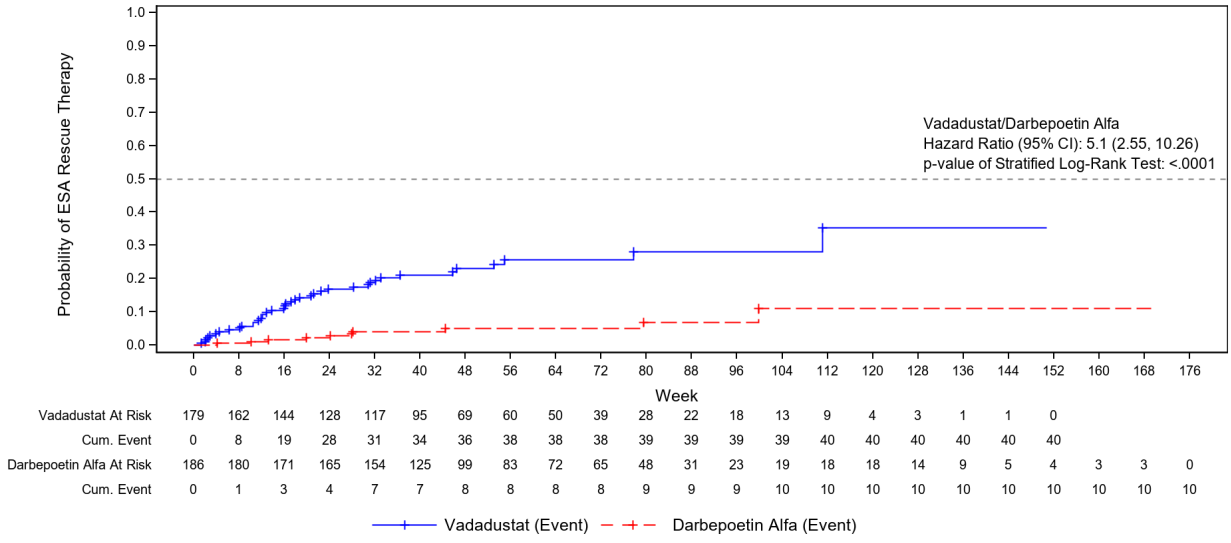
Proportion of Subjects That Received ESA Rescue Medications, Narrow Rescue Therapy

Table 43. Time to ESA Rescue Therapy - Narrow Rescue Therapy (Randomized Population), Trial 0016

Statistics	Vadadustat N=181	Darbepoetin Alfa N=188
Subjects with ESA rescue therapy, n (%)	40 (22.3)	10 (5.4)
Subjects censored, n (%)	139 (77.7)	176 (94.6)
Cumulative incidence (95% CI)		
24 Weeks	0.17 (0.12, 0.23)	0.02 (0.01, 0.06)
36 Weeks	0.20 (0.15, 0.27)	0.04 (0.02, 0.08)
40 Weeks	0.21 (0.15, 0.28)	0.04 (0.02, 0.08)
52 Weeks	0.23 (0.17, 0.31)	0.05 (0.02, 0.10)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	<0.0001	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	5.1 (2.55, 10.26)	

Source: Applicant's analysis in response to submitted information request

Figure 14. Kaplan-Meier Curve of Time to ESA Rescue Therapy- Narrow Rescue Therapy (Randomized Population), Trial 0016



Source: Applicant's analysis in response to submitted information request

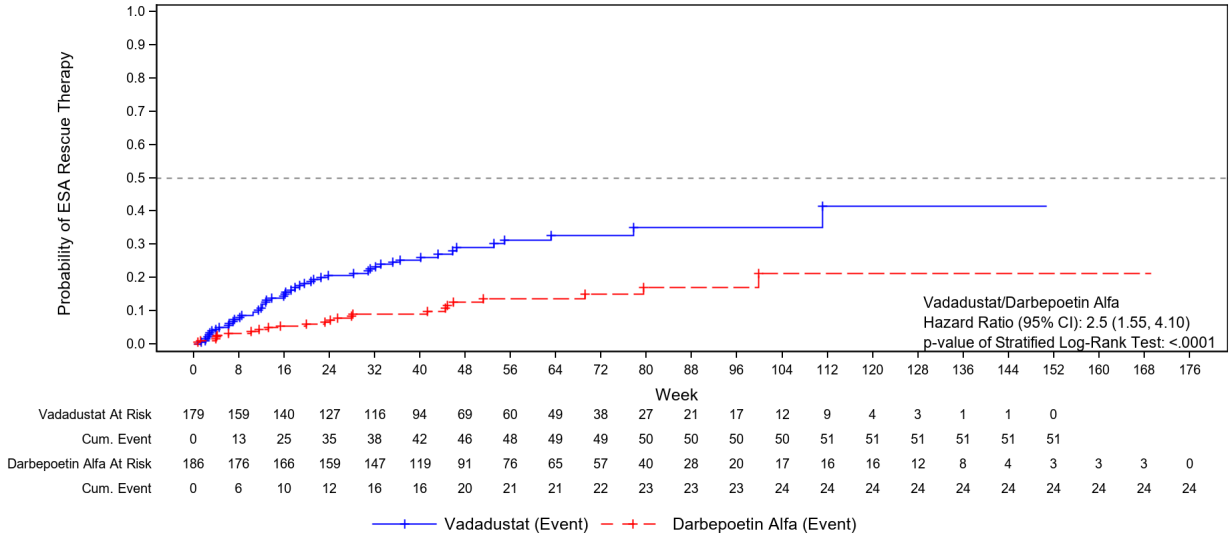
Proportion of Subjects That Received ESA Rescue Medications, Broad-on-Treatment Rescue Therapy

Table 44. Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0016

Statistics	Vadadustat N=181	Darbepoetin Alfa N=188
Subjects with ESA rescue therapy, n (%)	51 (28.5)	24 (12.9)
Subjects censored, n (%)	128 (71.5)	162 (87.1)
Cumulative incidence (95% CI)		
24 Weeks	0.21 (0.15, 0.28)	0.07 (0.04, 0.11)
36 Weeks	0.25 (0.19, 0.32)	0.09 (0.06, 0.14)
40 Weeks	0.25 (0.19, 0.33)	0.09 (0.06, 0.14)
52 Weeks	0.29 (0.23, 0.37)	0.14 (0.09, 0.21)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	<0.0001	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	2.50 (1.55, 4.10)	

Source: Applicant's analysis in response to submitted information request

Figure 15. Kaplan-Meier Curve of Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0016



Source: Applicant's analysis in response to submitted information request

Proportion of Subjects That Received RBC Transfusion, Narrow Rescue Therapy

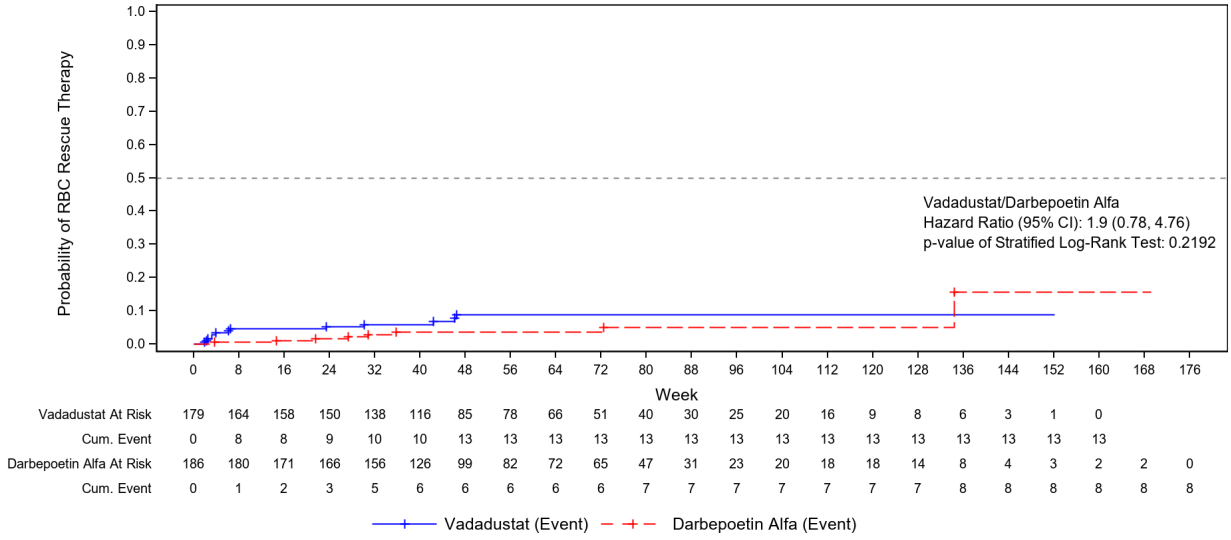
Table 45. Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0016

Statistics	Vadadustat N=181	Darbepoetin Alfa N=188
Subjects with RBC transfusion, n (%)	13 (7.3)	8 (4.3)
Subjects censored, n (%)	166 (92.7)	178 (95.7)
Cumulative incidence (95% CI)		
24 Weeks	0.05 (0.03, 0.10)	0.02 (0.01, 0.05)
36 Weeks	0.06 (0.03, 0.11)	0.04 (0.02, 0.08)

Statistics	Vadadustat N=181	Darbepoetin Alfa N=188
40 Weeks	0.06 (0.03, 0.11)	0.04 (0.02, 0.08)
52 Weeks	0.09 (0.05, 0.15)	0.04 (0.02, 0.08)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.22	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.9 (0.78, 4.76)	

Source: Applicant's analysis in response to submitted information request

Figure 16. Kaplan-Meier Curve of Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0016



Source: Applicant's analysis in response to submitted information request

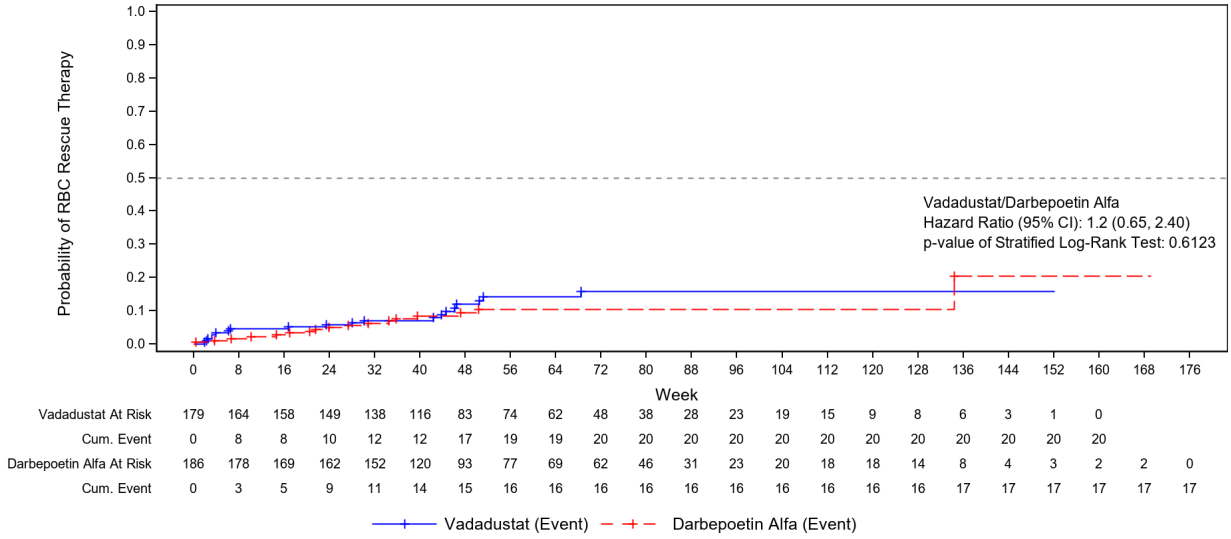
Proportion of Subjects That Received RBC Transfusion, Broad-on-Treatment Rescue Therapy

Table 46. Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0016

Statistics	Vadadustat N=181	Darbepoetin Alfa N=188
Subjects with RBC transfusion, n (%)	20 (11.2)	17 (9.1)
Subjects censored, n (%)	159 (88.8)	169 (90.9)
Cumulative incidence (95% CI)		
24 Weeks	0.06 (0.03, 0.11)	0.05 (0.03, 0.10)
36 Weeks	0.07 (0.04, 0.12)	0.08 (0.04, 0.13)
40 Weeks	0.07 (0.04, 0.12)	0.08 (0.05, 0.14)
52 Weeks	0.14 (0.09, 0.22)	0.10 (0.06, 0.17)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.61	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.2 (0.65, 2.40)	

Source: Applicant's analysis in response to submitted information request

Figure 17. Kaplan-Meier Curve of Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0016



Source: Applicant's analysis in response to submitted information request

Considering rescue therapy use, many more patients in the vadadustat arm recieved ESA rescue therapies than the darbepoetin alfa arm and they received the rescue significantly earlier, which was more apparent when the narrow definition of ESA rescue was used. Although not statistically significant, more patients in the vadadustat arm received RBC transfusions rescue (using either narrow or broad definitions) during the study than those in the darbepoetin alfa arm, which was more apparent when the narrow definition of RBC rescue was used. The Applicant conducted sensitivity analyses for both the primary and key secondary efficacy endpoints to further examine the impact of rescue use, according to the narrow definition, by setting all per-visit hemoglobin values to missing within four weeks after administration rescue therapy and results are consistent with the final Hb analysis results (see section III 16.3.3).

Subgroup Analyses for the Primary Endpoint, Trial 0016

The Applicant conducted subgroup analyses for various demographic and clinical characteristics groups and their results are presented in section III.16.2.3. The statistical reviewer confirmed their findings. Overall, the treatment effect of vadadustat compared to darbepoetin alfa was generally consistent across all prespecified subgroups, including regional subgroup results. However, the sample size for Europe and some subgroups is very small, limiting the ability to identify trends from the subgroup analysis results. In addition, conducting multiple subgroup analyses without any multiplicity adjustment could result in spurious findings due to chance, even if the observed result for one subgroup is seemingly very different from the other subgroups.

As noted previously, the Applicant used U.S.-approved darbepoetin alfa at the U.S. sites and non-U.S. approved darbepoetin alfa at the non-U.S. sites. Therefore, the review team assessed the performance of U.S.-approved and non-U.S.-approved darbepoetin alfa, and the impact, if any, on the conclusion of non-inferiority between vadadustat and darbepoetin alfa (see section II.6.3.2 and III.16.2.5).

6.2.5. Trial AKB-6548-CI-0017

6.2.5.1. Design, Trial 0017

Title

Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects With DD-CKD ($INNO_2VATE$ – Conversion)

Overview and Objectives

Trial 0017 was a multi-center, multi-national, randomized, open-label, sponsor-blinded, active-controlled trial of the efficacy and safety of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in adult subjects with DD-CKD (either peritoneal dialysis or hemodialysis) after conversion from ESA therapy.

The primary objective of this trial was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with DD-CKD.

Trial Design

Eligible subjects discontinued their ESA before the 2nd screening visit, which occurred at a minimum of 4 days from the baseline visit. Randomization took place at the baseline visit, in a 1:1 ratio, where subjects were randomized between receiving vadadustat or darbepoetin alfa. Subjects living in the U.S. received U.S.-approved darbepoetin alfa, while subjects living outside the U.S received non-U.S.-approved darbepoetin alfa. Enrolled subjects were also stratified by the following factors:

- Geographic region (United States versus Europe versus Rest of World)
- New York Heart Association (NYHA) heart failure Class 0 or I versus II or III
- Study entry Hb level (<10 versus ≥10 g/dL), based on the most recent central laboratory Hb measurement prior to the Baseline/Randomization visit

Following randomization, the trial consisted of five periods:

- Screening period (up to eight weeks)
- Conversion period (Weeks 0-23): period for converting to study medication, while maintaining Hb
- Maintenance period (Weeks 24-52): period on study medication during which efficacy will be assessed:
  - Primary evaluation period (Weeks 24-36)
  - Secondary evaluation period (Weeks 40-52)
- Long-term treatment period (Weeks 53-EOT)
- Follow-up period (EOT +4 weeks): subjects who discontinued study drug were followed to EOS to assess MACE.

Hemoglobin was monitored using a point of care device and was assessed with a CBC through the local or central laboratory. Hemoglobin measurements used to decide on study eligibility and

to calculate all efficacy endpoints were obtained using a central laboratory, while hemoglobin measurements used to decide on the need for dose adjustment could be obtained using any one of the three methods listed. Baseline Hb was used to determine study eligibility and was defined as the average of 2 Hb values measured by the central laboratory during the screening period, at least 4 days apart.

The need for dose adjustment was determined according to a treatment-specific dose adjustment algorithm (section III.15), which depended on the geographic location of the patient. In addition, subjects randomized to receive darbepoetin alfa were allowed to have dose adjustment based on the available prescribing information and local standard of care guidelines. The frequency of Hb assessment was every 2 weeks from weeks 0 to 12, every 4 weeks from weeks 12 to 52 and at least every 12 weeks thereafter with every 4-week frequency recommended by the Applicant. More frequent Hb assessments were indicated if modification of dosing or an unscheduled visit occurred due to clinical reasons.

The aim of the dosing strategy was to increase and maintain Hb levels of 10.0 g/dL to 11.0 g/dL in the United States and 10.0 g/dL to 12.0 g/dL outside of the United States throughout the trial. The difference in target Hb levels between the two geographic regions was based on the Agency's previous observation of greater risks for MACE when ESAs were used to target Hb levels greater than 11 g/dL. The use of ESA or RBC transfusion for rescue was allowed, up to the discretion of the investigator, but specific guidelines were provided in the trial protocol. The use of ESA rescue was discouraged if subjects were not experiencing worsening symptoms of anemia and had a Hb < 9.0 g/dL. Concomitant administration of RBC transfusion and study drug was allowed but concomitant administration of ESA rescue and study drug was not allowed. Additional important aspect of trial design and important protocol amendments can be found in section III.15.

There were three committees involved in conducting the trial:

- Executive Steering Committee: Oversaw the study and provided expert input to assure a high scientific standard. Member of the committee were blinded to the randomization and were recognized academic leaders, including those from the field of nephrology and cardiology. Details of the roles and responsibilities of the ESC were described in the ESC charter.
- Independent Data Monitoring Committee: Reviewed and discussed study safety data in an unblinded fashion during regularly scheduled meetings. The IDMC was composed of at least one nephrologist, one cardiologist and one biostatistician. Written records of their meetings and decisions were submitted by the Applicant and reviewed. Details of the roles and responsibilities of the IDMC were described in the IDMC charter.
- Endpoint Adjudication Committee: Independently adjudicated the primary safety endpoints of interest (i.e., all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, thromboembolic events, and hospitalization for heart failure) in a blinded fashion. Members of the committee were independent experts, selected prior to commencement of the trial, with experience and training in adjudication of the primary safety endpoints of interest. Details of the roles and responsibilities of the EAC were described in the EAC charter.

Key Eligibility Criteria

Inclusion criteria:

- At least 18 years of age
- Receiving chronic maintenance dialysis (either peritoneal or hemodialysis) for end-stage kidney disease for at least 12 weeks prior to Screening.
- Currently maintained on ESA therapy, with a dose received within 6 weeks prior to or during Screening.
- Mean Screening Hb between 8.0 and 11.0 g/dL (inclusive) in the United States and between 9.0 and 12.0 g/dL (inclusive) outside of the United States, as determined by the average of 2 Hb values measured by the central laboratory during Screening
- Serum ferritin ≥100 ng/mL and TSAT ≥20% during Screening
- Folate and vitamin B12 measurements ≥ lower limit of normal during Screening
- Understood the procedures and requirements of the study and provided written informed consent and authorization for protected health information disclosure

Exclusion criteria:

- Presented with anemia due to a cause other than CKD or with active bleeding or recent blood loss.
- Subjects with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia.
- RBC transfusion within 8 weeks prior to randomization.
- Anticipated to recover adequate kidney function to no longer require dialysis.
- AST, ALT, or total bilirubin >2.0 × ULN during Screening. Subjects with a history of Gilbert's syndrome were not excluded.
- Uncontrolled hypertension (confirmed DBP >110 mmHg or SBP >180 mmHg) during Screening.
- Severe HF during Screening (NYHA Class IV).
- Acute coronary syndrome (hospitalization for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for HF, or stroke within 12 weeks prior to or during Screening.
- History of active malignancy within 2 years prior to or during Screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ.
- History of DVT or PE within 12 weeks prior to randomization.
- History of hemosiderosis or hemochromatosis.
- History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list were not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis were not excluded).
- Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever was longer), prior to the Screening visit.

- Previous participation in this study, or previous participation in a study with an HIF prolyl-hydroxylase inhibitor other than vadadustat.
- Females who were pregnant or breast-feeding. Women of childbearing potential who were unable or unwilling to use an acceptable method of contraception.
- Non-vasectomized male subjects who were unable or unwilling to use an acceptable method of contraception.
- Any other reason that in the opinion of the investigator would make the subject not suitable for participation in the study.
- Hypersensitivity to darbepoetin alfa or vadadustat, or to any of their excipients.

Study Endpoints:

Primary efficacy endpoint:

- Mean change in Hb between baseline (mean pre-treatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36).

Key secondary efficacy endpoints:

- Mean change in Hb value between baseline (mean pre-treatment Hb) and the secondary evaluation period (Weeks 40-52)

Other secondary efficacy endpoints:

- Proportion of subjects with Hb values within the geography-specific target range during the primary evaluation period (Weeks 24-36)
- Proportion of subjects with Hb values within the geography-specific target range during the secondary evaluation period (Weeks 40-52)
- Proportion of time with Hb values within the target range during the primary evaluation period (Weeks 24-36)
- Proportion of time with Hb values within the target range during the secondary evaluation period (Weeks 40-52)
- Proportion of subjects with Hb increase of >1.0 g/dL from baseline to week 52
- Time to achieve Hb increase of >1.0 g/dL from baseline (censored at week 52)
- Mean change in Hb between baseline (mean pre-treatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36) stratified by pre-baseline ESA exposure
- Proportion of subjects receiving IV iron therapy from baseline to Week 52
- Mean monthly dose of IV elemental iron administered from baseline to Week 52 in subjects who have received IV iron
- ESA rescue
- Dose adjustments from baseline to Week 52
- Proportion of subjects receiving RBC transfusion(s) from baseline to Week 52

Safety endpoints:

- MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke
- Individual components of MACE:
  - All-cause mortality
  - Non-fatal MI
  - Non-fatal stroke

- TE events: ATE, DVT, PE, or VAT
- Hospitalization for HF
- Expanded MACE, defined as all-cause mortality, non-fatal MI, non-fatal stroke, hospitalization for HF, or TE event
- Fatal/non-fatal MI
- Fatal/non-fatal stroke
- Sudden death
- CV death
- Non-CV death
- Hospitalization
- Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
- Hb <8.0 g/dL
- Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
- AEs and SAEs
- Vital signs and clinical laboratory values
- Assessment of adrenal disorders as an AE of special interest, using a MedDRA high-level group term of adrenal gland disorders and MedDRA high-level term adrenal cortex tests

To ensure the ability to evaluate primary efficacy and safety endpoints, study completion was achieved when:

- 631 MACE events were reached in both trial 0016 and trial 0017, representing the DD-CKD trial population, and
- All enrolled subjects completed at least 36 weeks on trial (i.e., visit 13)

6.2.5.2. Statistical Analysis Plan, Trial 0017

Definitions of the Analysis Populations

The analysis populations were defined as follows:

- Randomized population: all subjects randomized. Analyses for this population were based on subjects' randomized treatment.
- Full analysis set (FAS) population: all subjects in the randomized population who received at least 1 dose of study drug and had at least 1 post-dose Hb. Analyses for this population were based on subjects' randomized treatment.
- Safety population: all subjects in the randomized population who received at least 1 dose of study drug. Analysis for this population were based on the actual treatment received. Subjects who received in error some vadadustat and some darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received drug.
- PP population: all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least 1 Hb assessment during the primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviations affecting the primary endpoint analyses (i.e., prior to Week 36). Analyses for this population were based on actual treatment received, as described for the Safety population.

Efficacy analyses utilized the Randomized, FAS, and PP populations while safety analyses (including analyses of MACE) utilized the Safety population. The randomized population was used for major efficacy analyses.

Analysis for the Primary Efficacy Endpoint

According to the Applicant's SAP and CSR, the primary efficacy endpoint is the change in average Hb between baseline and the primary efficacy period (Weeks 24 to 36). The primary analysis model used ANCOVA with multiple imputation. Missing data were imputed based on information of the group to which the subject was randomized. The primary analysis model contains treatment group, baseline Hb level, and two stratification factors (region and NYHA CHF class) as predictor variables. The randomization stratification factor of entry Hb level was not included in the model because of the inclusion of baseline Hb. The single master seed was used to generate all the multiple imputations runs for each trial. The noninferiority of vadadustat to darbepoetin alfa was to be demonstrated if the lower bound of the 95% confidence interval for the difference in estimated change from baseline in the 2 groups (vadadustat minus darbepoetin alfa) exceeded the noninferiority margin of -0.75. This ensures a type I error rate of 0.05 control based on 1-sided alfa of 0.025 for the primary analysis.

Analyses for the Key Secondary Efficacy Endpoint

According to the Applicant's SAP and CSR, the key secondary efficacy endpoint was the change in average Hb value between baseline and the secondary efficacy period (Weeks 40 to 52). Evaluation of the key secondary efficacy endpoint employed the same approach described for the primary endpoint assessing Weeks 40 to 52 instead of Weeks 24 to 36. The power for this endpoint for a noninferiority margin of -0.75 g/dL is expected to be close to the power of the primary endpoint, which is 90%. Similar to the primary endpoint, the Agency recommended the -0.75 non-inferiority margin, which has been used in other applications for treatment of anemia due to chronic kidney disease and is based on preserving at least 50% treatment effect of an ESA in the conversion studies.

Multiple Testing Approach

The key secondary efficacy endpoint was analyzed formally only if the primary analysis met the prespecified non-inferiority margin. The formal testing procedure for the key secondary efficacy endpoint would be stopped if the analysis failed to confirm non-inferiority of the primary efficacy endpoint using a 1-sided significance level of 2.5%.

Method for Handling of Missing Data

Standard multiple imputation of missing values based on the group to which the subject was randomized was used for all analyses for the primary and secondary efficacy outcomes to handle missing data.

6.2.5.3. Results of Analyses, Trial 0017

This section summarizes subjects' baseline demographics and clinical characteristics, disposition data, and major efficacy results for the maintenance treatment of anemia in subjects with DD-CKD from trial 0017.

Baseline Demographics and Clinical Characteristics, Trial 0017

Baseline Demographics of the randomized population data are summarized by treatment group in Table 47. Subjects' demographic characteristics were generally balanced between treatment groups.

Table 47. Baseline Demographic, Randomized Population, Trial 0017

Characteristics	Vadadustat N=1777	Darbepoetin Alfa N=1777	Total N=3554
Age[1] (Years)			
n	1777	1777	3554
Mean (SD)	57.9 (13.9)	58.4 (13.8)	58.1 (13.9)
Age category, n (%)			
<65 years	1167 (65.7)	1161 (65.3)	2328 (65.5)
≥65 years	610 (34.3)	616 (34.7)	1226 (34.5)
Sex, n (%)			
Male	990 (55.7)	1004 (56.5)	1994 (56.1)
Female	787 (44.3)	773 (43.5)	1560 (43.9)
Ethnicity, n (%)			
Hispanic or Latino	682 (38.4)	674 (37.9)	1356 (38.2)
Not Hispanic or Latino	1043 (58.7)	1040 (58.5)	2083 (58.6)
Not reported	36 (2.0)	47 (2.6)	83 (2.3)
Unknown	16 (0.9)	16 (0.9)	32 (0.9)
Race, n (%)			
American Indian or Alaska Native	19 (1.1)	30 (1.7)	49 (1.4)
Asian	76 (4.3)	99 (5.6)	175 (4.9)
Black or African American	432 (24.3)	444 (25.0)	876 (24.6)
Native Hawaiian or Pacific Islander	13 (0.7)	6 (0.3)	19 (0.5)
White	1135 (63.9)	1096 (61.7)	2231 (62.8)
Not Reported	52 (2.9)	52 (2.9)	104 (2.9)
Other	42 (2.4)	45 (2.5)	87 (2.4)
Multiple	8 (0.5)	5 (0.3)	13 (0.4)
Country, n (%)			
Argentina	36 (2.0)	52 (2.9)	88 (2.5)
Australia	17 (1.0)	21 (1.2)	38 (1.1)
Brazil	155 (8.7)	152 (8.6)	307 (8.6)
Bulgaria	102 (5.7)	106 (6.0)	208 (5.9)
Canada	25 (1.4)	23 (1.3)	48 (1.4)
France	18 (1.0)	22 (1.2)	40 (1.1)
Germany	6 (0.3)	11 (0.6)	17 (0.5)
Israel	14 (0.8)	18 (1.0)	32 (0.9)
Italy	4 (0.2)	8 (0.5)	12 (0.3)
Mexico	15 (0.8)	11 (0.6)	26 (0.7)
Poland	41 (2.3)	35 (2.0)	76 (2.1)
Portugal	12 (0.7)	18 (1.0)	30 (0.8)
Republic of Korea	45 (2.5)	47 (2.6)	92 (2.6)
Russian Federation	53 (3.0)	39 (2.2)	92 (2.6)
Serbia	66 (3.7)	65 (3.7)	131 (3.7)
Ukraine	73 (4.1)	47 (2.6)	120 (3.4)
United Kingdom	5 (0.3)	16 (0.9)	21 (0.6)
United States	1090 (61.3)	1086 (61.1)	2176 (61.2)
Height (cm)			
n	1749	1749	3498
Mean (SD)	167.4 (10.8)	167.0 (10.6)	167.2 (10.7)

Weight (kg)			
n	1753	1762	3515
Mean (SD)	80.3 (21.8)	80.0 (22.0)	80.1 (21.9)
BMI (kg/m^2)			
n	1730	1737	3467
Mean (SD)	28.6 (7.2)	28.6 (7.2)	28.6 (7.2)

Source: Study 0017 Clinical Study Report Table 11 (p. 63)
[1] Reported age on the case report forms.
[2] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
Abbreviations: BMI, body mass index; N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Subjects' baseline clinical characteristics of the randomized population are summarized by treatment group in Table 48.

Table 48. Baseline Clinical Characteristics, Randomized Population, Trial 0017

Characteristics	Vadadustat N=1777	Darbepoetin Alfa N=1777	Total N=3554
Randomization stratification factors, n (%)			
Region of enrollment[1]			
United States	1090 (61.3)	1086 (61.1)	2176 (61.2)
Europe	254 (14.3)	281 (15.8)	535 (15.1)
Rest of World	433 (24.4)	410 (23.1)	843 (23.7)
New York Heart Association HF Class			
Class 0 (no HF) or I	1545 (86.9)	1547 (87.1)	3092 (87.0)
Class II or III	232 (13.1)	230 (12.9)	462 (13.0)
Central lab baseline Hb category			
<10 g/dL	620 (34.9)	619 (34.8)	1239 (34.9)
≥10 g/dL	1157 (65.1)	1158 (65.2)	2315 (65.1)
IV iron, ESA & transfusion history, n (%)			
IV iron use prior to first dose of study drug			
Yes	1372 (77.3)	1326 (74.7)	2698 (76.0)
No	402 (22.7)	449 (25.3)	851 (24.0)
Missing	3	2	5
Received a transfusion within 8 weeks of screening period prior to randomization through to the first dose of study drug			
Yes	31 (1.7)	29 (1.6)	60 (1.7)
No	1746 (98.3)	1748 (98.4)	3494 (98.3)
Baseline ESA use, n (%)			
N	1765	1774	3539
Epoetin	970 (55.0)	967 (54.5)	1937 (54.7)
Darbepoetin Alfa	484 (27.4)	521 (29.4)	1005 (28.4)
Methoxy polyethylene glycol-epoetin β	311 (17.6)	286 (16.1)	597 (16.9)
Baseline ESA dose (U/kg/week), n (%)			
n	1742	1759	3501
Mean (SD)	117 (109)	112 (110)	114 (110)
≤90 U/kg/week	916 (52.6)	968 (55.0)	1884 (53.8)
>90 and <300 U/kg/week	724 (41.6)	693 (39.4)	1417 (40.5)
≥300 U/kg/week	102 (5.9)	98 (5.6)	200 (5.7)
Baseline iron use[2], n (%)			
0 - subjects not receiving any iron	660 (37.1)	721 (40.6)	1381 (38.9)
I - subjects receiving oral iron only	123 (6.9)	118 (6.6)	241 (6.8)
II - subjects receiving IV iron only	911 (51.3)	853 (48.0)	1764 (49.6)
III - subjects receiving IV and oral iron	83 (4.7)	85 (4.8)	168 (4.7)

Baseline IV iron dose (mg/week)			
n	610	560	1170
Mean (SD)	114 (257)	145 (475)	129 (378)
Baseline oral iron dose (mg/week)			
n	156	159	315
Mean (SD)	3684.4 (10026)	2712 (3649)	3193 (7520)
Diabetes mellitus, n (%)			
Yes	971 (54.6)	998 (56.2)	1969 (55.4)
No	806 (45.4)	779 (43.8)	1585 (44.6)
History of cardiovascular disease[3], n (%)			
Yes	868 (48.8)	932 (52.4)	1800 (50.6)
No	909 (51.2)	845 (47.6)	1754 (49.4)
History of retinal disorder, n (%)			
Yes	304 (17.1)	362 (20.4)	666 (18.7)
No	1473 (82.9)	1415 (79.6)	2888 (81.3)
Years since chronic dialysis initiated[4]			
n	1775	1777	3552
Mean (SD)	4.0 (4.0)	3.9 (4.0)	4.0 (4.0)
Baseline systolic blood pressure (mmHg)			
n	1777	1777	3554
Mean (SD)	143 (23)	143 (22)	143 (23)
Baseline diastolic blood pressure (mmHg)			
n	1777	1777	3554
Mean (SD)	76 (13)	76 (13)	76 (13)
Baseline heart rate (beats/min)			
n	1774	1776	3550
Mean (SD)	75 (11)	75 (12)	75 (11)

Source: Study 0017 Clinical Study Report Table 12 (p. 64)
Note: The percentage is calculated based on the number of subjects with non-missing data.
[1] Regions are defined by geographical location. Listing of countries can be found inn section III.17.4.2.
[2] ESA doses were converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin alfa to IV epoetin was 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin was 1:220; subcutaneous epoetin to IV epoetin was 1:1.25.
[3] Cardiovascular (CV) disease included coronary artery disease, myocardial infarction, stroke, and HF.
[4] The handling of the partial date of chronic dialysis initiated: If day was missing, day was set to 15th of the month. If month was missing, month and day were set to Jul 1. If year was missing, date was missing. Years since chronic dialysis initiated was calculated based on date of chronic dialysis initiated and date of Screening 1.
Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HF, heart failure; IV, intravenous; N, number of subjects; n, number of subjects within specific category; SD, standard deviation

Disposition, Trial 0017

Subject disposition information for Trial 0017 is summarized in Table 49 and Table 50.

A total of 4944 subjects were screened for entry into Trial 0017. Of these, 1390 subjects failed screening and 3554 subjects were enrolled and randomized in the study. The majority of subjects who failed screening did not meet one or more inclusion/exclusion criteria, with no specific pattern detected upon analysis. Of subjects randomized, 3537 subjects were included in the Safety population, and 3514 subjects were included in the FAS population. Overall, a lower percentage of each treatment group qualified for the per protocol population, with a much lower percentage (62.8% versus 81.1%) in the vadadustat treatment group than the control group of darbepoetin alfa.

Similar proportions of subjects in the vadadustat and darbepoetin alfa treatment groups completed the study. The incidence of discontinuations of study drug treatment (but continuing to be followed in the trial) was higher (899 [50.6%]) in the vadadustat treatment group compared with the darbepoetin alfa treatment group (653 [36.8%]). The primary reasons for discontinuation of study drug in the vadadustat treatment group were subjects no longer wants to

receive study drug (17.7%), death (8.3%) and subject receiving a kidney transplant (6.5%). The primary reasons for discontinuation of study drug in the darbepoetin alfa treatment group were subject no longer wants to receive study drug (12.3%), death (10.1%) and subject receiving a kidney transplant (5.7%).

Table 49. Patient Screening and Randomization, Trial 0017

Disposition	Value
No. subjects screened	4944
No. subjects not randomized	1390
No. screening failures	1390/4944 (28.1%)
No. subjects randomized	3554

Source: Study 0017 Clinical Study Report Figure 2 (p. 57)

Table 50. Subject Disposition, Trial 0017

Disposition Category	Vadadustat N=1777 n (%)	Darbepoetin Alfa N=1777 n (%)	Relative Risk	Risk Difference (%)
Subjects randomized	1777 (100)	1777 (100)	NA	NA
ITT/mITT population	1755 (98.8)	1759 (99.0)	NA	NA
Per protocol population	1116 (62.8)	1441 (81.1)	NA	NA
Safety population	1768 (99.5)	1769 (99.5)	NA	NA
Completed study drug	878 (49.4)	1124 (63.3)	0.78	-13.8
Discontinued study drug	899 (50.6)	653 (36.8)	1.38	13.8
Death	147 (8.3)	180 (10.1)	0.82	-1.9
Kidney transplant	116 (6.5)	102 (5.7)	1.14	0.8
Adverse event[1]	115 (6.5)	66 (3.7)	1.74	2.8
Lack of efficacy	70 (3.9)	6 (0.3)	11.67	3.6
Decision to Switch to ESA	3 (0.2)	1 (0.1)	3.00	0.1
Investigator's Decision[2]	95 (5.4)	45 (2.5)	2.11	2.8
Lack of Compliance	9 (0.5)	1 (0.1)	9.00	0.5
Lost to follow-up	8 (0.5)	9 (0.5)	0.89	-0.1
Global termination[3]/Sponsor Decision	12 (0.7)	16 (0.9)	0.75	-0.2
Patient wishes[4]	315 (17.7)	219 (12.3)	1.44	5.4
Completed study	1423 (80.1)	1419 (79.9)	1.00	0.2
Discontinued study	345 (19.4)	350 (19.7)	0.99	-0.3
Death	262 (14.7)	277 (15.6)	0.95	-0.8
Lost to follow-up	38 (2.1)	32 (1.8)	1.19	0.3
Kidney transplant	3 (0.2)	3 (0.2)	1.00	0
Patient wishes	38 (2.1)	37 (2.1)	1.03	0.1
Adverse event	2 (0.1)	1 (0.1)	2.00	0.1
Lack of efficacy	2 (0.1)	0 (0)	-	0.1

Source: SDTM datasets; Software: JMP
Abbreviation: FAS, full analysis set; ITT, intent to treat; mITT, modified intent to treat; N, number of subjects; n, number of subjects with at least one event
Note: Percentages were calculated based on all randomized subjects.
1, Discontinuation due to adverse events included discontinuation of study drug due unacceptable toxicity, drug tolerability and adverse events.
2, The investigator's decision to discontinue study drug was not due to occurrence of an adverse event. Further details were not provided by the Applicant.
3, When the target number of MACE was reached, global study termination was initiated, resulting in discontinuation of study drug and conducting end-of-study visits in all on-study subjects, regardless of their current study period status.
4, Patient wishes, as a reason for discontinuation of study drug, were not due to occurrence of an adverse event. In the majority of cases, discontinuation of study drug was associated with practical inconveniences of being enrolled on study, due to social external circumstances or not specified.

Analysis for the Primary Efficacy Endpoint, Trial 0017

The primary efficacy endpoint for this study was the change in average Hb between baseline and the primary efficacy period (Weeks 24 to 36).

The primary efficacy endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's primary efficacy results demonstrated a LS mean (and SEM) change from baseline to the average Hb over Weeks 24 to 36 of 0.2 (0) and 0.4 (0) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (and SEM) treatment difference was -0.2 (0) g/dL with a 95% CI of (-0.2, -0.1). The magnitude of change from baseline was small because subjects enrolled in trial 0017 were treated with ESA prior to enrollment. It is important to note that the change from baseline to the average Hb over the primary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa.

Although the lower bound of the 95% CI (-0.2) was above the prespecified non-inferiority margin of -0.75 g/dL, the upper bound of the 95% CI is less than 0. However, since the magnitude of difference between the upper bound and zero is very small (i.e., 0.1 g/dL), the clinical significance of this finding is limited. Therefore, the review team determined this is not a concern. The Applicant's analyses results are shown in Table 51.

Table 51. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population, Trial 0017

Visit Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	1777	1777	
Mean (SD)	10.3 (0.9)	10.23 (0.83)	
Weeks 24 to 36 (observed)			
n	1573	1623	
Mean (SD)	10.4 (1.0)	10.6 (1.0)	
Weeks 24 to 36 (observed + imputed)			
n	1777	1777	
Mean (SD)	10.4 (1.0)	10.5 (1.0)	
Change from baseline			
n	1777	1777	
Mean (SD)			
Least squares mean (SEM)	0.2 (0)	0.4 (0)	-0.2 (0)
95% CI	(0.1, 0.3)	(0.3, 0.4)	(-0.2, -0.1)

Source: Study 0017 Clinical Study Report Table 20 (p.78), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

The Applicant also performed a sensitivity analysis using MMRM with missing at random (MAR) assumption. MMRM results are not shown but they also showed non-inferiority of vadadustat to darbepoetin alfa for the primary endpoint.

Analysis for the Key Secondary Efficacy Endpoint, Trial 0017

The key secondary efficacy endpoint for this study was the change in average Hb levels between baseline and the secondary efficacy period (Weeks 40 to 52).

The key secondary endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's efficacy results demonstrated a LS mean (and SEM) change from baseline to the average over Weeks 40 to 52 of 0.2 (0) and 0.4 (0) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (and SEM) difference between treatment groups was -0.2 (0) g/dL with a 95% CI of (-0.3, -0.1). It is important to note that the change from baseline to the average Hb over the secondary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa.

Although the lower bound of the 95% CI (-0.3) was above the prespecified non-inferiority margin of -0.75 g/dL, the upper bound of the 95% CI is less than 0. However, since the magnitude of difference between the upper bound and zero is very small (i.e., 0.1 g/dL), the clinical significance of this finding is limited. Therefore, the review team determined this is not a concern. The Applicant's analyses results are shown in Table 52.

Table 52. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Randomized Population, Trial 0017

Visit Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	1777	1777	
Mean (SD)	10.3 (0.9)	10.2 (0.8)	
Weeks 40 to 52 (observed)			
n	1451	1515	
Mean (SD)	10.4 (1.0)	10.6 (1.0)	
Weeks 40 to 52 (observed + imputed)			
n	1777	1777	
Mean (SD)	10.4 (1.0)	10.6 (1.0)	
Change from baseline			
n	1777	1777	
Mean (SD)	0.2 (1.2)	0.4 (1.1)	
Least squares mean (SEM)	0.2 (0)	0.4 (0)	-0.2 (0)
95% CI	(0.2, 0.3)	(0.3, 0.5)	(-0.3, -0.1)

Source: Study 0017 Clinical Study Report Table 23 (p. 82), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Similar to the primary endpoint, the Applicant performed a sensitivity analysis using MMRM assuming data missing at random (MAR). The non-inferiority of vadadustat to darbepoetin alfa was also demonstrated for the randomized population for the key secondary endpoint analysis using MMRM (results not shown in this review).

The FDA statistical review team has confirmed the sponsor's primary and key secondary efficacy endpoint results and agreed that Trial 0017 demonstrated the non-inferiority of vadadustat to darbepoetin alfa. The Applicant's conducted analyses of selected important secondary efficacy endpoints are summarized in section III.16.3.4.

Important Secondary Efficacy Endpoints

Patients in the trial were allowed to receive RBC transfusions or ESA as a rescue therapy. As pre-specified secondary endpoints, the Applicant analyzed the following rescue-based endpoints,

whose analysis is essential to determine if there is any impact of rescue therapy on the non-inferiority conclusions:

- Proportion of subjects that received ESA rescue medications, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received ESA rescue medications, using the broad-on-treatment rescue therapy definition, where any exposure to ESA rescue is counted for any reason, as long it is not started after permanent study treatment discontinuation
- Proportion of subjects that received RBC transfusion, using the narrow rescue therapy definition, where rescue is given for worsening anemia (see section 15 for details), not starting after permanent study treatment discontinuation.
- Proportion of subjects that received RBC transfusion, using the broad-on-treatment rescue therapy definition, where any exposure to RBC transfusion is counted for any reason, as long it is not started after permanent study treatment discontinuation

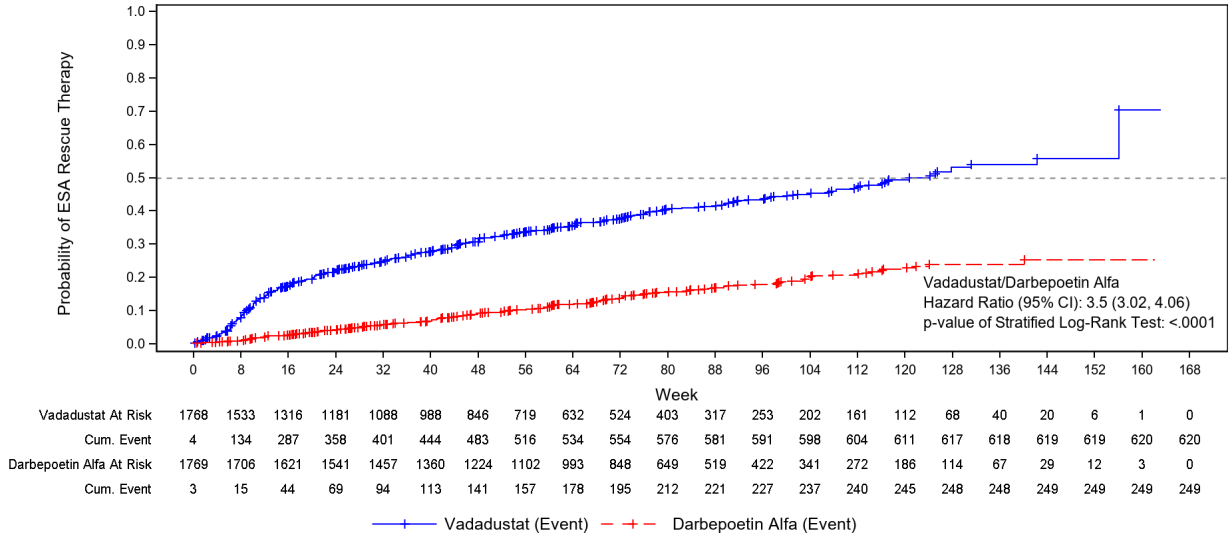
Proportion of Subjects That Received ESA Rescue Medications, Narrow Rescue Therapy

Table 53. Time to ESA Rescue Therapy - Narrow Rescue Therapy (Randomized Population), Trial 0017

Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777
Subjects with ESA rescue therapy, n (%)	620 (35.1)	249 (14.1)
Subjects censored, n (%)	1148 (64.9)	1520 (85.9)
Cumulative incidence (95% CI)		
24 Weeks	0.22 (0.20, 0.24)	0.04 (0.03, 0.05)
36 Weeks	0.26 (0.24, 0.28)	0.06 (0.05, 0.08)
40 Weeks	0.28 (0.26, 0.30)	0.07 (0.06, 0.08)
52 Weeks	0.32 (0.30, 0.35)	0.10 (0.08, 0.11)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	<0.0001	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	3.5 (3.02, 4.06)	

Source: Applicant's analysis in response to submitted information request

Figure 18. Kaplan-Meier Curve of Time to ESA Rescue Therapy- Narrow Rescue Therapy (Randomized Population), Trial 0017



Source: Applicant's analysis in response to submitted information request

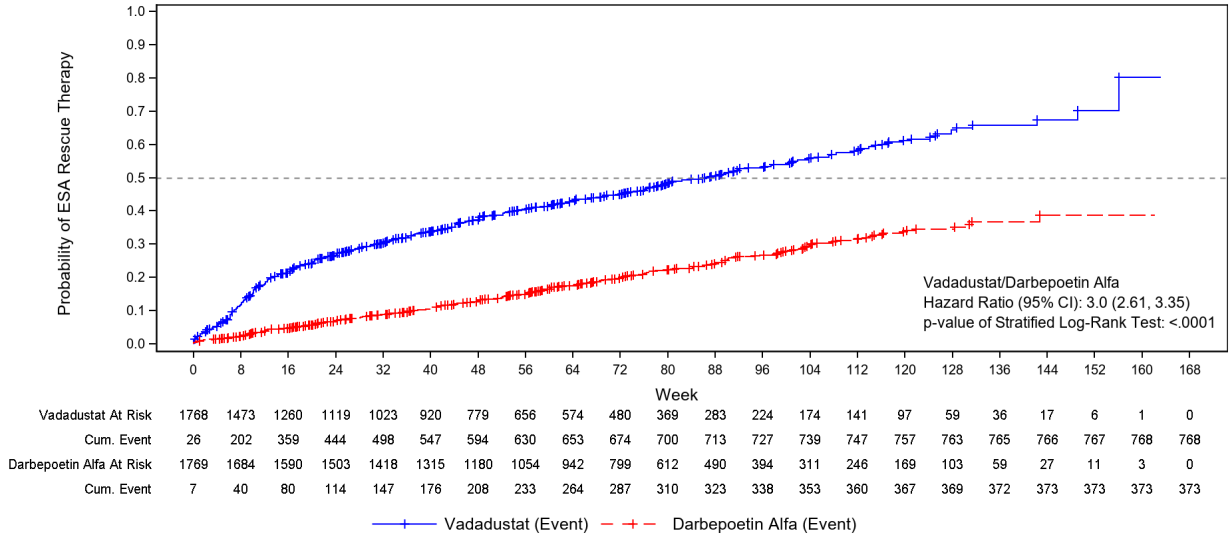
Proportion of Subjects That Received ESA Rescue Medications, Broad-on-Treatment Rescue Therapy

Table 54. Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0017

Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777
Subjects with ESA rescue therapy, n (%)	768 (43.4)	373 (21.1)
Subjects censored, n (%)	1000 (56.6)	1396 (78.9)
Cumulative incidence (95% CI)		
24 Weeks	0.27 (0.25, 0.29)	0.07 (0.06, 0.08)
36 Weeks	0.32 (0.30, 0.34)	0.10 (0.08, 0.11)
40 Weeks	0.34 (0.31, 0.36)	0.11 (0.09, 0.12)
52 Weeks	0.39 (0.36, 0.41)	0.14 (0.12, 0.16)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	<0.0001	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	3.0 (2.61, 3.35)	

Source: Applicant's analysis in response to submitted information request

Figure 19. Kaplan-Meier Curve of Time to ESA Rescue Therapy - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0017



Source: Applicant's analysis in response to submitted information request

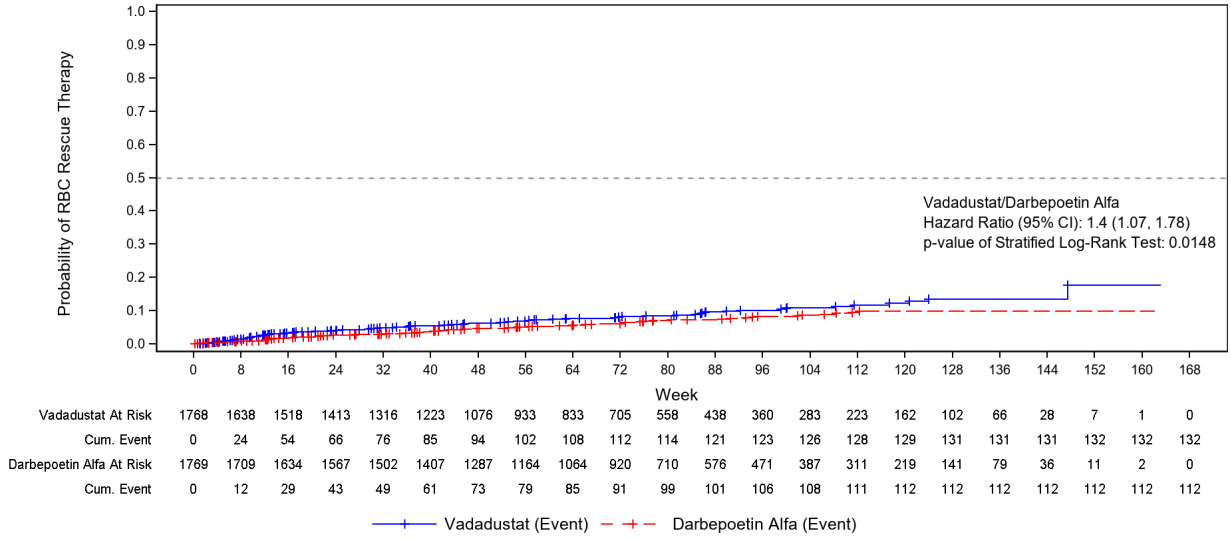
Proportion of Subjects That Received RBC Transfusion, Narrow Rescue Therapy

Table 55. Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0017

Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777
Subjects with RBC transfusion, n (%)	132 (7.5)	112 (6.3)
Subjects censored, n (%)	1636 (92.5)	1657 (93.7)
Cumulative incidence (95% CI)		
24 Weeks	0.04 (0.03, 0.05)	0.03 (0.02, 0.03)
36 Weeks	0.05 (0.04, 0.06)	0.03 (0.02, 0.04)
40 Weeks	0.05 (0.04, 0.07)	0.04 (0.03, 0.05)
52 Weeks	0.06 (0.05, 0.08)	0.05 (0.04, 0.06)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.01	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.4 (1.07, 1.78)	

Source: Applicant's analysis in response to submitted information request

Figure 20. Kaplan-Meier Curve of Time to RBC Transfusion - Narrow Rescue Therapy (Randomized Population), Trial 0017



Source: Applicant's analysis in response to submitted information request

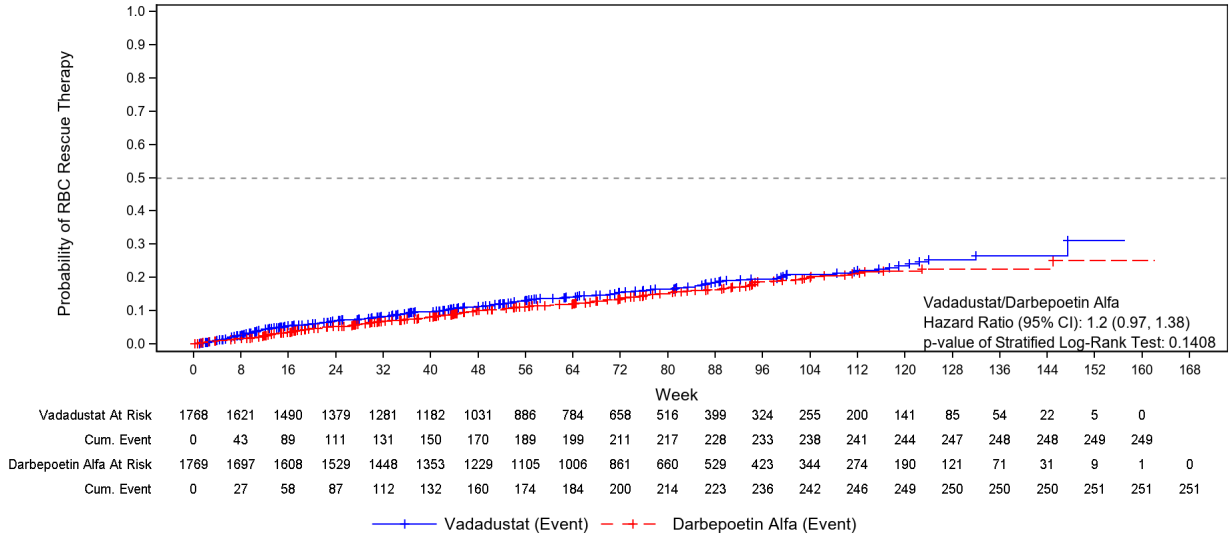
Proportion of Subjects That Received RBC Transfusion, Broad-on-Treatment Rescue Therapy

Table 56. Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0017

Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777
Subjects with red blood cell transfusion, n (%)	249 (14.0)	251 (14.1)
Subjects censored, n (%)	1528 (86)	1526 (85.9)
Cumulative incidence (95% CI)		
24 Weeks	0.07 (0.06, 0.08)	0.05 (0.04, 0.06)
36 Weeks	0.09 (0.08, 0.11)	0.07 (0.06, 0.09)
40 Weeks	0.10 (0.08, 0.11)	0.08 (0.07, 0.09)
52 Weeks	0.12 (0.10, 0.14)	0.10 (0.09, 0.12)
Treatment comparison		
Nominal p-value of Stratified Log-Rank Test	0.14	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.20 (0.97, 1.38)	

Source: Applicant's analysis in response to submitted information request

Figure 21. Kaplan-Meier Curve of Time to RBC Transfusion - Broad-on-Treatment Rescue Therapy (Randomized Population), Trial 0017



Source: Applicant's analysis in response to submitted information request

Similar to Study 0016, many more patients in the vadadustat arm received ESA rescue therapies than those in the darbepoetin alfa arm and they received rescue significantly earlier, which was more apparent when the narrow definition of ESA rescue was used. Although not statistically significant, more patients in the vadadustat arm received RBC transfusions rescue (using either narrow or broad definitions) during the study than those in darbepoetin alfa, which was more apparent when the narrow definition of ESA rescue was used (HR 1.4 for narrow definition and 1.2 for broad definition).The Applicant conducted sensitivity analyses for both the primary and key secondary efficacy endpoints to further examine the impact of rescue use, according to the narrow definition, by setting all per-visit hemoglobin values to missing within four weeks after administration rescue therapy and results are consistent with the final Hb analysis results (see III16.3.4).

Subgroup Analyses for the Primary Endpoint, Trial 0017

The Applicant conducted subgroup analyses for various demographic and clinical characteristics groups and their results are presented in section III.16.2.4. The statistical reviewer confirmed their findings. Overall, the treatment effect of vadadustat compared to darbepoetin alfa appeared consistent across all prespecified subgroups including regional subgroups as well as their darbepoetin alfa arm's performance (see section II.6.3.2 and III.16.2.5). However, the sample sizes for some subgroups were small and thus the ability to identify trends from the subgroup analysis results is limited. In addition, conducting multiple subgroup analyses without any multiplicity adjustment could result in spurious findings due to chance, even if the observed result for one subgroup is seemingly very different from the other subgroups.

6.2.6. Results of Analyses for the DD Trials, Trials 0016 and 0017

This section gives a side-by-side comparison between Trials 0016 and 0017, in relation to baseline demographics and clinical characteristics, subject disposition, and primary analyses

results for the primary and the key secondary efficacy endpoints to support the efficacy of oral vadadustat in subjects with DD-CKD.

Baseline Demographics and Clinical Characteristics, Trial 0016 and 0017

Baseline demographics of the randomized population for Trials 0016 and 0017 are summarized by treatment group in Table 57.

Table 57. Baseline Demographic, Randomized Population, Trials 0016 and 0017

	Trial 0016		Trial 0017	
Characteristics	Vadadustat N=181	Darbepoetin Alfa N=188	Vadadustat N=1777	Darbepoetin Alfa N=1777
Age[1] (Years)				
n	181	188	1777	1777
Mean (SD)	56.5 (14.80)	55.6 (14.60)	57.9 (13.86)	58.4 (13.84)
Age category, n (%)				
<65 years	122 (67.4)	137 (72.9)	1167 (65.7)	1161 (65.3)
≥65 years	59 (32.6)	51 (27.1)	610 (34.3)	616 (34.7)
Sex, n (%)				
Male	107 (59.1)	113 (60.1)	990 (55.7)	1004 (56.5)
Female	74 (40.9)	75 (39.9)	787 (44.3)	773 (43.5)
Ethnicity, n (%)				
Hispanic or Latino	71 (39.2)	66 (35.1)	682 (38.4)	674 (37.9)
Not Hispanic or Latino	104 (57.5)	118 (62.8)	1043 (58.7)	1040 (58.5)
Not reported	5 (2.8)	3 (1.6)	36 (2.0)	47 (2.6)
Unknown	1 (0.6)	1 (0.5)	16 (0.9)	16 (0.9)
Race, n (%)				
American Indian or Alaska Native	1 (0.6)	0	19 (1.1)	30 (1.7)
Asian	12 (6.6)	8 (4.3)	76 (4.3)	99 (5.6)
Black or African American	38 (21.0)	35 (18.6)	432 (24.3)	444 (25.0)
Native Hawaiian or Pacific Islander	0	0	13 (0.7)	6 (0.3)
White	129 (71.3)	143 (76.1)	1135 (63.9)	1096 (61.7)
Not reported	0	1 (0.5)	52 (2.9)	52 (2.9)
Other	0	1 (0.5)	42 (2.4)	45 (2.5)
Multiple	1 (0.6)	0	8 (0.5)	5 (0.3)
Country, n (%)				
Argentina	3 (1.7)	5 (2.7)	36 (2.0)	52 (2.9)
Australia	--	--	17 (1.0)	21 (1.2)
Brazil	18 (9.9)	20 (10.6)	155 (8.7)	152 (8.6)
Bulgaria	--	--	102 (5.7)	106 (6.0)
Canada	--	--	25 (1.4)	23 (1.3)
France	--	--	18 (1.0)	22 (1.2)
Germany	0	0	6 (0.3)	11 (0.6)
Israel	--	--	14 (0.8)	18 (1.0)
Italy	6 (3.3)	1 (0.5)	4 (0.2)	8 (0.5)
Mexico	1 (0.6)	0	15 (0.8)	11 (0.6)
Poland	11 (6.1)	9 (4.8)	41 (2.3)	35 (2.0)
Portugal	9 (5.0)	6 (3.2)	12 (0.7)	18 (1.0)
Republic of Korea	6 (3.3)	3 (1.6)	45 (2.5)	47 (2.6)
Russian Federation	4 (2.2)	6 (3.2)	53 (3.0)	39 (2.2)
Serbia	--	--	66 (3.7)	65 (3.7)
Ukraine	26 (14.4)	36 (19.1)	73 (4.1)	47 (2.6)
United Kingdom	--	--	5 (0.3)	16 (0.9)

Characteristics	Trial 0016 Vadadustat N=181	Trial 0016 Darbepoetin Alfa N=188	Trial 0017 Vadadustat N=1777	Trial 0017 Darbepoetin Alfa N=1777
United States	97 (53.6)	102 (54.3)	1090 (61.3)	1086 (61.1)
Height (cm)				
n	178	184	1749	1749
Mean (SD)	167.6 (10.7)	166.9 (9.0)	167.4 (10.8)	167.0 (10.6)
Weight (kg)				
n	177	184	1753	1762
Mean (SD)	77.9 (20.6)	77.6 (19.7)	80.3 (21.8)	80.0 (22.0)
BMI (kg/m^2)				
n	174	181	1730	1737
Mean (SD)	27.6 (6.1)	27.5 (6.0)	28.6 (7.2)	28.6 (7.2)

Source: Study 0016 Clinical Study Report Table 11 (p. 64); Study 0017 Clinical Study Report Table 11 (p. 63)
[1] Reported age on the case report forms.
[2] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
Abbreviations: N, number of subjects; n, number of subjects within specific category; SD, standard deviation; --: not applicable

Baseline clinical characteristics of the randomized population for Trials 0016 and 0017 are summarized by treatment group in Table 58.

Table 58. Baseline Clinical Characteristics, Randomized Population, Trials 0016 and 0017

Characteristics	Trial 0016 Vadadustat N=181	Trial 0016 Darbepoetin Alfa N=188	Trial 0017 Vadadustat N=1777	Trial 0017 Darbepoetin Alfa N=1777
Randomization stratification factors, n (%)				
Region of enrollment[1]				
United States	97 (53.6)	102 (54.3)	1090 (61.3)	1086 (61.1)
Europe	26 (14.4)	16 (8.5)	254 (14.3)	281 (15.8)
Rest of World	58 (32.0)	70 (37.2)	433 (24.4)	410 (23.1)
New York Heart Association HF Class				
Class 0 (no HF) or I	162 (89.5)	162 (86.2)	1545 (86.9)	1547 (87.1)
Class II or III	19 (10.5)	26 (13.8)	232 (13.1)	230 (12.9)
Central lab baseline Hb category				
<9.5 g/dL for 0016 / <10 g/dL for 0017	94 (51.9)	99 (52.7)	620 (34.9)	619 (34.8)
≥9.5 g/dL for 0016 / ≥10 g/dL for 0017	87 (48.1)	89 (47.3)	1157 (65.1)	1158 (65.2)
IV iron, ESA & transfusion history, n (%)				
IV iron use prior to first dose of study drug				
Yes	119 (65.7)	140 (74.5)	1372 (77.3)	1326 (74.7)
No	62 (34.3)	48 (25.5)	402 (22.7)	449 (25.3)
Missing	--	--	3	2
Received a transfusion within 8 weeks of screening period prior to randomization through to the first dose of study drug				
Yes	6 (3.3)	9 (4.8)	31 (1.7)	29 (1.6)
No	175 (96.7)	179 (95.2)	1746 (98.3)	1748 (98.4)
Baseline ESA use, n (%)				
n	92	85	1765	1774
Epoetin	54 (58.7)	44 (51.8)	970 (55.0)	967 (54.5)
Darbepoetin Alfa	18 (19.6)	21 (24.7)	484 (27.4)	521 (29.4)
Methoxy polyethylene glycol-epoetin β	20 (21.7)	20 (23.5)	311 (17.6)	286 (16.1)

Characteristics	Trial 0016 Vadadustat N=181	Trial 0016 Darbepoetin Alfa N=188	Trial 0017 Vadadustat N=1777	Trial 0017 Darbepoetin Alfa N=1777
Baseline ESA dose (U/kg/week), n (%)				
n	90	83	1742	1759
Mean (SD)	155 (113)	148 (115)	117 (109)	112 (110)
≤90 U/kg/week	36 (40.0)	30 (36.1)	916 (52.6)	968 (55.0)
>90 and <300 U/kg/week	45 (50.0)	47 (56.6)	724 (41.6)	693 (39.4)
≥300 U/kg/week	9 (10.0)	6 (7.2)	102 (5.9)	98 (5.6)
Baseline iron use[2], n (%)				
0 - subjects not receiving any iron	52 (28.7)	56 (29.8)	660 (37.1)	721 (40.6)
I - subjects receiving oral iron only	19 (10.5)	9 (4.8)	123 (6.9)	118 (6.6)
II - subjects receiving IV iron only	92 (50.8)	110 (58.5)	911 (51.3)	853 (48.0)
III - subjects receiving IV and oral iron	18 (9.9)	13 (6.9)	83 (4.7)	85 (4.8)
Baseline IV iron dose (mg/week)				
n	68	75	610	560
Mean (SD)	567 (3380)	403 (1018)	114 (257)	145 (475)
Baseline oral iron dose (mg/week)				
n	29	20	156	159
Mean (SD)	3767 (7607)	2197 (1813)	3684 (10026)	2712 (3649)
Diabetes mellitus, n (%)				
Yes	105 (58.0)	96 (51.1)	971 (54.6)	998 (56.2)
No	76 (42.0)	92 (48.9)	806 (45.4)	779 (43.8)
History of cardiovascular disease[3], n (%)				
Yes	69 (38.1)	73 (38.8)	868 (48.8)	932 (52.4)
No	112 (61.9)	115 (61.2)	909 (51.2)	845 (47.6)
History of retinal disorder, n (%)				
Yes	37 (20.4)	35 (18.6)	304 (17.1)	362 (20.4)
No	144 (79.6)	153 (81.4)	1473 (82.9)	1415 (79.6)
Years since chronic dialysis initiated[4]				
n	179	186	1775	1777
Mean (SD)	0.14 (0.09)	0.15 (0.29)	4.00 (4.02)	3.94 (4.01)
Baseline systolic blood pressure (mmHg)				
n	181	188	1777	1777
Mean (SD)	143 (22)	143 (20)	143 (23)	143 (22)
Baseline diastolic blood pressure (mmHg)				
n	181	188	1777	1777
Mean (SD)	77 (13)	78.8 (13)	76.3 (13)	76 (13)
Baseline heart rate (beats/min)				
n	181	188	1774	1776
Mean (SD)	76 (11)	75 (10)	75 (11)	75 (12)

Source: Study 0016 Clinical Study Report Table 12 (p. 65); Study 0017 Clinical Study Report Table 12 (p. 64)
Note: The percentage is calculated based on the number of subjects with non-missing data.
[1] Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
[2] ESA doses were converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin alfa to IV epoetin was 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin was 1:220; subcutaneous epoetin to IV epoetin was 1:1.25.
[3] Cardiovascular (CV) disease included coronary artery disease, myocardial infarction, stroke, and HF. 4 The handling of the partial date of chronic dialysis initiated: If day was missing, day was set to 15th of the month. If month was missing, month and day were set to Jul 1. If year was missing, date was missing. Years since chronic dialysis initiated was calculated based on date of chronic dialysis initiated and date of Screening 1.
Abbreviations: ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HF, heart failure; IV, intravenous; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; --: not applicable

Disposition, Trials 0016 and 0017

Subject disposition information for Trials 0016 and 0017 is summarized in Table 59 and Table 60.

Table 59. Subject Screening and Randomization, Trial 0016 and 0017

Disposition	Trial 0016	Trial 0017
No. subjects screened	677	4944
No. subjects not randomized	308	1390
No. screening failures	308/677 (45.5%)	1390/4944 (28.1%)
No. subjects randomized	369	3554

Source: Study 0016 Clinical Study Report Figure 2 (p. 58); Study 0017 Clinical Study Report Figure 2 (p. 57)

Table 60. Subject Disposition, Trials 0016 and 0017

	Trial 0016		Trial 0017	
Disposition Category	Vadadustat N=181 n (%)	Darbepoetin Alfa N=188 n (%)	Vadadustat N=1777 n (%)	Darbepoetin Alfa N=1777 n (%)
Subjects randomized	181 (100)	188 (100)	1777 (100)	1777 (100)
FAS population	178 (98.3)	186 (98.9)	1755 (98.8)	1759 (99.0)
Per protocol population	107 (59.1)	142 (75.5)	1116 (62.8)	1441 (81.1)
Safety population	179 (98.9)	186 (98.9)	1768 (99.5)	1769 (99.5)
Completed study drug	121 (66.9)	139 (73.9)	878 (49.4)	1124 (63.3)
Discontinued study drug	58 (32.0)	47 (25.0)	890 (50.2)	645 (36.3)
Death	1 (0.6)	11 (5.9)	147 (8.3)	180 (10.1)
Kidney transplant	7 (3.9)	13 (6.9)	116 (6.5)	102 (5.7)
Adverse event[1]	16 (8.8)	6 (3.2)	115 (6.5)	66 (3.7)
Lack of efficacy	1 (0.6)	0 (0)	70 (3.9)	6 (0.3)
Decision to Switch to ESA	0 (0)	0 (0)	3 (0.2)	1 (0.1)
Investigator's Decision[2]	11 (6.1)	3 (1.6)	95 (5.4)	45 (2.5)
Lack of Compliance	0 (0)	0 (0)	9 (0.5)	1 (0.1)
Lost to follow-up	1 (0.6)	1 (0.5)	8 (0.5)	9 (0.5)
Global termination[3]/Sponsor Decision	0 (0)	0 (0)	12 (0.7)	16 (0.9)
Patient wishes[4]	21 (11.6)	13 (6.9)	315 (17.7)	219 (12.3)
Completed study	159 (87.9)	163 (86.7)	1423 (80.1)	1419 (79.9)
Discontinued study	20 (11.1)	23 (12.2)	345 (19.4)	350 (19.7)
Death	15 (8.3)	19 (10.1)	262 (14.7)	277 (15.6)
Lost to follow-up	3 (1.7)	2 (1.1)	38 (2.1)	32 (1.8)
Kidney transplant	0 (0)	1 (0.5)	3 (0.2)	3 (0.2)
Patient wishes	2 (1.1)	1 (0.5)	38 (2.1)	37 (2.1)
Adverse event	0 (0)	0 (0)	2 (0.1)	1 (0.1)
Lack of efficacy	0 (0)	0 (0)	2 (0.1)	0 (0)

Source: SDTM datasets; Software: JMP
Abbreviation: FAS, full analysis set; N, number of subjects; n, number of subjects with at least one event
Note: Percentages were calculated based on all randomized subjects.
1, Discontinuation due to adverse events included discontinuation of study drug due unacceptable toxicity, drug tolerability and adverse events.
2, The investigator's decision to discontinue study drug was not due to occurrence of an adverse event. Further details were not provided by the Applicant.
3, When the target number of MACE was reached, global study termination was initiated, resulting in discontinuation of study drug and conducting end-of-study visits in all on-study subjects, regardless of their current study period status.
4, Patient wishes, as a reason for discontinuation of study drug, were not due to occurrence of an adverse event. In the majority of cases, discontinuation of study drug was associated with practical inconveniences of being enrolled on study, due to social external circumstances or not specified.

Analysis of the Primary Efficacy Endpoint, Trials 0016 and 0017

According to the Applicant's SAPs and CSRs, the primary efficacy endpoint for both studies was the change in average Hb between baseline and the primary efficacy period (Weeks 24 to 36).

The primary efficacy endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's primary efficacy results were confirmed by the

statistical review team. Although the lower bound of the 95% CIs were both above the prespecified non-inferiority margin of -0.75 g/dL for both trials, the upper bound of the 95% CI was less than 0 in both trials (Table 61). However, since the magnitude of difference between the upper bound and zero was very small (i.e., 0.1 g/dL) for both trials, the clinical significance of this finding is limited, and the review team determined this is not a concern for establishing the efficacy of vadadustat for the treatment of anemia in the DD-CKD population. There were notable differences in the use of rescue therapy between the vadadustat and darbepoetin alfa arms, which is discussed below and in section II.6.3.1. More detailed efficacy analysis results for the primary efficacy endpoint for different patient populations for trials 0016 and 0017 can be found in sections II.6.2.4.3 and II.6.2.5.3, respectively.

Table 61. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputation), Randomized Population, Trial 0016 and 0017

	Trial 0016			Trial 0017		
Visit Statistics	Vadadustat N=181	Darbepoetin Alfa N=188	Treatment Comparison Vadadustat – Darbepoetin Alfa	Vadadustat N=1777	Darbepoetin Alfa N=1777	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline						
n	181	188		1777	1777	
Mean (SD)	9.4 (1.1)	9.2 (1.1)		10.3 (0.9)	10.2 (0.8)	
Weeks 24 to 36 (observed)						
n	157	171		1573	1623	
Mean (SD)	10.4 (1.1)	10.7 (0.9)		10.4 (1.0)	10.6 (1.0)	
Weeks 24 to 36 (observed + imputed)						
n	181	188		1777	1777	
Mean (SD)	10.4 (1.1)	10.6 (0.9)		10.4 (1.0)	10.5 (1.0)	
Change from baseline						
n	181	188		1777	1777	
Mean (SD)	1.0 (1.3)	1.4 (1.4)		0.1 (1.1)	0.3 (1.1)	
Least squares mean (SEM)	1.3 (0.1)	1.6 (0.1)	-0.3 (0.1)	0.2 (0)	0.4 (0)	-0.2 (0)
95% CI	(1.1, 1.2)	(1.4, 1.8)	(-0.5, -0.1)	(0.1, 0.3)	(0.3, 0.4)	(-0.2, -0.1)

Source: Study 0016 Clinical Study Report Table 19 (p. 78); Study 0017 Clinical Study Report Table 20 (p.78); Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Analysis of the Key Secondary Efficacy Endpoint, Trials 0016 and 0017

According to the Applicant's SAPs and CSRs, the key secondary efficacy endpoint for both studies was the change in average Hb between baseline and the secondary efficacy period (Weeks 40 to 52).

The key secondary endpoint was analyzed using ANCOVA with multiple imputation based on the randomized population. The Applicant's key secondary efficacy endpoint results were confirmed by the statistical review team. Although the lower bound of the 95% CIs were both above the prespecified non-inferiority margin of -0.75 g/dL for both trials, the upper bound of the 95% CI was less than 0 in the larger trial 0017 (Table 62). However, since the magnitude of difference between the upper bound and zero was very small (i.e., 0.1 g/dL), the clinical significance of this finding is limited, and the review team determined this is not a concern. More detailed efficacy analysis results for the key secondary efficacy endpoint for different patient populations for Trials 0016 and 0017 can be found in sections II.6.2.4.3 and II.6.2.5.3, respectively.

Table 62. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Randomized Population, Trials 0016 and 0017

	Trial 0016			Trial 0017		
Visit Statistics	Vadadustat N=181	Darbepoetin Alfa N=188	Treatment Comparison Vadadustat – Darbepoetin Alfa	Vadadustat N=1777	Darbepoetin Alfa N=1777	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline						
n	181	188		1777	1777	
Mean (SD)	9.4 (1.1)	9.2 (1.1)		10.3 (0.9)	10.2 (0.8)	
Weeks 40 to 52 (observed)						
n	133	145		1451	1515	
Mean (SD)	10.5 (1.1)	10.6 (1.1)		10.4 (1.0)	10.6 (1.0)	
Weeks 40 to 52 (observed + imputed)						
n	181	188		1777	1777	
Mean (SD)	10.5 (1.2)	10.6 (1.1)		10.4 (1.0)	10.1 (1.0)	
Change from baseline						
n	181	188		1777	1777	
Mean (SD)	1.2 (1.4)	1.4 (1.6)		0.2 (1.2)	0.4 (1.1)	
Least squares mean (SEM)	1.4 (0.1)	1.5 (0.1)	-0.1 (0.1)	0.2 (0)	0.4 (0)	-0.2 (0)
95% CI	(1.2, 1.7)	(1.2, 1.8)	(-0.3, 0.2)	(0.2, 0.3)	(0.3, 0.5)	(-0.3, -0.1)

Source: Study 0016 Clinical Study Report Table 22 (p. 82); Study 0017 Clinical Study Report Table 23 (p. 82); Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Summary:

After conducting a thorough evaluation of the data from the vadadustat INNO$_2$VATE program, we concluded that the enrolled patient population is appropriately reflective of the patient population with DD-CKD associated anemia. In addition, the two treatment arms are balanced, in relation to baseline demographic and clinical characteristics, with appropriate representation across ages, genders and races/ethnicities.

Based on results of the primary and key secondary analysis, evaluating hemoglobin response at the primary efficacy period (i.e., weeks 24 to 36) and the secondary efficacy period (i.e., weeks 40 to 52) respectively, the non-inferiority of vadadustat, compared to darbepoetin alfa, was established in the DD-CKD population. Although there was a higher rate of rescue therapy in patients with DD-CKD on vadadustat compared to patients treated with on-study darbepoetin alfa, sensitivity analyses that set Hb values within 4 weeks after rescue therapy as missing yielded efficacy results consistent with that of the primary efficacy analysis (see section II.6.3.1). It is important to note that the change from baseline to the average Hb over the primary and secondary treatment period in the darbepoetin alpha arm was consistent with historical Hb-based response observed in previous similar trials with darbepoetin alfa. In addition, the difference in darbepoetin alfa product source did not impact efficacy conclusions (See section II.6.3.2). Other pre-specified subgroup sensitivity analyses showed results generally consistent with the primary efficacy analysis (except for some subgroups with very small sample size), and thus are supportive of the efficacy of vadadustat across the different sub-groups.

There were no efficacy endpoints that directly measured how patients feel, function, or survive (e.g., patient-reported outcomes). As noted previously, hematologic response and reduction in RBC transfusions have been used for traditional approval for drugs intended to treat anemia of CKD. Trials 0016 and 0017 showed that vadadustat is non-inferior to darbepoetin alfa on hematologic response. The trials were not designed to show non-inferiority or superiority of vadadustat to darbepoetin alfa on RBC transfusions; however, the RBC transfusion data across the two trials consistently showed an unfavorable trend with vadadustat vs. darbepoetin alfa (narrow RBC transfusion rescue HR 1.9 in trial 0016 and HR 1.4 in trial 0017). We recognize that avoidance of RBC transfusion represents an important benefit as it helps limit alloreactivity, a critical risk factor for renal allograft rejection. The unfavorable trend on RBC transfusion with vadadustat vs. darbepoetin alfa raises concerns. RBC transfusions should be further assessed in any new trial(s) that the Applicant conducts to address the safety deficiencies identified in this application.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Impact of Rescue Therapy Use on the Non-Inferiority Efficacy Conclusion of Vadadustat

Issue:

Patients on vadadustat had a higher rate of ESA rescue in all four phase 3 trials and had a higher rate of RBC transfusion rescue in trials 0016 and 0017, compared to patients on darbepoeitin

alfa. We assessed whether the imbalance in rescue therapy use impacted the conclusions of non-inferiority of vadadustat to darbepoetin alfa on Hb response.

Background:

Hemoglobin response from baseline to weeks 24 to 52 of treatment and reduction in transfusion need have been accepted surrogate endpoints for establishing efficacy in patients with anemia of CKD, based on their relationship to clinically relevant endpoints reflecting how patients feel, function, or survive. The phase 3 trials used to evaluate the efficacy of vadadustat in the NDD-CKD population and the DD-CKD population used Hb response at the primary efficacy period (i.e., weeks 24 to 36) and the secondary efficacy period (i.e., weeks 40 to 52) as the primary and key secondary efficacy endpoints, respectively. The pre-specificed non-inferiority comparisons for all phase 3 trials were conducted based on patients' Hb performance, using -0.75 g/dL as the non-inferiority margin, which was appropriately justified based on previous applications for drugs intended to treat anemia of CKD and the Applicant's conducted meta-analyses. An evaluation of the rate of both ESA rescue and RBC transfusion rescue was conducted as a secondary efficacy endpoint in all phase 3 trials to further evaluate the robustness of the efficacy results.

Assessment:

Overall, all phase 3 trials met their primary and key secondary efficacy endpoints based on the pre-specified non-inferiority criteria, thus demonstrating non-inferiority of vadadustat to darbepoetin alpha. However, in the two phase 3 trials conducted in the DD-CKD population, we observed that the entire 95% CIs was less than zero. This finding is uncommon but it can occur in programs where there is a need to have trials powered, not only for major efficacy endpoints, but also for major surivival-based safety endpoints, such as MACE, normally requiring many more patients. Furthermore, since the magnitude of difference between the upper bound and zero is very small (i.e., 0.1 g/dL), the clinical significance of this finding is limited and the review team determined this is not a concern.

The evaluation of rates of ESA rescue showed that patients on vadadustat had a higher rate of ESA rescue in all four phase 3 trials, with both the narrow and broad definition for ESA rescue. However, because the narrow definition of ESA rescue is more specific, with less confounding, results from its analysis will be the focus of this assessment. The HR (95% CI) for the narrow definition of ESA rescue for trials 0014, 0015, 0016 and 0017 is 1.6 (1.1, 2.2), 2.6 (1.8, 3.7), 5.1 (2.6, 10.3) and 3.5 (3.0, 4.1), respectively.

The evaluation of rates of RBC transfusion rescue showed that patients on vadadustat, who were on baseline ESA therapy, had a higher rate of RBC transfusion rescue in trials 0016 and 0017. This was observed with the narrow definition for RBC transfusion rescue, which was used as the main focus of this assessment because it is more specific, with less confounding. The HR (95% CI) for the narrow definition of RBC transfusion rescue for trials 0016 and 0017 is 1.9 (0.78, 4.76) and 1.4 (1.07, 1.78), respectively. While the HR (95% CI) for the narrow definition of RBC transfusion rescue for trial 0015 was 1.2 (0.84, 1.74), which also appears elevated, this difference was based on a 3-event difference between treatment arms, limiting conclusions.

The Applicant conducted sensitivity analyses to assess the impact of the differential ESA and RBC transfusion rescue therapy use between vadadustat and darbepoietin alfa on the primary and key secondary endpoints. This analysis assigned missing values to Hb values measured within 4 weeks after rescue therapy, and showed results consistent with the primary efficacy analyses.

However, the higher rate of ESA rescue in both the NDD-CKD and DD-CKD populations, and the higher rate of RBC transfusion rescue in the DD-CKD population, observed in the vadadustat treatment arms, introduces uncertainty in the efficacy conclusions of vadadustat in the treatment of anemia of CKD. Furthermore, the higher RBC transfusion rescue raises concerns because one of the benefits of treating anemia is the avoidance of RBC transfusions as it helps limit alloreactivity, a critical risk factor for renal allograft rejection. Overall, these findings raise concerns about the Applicant's non-inferiority-based efficacy conclusion, in the absence of additional evidence of effectiveness demonstrating an impact on how a patient feels, functions or survives.

Conclusion:

All phase 3 trials in the NDD-CKD and DD-CKD population met the primary and key secondary efficacy endpoints, based on the pre-specified Hb reponse criteria. However, patients on vadadustat had a higher rate of ESA rescue in all four phase 3 trials and had a higher rate of RBC transfusion rescue in trials 0016 and 0017, compared to patients on darbepoeitin alfa. Sensitivity analyses treating Hb values obtained within four weeks after rescue therapy as missing, showed the non-inferiority results on Hb to be robust for the primary and key secondary efficacy endpoints. However, there was a higher rate of rescue therapies with vadadustat, compared to darbepoetin alfa, which introduces uncertainty in the efficacy conclusions of vadadustat in the treatment of anemia of CKD and its ability to limit alloreactivity by reducing the need for RBC transfusions. . This concern will be communicated in the Complete Response letter and the Applicant will be asked to further assess rescue therapy, including ESA and RBC transfusions, in new trial(s) that will be conducted to resolve the safety concerns.

6.3.2. Impact of US vs. Non-US Darbepoetin Alfa on the Efficacy Results

Issue:

The Applicant compared vadadustat to darbepoetin alfa in the four pivotal phase 3 trials and used darbepoetin alfa approved in other countries for the non-U.S. sites. We assessed the impact of the non-US approved darbepoetin alfa on the conclusion of non-inferiority for the primary efficacy endpoint.

Background:

Trials 0014, 0015, 0016, and 0017 were global studies. The Applicant used U.S. approved darbepoetin alfa as the active comparator at the US sites and dabepoetin alfa approved in other countries for the non-US sites. US darbepoetin alfa became a deemed biologic in March 2020, and the vadadustat NDA does not contain detailed analytical or clinical pharmacology data comparing the U.S. and non-U.S. approved darbepoetin alfa. We assessed the impact, if any, of

the different sources of darbepoetin alfa on the conclusion of non-inferiority of vadadustat to darbepoetin alfa on the primary efficacy endpoint (change from baseline in Hb to the average over Week 24-36) and key secondary efficacy endpoint (change from baseline in Hb to the average over Week 40-52).

Assessment:

Our first set of analyses compared the within group change from baseline to the average Hb over Week 24-36 for U.S.-darbepoetin alfa versus non-U.S.-darbepoetin alfa.

This analysis showed a numerically smaller within group change from baseline for US darbepoetin alfa (1.0 g/dL) in trials 0014 and 0016 compared to non-US darbepoetin alfa (1.6-1.8 g/dL). In contrast, for trials 0015 and 0017, the mean change from baseline for US darbepoetin alfa (0.3 g/dL) was similar to that of non-U.S. darbepoetin alfa (0.2-0.4 g/dL). Analyses comparing the within group change from baseline to the average Hb over Week 40-52 for U.S.-darbepoetin alfa versus non-U.S.-darbepoetin alfa has similar results to analyses of the primary efficacy endpoint.

Given the potential differences in darbepoetin alfa performance at the U.S. versus non-U.S. sites in trials 0014 and 0016, we assessed the impact of U.S. versus non-U.S. darbepoetin alfa on the conclusion of non-inferiority of vadadustat to darbepoetin alfa on the primary efficacy endpoint.

In trial 0014, the mean treatment difference (95% CI) for vadadustat minus dabepoietin alfa for the primary efficacy endpoint was 0.2 g/dL (0.0, 0.3) for the US compared to 0.3 g/dL (-0.1, 0.6) for Europe and -0.2 (-0.4, 0) for the rest of the world. In trial 0016, the mean treatment difference (95% CI) between vadadustat and dabepoietin alfa for the primary efficacy endpoint was -0.3 g/dL (-0.6, -0.1) for the US compared to -0.6 g/dL (-1.3, 0.1) for Europe and -0.2 (-0.6, 0.2) for the rest of the world. These differences in the treatment effect across geographic regions were small, most of these results had overlapping confidence intervals and, importantly, vadadustat was consistently non-inferior to darbepoetin alfa on the primary efficacy endpoint in all regions, including the US. Results of the same analyses on the key secondary efficacy endpoint were similar to results of the primary efficacy endpoint.

In trials 0015 and 0017, the mean treatment differences (95% CI) between vadadustat and darbepoetin alfa for the primary efficacy endpoint were virtually identical across the geographic regions. In trial 0015, the mean treatment difference (95% CI) between vadadustat and dabepoietin alfa for the primary efficacy endpoint was 0.0 g/dL (-0.1, 0.2) for the US compared to 0.0 g/dL (-0.2, 0.2) for Europe and 0.0 (-0.2, 0.1) for the rest of the world. In trial 0017, the mean treatment difference (95% CI) between vadadustat and dabepoietin alfa for the primary efficacy endpoint was -0.2 g/dL (-0.3, -0.1) for the US compared to -0.2 g/dL (-0.3, 0.0) for Europe and -0.1 (-0.2, 0.1) for the rest of the world. For these trials, vadadustat was consistently non-inferior to darbepoetin alfa on the primary efficacy endpoint in all regions, including the United States. Results of the same analyses on the key secondary efficacy endpoint were similar to results of the primary efficacy endpoint.

Conclusion:

The different sources of darbepoetin alfa used at the U.S. versus non-U.S. sites did not impact the conclusion of non-inferiority for vadadustat versus darbepoetin alfa.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Toxicological characterization of vadadustat was assessed in mice (3-month), rats (4-week, 3-month, 6-month, embryo-fetal development), dogs (4-week, 3-month, 9-month) and rabbits (embryo-fetal development) using repeat-dose toxicology studies. Pharmacology-related effects were observed in all of these species including increases in red blood cell indices (red blood cell count, hemoglobulin, hematocrit). Additionally, polycythemia-related fibrin thrombosis and tissue necrosis in multiple organs and/or mortalities were observed in these animal species. No definitive risks were identified from in vitro and in vivo safety pharmacology assessments and these studies are discussed in detail in section III.13.1.2.

The predominate toxicity observed in nonclinical studies can be reasonably attributed to the exaggerated pharmacological effects of excessive erythropoiesis; the toxicity was marked by thromboses, tissue necrosis, and mortalities. Exposure in animals at the 'no observed adverse effect level' (NOAEL) were all below human exposure at the clinical dose of 600 mg QD (Table 63). Key to interpreting the toxicology data is to understand that the nonclinical toxicology studies were conducted in healthy and non-anemic animals, in which vadadustat produces polycythemia. The findings in the nonclinical program demonstrate that vadadustat is capable, mechanistically, of increasing erythropoiesis to a point of polycythemia and thus leading to adverse sequalae such as thromboses. However, a similar exposure-response to vadadustat would not necessarily occur in patients with anemia for whom increased erythropoiesis is the intent of treatment, and for which the degree of induced erythropoiesis is a primary efficacy and safety monitoring endpoint.

Lacrimal gland atrophy in males with a dose-related incidence and/or severity (minimum to moderate) was observed in the 3-month toxicology study in mice. Considering the hematology findings at the corresponding dose levels, the lacrimal gland findings were attributed to effects of increased blood viscosity.

A microscopic change unique to the dog was noted in the adrenal gland cortex which displayed hypertrophied cell aggregation and increased mononuclear cell infiltration. The identity of the hypertrophied cells is unknown but is presumed to be histiocytes or adrenal cortical cells. The incidence of this finding was independent of pharmacodynamic effects. A partial recovery was observed after 3 months of a treatment-free period in both the 3-month and 9-month dog studies. This finding appears to be subclinical as no adrenal functionality changes were observed. Other general toxicology findings are discussed in more detail in section III.13.1.4.1.

Vadadustat is not extensively metabolized in animals or humans and there are no unique human metabolites. The major elimination pathway in rats and dogs is hepatobiliary elimination into feces while the major elimination route in humans is urinary elimination. No safety concerns were identified with vadadustat metabolites. Details of metabolism and elimination of vadadustat are discussed in section III.13.1.3.

Vadadustat did not affect fertility or cause teratogenicity, although lower fetal weight (-7%), lower pup weight (-5% to -11%), and reduced fetal skeletal ossifications occurred at dose levels associated with maternal toxicity. Additionally, an increased post-implantation loss was observed

in a dose-ranging study in rats, which was not reproduced in the definitive study. See details in section III.13.1.4.4.

No safety concerns were identified from genotoxicity or carcinogenicity studies. See details in section III.13.1.4.2 and III.13.1.4.3.

In summary, the predominate risk identified in the nonclinical program related to the primary pharmacological intent of increasing erythropoiesis. No other outstanding nonclinical safety issues of significant concern were observed at clinically relevant exposures in the nonclinical toxicology program. Therefore, the nonclinical pharmacology/toxicology data support approval of this NDA.

Table 63. Exposure Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (µg.h/mL)	Exposure Margins* (multiples)	Basis for NOAEL
3-month, mouse	150	310	0.47x	Mortalities at 200 mg/kg/day
3-month, rat	40	213.8	0.33x	Mortalities at ≥70 mg/kg/day
6-month, rat	20	124.4	0.19x	Stomach findings (mucosal necrosis, hemorrhage, edema, and mixed cell infiltration) at ≥40 mg/kg/day
3-month, dog	45	216	0.33x	HD of 90 mg/kg/day was reduced to 65 mg/kg/day to reduce the potential development of polycythemia
9-month, dog	25	32.3	0.05x	Mortality at 50 mg/kg/day.

Source: Reviewer constructed summary table.
*Exposure multiples were based on population pharmacokinetics analysis from phase 3 trials, where the maximum clinical dose of 600 mg/day resulted in systemic geometric mean exposures of AUC0-24hr of 654.9 µg.h/mL
Abbreviations: HD, human dosage; NOAEL, no observed adverse effect level.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Vadadustat is a small molecule inhibitor of HIF-PH enzymes, which mimics the physiological effects of hypoxia inside the cell, leading to increased production of EPO and improved oxygen-carrying capacity through increased production of red cells and elevation of Hb levels. Currently, the standard of care for the treatment of anemia due to CKD is ESA, which include Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa) and Mircera (pegylated epoetin alfa or epoetin beta). ESAs are approved for the treatment of anemia due to CKD, including patients on dialysis and not on dialysis. Given the similar end effect of increased EPO, as a common mechanism of action between vadadustat and ESAs, safety concerns observed with ESAs were considered potential safety concerns in our safety evaluation of vadadustat.

Prescribing information (PI) for ESAs contain a boxed warning for increased risk of death, serious adverse cardiovascular reactions such as myocardial infarction and congestive heart failure, stroke, venous thromboembolism, and thrombosis of vascular access. Even though this risk was observed when Hb level were >11 g/dL in ESA trials, there has not been an identified safe hemoglobin target level or dosing strategies for ESAs. As a result, the PI recommends using the lowest ESA dose sufficient to reduce the need for red blood cell transfusions. In addition, the

PIs for ESAs include the following relevant safety concerns in the warnings and precautions sections:

- Hypertension, worsening or new onset, with a contraindication in patients with uncontrolled hypertension
- Increase risk for seizures in patients with CKD
- Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash and urticaria
- Severe cutaneous reactions, including blistering and skin exfoliation

Roxadustat is a first-in-class HIF-PH inhibitor, using the same mechanism of action as vadadustat, targeting the same indications and patient population, and having a similar clinical development program to vadadustat. It is important to note that, after an extensive review of the safety data provided and upon consultation with an advisory committee, the Agency issued a complete response letter for roxadustat, citing serious safety concerns that were echoed by the members of the advisory committee, of similar nature to those experienced with the ESAs. A summary of these safety concerns included:

- Risk of major adverse cardiovascular events (MACE) in the NDD-CKD and DD-CKD population, where MACE includes non-fatal myocardial infarction, non-fatal stroke, and all-cause mortality.
- Risk of deep venous thrombosis in the NDD-CKD population
- Risk of vascular access thrombosis in the DD-CKD population
- Risk of serious infections in both the NDD-CKD and DD-CKD population
- Risk of systemic hypertension in both the NDD-CKD and DD-CKD population
- Risk of seizures in both the NDD-CKD and DD-CKD population

In addition, there was an observed higher rate of end stage renal disease in the NDD-CKD population and higher rate of hyperkalemia in both the NDD-CKD and DD-CKD population.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Vadadustat was approved in Japan on June 29, 2020, for the treatment of anemia due to CKD and was launched in Japan on August 26, 2020. From the launch date to the data cutoff date of October 15, 2020, the Applicant reported five related SAEs (anemia, angina pectoris, asthenia, gastrointestinal hemorrhage, and melena) and two deaths (due to asthenia and cardiac failure). The Applicant did not report the extent of vadadustat use over this period in Japan. The most commonly reported non-serious AEs were nausea, diarrhea, and decrease appetite. Overall, there are no new safety concerns with vadadustat based on the available post-marketing data from Japan.

7.4. FDA Approach to the Safety Review

The safety review of vadadustat was divided into two populations of patients with CKD: those who were not dependent on chronic dialysis, and those who were dependent on chronic dialysis as follows:

- Evaluation of safety in the NDD-CKD population, which was based on data from:
  - Two completed phase 3 global trials: AKB-6548-CI-0014 (PRO_2TECT – CORRECTION) and AKB-6548-CI-0015 (PRO_2TECT – CONVERSION). A summary of the design of the two trials can be found in section II.6.2.1.1 and II.6.2.2.1, respectively. Trials were analyzed separately and using a pooled approach.
  - One completed phase 3 trial in Japan: MT-6548-J01. A descriptive summary of the design and results of this trial can be found in section III.17.3. Trial was not pooled with global phase 3 trials due to significant differences in the trial populations.
  - Five early phase completed trials: AKB-6548-CI-0003, AKB-6548-CI-0004, AKB-6548-CI-0005, AKB-6548-CI-0007 and AKB-6548-CI-0021. A descriptive summary of the design and results of each of the trials can be found in section III.17.1. Trials were not pooled due to significant differences in trial design.
- Evaluation of safety in the DD-CKD population, which was based on data from:
  - Two completed phase 3 trials: AKB-6548-CI-0016 ($INNO_2VATE$ – CORRECTION/CONVERSION) and AKB-6548-CI-0017 ($INNO_2VATE$ – CONVERSION). A summary of the design of the two trials can be found in section II.6.2.4.1 and II.6.2.5.1, respectively. Trials were analyzed separately and using a pooled approach.
  - Three completed phase 3 trials in Japan: MT-6548-J02, MT-6548-J03 and MT-6548-J04. A descriptive summary of the design and results of each of the trials can be found in section III.17.3. Trials were not pooled with global phase 3 trials due to significant differences in the trial populations.
  - Five early phase completed trials: AKB-6548-CI-0009, AKB-6548-CI-0011, AKB-6548-CI-0025, AKB-6548-CI-0034 and AKB-6548-CI-0022. A descriptive summary of the design and results of each of the trials can be found in section III.17.2. Trials were not pooled due significant differences in trial design.

Descriptive safety evaluation of early phase trials in the NDD-CKD population, early phase trials in the DD-CKD population and phase 2/3 trials in Japan showed similar safety signals to the evaluation conducted using the global phase 3 trials, without revealing any new safety signals. Specifically, there was confirmation of the presence of increased hepatotoxicity and gastrointestinal adverse events in subjects with anemia of CKD, who were treated with vadadustat, and of increased risk of thromboembolism, especially vascular-associated thrombosis, in subjects with DD-CKD. See sections III.17.1, III.17.2 and III.17.3 for details.

The Safety population was defined as all subjects in the randomized population who received at least one dose of study drug and analysis was based on the actual treatment received. Adverse events (AEs) were reported by verbatim term and coded and categorized using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. To assess the reliability and quality of the data, the clinical reviewer compared the coding of verbatim reported adverse event terms (AETERM), the MedDRA lowest coded level (AELLT) and the MedDRA preferred term (AEDECOD) for 14,010 AEs in the safety dataset of trial 0014, 12,023 in the safety dataset of trial 0015, 2,273 AEs in the safety dataset of trial 0016 and 27,455 AEs in the safety dataset of trial 0017. Overall, the coding was consistently performed between the terms. However, there were inconsistences found in the translation of verbatim terms to MedDRA-based terms that

needed correction, resulting in re-coding of preferred terms (PTs). In general, there were two broad categories of PTs that required re-coding to avoid potential dilution of a safety signal:

- PT that was not specific enough, such as categorizing a skin infection as a non-specific infection, instead of specifying it as a cellulitis, as described in the verbatim term
- PT that was incorrectly categorized, such as categorizing a thrombosed fistula as a fistula site complication, instead of appropriately categorizing it as a fistula thrombosis, as described in the verbatim term

In addition, detailed evaluation of the MedDRA PTs and system organ classes (SOCs) to ensure appropriate splitting was conducted to allow for meaningful and consistent evaluation of adverse reactions.

A list of PTs defining each meaningful and consistent grouping of adverse events was obtained from review of all PT-based adverse events used in the four phase 3 trials. If a specific PT was not listed, at least once, as an adverse event in any of the four phase 3 trials, it was not included in the grouping definition. To ensure consistency among other approaches used for grouping PTs, such as SMQs and FMQs, results from analyses conducted by the CDS team were compared to results obtained from the reviewer's analyses, which were consistent across all phase 3 trials. This approach was consistently performed across all subjects and specific definitions of groupings of PTs are provided in section III.17.4.3.Overall, the safety review focused on evaluating the safety profile of vadadustat, compared to the active-control arm of darbepoetin alfa, using a frequency-based first-event approach, an exposure-adjusted first-event approach, and a time-to-first-event analysis approach. Specifically, we evaluated the following aspects:

- Presence of any treatment emergent adverse event (TEAE), any severe TEAE, any serious adverse event (SAE), any TEAE leading to death, and any TEAE leading to discontinuation
- Causes of death in the on-study (defined in section III.17.4.1) population and characteristics of this population
- Specific SAE that occurred in ≥2% of subjects in the vadadustat arm
- Specific TEAE leading to discontinuation that occurred in >2 subjects
- Specific TEAE that occurred in ≥5% of subjects in the vadadustat arm
- Specific TEAE of special interest, based on preclinical and clinical experience, including findings from other related drugs, and known drug-class safety findings

Please refer to section III.17.4.4 for definitions of safety-related terms used in our safety review approach.

Several AEs of special interest were assessed as part of the safety analysis in Trials 0014, 0015, 0016, and 0017, as follows:

- MACE, defined as a composite of non-fatal MI, non-fatal stroke, and all-cause mortality. MACE was the pre-specified primary safety endpoint.
- Key secondary CV-related endpoints, which the Applicant planned to statistically test in the following order only if the pre-specified risk margin was ruled out in the primary safety endpoint:
  - MACE2, defined as a composite of MACE, hospitalization for HF, or TE event excluding VAT
  - CV MACE, defined as a composite of CV death, non-fatal MI, and non-fatal stroke

- CV death
- All-cause mortality

- Other secondary CV-related endpoints were:
  - Individual components of MACE
  - TE events, which were assessed based on two approaches:
    - The Applicant's pre-specified adjudication data, defined as a composite of ATE, DVT, PE and VAT
    - The Agency's definition using PT terms (see section III.17.4.3 for specific definitions), which was conducted using two approaches:
      - TE events (narrow), defined using PT terms relevant to venous thromboembolism (VTE) and ATE.
      - TE events (broad), defined using PT terms relevant to VTE, arterial thrombosis, non-fatal MI, non-fatal stroke, arteriovenous (AV) connection stenosis, transient ischemic attack (TIA), and non-adjudicated thrombosis-related death.
  - MACE+, defined as a composite of MACE and TE events
  - Other individual non-adjudicated thrombosis-related AEs, such as TIA, AV connection stenosis, and thrombosis-related death.

Of note, only the following AEs of special interest were independently adjudicated by the Endpoint Adjudication Committee (EAC) once they were reported by the investigator: MACE, non-fatal MI, non-fatal stroke, all-cause mortality (including CV death), hospitalization for unstable angina (to avoid potentially missing a non-fatal MI), hospitalization for HF and TE events (including ATE, DVT, PE and VAT). Upon review of the narratives provided by the Applicant, there were significant inconsistencies observed in the adjudication process of the TE events, especially in relation to cases with vascular-access thrombosis, such as exclusion of cases without sufficient justification, based on the reviewer's analysis of the narratives, which led to exclusion of ~40% of cases with possible vascular-access thrombosis. In addition, the Applicant's TE event grouping included several cases of chronic stenotic lesions, which did not fit the pre-specified definition. Furthermore, given the pathophysiological difference between arterial and venous thrombosis, the reviewer did not agree with the grouping of these pathophysiologically distinct events. As a result of these findings, in addition to utilizing the Applicant's TE event grouping as a safety endpoint, the reviewer conducted sensitivity analyses using Agency-defined grouping definitions, based on the approach described above.

The analyses of the primary and secondary safety endpoints used pooled data from the two pivotal trials of each program (PRO$_2$TECT: 0014 and 0015; INNO$_2$VATE: 0016 and 0017). Both were designed to rule out a risk margin of 1.25 with 80% power and 2.5% one-sided type I error rate for the primary safety endpoint, MACE. The Applicant estimated a total of 631 MACE events (first event) in each program to be sufficient. Agreement on both the non-inferiority margin and the estimated number of events needed was reached between the Agency and the Applicant prior to conducting the phase 3 trials. Analyses and conclusions of the safety evaluation obtained from the above-mentioned trials can be found in section II.7.6.

The safety statistical review team analyzed and summarized the safety data for the pre-specified primary and key secondary safety endpoints. Below are important aspects of the analysis approach used by the safety statistical review team:

- The pre-specified primary analysis method used a study-stratified Cox proportional hazard model to analyze the time to first MACE event. The pre-specified covariates adjusted in the model were baseline hemoglobin level, age (<65 versus ≥65 years), sex, race, history of CV disease, diabetes status, region, and NYHA class (NYHAC).
- The region variable in the SAP was defined as the Applicant-defined geographic-based approach, while FDA's analyses used the practice-of-care measures approach (see section III.17.4.2 for exact definitions of the variables). In our analysis, we used the practice-of-care measures approach to sufficiently account for variations in access and/or delivery of medical care, which may contribute to the observed differences in outcomes and is not accounted for by the traditional geographic-based approach, initially proposed by the Applicant. This approach was discussed with the Applicant, who was in agreement with its implementation.
- All other secondary endpoints including TE events were analyzed using the same study-stratified Cox proportional hazard model in FDA's primary analyses.
- The Applicant's and FDA's analyses, both used on-study analysis as primary. The on-study analysis followed subjects until the date of last contact or date of event, whichever came first.
- To take difference in duration of drug exposure into consideration, we conducted a post-hoc on-treatment (OT) +7 analysis, which followed subjects until the date of last contact, date of event, or 7 days after the last dose, whichever came first.
- Additionally, a prespecified sensitivity meta-analysis of MACE, using the inverse variance method to assess the robustness of the results from the primary analysis was conducted by the Applicant and confirmed by FDA.

The clinical review team analyzed and summarized all other aspects of the safety data using an unadjusted univariate on-study analysis approach. Clinical trial data were independently analyzed using JMP and R statistics software. Using the frequency-based analysis approach, a safety signal was considered for evaluation if the relative risk was ≥1.1 and the risk difference was ≥1%. Using the exposure-adjusted analysis approach, a safety signal was considered for evaluation if the relative risk was ≥1.1. Using the time-to-first-event analysis approach, a safety signal was considered for evaluation only if the hazard ratio was ≥1.1. Exploratory analyses were conducted to evaluate the impact of both baseline and post-baseline, clinically significant, covariates on the unadjusted on-study time-to-first-event analysis of the following key safety endpoints: MACE, CV MACE, TE events (broad), and VTE. Definitions of the covariates used can be found in section III.17.4.5. Summary of relevant exploratory covariate analyses can be found in section III.17.5.

Due to the early detection of drug-related hepatoxicity requiring quarterly hepatic evaluation reports, the drug-induced liver injury (DILI) team was consulted to evaluate the hepatotoxic potential of vadadustat. Given the known renal-based toxicities of the drug class and the trial population of subjects with CKD, the clinical review team consulted the Division of Cardiology and Nephrology for their specialty-specific input. Finally, in relation to on-study laboratory evaluation, the following laboratory markers were serially measured throughout the trial period for all phase 3 trials, thus allowing for comprehensive evaluation of the change in mean values over time and evaluation of severity-based outliers:

- Biochemistry markers: sodium, potassium, chloride, bicarbonate, glucose, calcium, magnesium, phosphate, total protein, albumin, creatine kinase, urea nitrogen, creatinine, eGFR, ALT, AST, alkaline phosphatase, and bilirubin.
- Hematology markers: white blood cell count (WBC), hemoglobin, platelets, lymphocytes, neutrophils, and eosinophils.
- Coagulation markers: activated partial thromboplastin time and prothrombin time
- Lipid profile components: HDL cholesterol and LDL cholesterol

The following laboratory markers were not evaluated: amylase and lipase. A laboratory-based safety signal was considered for evaluation if the risk difference in outlier analysis was ≥1%.

7.5. Adequacy of Clinical Safety Database

For the NDD-CKD population, a total of 3511 subjects were randomized in trial 0014 and 0015, of which 3506 subjects received at least one dose of study drug. Due to significant data quality issues reported by the Applicant in one of the sites enrolling subjects from the NDD-CKD population, a total of 35 enrolled subjects who received study drug were excluded from the safety population. As a result, the safety population for the NDD-CKD population is composed of 3471 subjects, 1739 subjects who received vadadustat and 1732 subjects who received darbepoetin alfa. Exposure characteristics of the individual trials 0014 and 0015, and of the pooled NDD-CKD population, are summarized in Table 64 and Table 66, respectively.

Overall, >50% subjects were exposed to the study drug for >1 year, regardless of treatment assignment. The full on-study follow-up time was also similar in the two arms, 3113 person-years (PYs) and 3174 PYs in the vadadustat and darbepoetin alfa arms, respectively. Similar follow-up time was also observed when the full on-treatment period was examined between study arms (2307 PYs for the vadadustat arm and 2505 PYs for the darbepoetin alfa arm). However, subjects on vadadustat had a shorter average duration of treatment by approximately seven weeks, with a higher proportion discontinuing study drug within the first 3-6 months, compared to subjects on darbepoetin alfa. Subjects on vadadustat experienced a lower proportion of dose interruption and decreases in dose levels, with subjects on darbepoetin alfa having a higher number of dose adjustments. However, the total duration of dose interruptions was comparable between the two treatment arms, resulting in an approximate nine-week period of drug interruption.

Table 64. Exposure Characteristics, Safety Population, Trial 0014, and Trial 0015

	Trial 0014		Trial 0015	
Variable	**Vadadustat N=878**	**Darbepoetin Alfa N=870**	**Vadadustat N=861**	**Darbepoetin Alfa N=862**
Duration of treatment[1] (weeks)				
Mean (SD)	66.8 (46.7)	71.6 (48.5)	71.7 (48.6)	79.3 (48.3)
Median (25% to 75% IQR)	57.1 (31.9- 97.3)	63.8 (35.7- 101.1)	61.3 (34.6-105.3)	70.4 (37-120.8)
Min, Max	0.1, 204.1	0.1, 208.1	0.1, 202.1	0.1, 201.7
Total exposure (person years)	1124	1195	1183	1310
Subjects treated, by duration				
<3 months, n (%)	114 (13.0)	111 (12.8)	95 (11.0)	59 (6.8)
3 to <6 months, n (%)	100 (11.4)	76 (8.7)	76 (8.8)	73 (8.5)
≥6 months, n (%)	664 (75.6)	683 (78.5)	690 (80.1)	730 (84.7)
≥1 year, n (%)	423 (48.2)	453 (52.1)	438 (50.9)	496 (57.5)
≥2 years, n (%)	133 (15.2)	165 (19.0)	190 (22.1)	232 (26.9)
≥3 years, n (%)	23 (2.6)	33 (3.8)	37 (4.3)	29 (3.4)
Dose interruption occurred?, n (%)	481 (54.8)	491 (56.4)	440 (51.1)	494 (57.3)
Number of dose interruption: Median (25% to 75% IQR, min-max)	2 (1-3, 1-79)	2 (1-3, 1-16)	2 (1-3, 1-17)	2 (1-3, 1-19)
Duration of dose interruption (weeks): Median (25% to 75% IQR, min-max)	9 (4-19.5, 0.3-98.7)	10 (5-19.6, 0.3-119)	8 (3.8-16.1, 0.3-104.9)	8.2 (4-16.8, 0.1-107.9)
Number of dose adjustments: Median (25% to 75% IQR, min-max)	3 (2-6, 1-24)	6 (3-9, 1-31)	4 (2-6, 1-20)	5 (3-10, 1-35)
Dose decrease occurred?, n (%)	596 (67.9)	674 (77.5)	620 (72)	702 (81.4)
Number of dose decrease: Median (25% to 75% IQR, min-max)	2 (1-3, 1-12)	3 (1-4, 1-15)	1 (1-2, 1-8)	2 (1-4, 1-15)
Duration of treatment without drug interruption periods[2] (weeks)				
Mean (SD)	58.5 (41.6)	62.9 (44.1)	65 (45.3)	71.2 (45.3)
Median (25% to 75% IQR)	48.6 (26.3-84.5)	53.1 (29.9-88.1)	53.1 (30.9-97.7)	62.3 (33.8-107.9)
Min, Max	0.1, 191.4	0.1, 192.9	0.1, 198.3	0.1, 191.9
Total Exposure (person years)	984	1048	1073	1176

Source: SDTM dataset; software: JMP
[1]Duration of treatment calculated as follows: [(date of last dose – date of first dose) +1]
[2]Duration of treatment calculated by subtracting the total period of drug interruption from the standard duration of treatment.
Abbreviations: N, number of subjects in group; n, number of subjects with exposure characteristic; SD, standard deviation; IQR, Interquartile range.

For the DD-CKD population, a total of 3923 subjects were randomized, of which 3902 subjects received at least one dose of study drug. There were no data quality issues reported by the Applicant or detected during our review, thus no exclusion of sites or subjects occurred. As a result,

the safety population for the DD-CKD population is composed of 3902 subjects, 1947 subjects who received vadadustat, and 1955 subjects who received darbepoetin alfa. Exposure characteristics of the individual trials 0016 and 0017, and of the pooled DD-CKD population, is summarized in Table 65 and Table 66, respectively.

Overall, >40% subjects were exposed to the study drug for >1 year, regardless of assignment. The follow-up time was comparable between the two arms, 3222 PY and 3246 PY in the vadadustat and darbepoetin alfa arms, respectively. Similar follow-up time was also observed when the full on-treatment period was examined between study arms (2218 PYs for the vadadustat arm and 2670 PYs for the darbepoetin alfa arm). However, subjects on vadadustat had a shorter duration of treatment of approximately 8 weeks, with a higher proportion of vadadustat-treated patients in the pooled DD population discontinuing study drug within the first 3-6 months, compared to subjects on darbepoetin alfa. Subjects on vadadustat experienced a lower proportion of dose interruption and decreases in dose levels, with subjects on darbepoetin alfa having a higher number of dose adjustments. However, the total duration of dose interruptions was comparable between the two arms, resulting in an approximate 10-week period of drug interruption.

Table 65. Exposure Characteristics, Safety Population, Trial 0016, and Trial 0017

	Trial 0016		Trial 0017	
Variable	**Vadadustat N=179**	**Darbepoetin Alfa N=186**	**Vadadustat N=1768**	**Darbepoetin Alfa N=1769**
Duration of treatment[1] (weeks)				
Mean (SD)	52.8 (34.4)	59.5 (35.6)	60.1 (37.8)	72.5 (36.6)
Median (25% to 75% IQR)	45 (28.9-72.9)	50.1 (36-80.1)	56.1 (28.9-85.4)	72.1 (44.9-98.7)
Min, Max	0.4, 150.7	1.1, 169.1	0.1, 163.1	0.1, 161.9
Total Exposure (person years)	181	212	2037	2458
Subjects treated, by duration				
<3 months, n (%)	31 (17.3)	16 (8.6)	276 (15.6)	131 (7.4)
3 to <6 months, n (%)	18 (10.1)	26 (14.0)	238 (13.5)	140 (7.9)
≥6 months, n (%)	130 (72.6)	144 (77.4)	1254 (70.9)	1498 (84.7)
≥1 year, n (%)	65 (36.3)	76 (41.0)	791 (44.7)	1081 (61.1)
≥2 years, n (%)	8 (4.5)	14 (7.5)	142 (8.0)	186 (10.5)
≥3 years, n (%)	0 (0)	0 (0)	1 (0.1)	1 (0.7)
Dose interruption occurred?, n (%)	91 (50.8)	118 (63.4)	1078 (61.0)	1180 (66.7)
Number of dose interruption: Median (25% to 75% IQR, min-max)	2 (1-3, 1-6)	2 (1-3, 1-10)	2 (1-3, 1-12)	3 (1-5, 1-22)
Duration of dose interruption (weeks): Median (25% to 75% IQR, min-max)	8.3 (3.9-20, 0.1-54.6)	9.6 (4.4-18.2, 1-54.4)	10.7 (4.4-20.6, 0.3-98.9)	11.8 (4.7-23, 0.1-106)
Number of dose adjustments: Median (25% to 75% IQR, min-max)	2 (2-4, 0-12)	4 (2-7, 0-32)	3 (2-5, 0-15)	6 (3-10, 0-41)

Variable	Trial 0016		Trial 0017	
	Vadadustat N=179	Darbepoetin Alfa N=186	Vadadustat N=1768	Darbepoetin Alfa N=1769
Dose decrease occurred?, n (%)	106 (59.2)	150 (80.7)	1118 (63.2)	1505 (85.1)
Number of dose decrease: Median (25% to 75% IQR, min-max)	1 (0-2, 0-6)	2 (1-3, 0-17)	1 (0-2, 0-8)	3 (1-4, 0-16)
Duration of treatment without drug interruption periods[2] (weeks)				
Mean (SD)	45.9 (30.7)	51.0 (31.4)	50.9 (34)	61.6 (32)
Median (25% to 75% IQR)	40.1 (23.1-65.0)	44.1 (28.7-67.9)	47.1 (21.6-74.4)	60.9 (39.1-83.1)
Min, Max	0.4, 136	1.1, 128.3	0, 156	0.1, 157.3
Total Exposure (person years)	158	182	1726	2090

Source: SDTM dataset; software: JMP
[1]Duration of treatment calculated as follows: [(date of last dose – date of first dose) +1]
[2]Duration of treatment calculated by subtracting the total period of drug interruption from the standard duration of treatment.
Abbreviations: N, number of subjects in group; n, number of subjects with exposure characteristic; SD, standard deviation; IQR, Interquartile range.

Table 66. Exposure Characteristics, Safety Population, Pooled Trial 0014 and 0015, and Pooled Trial 0016 and 0017

Variable	Pooled Trial 0014 and 0015		Pooled Trial 0016 and 0017	
	Vadadustat N=1739	Darbepoetin Alfa N=1732	Vadadustat N=1947	Darbepoetin Alfa N=1955
Duration of treatment[1] (weeks)				
Mean (SD)	69.2 (47.7)	75.5 (48.5)	59.4 (37.6)	71.3 (36.7)
Median (25% to 75% IQR)	59.4 (33.3-101.9)	67 (36.1-112.1)	55.9 (28.9-85)	71.7 (43.9-96)
Min, Max	0.1, 204.1	0.1, 208.1	0.1, 163.1	0.1, 169.1
Total Exposure (person years)	2308	2505	2218	2670
Subjects treated, by duration				
<3 months, n (%)	209 (12.02)	170 (9.82)	307 (15.77)	147 (7.52)
3 to <6 months, n (%)	176 (10.12)	149 (8.6)	256 (13.15)	166 (8.49)
≥6 months, n (%)	1354 (77.86)	1413 (81.58)	1384 (71.08)	1642 (83.99)
≥1 year, n (%)	861 (49.51)	949 (54.79)	856 (43.97)	1157 (59.18)
≥2 years, n (%)	323 (18.57)	397 (22.92)	150 (7.70)	200 (10.23)
≥3 years, n (%)	60 (3.45)	62 (3.58)	1 (0.05)	1 (0.05)
Dose interruption occurred?, n (%)	921 (53)	985 (56.9)	1169 (60.04)	1298 (66.39)
Number of dose interruption: Median (25% to 75% IQR, min-max)	2 (1-3, 1-79)	2 (1-3, 1-19)	2 (1-3, 1-12)	2 (1-5, 1-22)
Duration of dose interruption (weeks): Median (25% to 75% IQR, min-max)	8.4 (3.9-17.8, 0.3-104.9)	9 (4.1-18.1, 0.1-119)	10.6 (4.3-20.6, 0.1-98.9)	11.6 (4.7-22.6, 0.1-106)

Variable	Pooled Trial 0014 and 0015		Pooled Trial 0016 and 0017	
	Vadadustat N=1739	Darbepoetin Alfa N=1732	Vadadustat N=1947	Darbepoetin Alfa N=1955
Number of dose adjustments: Median (25% to 75% IQR, min-max)	3 (2-6, 1-24)	5 (3-9, 1-35)	2 (2-5, 0-15)	6 (3-10, 0-41)
Dose decrease occurred?, n (%)	1216 (69.9)	1376 (79.5)	1224 (62.87)	1655 (85.66)
Number of dose decrease: Median (25% to 75% IQR, min-max)	2 (1-3, 1-12)	3 (1-4, 1-15)	1 (0-2, 0-8)	2 (1-4, 0-17)
Duration of treatment without drug interruption periods (weeks)[2]				
Mean (SD)	61.7 (43.6)	67 (44.8)	50.5 (33.7)	60.6 (32.1)
Median (25% to 75% IQR)	51.6 (29.1-90)	57.1 (32.1-98.5)	46.3 (22-74)	59.4 (37.7-82.1)
Min, Max	0.1, 198.3	0.14, 192.9	0, 156	0.1, 157
Total Exposure (person years)	2057	2224	1884	2272

Source: SDTM dataset; software: JMP
Abbreviations: N, number of subjects in group; n, number of subjects with exposure characteristic; SD, standard deviation; IQR, Interquartile range.
[1]Duration of treatment calculated as follows: [(date of last dose – date of first dose) +1]
[2]Duration of treatment calculated by subtracting the total period of drug interruption from the standard duration of treatment
Abbreviations: N, number of subjects in group; n, number of subjects with exposure characteristic; SD, standard deviation; IQR, Interquartile range..

Summary:

Overall, we did not identify any major data quality or integrity issues that precluded performing a thorough safety review. The safety database is adequate for the comprehensive safety assessment of vadadustat for the proposed indication, patient population, dosage regimen and duration. In relation to the study site excluded from the safety database in the NDD-CKD population, a thorough evaluation of baseline characteristics, study drug assignment and adverse event occurrence was conducted. In addition, appropriate sensitivity analysis of overall results and conclusions, with and without the excluded data, was conducted, which concluded that the exclusion of these patients did not impact the overall conclusion of the review.

The difference of exposure observed between vadadustat and darbepoietin alfa may be explained by the early discontinuation of vadadustat due to adverse events, generally within the first 6 months of therapy. This finding is further supported by the dropout analysis of the phase 3 trials. Another factor impacting the total duration of exposure is the significant total duration of drug interruption, mainly due to adherence to drug adjustment protocols, which allowed for the safe administration of the study drug. Given the impact of these two factors on actual drug exposure, the clinical review team utilized an exposure-adjustment approach in their analysis that corrected for the total exposure (in person-years), by removing the drug interruption periods. This approach does not sufficiently account for residual PD effects of the study drug and results will be considered as a sensitivity analysis due to this limitation.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, NDD-CKD

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Pooled Trials 0014 and 0015

Table 67 provides a frequency-based overview of TEAEs reported in the safety population during the on-study period for the NDD-CKD population, obtained from the pooled trials 0014 and 0015, while Table 68 provides the exposure-adjusted analysis of the same data. Based on the frequency-based analysis, there were no clinically significant differences between study arms in relation to TEAE occurrence, severe AE occurrence, SAE occurrence, and fatal SAE occurrence. However, based on exposure-adjusted analysis, subjects on vadadustat experienced a higher rate of severe AE, SAE, and fatal SAE, compared to subjects on darbepoetin alfa. Both frequency-based and exposure-adjusted analysis demonstrated that subjects on vadadustat experienced a higher rate of AE leading to permanent treatment discontinuation and AE leading to dose modification, such as interruption and dose reduction of study drug, when compared to subjects on darbepoetin alfa.

Table 67. Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Pooled Trials 0014 and 0015

Event	Vadadustat N=1739 n (%)	Darbepoetin Alfa N=1732 n (%)	Relative Risk	Risk Difference (%)
Any treatment-emergent AE	1565 (90.0)	1553 (89.7)	1.00	0.3
Severe AEs	815 (46.9)	782 (45.2)	1.04	1.7
SAEs	1077 (61.9)	1049 (60.6)	1.02	1.4
SAEs with fatal outcome	319 (18.3)	307 (17.7)	1.03	0.6
AEs leading to permanent discontinuation of study drug	164 (9.4)	104 (6)	1.57	3.4
AEs leading to dosage modification of study drug	349 (20.1)	198 (11.4)	1.76	8.6
AEs leading to interruption of study drug	324 (18.6)	178 (10.3)	1.81	8.4
AEs leading to reduction of study drug	35 (2.0)	21 (1.2)	1.66	0.80
AEs leading to dosage delay of study drug	0	0	0	0

Source: ADEM and SDTM datasets; Software: R and JMP
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

Table 68. Exposure-Adjusted Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0014 and 0015

Event	Vadadustat N=2057 PY (/ 100 yrs)	Darbepoetin Alfa N=2224 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Any treatment-emergent AE	76.08	69.83	1.09	6.25
Severe AEs	39.62	35.16	1.13	4.46
SAEs	52.36	47.17	1.11	5.19
SAEs with fatal outcome	15.51	13.8	1.12	1.71
AEs leading to permanent discontinuation of study drug	7.97	4.68	1.70	3.29
AEs leading to dosage modification of study drug	16.97	8.90	1.91	8.07
AEs leading to interruption of study drug	15.75	8.00	1.97	7.75
AEs leading to reduction of study drug	1.70	0.94	1.81	0.76
AEs leading to dosage delay of study drug	0	0 (0)	0	0

Source: SDTM datasets; Software: JMP
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; SAE, serious adverse event

Summary:

In the NDD-CKD population, vadadustat is associated with a higher rate of AEs leading to permanent discontinuation and AEs leading to dosage modification of study drug. In addition, vadadustat maybe associated with higher rates of severe TEAEs, SAEs and fatal SAEs in the NDD-CKD population.

7.6.1.2. Deaths, Pooled Trials 0014 and 0015

A total of 626 subjects died during the on-study period for the NDD-CKD population, obtained from the pooled trials 0014 and 0015, with 319 subjects receiving vadadustat and 307 subjects receiving darbepoetin alfa, as summarized in Table 69. The rates of all-cause mortality are comparable between the two treatment arms, with a trend towards a higher relative risk of death due to cerebrovascular causes with vadadustat compared to darbepoetin alfa. Table 70 summarizes key characteristics of patients who died while on-study. There were no observed clinically significant differences in key demographic characteristics but subjects on vadadustat had a shorter drug exposure duration prior to death and experienced a slightly earlier study day of death.

Table 69. Deaths in Safety Population, on-Study Period, Pooled Trial 0014 and 0015

Deaths	Vadadustat N=1739 n (%)	Darbepoetin Alfa N=1732 n (%)	Relative Risk	Risk Difference (%)
Treatment-emergent deaths[1]	319 (18.3)	307 (17.7)	1.03	0.6
Acute cardiovascular/vascular causes	82 (4.7)	82 (4.7)	1.00	0
Cerebrovascular causes	19 (1.1)	9 (0.5)	2.10	0.6
Infectious causes	48 (2.8)	41 (2.4)	1.17	0.4
Renal/electrolyte disturbances causes	58 (3.3)	68 (3.9)	0.85	-0.6
Acute respiratory causes	15 (0.9)	13 (0.8)	1.47	0.1
Oncological causes	12 (0.7)	21 (1.2)	0.57	-0.5
Non-specific/unknown causes	73 (4.2)	60 (3.5)	1.21	0.7
Other causes	12 (0.7)	13 (0.6)	0.92	-0.1

Source: ADEM and SDTM datasets; Software: R and JMP
[1] Grouping definitions for causes of death can be found in section III.17.4.1.
Abbreviations: N, number of subjects in group; n, number of deaths.

Table 70. Characteristics of Subjects Experiencing Death During on-Study Period in the Safety Population, Pooled Trial 0014 and 0015

Characteristic	Vadadustat N=319	Darbepoetin Alfa N=307
Age (years), mean (SD)	70.6 (13.7)	70.8 (13.3)
Male, n (%)	162 (51)	154 (50)
U.S. subjects, n (%)	155 (49)	170 (55)
Subjects in developed countries[1], n (%)	174 (55)	184 (60)
Maximal Dose[2], median (25%-75% IQR)	450 (300 – 600)	0.53 (0.33 – 0.84)
Final Dose[2], median (25%-75% IQR)	450 (300 – 600)	0.39 (0.19 – 0.68)
Duration of Exposure (days), median (25%-75% IQR)	226 (96 – 396)	259 (124 – 466)
Study day of death, median (25%-75% IQR)	365 (201 – 593)	371 (215 – 659)

Source: SDTM datasets; Software: JMP
[1] Developed countries are defined by the availability and advancement of the practice of medicine, based on information collected by the world health organization. Listing of countries according to “developed” versus “developing” status can be found in section III.17.4.2
[2] The dosage unit for subjects on vadadustat is mg. The dosage unit for patient on darbepoetin alfa is µg/kg/week.
Abbreviations: IQR, Interquartile range; N, total number of deaths in group; n, number of subjects; U.S., United States.

Summary:

In the NDD-CKD population, the rates of all-cause mortality are comparable between the two treatment arms. However, there may be a trend towards a higher relative risk of death due to cerebrovascular causes, in patients on vadadustat. In addition, patients on vadadustat had a shorter drug exposure duration prior to death.

7.6.1.3. Serious Adverse Events, Pooled Trials 0014 and 0015

There were 6432 SAEs in 2126 subjects in the NDD-CKD population, with 3264 SAEs occurring in the vadadustat arm and 3168 SAEs occurring in the darbepoetin alfa arm. Table 71 provides a frequency-based comparison of thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for the NDD-CKD population, obtained from the pooled trials 0014 and 0015. There was a numerically higher occurrence of acute arterial thrombotic SAEs in the vadadustat arm, such as unadjudicated CV thrombosis and TIA, while occurrence was similar between study arms in unadjudicated cerebrovascular accident (CVA). The occurrence of chronic/sub-acute thrombotic SAEs, such as atherosclerotic disease and AV connection stenosis, was also similar between study arms. In contrast, there was a numerical trend toward higher occurrence of acute venous thrombotic SAEs in the darbepoetin arm. There were no other concerning SAEs that occurred at an incidence of <2%.

Table 71. Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Pooled Trial 0014 and 0015

Serious Adverse Event[1]	Vadadustat N=1739 n (%)	Darbepoetin Alfa N=1732 n (%)	Relative Risk	Risk Difference (%)
Atherosclerotic disease	49 (2.8)	49 (2.8)	1.00	0
Cardiac disorders (SOC)	281 (16.2)	292 (16.9)	0.96	-0.7
Unadjudicated cardiovascular thrombotic event	86 (5.0)	79 (4.6)	1.08	0.4
Unadjudicated cardiac life-threatening event	55 (3.2)	54 (3.1)	1.01	0
Unadjudicated cardiac failure	140 (8.1)	155 (9.0)	0.90	-0.9
Nervous system disorders (SOC)	124 (7.1)	117 (6.8)	1.06	0.4
Unadjudicated cerebrovascular accident	40 (2.3)	42 (2.4)	0.95	-0.1
Transient ischemic attack	12 (0.7)	6 (0.4)	1.99	0.3
Product issues (SOC)	5 (0.3)	10 (0.6)	0.50	-0.3
AV connection stenosis	4 (0.2)	5 (0.3)	0.80	-0.1
AV fistula maturation failure	2 (0.1)	0 (0)	-	0.1
Respiratory, thoracic, and mediastinal disorders (SOC)	113 (6.5)	135 (7.8)	0.83	-1.3
Vascular disorders (SOC)	105 (6.0)	120 (6.9)	0.87	-0.9
VTE disease	22 (1.3)	31 (1.8)	0.71	-0.5
Arterial thrombosis	5 (0.3)	3 (0.2)	1.66	0.1

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat and at a higher incidence than in the darbepoetin alfa arm are considered SAEs of interest. The PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class; MedDRA, Medical Dictionary for Regulatory Activities; AV, Arteriovenous; VTE, venous thromboembolism.

Table 72 provides a frequency-based comparison of non-thrombotic SAE occurrence, by system organ class and FDA groupings, reported in the safety population during the on-study period for the NDD-CKD population, obtained from the pooled trials 0014 and 0015. The following SAEs had a numerically higher occurrence in the vadadustat arm: any bleeding, GI bleeding, diarrhea, abdominal pain, hepatobiliary disorders, and acute kidney injury. The following SAEs had a numerical trend toward higher occurrence in the darbepoetin alfa arm: hypertension,

hypertension emergency, and cancer. Infections, falls, fractures, seizures, and hyperkalemia were similar between study arms.

Table 72. Non-Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Pooled Trial 0014 and 0015

Serious Adverse Event[1]	Vadadustat N=1739 n (%)	Darbepoetin Alfa N=1732 n (%)	Relative Risk	Risk Difference (%)
Hypertension	17 (1.0)	22 (1.3)	0.77	-0.3
Hypertension emergency	25 (1.4)	42 (2.4)	0.59	-1.0
Seizures	7 (0.4)	5 (0.3)	1.39	0.1
Blood and lymphatic system disorders (SOC)	58 (3.3)	66 (3.8)	0.88	-0.5
Any bleeding adverse event	83 (4.8)	76 (4.4)	1.09	0.4
GI bleeding	46 (2.7)	39 (2.3)	1.17	0.4
Gastrointestinal disorders (SOC)	123 (7.1)	104 (6.0)	1.18	1.1
GI acid-related disease	18 (1.0)	18 (1.0)	1.00	0
Any gastrointestinal symptoms	31 (1.8)	17 (1.0)	1.82	0.8
Diarrhea	13 (0.8)	5 (0.3)	2.59	0.5
Nausea	2 (0.1)	1 (0.1)	1.99	0.1
Abdominal pain	10 (0.6)	1 (0.1)	9.96	0.5
Constipation	2 (0.1)	4 (0.2)	0.50	-0.1
Hepatobiliary disorders (SOC)	33 (1.9)	18 (1.0)	1.83	0.9
Hepatotoxicity	38 (2.2)	35 (2.0)	1.08	0.2
Infections and infestations (SOC)	327 (18.8)	339 (19.6)	0.96	-0.8
Systemic infection	131 (7.5)	131 (7.6)	1.00	0
Localized infection	241 (13.9)	244 (14.1)	0.98	-0.2
Injury, poisoning and procedural complications (SOC)	100 (5.8)	111 (6.4)	0.90	-0.7
Falls	20 (1.2)	21 (1.2)	0.95	-0.1
Fractures	50 (2.9)	51 (2.9)	0.98	-0.1
Metabolism and nutrition (SOC)	185 (10.6)	168 (9.7)	1.10	0.9
Neoplasm benign, malignant, and unspecified (SOC)	59 (3.4)	69 (4.0)	0.85	-0.6
Cancer	54 (3.1)	63 (3.6)	0.85	-0.5
Renal and urinary disorders (SOC)	631 (36.3)	631 (36.4)	1.00	-0.1
Acute kidney Injury	76 (4.4)	71 (4.1)	1.07	0.3
Hyperkalemia	33 (1.9)	35 (2.0)	0.94	-0.1
Hyperphosphatemia	0 (0)	0 (0)	0	0

Source: ADEM and SDTM datasets; Software: R and JMP

[1] MedDRA PTs that occurred at ≥2% in the vadadustat and at a higher incidence than in the darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.

Abbreviations: N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class; MedDRA, Medical Dictionary for Regulatory Activities; GI, gastrointestinal.

Summary:

In the safety evaluation of thrombotic SAEs in the NDD-CKD population, we detected a numerically higher occurrence of acute arterial thrombotic SAEs (unadjudicated CV thrombosis, TIA) in the vadadustat arm, compared to the darbepoetin alfa arm. This finding constitutes a major safety review issue. In relation to non-thrombotic SAEs, we detected a numerically higher occurrence of diarrhea, abdominal pain, GI bleeding, and hepatobiliary disorders in the vadadustat arm, compared to the darbepoetin alfa arm. These findings constitute major safety

review issues. There was also a higher occurrence of acute kidney injury in the vadadustat arm, which warrants further investigation.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Pooled Trials 0014 and 0015

In the NDD-CKD population, vadadustat is associated with higher rate of AEs leading to permanent discontinuation, compared to darbepoetin alfa (9.4% versus 6.0%). As shown in Table 73, the majority of this difference is attributable to the following AEs: GI symptoms (i.e., mainly abdominal pain, nausea, vomiting, and diarrhea), hepatotoxicity, and GI bleeding. Exposure adjustment of the overall rate of AEs leading to permanent discontinuation and their specific etiologies resulted in similar conclusions (exposure-adjusted analyses).

Table 73. Adverse Events Leading to Discontinuation, Safety Population, Pooled Trial 0014 & 0015

FDA Grouped PTs[1]	Vadadustat N=1739 n (%)	Darbepoetin Alfa N=1732 n (%)	Relative Risk	Risk Difference (%)
Subjects with at least 1 AE leading to discontinuation	164 (9.4)	104 (6)	1.57	3.4
End-stage renal disease	65 (3.7)	65 (3.8)	1.00	0
GI symptoms	25 (1.4)	1 (0.1)	24.00	1.4
Hepatotoxicity	12 (0.7)	0 (0)	-	0.7
Cancer	9 (0.5)	9 (0.5)	1.00	0
GI bleeding	5 (0.3)	0 (0)	-	0.3
Localized infection	5 (0.3)	4 (0.2)	1.26	0.1
Cardiac function failure	4 (0.2)	2 (0.1)	1.92	0.1
Acute kidney injury	3 (0.2)	1 (0.1)	2.83	0.1
Systemic infection	3 (0.2)	3 (0.2)	1.00	0
Unadjudicated cardiovascular thrombosis	2 (0.1)	2 (0.1)	1.00	0
Unadjudicated cerebrovascular accident	2 (0.1)	3 (0.2)	0.71	-0.1
GI acid disease	2 (0.1)	1 (0.1)	2.00	0.1
Hyperkalemia	2 (0.1)	1 (0.1)	2.00	0.1
Hypertension	2 (0.1)	4 (0.2)	0.52	-0.1
Rhabdomyolysis	2 (0.1)	0 (0)	-	0.1
Seizure	2 (0.1)	0 (0)	-	0.1

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3. PTs were included if they were AEs of interest or if occur in >2 subjects in the vadadustat arm.
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities; GI, gastrointestinal

Summary:

In the NDD-CKD population, vadadustat is associated with a higher rate of AEs leading to permanent discontinuation, with the most common etiologies being GI events and hepatotoxicity. These findings constitute major safety review issues.

7.6.1.5. Treatment-Emergent Adverse Events, Pooled Trials 0014 and 0015

There were 26,033 TEAEs in 3118 subjects in the NDD-CKD population, with 12,940 TEAEs occurring in the vadadustat arm and 13,093 TEAEs occurring in the darbepoetin alfa arm. Table 74 provides a frequency-based comparison of specific TEAE occurrence reported in the

safety population during the on-study period for the NDD-CKD population, obtained from the pooled trials 0014 and 0015, while Table 75 provides the exposure-adjusted analysis of the same data. The frequency-based analysis demonstrated that:

- The following TEAEs had a numerical trend toward higher occurrence in the vadadustat arm: TIA, AV fistula maturation failure, cerebrovascular atherosclerotic disease, GI acid-related disease, GI symptoms of diarrhea, nausea, and abdominal pain, acute kidney injury and hyperphosphatemia.
- The following TEAEs had a numerical trend toward higher occurrence in the darbepoetin alfa arm: unadjudicated CVA, VTE, access-related VTE, AV connection stenosis, most atherosclerotic diseases, hypertension and hypertensive-related AEs, fractures, cancer, and hyperkalemia.

There were no clinically significant differences between study arms in the remainder of the TEAEs. Adrenal disorders, as an adverse event of special interest (AESI), were reported as an adrenal mass in two subjects in the vadadustat arm vs. one subject in the darbepoetin alpha arm (0.1% vs. 0.1%) in the NDD-CKD population. All adrenal function assessments using an ACTH stimulation test were normal. The results from the exposure-adjusted analysis were consistent with the results from the frequency-based analysis but subjects on vadadustat experienced a higher rate of the following additional TEAEs: unadjudicated CV thrombosis, hepatotoxicity, any bleeding, and GI bleeding.

Rhabdomyolysis occurred in 14 subjects in the NDD-CKD population (10 subjects on vadadustat and 4 subjects on darbepoetin alfa), with 2 of 14 subjects being severe (both subjects being on vadadustat), 8 of 14 subjects being moderate (6 subjects on vadadustat and 2 subjects on darbepoetin alfa) and 4 of 14 subjects being mild (2 subjects on vadadustat and 2 subjects on darbepoetin alfa). Events were considered as a SAE in 8 of 14 subjects (6 subjects on vadadustat and 2 subjects on darbepoetin alfa) and 2 events led to permanent study drug discontinuation (all subjects being on vadadustat). Higher rates of moderate elevation in creatine phosphokinase (CPK) was observed in subjects on vadadustat, compared to subjects on darbepoetin alfa, in trial 0014 only. Overall, rhabdomyolysis in the NDD-CKD population was more prevalent in the vadadustat arm.

There is a drug interaction between vadadustat and statins. As noted in section II.8.2, vadadustat is known to increase the exposure of atorvastatin, simvastatin, and rosuvastatin, but not pravastatin. Additional information was collected from the patient narratives of the 10 subjects randomized to vadadustat who experienced rhabdomyolysis to explore whether drug interaction of vadadustat with statins was causative to the rhabdomyolysis events. First, subjects who were on a maximum approved dose of statins were identified because drug interaction with vadadustat will increase the systemic exposure of statins beyond the approved range of exposures, thus increasing the risk for statin adverse events. Out of the 10 subjects, only 2 subjects were at the maximally approved dose of statin. Of the 2 subjects, 1 subject was on rosuvastatin 10 mg when the rhabdomyolysis event occurred, 5 months after initiation of the statin. The other subject was on simvastatin 40 mg since 2012, but upon 7 months into concomitant use of vadadustat and the statin, rhabdomyolysis occurred. These two subjects are potential cases for drug interaction being causative to rhabdomyolysis events.

There were 4 subjects who experienced rhabdomyolysis 3 days (atorvastatin 20 mg), 10 months (atorvastatin 20 mg), 1.5 years (atorvastatin 40 mg), and >2 years (atorvastatin 10 mg) after concomitant use of vadadustat and the statin. However, these are less probable cases for drug

interaction being causative, either because the rhabdomyolysis events happened much later following concomitant use of vadadustat and statin, and/or these subjects were at lower than the maximum approved dose of statin. The highest approved dose for atorvastatin is 80 mg and there is no dose adjustment required for renal impaired subjects. Of the remaining 4 subjects, 2 were on pravastatin which does not interact with vadadustat, and 2 subjects did not report any statin use.

Based on the available data and analyses, it is difficult to delineate a clear causation for drug interaction leading to the rhabdomyolysis events in the vadadustat arm in the NDD-CKD population. Given the rarity of these events and the presence of clinical risk factors, obtained from review of the individual narratives, that may explain their occurrence, we concluded that the occurrence of rhabdomyolysis may not be related to study drug in the NDD-CKD population.

The incidence of therapeutic phlebotomy in the NDD-CKD population, to treat excessive Hb response and avoid the risk of complications, was examined. Therapeutic phlebotomy was used in 37 patients: 15 patients on vadadustat and 22 patients on darbepoetin alfa. Overall, therapeutic phlebotomy was used infrequently, occuring more in the dabepoetin alfa arm, as a treatment of excessive Hb response.

In assessing vitals signs for safety signals, there were no clinically significant differences between trial arms in relation to median, maximum and minimum values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate, throughout the on-study period. In addition, there were no findings of outlier risk difference ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in maximum SBP, maximum DBP, occurrence of hypotension, and evaluation of heart rate.

Table 74. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects on Vadadustat and TEAEs of Special Interest, Safety Population, Pooled Trial 0014 and 0015

FDA Grouped PTs[1]	Vadadustat N=1739 n (%)	Darbepoetin Alfa N=1732 n (%)	Relative Risk	Risk Difference (%)
Unadjudicated cardiovascular thrombosis	92 (5.3)	87 (5.0)	1.05	0.3
Unadjudicated cardiac life-threatening event	55 (3.2)	54 (3.1)	1.01	0
Unadjudicated cerebrovascular accident	40 (2.3)	51 (2.9)	0.78	-0.6
Transient ischemic attack	14 (0.8)	7 (0.4)	2.03	0.4
Arterial thrombosis	7 (0.4)	6 (0.4)	1.14	0.1
VTE disease	57 (3.3)	66 (3.8)	0.86	-0.5
Access-related VTE	20 (1.2)	28 (1.6)	0.71	-0.5
Access unrelated VTE	39 (2.2)	41 (2.4)	0.95	-0.1
AV connection stenosis	12 (0.7)	19 (1.1)	0.63	-0.4
AV fistula maturation failure	6 (0.4)	2 (0.1)	2.92	0.2
Atherosclerotic disease	123 (7.1)	139 (8.0)	0.88	-1.0
Coronary disease	49 (2.8)	57 (3.3)	0.86	-0.5
Cerebrovascular disease	23 (1.3)	10 (0.6)	2.28	0.7
Vascular disease	63 (3.6)	80 (4.6)	0.78	-1.0
Unadjudicated cardiac function failure	178 (10.2)	193 (11.1)	0.92	-0.9
Hypertension	302 (17.4)	343 (19.8)	0.88	-2.4
Hypertension emergency	46 (2.7)	70 (4.0)	0.66	-1.4
Hypertension caused pathology	12 (0.7)	15 (0.9)	0.79	-0.2

FDA Grouped PTs[1]	Vadadustat N=1739 n (%)	Darbepoetin Alfa N=1732 n (%)	Relative Risk	Risk Difference (%)
Seizures	12 (0.7)	12 (0.7)	1.00	0
Hepatotoxicity	75 (4.3)	69 (4.0)	1.08	0.3
Systemic infection	213 (12.3)	221 (12.8)	0.96	-0.5
Localized infection	615 (35.4)	640 (37.0)	0.96	-1.6
Any bleeding adverse event	262 (15.1)	245 (14.2)	1.07	0.9
GI bleeding	133 (7.7)	128 (7.4)	1.04	0.3
Mucocutaneous bleeding	91 (5.2)	87 (5.0)	1.04	0.2
Visceral bleeding	33 (1.9)	35 (2.0)	0.94	-0.1
GU bleeding	37 (2.1)	29 (1.7)	1.28	0.5
GI acid-related disease	158 (9.1)	142 (8.2)	1.11	0.9
Any gastrointestinal symptoms	583 (33.5)	455 (26.3)	1.28	7.3
Diarrhea	241 (13.9)	163 (9.4)	1.47	4.5
Nausea	161 (9.3)	129 (7.5)	1.24	1.8
Abdominal pain	95 (5.5)	74 (4.3)	1.28	1.2
Constipation	119 (6.8)	114 (6.6)	1.04	0.3
Falls	153 (8.8)	152 (8.8)	1.00	0
Fractures	100 (5.8)	116 (6.7)	0.86	-1.0
Cancer	96 (5.5)	108 (6.2)	0.88	-0.7
End stage renal disease	548 (31.5)	560 (32.3)	0.97	-0.8
Acute kidney injury	120 (6.9)	109 (6.3)	1.10	0.6
Peripheral edema	197 (11.3)	189 (10.9)	1.04	0.4
Hyperkalemia	189 (10.9)	221 (12.8)	0.85	-1.9
Hyperphosphatemia	109 (6.3)	93 (5.4)	1.17	0.9
Metabolic acidosis	101 (5.8)	76 (4.4)	1.32	1.4
Hypoglycemia	106 (6.1)	104 (6.0)	1.02	0.1
Back pain	95 (5.5)	82 (4.7)	1.17	0.8
Hypotension	100 (5.8)	89 (5.1)	1.14	0.7
Arthralgia	93 (5.4)	95 (5.5)	0.98	-0.1
Cough	88 (5.1)	96 (5.5)	0.93	-0.4
Vomiting	100 (5.8)	94 (5.4)	1.07	0.4

Source: SDTM datasets; Software: JMP
1, Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism.

Table 75. Exposure-Adjusted Treatment-Emergent Adverse Events, Safety Population, Pooled Trial 0014 and 0015

FDA Grouped PTs[1]	Vadadustat N= 2057 PY (/ 100 yrs)	Darbepoetin Alfa N=2224 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Unadjudicated cardiovascular thrombosis	4.47	3.91	1.14	0.56
Unadjudicated cardiac life-threatening event	2.67	2.43	1.10	0.24
Unadjudicated cerebrovascular accident	1.95	2.29	0.85	-0.34
Transient ischemic attack	0.68	0.31	2.19	0.37
Arterial thrombosis	0.34	0.27	1.26	0.07
VTE disease	2.77	2.97	0.93	-0.2
Access-related VTE	0.97	1.26	0.77	-0.29
Access unrelated VTE	1.9	1.84	1.03	0.06

FDA Grouped PTs[1]	Vadadustat N= 2057 PY (/ 100 yrs)	Darbepoetin Alfa N=2224 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
AV connection stenosis	0.58	0.85	0.68	-0.27
AV fistula maturation failure	0.29	0.09	3.22	0.2
Atherosclerotic disease	5.98	6.25	0.96	-0.27
Coronary disease	2.38	2.56	0.93	-0.18
Cerebrovascular disease	1.12	0.45	2.49	0.67
Vascular disease	3.06	3.6	0.85	-0.54
Unadjudicated cardiac function failure	8.65	8.68	1	-0.03
Hypertension	14.68	15.42	0.95	-0.74
Hypertension emergency	2.24	3.15	0.71	-0.91
Hypertension caused pathology	0.58	0.67	0.87	-0.09
Seizures	0.58	0.54	1.07	0.04
Hepatotoxicity	3.65	3.1	1.18	0.55
Systemic infection	10.35	9.94	1.04	0.41
Localized infection	29.9	28.78	1.04	1.12
Any bleeding adverse event	12.74	11.02	1.16	1.72
GI bleeding	6.47	5.76	1.12	0.71
Mucocutaneous bleeding	4.42	3.91	1.13	0.51
Visceral bleeding	1.6	1.57	1.02	0.03
GU bleeding	1.8	1.3	1.38	0.5
GI acid-related disease	7.68	6.38	1.2	1.3
Any gastrointestinal symptoms	28.34	20.46	1.39	7.88
Diarrhea	11.72	7.33	1.6	4.39
Nausea	7.83	5.8	1.35	2.03
Abdominal pain	4.62	3.33	1.39	1.29
Constipation	5.79	5.13	1.13	0.66
Falls	7.44	6.83	1.09	0.61
Fractures	4.86	5.22	0.93	-0.36
Cancer	4.67	4.86	0.96	-0.19
End stage renal disease	26.64	25.18	1.06	1.46
Acute kidney injury	5.83	4.9	1.19	0.93
Peripheral edema	9.58	8.5	1.13	1.08
Hyperkalemia	9.19	9.94	0.92	-0.75
Hyperphosphatemia	5.3	4.18	1.27	1.12

Source: SDTM datasets; Software: JMP

[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3

Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

Summary:

In the safety evaluation of frequency-based and exposure-adjusted TEAEs in the NDD-CKD population, we detected a higher occurrence of CV thrombosis, TIA, AV fistula maturation failure, hepatotoxicity, GI acid-related disease, GI bleeding, GI symptoms, acute kidney injury and hyperphosphatemia. These findings constitute major safety review issues. Adrenal disorders, as an AESI, were assessed with no detected safety signal. Even though rhabdomyolysis was more prevalent with vadadustat treatment, given the rarity of these events and the presence of appropriate clinical risk factors, the occurrence of rhabdomyolysis may not be related to study drug in the NDD-CKD population. However, given the numerical imbalance in this population, rhabdomyolysis should be an adverse event of interest in any future vadadustat trial.

7.6.1.1. Laboratory Findings, Pooled Trials 0014 and 0015

Clinically relevant laboratory abnormalities in the NDD-CKD population are presented in sections pertaining to the safety review issues of the respective organ system. Specifically, liver biochemistries are presented in section II.7.7.3. Table 76 shows other laboratory abnormalities that reached the outlier risk difference threshold of ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in the NDD-CKD population. Elevation of serum creatinine, decrease in eGFR and decrease in platelets, of all severities, was higher in the darbepoetin arm, compared to the vadadustat arm, in the NDD-CKD population. There were no clinically significant differences between trial arms in relation to the change in mean values of laboratory parameters from baseline to end of treatment values.

Table 76. Subjects Meeting Laboratory Abnormality Criteria From Baseline to ≥ Week 36, Risk Difference ≥1% Higher in Vadadustat Arm, Safety Population, Pooled Trial 0014 and 0015

Laboratory Analysis	Vadadustat N=1739	Darbepoetin Alfa N=1732	Risk Difference (%)
High sodium (mEq/L)	N=1538	N=1570	
Mild[1], n (%)	296 (19.2)	286 (18.2)	1.0
High chloride (mEq/L)	N=1537	N=1570	
Mild[2], n (%)	371 (24.1)	345 (22.0)	2.2

Source: ADEM datasets; Software: R.
[1] Mild high sodium defined as >144 mEq/L. [2] Mild high chloride defined as >108 mEq/L.
Abbreviations: N, number of subjects; n, number of subjects with abnormality.

7.6.1.2. Adverse Events of Special Interest

7.6.1.2.1. MACE and Other CV Outcomes

Table 77 summarizes the results from the Applicant's pre-specified analyses of MACE and key secondary outcomes. There were 382 (22.0%) and 344 (19.9%) subjects who had at least one adjudicated MACE event in the vadadustat and darbepoetin arms, respectively. Non-inferiority MACE risk in vadadustat compared to darbepoetin was not established in the pre-specified primary analysis. The estimated hazard ratio (HR) and corresponding 95% confidence interval (CI) were 1.17 (1.01, 1.36); the upper bound of the 95% CI was greater than the pre-specified risk margin of 1.25 and the interval did not include 1, with the increase driven by nonfatal myocardial infarction and nonfatal stroke (Figure 23). Estimated HRs of all other secondary outcomes were greater than one, although for CV death the estimate was nearly one.

Table 77. Number (%) of Subjects and HRs (95% CI) of MACE and Key Secondary CV Outcomes in NDD-CKD Population. Pre-Specified Analyses

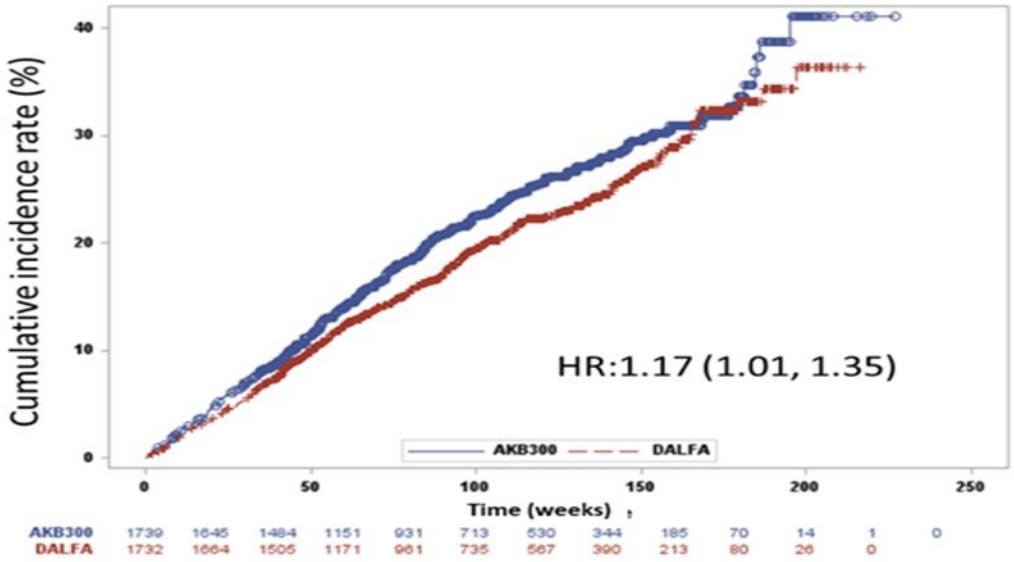
Outcome	Vadadustat N=1739 n (%)	Darbepoetin N=1732 n (%)	HR (95% CI)
MACE	382 (22.0)	344 (19.9)	1.17, (1.01, 1.36)
MACE 2	451 (25.9)	424 (24.5)	1.11, (0.97, 1.27)
CV MACE	198 (11.4)	178 (10.3)	1.16, (0.95, 1.42)
CV Death	127 (7.3)	131 (7.6)	1.01, (0.79, 1.29)
All Death	319 (18.3)	307 (17.7)	1.09, (0.93, 1.27)

Source: Generated by statistical reviewer from adtte.xpt, adsl.xpt datasets from PRO2TECT program.

Abbreviations: CI, confidence interval; CV Death, cardiovascular death; CV MACE, composite outcome of cardiovascular death, non-fatal MI or non-fatal stroke; HR, hazard ratio; MACE 2, MACE plus hospitalization for heart failure or thromboembolic event excluding vascular access thrombosis.

The FDA's on-study analysis of MACE using the modified region variable, was consistent with the pre-specified analysis (HR, 1.17; 95% CI, 1.01,1.35). In addition, the result from the sensitivity meta-analysis using inverse variance (on-study analysis) was also similar (HR, 1.16; 95% CI, 1.01, 1.35). The OT +7 MACE analysis results (HR, 1.50; 95% CI, 1.22, 1.85) were numerically higher. The Applicant's cumulative incidence rate of MACE (Figure 22) also illustrated a consistently higher risk of MACE over time in the vadadustat arm, compared to the darbepoetin arm.

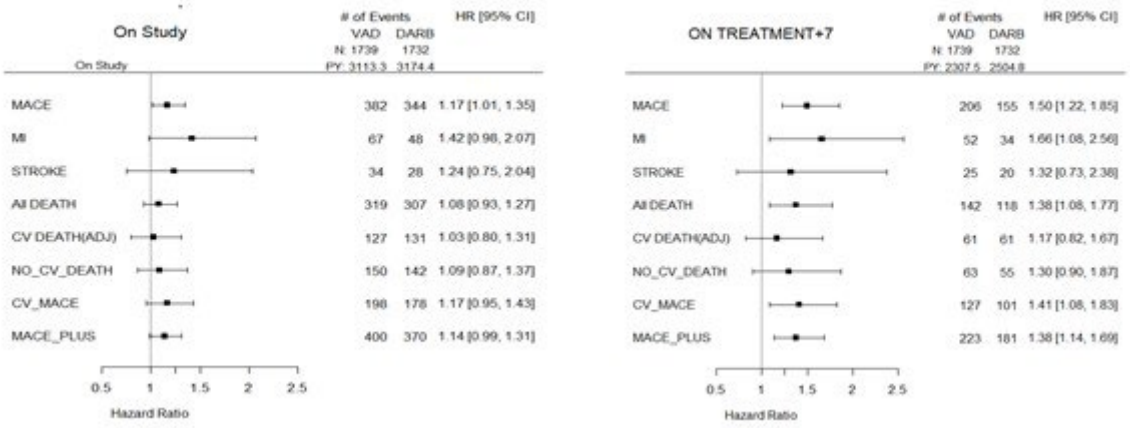
Figure 22. Cumulative Incidence Rate of MACE in NDD-CKD Population: on-Study Analysis



Source: Generated by statistical reviewer from adtte.xpt, adsl.xpt datasets from PRO2TECT program.
Abbreviation: AKB300, vadadustat; DALFA, darbepoetin alfa. HR, hazard ratio.

Figure 23 is the forest plot that summarizes the results of all CV outcomes from the reviewer's analyses. The estimated HRs of all other CV outcomes were greater than one. The estimated HRs of all CV outcomes were larger in the OT +7 analyses than those in the on-study analysis.

Figure 23. Risk of MACE, Death and Other CV Outcomes in NDD-CKD Population



Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from PRO2TECT program.
Abbreviations: MACE, major adverse cardiovascular event; MI, non-fatal myocardial infarction; CV DEATH(ADJ), death caused by cardiovascular events; NO_CV_DEATH, death unrelated to cardiovascular events; CV_MACE, composite outcome of non-fatal MI, non-fatal stroke and CV death; MACE_PLUS, composite outcome of non-fatal MI, non-fatal stroke, all-cause mortality and thromboembolic event; HR, hazard ratio; CI, confidence interval; VAD, vadadustat; DARB, darbepoetin alfa; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25) for on-treatment analysis.

Regarding death, a larger proportion of subjects assigned to vadadustat died (18.3%) compared to those to darbepoetin (17.7%). In both arms, the proportion of non-cardiovascular deaths was higher than CV-related deaths. (Table 78). The risk of all-cause mortality was slightly higher in the vadadustat arm compared to the darbepoetin arm (HR, 1.08; 95% CI, 0.93, 1.27). When accounting for the difference in duration of drug exposure (OT +7 analysis), the estimated HR (95% CI) of all-cause mortality was 1.38 (1.08, 1.77).

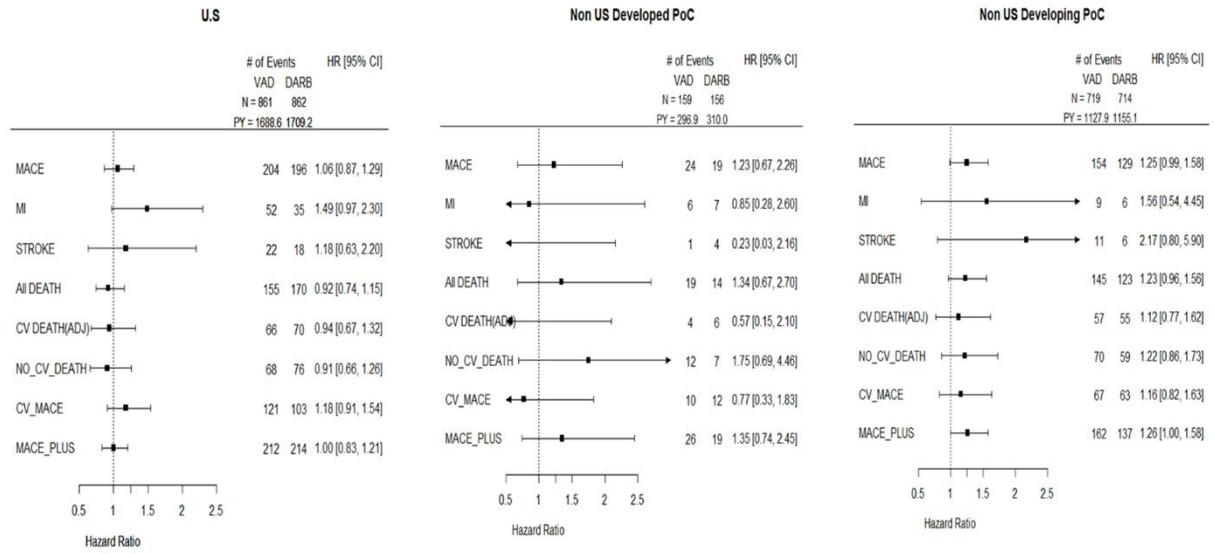
Table 78. Subjects Who Died During Study Period by Cause of Death in NDD-CKD Population

Cause of Death	Vadadustat N=1739 n (%)	Darbepoetin N=1732 n (%)
All death	319 (18.3)	307 (17.7)
CV death	127 (7.3)	131 (7.6)
Non-CV death	150 (8.6)	142 (8.2)
Unknown	42 (2.4)	34 (2.0)

Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt datasets from PRO2TECT program.
Abbreviations: CV, cardiovascular; N, number of subjects in group; n, number of subjects with serious adverse event; NDD-CKD, non-dialysis dependent-chronic kidney disease

Figure 24 presents the on-study analysis results by region (FDA's definition). A total of 1,723 subjects (49.6%) were recruited from the United States. The estimated HRs (95% CI) of MACE were 1.06 (0.87, 1.29), 1.23 (0.67, 2.26) and 1.25 (0.99, 1.58) for United States, non-U.S. developed practice-of-care (PoC) region and non-U.S. developing PoC region, respectively. In the U.S. population, non-fatal MI was the most noticeable CV outcome that showed a possible increased risk in the vadadustat arm compared to the darbepoetin arm (HR, 1.49; 95% CI, 0.97, 2.30).

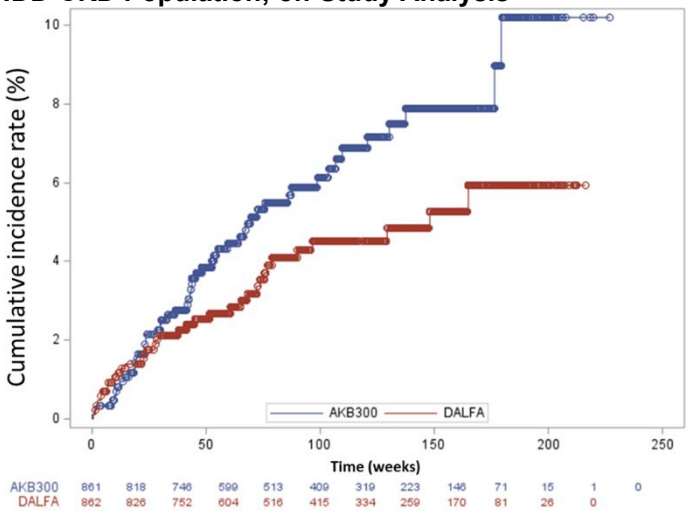
Figure 24. Risk of MACE, Death and Other CV Outcomes by Region in NDD-CKD Population: on-Study Analyses



Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from PRO2TECT program.
Abbreviations: MACE, major adverse cardiovascular event; MI, non-fatal myocardial infarction; CV DEATH(ADJ), death caused by cardiovascular events; NO_CV_DEATH, death unrelated to cardiovascular events; CV_MACE, composite outcome of non-fatal MI, non-fatal stroke and CV death; MACE_PLUS, composite outcome of non-fatal MI, non-fatal stroke, all-cause mortality and thromboembolic event; HR, hazard ratio; CI, confidence interval; VAD, vadadustat; DARB, darbepoetin alfa; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25) for on-treatment analysis.

Figure 25 shows the cumulative incidence rate of nonfatal MI in the U.S. population. The plots show a clear separation between the two groups over time. The analyses in the non-U.S. developed PoC region did not yield meaningful results because of the small sample size and limited number of events. In the non-U.S. developing region, the estimated risk of all CV outcomes was higher in the vadadustat arm with a HR >1.

Figure 25. Cumulative Incidence Rate of Non-Fatal Myocardial Infarction in the U.S. Population: NDD-CKD Population; on-Study Analysis



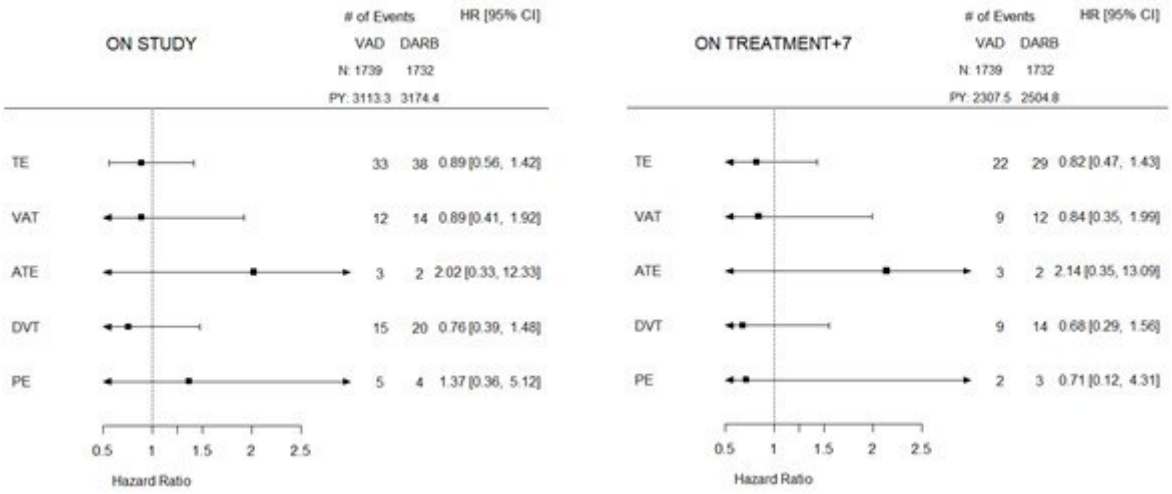
Source: Generated by statistical reviewer from adtte.xpt, adsl.xpt datasets from PRO2TECT program.
Abbreviation: AKB300, vadadustat; DALFA, darbepoetin alfa. HR, hazard ratio.

Subgroup analyses of MACE by other baseline variables are presented in section III.17.6.

7.6.1.2.2. Thromboembolic Events

Figure 26 includes the forest plots of thromboembolic events based on the Applicant's adjudicated data. There were 33 (1.9%) and 38 (2.2%) subjects who had at least one TE event during the study in the vadadustat and darbepoetin arms, respectively. The estimated HR of the adjudicated TE events was 0.89 (0.56, 1.42) in the on-study analysis. The OT +7 analysis results were consistent with the on-study analysis results.

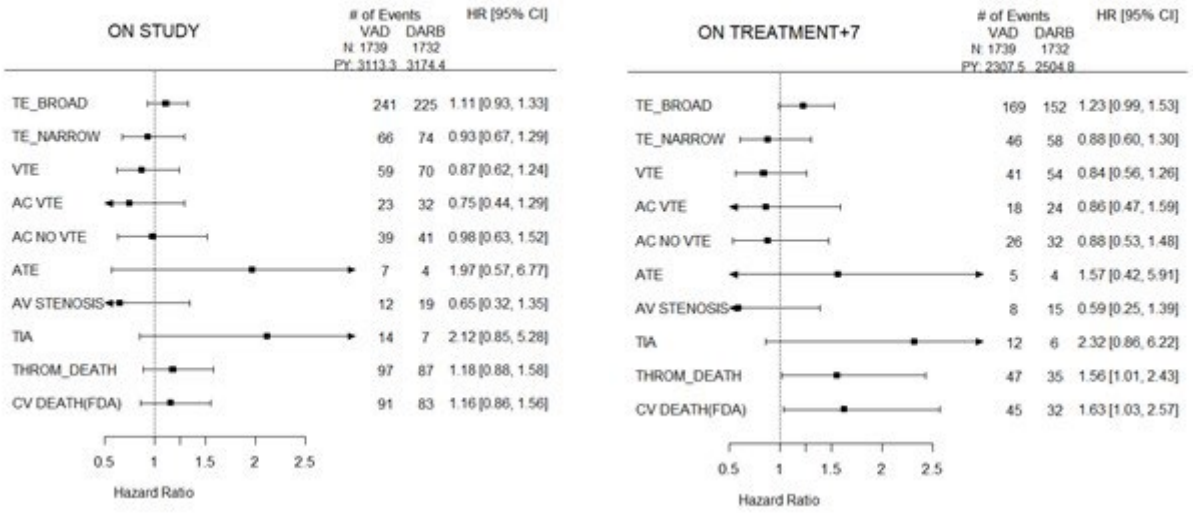
Figure 26. Risk of Thromboembolic Event and Sub-Outcomes Based on Adjudicated Data in NDD-CKD Population



Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from PRO2TECT program.
Abbreviations: TE, applicant's adjudicated thromboembolic events including arterial thrombosis, deep vein thrombosis, pulmonary embolism and vascular access thrombosis; VAT, vascular access thrombosis; ATE, arterial thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; HR, hazard ratio; CI, confidence interval; VAD, vadadustat; DARB, darbepoetin alfa; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25)for on-treatment analysis.

A greater number of TE events were identified using the Agency's definition (see section II.7.4 for details of definition) – 66 (3.8%) and 74 (4.3%) events in the vadadustat and darbepoetin arms, respectively (Figure 27). The estimated HR using the Agency's narrow TE definition (HR, 0.94; 95% CI, 0.67-1.29) was similar to the that using the Applicant's adjudicated data. The estimated risk of thrombosis-related death using the Agency's definition was higher in the vadadustat arm (HR, 1.18; 95% CI, 0.88, 1.58). HRs of ATE and TIA were estimated to be greater than one, but the number of events was small in both arms.

Figure 27. Risk of Thromboembolic Events and Sub-Outcomes Based on Agency's Definition in NDD-CKD Population



Source: Generated by statistical reviewer from ae.xpt, adsl.xpt datasets from PRO2TECT program.
Abbreviations: TE_BROAD, FDA's broad definition; TE_NARROW, FDA's definition including venous thrombosis and arterial thrombosis only; VTE, venous thrombosis; AC VTE, access-related venous thrombosis; AC NO VTE, access unrelated venous thrombosis; AV STENOSIS, arteriovenous connection stenosis; TIA, transient ischemic attack; THROM_DEATH, thrombosis-related death; CV DEATH(FDA), FDA's own definition of cardiovascular death; HR, hazard ratio; CI, confidence interval; VAD, vadadustat; DARB, darbepoetin alfa; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25)for on-treatment analysis.

The results by region did not provide meaningful results in the non-U.S. regions because of the small numbers of thromboembolic events (Table 79). In the U.S. population, vadadustat did not show an increased risk of thromboembolic events (HR, 0.60; 95% CI, 0.32, 1.12). The OT +7 analysis results were consistent with the on-study analysis results (data not shown).

Table 79. Number of Subjects With Thromboembolic Events and HR Based on Adjudicated Data in NDD-CKD Population

	United States		Non-U.S. Developed PoC		Non-U.S. Developing PoC	
Variable	Vadadustat N=861	Darbepoetin N=862	Vadadustat N=159	Darbepoetin N=156	Vadadustat N=719	Darbepoetin N=714
n (%)	16 (1.9)	27 (3.1)	2 (1.3)	1 (0.6)	15 (2.1)	10 (1.4)
HR (95% CI)	0.60 (0.32, 1.12)		2.98 (0.16, 56.10)		1.61 (0.72, 3.59)	

Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from PRO2TECT program.
Abbreviation: CI, confidence interval; HR, hazard ratio; NDD-CKD, non-dialysis dependent-chronic kidney disease; PoC, practice of care

7.6.2. Safety Findings and Concerns, Trial 0014

7.6.2.1. Overall Treatment-Emergent Adverse Event Summary, Trial 0014

Table 80 provides a frequency-based overview of TEAEs reported in the safety population during the on-study period for trial 0014, while Table 81 provides the exposure-adjusted analysis of the same data. Overall, there were no clinically significant differences between study arms in relation to TEAE occurrence and SAE occurrence. However, subjects on vadadustat experienced

a higher rate of severe AEs and fatal SAEs, compared to subjects on darbepoetin alfa, which was further appreciated in the exposure-adjusted analysis. Both frequency-based and exposure-adjusted analysis demonstrated that subjects on vadadustat experienced a higher rate of AEs leading to permanent treatment discontinuation and AEs leading to dose modification, such as interruption and dose reduction of study drug, when compared to subjects on darbepoetin alfa.

Table 80. Frequency-Based Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0014

Event	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Any treatment-emergent AE	798 (90.9)	797 (91.6)	0.99	-0.7
Severe AEs	463 (52.7)	432 (49.7)	1.06	3.1
SAEs	573 (65.3)	561 (64.5)	1.01	0.8
SAEs with fatal outcome	180 (20.5)	168 (19.3)	1.06	1.2
AEs leading to permanent discontinuation of study drug	84 (9.6)	60 (6.9)	1.39	2.7
AEs leading to dosage modification of study drug	167 (19.0)	121 (13.9)	1.37	5.1
AEs leading to interruption of study drug	148 (16.9)	106 (12.2)	1.38	4.7
AEs leading to reduction of study drug	21 (2.4)	16 (1.8)	1.30	0.6
AEs leading to dosage delay of study drug	0 (0)	0 (0)	0	0

Source: ADEM and SDTM datasets; Software: R and JMP
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

Table 81. Exposure-Adjusted Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0014

Event	Vadadustat N=984 PY (/ 100 yrs)	Darbepoetin Alfa N=1048 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Any treatment-emergent AE	81.10	76.05	1.07	5.05
Severe AEs	47.05	41.22	1.14	5.83
SAEs	58.23	53.53	1.09	4.70
SAEs with fatal outcome	18.29	16.03	1.14	2.26
AEs leading to permanent discontinuation of study drug	8.54	5.73	1.49	2.81
AEs leading to dosage modification of study drug	16.97	11.55	1.47	5.42
AEs leading to interruption of study drug	15.04	10.12	1.49	4.92
AEs leading to reduction of study drug	2.13	1.53	1.39	0.60
AEs leading to dosage delay of study drug	0	0 (0)	0	0

Source: SDTM datasets; Software: JMP
Abbreviations: AE, adverse event; SAE, serious adverse event; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; N, number of subjects in group; n, number of subjects with at least one event

7.6.2.2. Deaths, Trial 0014

A total of 348 subjects died during the on-study period of trial 0014, with 180 subjects on vadadustat and 168 subjects on darbepoetin alfa, as summarized in Table 82. Even though the

rates of all-cause mortality are comparable between the two treatment arms, subjects on vadadustat experienced a higher rate of death due to acute cardiovascular/vascular, cerebrovascular, infectious, and non-specific/unknown causes. Analysis of EAC-confirmed thrombotic deaths, which account for 26% of all causes of deaths, revealed a relative risk of 1.45, with a risk difference of 1.9%, in subjects on vadadustat. Table 83 summarizes key characteristics of subjects who died while on-study. There were no observed clinically significant differences in key demographic characteristics, drug exposure duration and study day of death.

Table 82. Deaths in Safety Population, on-Study Period, Trial 0014

Deaths	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Treatment-emergent deaths[1]	180 (20.5)	168 (19.3)	1.06	1.2
Acute cardiovascular/vascular causes	45 (5.1)	34 (3.9)	1.31	1.2
Cerebrovascular causes	9 (1.0)	3 (0.3)	3.03	0.7
Infectious causes	31 (3.5)	23 (2.6)	1.34	0.9
Renal/Electrolyte disturbances causes	41 (4.7)	47 (5.4)	0.86	-0.7
Acute respiratory causes	4 (0.5)	8 (0.9)	0.50	-0.5
Oncological causes	3 (0.3)	8 (0.9)	0.37	-0.6
Non-specific/Unknown causes	41 (4.7)	37 (4.3)	1.10	0.4
Other causes	6 (0.7)	8 (0.9)	0.74	-0.2

Source: ADEM and SDTM datasets; Software: R and JMP
[1] Grouping definitions for causes of death can be found in section III.17.4.1.
Abbreviations: N, number of subjects in group; n, number of deaths.

Table 83. Characteristics of Subjects Experiencing Death During on-Study Period in the Safety Population, Trial 0014

Characteristic	Vadadustat N=180	Darbepoetin Alfa N=168
Age (years) – mean (SD)	68.9 (14.5)	68.7 (14.5)
Male, n (%)	90 (50)	84 (50)
U.S. subjects, n (%)	92 (51)	101 (60)
Subjects in developed countries[1], n (%)	94 (52)	106 (63)
Maximal dose[2], median (25% to 75% IQR)	600 (300 – 600)	0.55 (0.35 – 0.78)
Final dose[2], median (25% to 75% IQR)	450 (300 – 600)	0.43 (0.19 – 0.70)
Duration of exposure (days), median (25% to 75% IQR)	210 (75 – 380)	221 (105 – 372)
Study day of death, median (25% to 75% IQR)	326 (156 – 591)	335 (190 – 626)

Source: SDTM datasets; Software: JMP
[1] Developed countries are defined by the availability and advancement of the practice of medicine, based on information collected by the world health organization. Listing of countries according to "developed" versus "developing" status can be found in section III.17.4.2.
[2] The dosage unit for subjects on vadadustat is mg. The dosage unit for subject on darbepoetin alfa is µg/kg/week.
Abbreviations: IQR, Interquartile range N, total number of deaths in group; n, number of subjects; U.S., United States.

7.6.2.3. Serious Adverse Events, Trial 0014

There were 3,548 SAEs in 1,134 subjects in trial 0014, with 1,823 SAEs occurring in the vadadustat arm and 1,725 SAEs occurring in the darbepoetin alfa arm. Table 84 provides a frequency-based comparison of thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for trial 0014. Given the relatively small number of individual thrombotic SAEs, there were no clinically significant differences between study arms. However, TIA (0.7% vs. 0.4%) and VTE (1.5% vs. 1.2%) had a numerically higher occurrence in the vadadustat arm, while unadjudicated CVA

(2.2% vs. 3.1%) had a numerical trend toward higher occurrence in the darbepoetin alfa arm. There were no other concerning SAEs that occurred at an incidence of <2%.

Table 84. Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings[1], Safety Population, Trial 0014

Adverse Events	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Atherosclerotic disease	32 (3.65)	30 (3.45)	1.06	0.2
Cardiac disorders (SOC)	158 (18.00)	147 (16.90)	1.07	1.1
Unadjudicated cardiovascular thrombotic event	40 (4.56)	43 (4.94)	0.92	-0.38
Unadjudicated cardiac life-threatening event	38 (4.33)	30 (3.45)	1.26	0.88
Unadjudicated cardiac function failure	79 (9.00)	79 (9.08)	0.99	-0.08
Nervous system disorders (SOC)	66 (7.52)	71 (8.16)	0.92	-0.64
Unadjudicated cerebrovascular accident	19 (2.16)	27 (3.10)	0.70	-0.94
Transient ischemic attack	6 (0.68)	3 (0.35)	1.98	0.33
Product issues (SOC)	5 (0.60)	5 (0.58)	1.04	0.02
AV connection stenosis	2 (0.23)	2 (0.23)	0.99	0
AV fistula maturation failure	0 (0)	0 (0)	-	0
Respiratory, thoracic, and mediastinal disorders (SOC)	63 (7.18)	68 (7.82)	0.92	-0.64
Vascular disorders (SOC)	56 (6.38)	70 (8.05)	0.79	-1.67
VTE disease	13 (1.48)	10 (1.15)	1.29	0.33
Arterial thrombosis	1 (0.11)	3 (0.35)	0.33	-0.24

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class; MedDRA, Medical Dictionary for Regulatory Activities; AV, Arteriovenous; VTE, venous thromboembolism.

Table 85 provides a frequency-based comparison of non-thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for trial 0014. The following SAEs had a numerical trend toward higher occurrence in the vadadustat arm: any bleeding, GI bleeding, diarrhea, abdominal pain, hepatobiliary disorders, and falls. The following SAEs had a numerical trend toward higher occurrence in the darbepoetin alfa arm: hypertension, hypertension emergency, fractures, cancer, and hyperkalemia. Infections and acute kidney injury were similar between study arms.

Table 85. Non-Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings1, Safety Population, Trial 0014

Adverse Events	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Hypertension	9 (1.03)	11 (1.26)	0.82	-0.23
Hypertension emergency	16 (1.82)	25 (2.87)	0.63	-1.05
Seizures	4 (0.46)	3 (0.35)	1.32	0.11
Blood and lymphatic system disorders (SOC)	34 (3.87)	37 (4.25)	0.91	-0.38
Any bleeding adverse event	49 (5.58)	39 (4.48)	1.24	1.1
GI bleeding	24 (2.73)	20 (2.30)	1.19	0.43

Adverse Events	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Gastrointestinal disorders (SOC)	67 (7.63)	56 (6.44)	1.19	1.19
GI acid-related disease	8 (0.91)	10 (1.15)	0.79	-0.24
Any gastrointestinal symptoms	20 (2.28)	10 (1.15)	1.98	1.13
Diarrhea	9 (1.03)	3 (0.35)	2.97	0.68
Nausea	2 (0.23)	0 (0)	-	0.23
Abdominal pain	5 (0.57)	0 (0)	-	0.57
Constipation	1 (0.11)	3 (0.35)	0.33	-0.24
Hepatobiliary disorders (SOC)	17 (1.94)	7 (0.81)	2.40	1.13
Hepatotoxicity	23 (2.62)	15 (1.72)	1.52	0.90
Infections and infestations (SOC)	172 (19.59)	185 (21.26)	0.92	-1.67
Systemic infection	79 (9.00)	76 (8.74)	1.03	0.26
Localized infection	121 (13.78)	131 (15.06)	0.92	-1.28
Injury, poisoning and procedural complications (SOC)	46 (5.24)	57 (6.55)	0.80	-1.31
Falls	12 (1.37)	9 (1.04)	1.32	0.33
Fractures	22 (2.51)	30 (3.45)	0.73	-0.94
Metabolism and nutrition (SOC)	105 (11.96)	95 (10.92)	1.10	1.04
Neoplasm benign, malignant, and unspecified (SOC)	26 (2.96)	37 (4.25)	0.71	-1.25
Cancer	23 (2.62)	31 (3.56)	0.74	-0.94
Renal and urinary disorders (SOC)	360 (41.00)	349 (40.11)	1.02	0.89
Acute kidney injury	42 (4.78)	40 (4.60)	1.04	0.18
Hyperkalemia	20 (2.28)	26 (3.00)	0.76	-0.72
Hyperphosphatemia	0 (0)	0 (0)	-	0

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial 0014

In trial 0014, vadadustat is associated with higher rate of AEs leading to permanent discontinuation, compared to darbepoetin alfa (9.6% versus 6.9%). As shown in Table 86, the majority of this difference is attributable to the following AEs: GI symptoms (i.e., mainly abdominal pain, nausea, vomiting, and diarrhea) and hepatotoxicity. Exposure adjustment of the overall rate of AEs leading to permanent discontinuation and their specific etiologies resulted in similar conclusions (exposure-adjusted analyses).

Table 86. Adverse Events Leading to Discontinuation, Safety Population, Trial 0014

FDA Grouped PTs[1]	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Subjects with at least one AE leading to discontinuation	84 (9.57)	60 (6.90)	1.39	2.67
End stage renal disease	33 (3.76)	35 (4.02)	0.94	-0.26
GI symptoms	10 (1.14)	2 (0.23)	4.96	0.91
Hepatotoxicity	8 (0.91)	0 (0)	-	0.91
Cancer	4 (0.46)	4 (0.46)	1.00	0.00
GI bleeding	1 (0.11)	0 (0)	-	0.11
Localized infection	3 (0.34)	4 (0.46)	0.74	-0.12

FDA Grouped PTs[1]	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Cardiac function failure	1 (0.11)	1 (0.11)	1.00	0.00
Acute kidney injury	2 (0.23)	1 (0.11)	2.09	0.12
Systemic infection	2 (0.23)	2 (0.23)	1.00	0.00
Unadjudicated cardiovascular thrombosis	1 (0.11)	1 (0.11)	1.00	0.00
Unadjudicated cerebrovascular accident	1 (0.11)	2 (0.23)	0.48	-0.12
GI acid disease	1 (0.11)	1 (0.11)	1.00	0.00
Hyperkalemia	1 (0.11)	1 (0.11)	1.00	0.00
Hypertension	2 (0.23)	3 (0.34)	0.68	-0.11
Rash	1 (0.11)	1 (0.11)	1.00	0.00
Arthralgias	1 (0.11)	1 (0.11)	1.00	0.00
Pleural effusion	0 (0)	2 (0.23)	0.00	-0.23
Seizure	1 (0.11)	0 (0)	-	0.11

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3. PTs were included if they were AEs of interest or if occur in >2 subjects in the vadadustat arm.
Abbreviations: AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term

7.6.2.5. Treatment-Emergent Adverse Events, Trial 0014

There were 14,010 TEAEs in 1,595 subjects in trial 0014, with 7,011 TEAEs occurring in the vadadustat arm and 6,999 TEAEs occurring in the darbepoetin alfa arm. Table 87 provides a frequency-based comparison of specific TEAE occurrence reported in the safety population during the on-study period for trial 0014, while Table 88 provides the exposure-adjusted analysis of the same data. The frequency-based analysis demonstrated that:

- The following TEAEs had a numerically higher occurrence in the vadadustat arm: TIA, cerebrovascular atherosclerotic disease, hepatotoxicity, certain sub-types of bleeding, diarrhea, nausea, abdominal pain, and acute kidney injury.
- The following TEAEs had a numerically higher occurrence in the darbepoetin alfa arm: unadjudicated CVA, most atherosclerotic diseases, hypertensive and hypertensive emergencies, fractures, cancer, and hyperkalemia.

There were no clinically significant differences between study arms in the remainder of the TEAEs. Adrenal disorders, as an AESI, were reported as an adrenal mass in one subject in each treatment arm (0.1% vs. 0.1%) in trial 0014. All adrenal function assessments using an ACTH stimulation test were normal. The results from the exposure-adjusted analysis were consistent with the results from the frequency-based analysis but subjects on vadadustat experienced a higher rate of the following additional TEAEs: GI acid-related disease, and fluid overload.

Rhabdomyolysis occurred in 7 subjects in trial 0014 (4 subjects on vadadustat and 3 subjects on darbepoetin alfa), with a moderate degree of severity in 6 of 7 subjects (4 subjects on vadadustat and 2 subjects on darbepoetin alfa), 5 of 7 events considered as a SAE (3 subjects on vadadustat and 2 subjects on darbepoetin alfa) and none of the events leading to permanent study drug discontinuation. Higher rates of moderate elevation in creatine phosphokinase (CPK) was observed in subjects on vadadustat, compared to subjects on darbepoetin alfa (2.5% vs. 1.6%). Overall, the occurrence and severity of rhabdomyolysis is balanced between treatment arms, is considered rare and, after review of the individual narratives, may be due to the presence of clinical risk factors.

The incidence of therapeutic phlebotomy in trial 0014, to treat excessive Hb response and avoid the risk of complications, was examined. Therapeutic phlebotomy was used in 31 patients, 12 patients on vadadustat and 19 patients on darbepoetin alfa. Overall, therapeutic phlebotomy was used infrequently, occuring more in the dabepoetin alfa arm, as a treatment of excessive Hb response.

In assessing vitals signs for safety signals, there were no clinically significant differences between trial arms in relation to median, maximum and minimum values of SBP, DBP and HR, throughout the on-study period. In addition, there were no findings of outlier risk difference ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in maximum SBP, maximum DBP, occurrence of hypotension, and evaluation of HR.

Table 87. Frequency-Based Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects on Vadadustat and TEAEs of Special Interest, Safety Population, Trial 0014

FDA Grouped PTs[1]	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Unadjudicated cardiovascular thrombosis	43 (4.9)	46 (5.29)	0.93	-0.39
Unadjudicated cardiac life-threatening event	38 (4.33)	30 (3.45)	1.26	0.88
Unadjudicated cerebrovascular accident	19 (2.16)	31 (3.56)	0.61	-1.40
Transient ischemic attack	8 (0.91)	3 (0.34)	2.68	0.57
Arterial thrombosis	3 (0.34)	4 (0.46)	0.74	-0.12
VTE disease	32 (3.64)	29 (3.33)	1.09	0.31
Access-related VTE	13 (1.48)	14 (1.61)	0.92	-0.13
Access unrelated VTE	19 (2.16)	16 (1.84)	1.17	0.32
AV connection stenosis	5 (0.8)	5 (0.6)	1.00	0
AV fistula maturation failure	2 (0.2)	2 (0.2)	1.00	0
Atherosclerotic disease	71 (8.1)	81 (9.3)	0.87	-1.2
Coronary disease	30 (3.4)	35 (4.0)	0.85	-0.6
Cerebrovascular disease	12 (1.4)	5 (0.6)	2.4	0.8
Vascular disease	37 (4.2)	48 (5.5)	0.76	-1.3
Unadjudicated cardiac function failure	102 (11.6)	100 (11.5)	1.01	0.1
Hypertension	166 (18.9)	206 (23.7)	0.8	-4.8
Hypertension emergency	27 (3.1)	43 (4.9)	0.62	-1.9
Hypertension caused pathology	9 (1.0)	9 (1.0)	1.00	0
Seizures	7 (0.8)	9 (1.0)	0.78	-0.2
Hepatotoxicity	42 (4.8)	32 (3.7)	1.3	1.1
Systemic infection	116 (13.2)	119 (13.7)	0.97	-0.5
Localized infection	303 (34.5)	323 (37.1)	0.93	-2.6
Any bleeding adverse event	142 (16.2)	135 (15.5)	1.04	0.7
GI bleeding	74 (8.4)	67 (7.7)	1.09	0.7
Mucocutaneous bleeding	42 (4.8)	51 (5.9)	0.82	-1.1
Visceral bleeding	22 (2.5)	19 (2.2)	1.15	0.3
GU bleeding	25 (2.9)	16 (1.8)	1.55	1.0
GI acid-related disease	85 (9.7)	78 (9.0)	1.08	0.7
Any gastrointestinal symptoms	320 (36.5)	245 (28.2)	1.29	8.3
Diarrhea	122 (13.9)	87 (10.0)	1.39	3.9
Nausea	88 (10.0)	71 (8.2)	1.23	1.9
Abdominal pain	48 (5.5)	33 (3.8)	1.44	1.7
Constipation	75 (8.5)	75 (8.6)	0.99	-0.1
Falls	84 (9.6)	87 (10.0)	0.96	-0.4
Fractures	51 (5.8)	58 (6.7)	0.87	-0.9
Cancer	48 (5.5)	53 (6.1)	0.9	-0.6
End stage renal disease	305 (34.7)	306 (35.2)	0.99	-0.4

FDA Grouped PTs[1]	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Relative Risk	Risk Difference (%)
Acute kidney injury	69 (7.9)	62 (7.1)	1.1	0.7
Peripheral edema	110 (12.5)	91 (10.5)	1.2	2.1
Fluid overload	73 (8.3)	69 (7.9)	1.05	0.4
Hyperkalemia	108 (12.3)	136 (15.6)	0.79	-3.3
Hyperphosphatemia	64 (7.2)	63 (7.2)	1.01	0.1
Metabolic acidosis	66 (7.5)	52 (6.0)	1.25	1.5
Hypoglycemia	60 (6.8)	65 (7.5)	0.91	-0.7
Back pain	57 (6.5)	45 (5.2)	1.25	1.3
Hypotension	52 (5.9)	55 (6.3)	0.94	-0.4
Arthralgia	48 (5.5)	47 (5.4)	1.02	0.1
Cough	47 (5.4)	58 (6.7)	0.81	-1.3
Dizziness	47 (5.4)	35 (4.0)	1.35	1.4
Headache	46 (5.2)	44 (5.1)	1.02	0.1

Source: SDTM datasets; Software: JMP
1, Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

Table 88. Exposure-Adjusted Treatment-Emergent Adverse Events, Safety Population, Trial 0014

FDA Grouped PTs[1]	Vadadustat N=984 PY (/ 100 yrs)	Darbepoetin Alfa N=1048 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Unadjudicated cardiovascular thrombosis	4.37	4.39	1.00	-0.02
Unadjudicated cardiac life-threatening event	3.86	2.86	1.35	1.00
Unadjudicated cerebrovascular accident	1.93	2.96	0.65	-1.03
Transient ischemic attack	0.81	0.29	2.79	0.52
Arterial thrombosis	0.30	0.38	0.79	-0.08
VTE disease	3.25	2.77	1.17	0.48
Access-related VTE	1.32	1.34	0.99	-0.02
Access unrelated VTE	1.93	1.53	1.26	0.4
AV connection stenosis	0.51	0.48	1.06	0.03
AV fistula maturation failure	0.2	0.19	1.05	0.01
Atherosclerotic disease	7.22	7.73	0.93	-0.51
Coronary disease	3.05	3.34	0.91	-0.29
Cerebrovascular disease	1.22	0.48	2.54	0.74
Vascular disease	3.76	4.58	0.82	-0.82
Unadjudicated cardiac function failure	10.37	9.54	1.09	0.83
Hypertension	16.87	19.66	0.86	-2.79
Hypertension emergency	2.74	4.1	0.67	-1.36
Hypertension caused pathology	0.91	0.86	1.06	0.05
Seizures	0.71	0.86	0.83	-0.15
Hepatotoxicity	4.27	3.05	1.4	1.22
Systemic infection	11.79	11.35	1.04	0.44
Localized infection	30.79	30.82	1	-0.03
Any bleeding adverse event	14.43	12.88	1.12	1.55
GI bleeding	7.52	6.39	1.18	1.13
Mucocutaneous bleeding	4.27	4.87	0.88	-0.6
Visceral bleeding	2.24	1.81	1.24	0.43
GU bleeding	2.54	1.53	1.66	1.01

FDA Grouped PTs[1]	Vadadustat N=984 PY (/ 100 yrs)	Darbepoetin Alfa N=1048 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
GI acid-related disease	8.64	7.44	1.16	1.2
Any gastrointestinal symptoms	32.52	23.38	1.39	9.14
Diarrhea	12.4	8.3	1.49	4.1
Nausea	8.94	6.77	1.32	2.17
Abdominal pain	4.88	3.15	1.55	1.73
Constipation	7.62	7.16	1.06	0.46
Falls	8.54	8.3	1.03	0.24
Fractures	5.18	5.53	0.94	-0.35
Cancer	4.88	5.06	0.96	-0.18
End stage renal disease	31	29.2	1.06	1.8
Acute kidney injury	7.01	5.92	1.18	1.09
Peripheral edema	11.18	8.68	1.29	2.5
Fluid overload	7.42	6.58	1.13	0.84
Hyperkalemia	10.98	12.98	0.85	-2
Hyperphosphatemia	6.5	6.01	1.08	0.49

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

7.6.2.6. Laboratory Findings, Trial 0014

Table 89 shows laboratory abnormalities that reached the outlier risk difference threshold of ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in trial 0014. In contrast to trial 0014, a decrease in platelets of all severities was higher in the darbepoetin arm, compared to the vadadustat arm, in trial 0015. There were no clinically significant differences between trial arms in relation to the change in mean values of laboratory parameters from baseline to end of treatment values.

Table 89. Subjects Meeting Laboratory Abnormality Criteria From Baseline to ≥ Week 36, Risk Difference ≥1% Higher in Vadadustat Arm, Safety Population, Trial 0014

Laboratory Analysis	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Risk Difference (%)
High sodium (mEq/L)	N=756	N=774	
Mild[1]	125 (16.5)	117 (15.1)	1.4
High chloride (mEq/L)	N=755	N=774	
Mild[2]	167 (22.1)	160 (20.7)	1.4
Low bicarbonate (mEq/L)	N=757	N=776	
Moderate[3]	337 (44.5)	337 (43.4)	1.1
Severe[4]	151 (19.9)	145 (18.7)	1.3
High magnesium (mg/dL)	N=755	N=774	
Mild[5]	377 (49.9)	372 (48.1)	1.9
High CPK (mg/dL)	N=755	N=773	
Moderate[6]	19 (2.5)	12 (1.6)	1.0
High BUN (mg/dL)	N=756	N=774	
Mild[7]	739 (97.8)	746 (96.4)	1.4
Severe[8]	697 (92.2)	705 (91.1)	1.1
Low eGFR (ml/min/1.73 m^2)	N=857	N=852	
Mild[9]	542 (63.2)	527 (61.9)	1.4

Laboratory Analysis	Vadadustat N=878 n (%)	Darbepoetin Alfa N=870 n (%)	Risk Difference (%)
Moderate[10]	234 (27.3)	214 (25.1)	2.2
High eosinophils (cells/µL)	N=743	N=769	
Mild[11]	96 (12.9)	84 (10.9)	2.0

Source: ADEM datasets; Software: R.
[1] Mild high sodium defined as > 144 mEq/L.
[2] Mild high chloride defined as > 108 mEq/L.
[3] Moderate low bicarbonate defined as < 18 mEq/L.
[4] Severe low bicarbonate defined as < 15 mEq/L.
[5] Mild high magnesium defined as > 2.3 mg/dL.
[6] Moderate high CPK defined as > 5x ULN.
[7] Mild high BUN defined as > 23 mg/dL.
[8] Severe high BUN defined as > 31 mg/dL.
[9] Mild low eGFR defined as ≥25% decrease from baseline.
[10] Moderate low eGFR defined as ≥50% decrease from baseline.
[11] Mild high eosinophils defined as > 650 cells/µL.
Abbreviations: BUN, blood urea nitrogen; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; N, number of subjects; n, number of subjects with abnormality; ULN, upper limit of normal

7.6.3. Safety Findings and Concerns, Trial 0015

7.6.3.1. Overall Adverse Event Summary, Trial 0015

Table 90 provides a frequency-based overview of TEAEs reported in the safety population during the on-study period for trial 0015, while Table 91 provides the exposure-adjusted analysis of the same data. Overall, there were no clinically significant differences between study arms in relation to TEAE occurrence, severe AEs occurrence, SAE occurrence and fatal SAE occurrence, based on the frequency-based analysis. However, subjects on vadadustat experienced a higher rate of TEAE, severe AEs, SAEs, and fatal SAEs, compared to subjects on darbepoetin alfa, when analysis was adjusted for exposure. Both frequency-based and exposure-adjusted analysis demonstrated that subjects on vadadustat experienced a higher rate of AEs leading to permanent treatment discontinuation and AEs leading to dose modification, such as interruption and dose reduction of study drug, when compared to subjects on darbepoetin alfa.

Table 90. Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0015

Event	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Any treatment-emergent AE	767 (89.1)	756 (87.7)	1.02	1.4
Severe AEs	352 (40.9)	350 (40.6)	1.01	0.3
SAEs	504 (58.5)	488 (56.6)	1.03	1.9
SAEs with fatal outcome	139 (16.1)	139 (16.1)	1.00	0
AEs leading to permanent discontinuation of study drug	80 (9.3)	44 (5.1)	1.82	4.2

Event	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
AEs leading to dosage modification of study drug	182 (21.1)	77 (8.9)	2.37	12.2
AEs leading to interruption of study drug	176 (20.4)	72 (8.4)	2.45	12.1
AEs leading to reduction of study drug	14 (1.6)	5 (0.6)	2.81	1.1
AEs leading to dosage delay of study drug	0	0	0	0

Source: ADEM and SDTM datasets; Software: R and JMP
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

Table 91. Exposure-Adjusted Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0015

Event	Vadadustat N=1073 PY (/ 100 yrs)	Darbepoetin Alfa N=1176 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Any treatment-emergent AE	71.48	64.29	1.11	7.19
Severe AEs	32.81	29.76	1.10	3.05
SAEs	46.97	41.5	1.13	5.47
SAEs with fatal outcome	12.95	11.82	1.10	1.13
AEs leading to permanent discontinuation of study drug	7.46	3.74	1.99	3.72
AEs leading to dosage modification of study drug	16.96	6.55	2.59	10.41
AEs leading to interruption of study drug	16.40	6.12	2.68	10.28
AEs leading to reduction of study drug	1.31	0.43	3.05	0.88
AEs leading to dosage delay of study drug	0	0 (0)	0	0

Source: SDTM datasets; Software: JMP
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment.

7.6.3.2. Deaths, Trial 0015

A total of 278 subjects died during the on-study period of trial 0015, with 139 subjects on vadadustat and 139 subjects on darbepoetin alfa, as summarized in Table 92. The rates of all-cause mortality are comparable between the two treatment arms, with no clear differences upon evaluation of specific causes of death, considering the small numbers of events for some of the analyses. Table 93 summarizes key characteristics of subjects who died while on-study. There were no observed clinically significant differences in key demographic characteristics but subjects on vadadustat had shorter drug exposure duration prior to death and experienced an earlier study day of death.

Table 92. Deaths in Safety Population, on-Study Period, Trial 0015

Deaths	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Treatment-emergent deaths[1]	139 (16.1)	139 (16.1)	1.00	0
Acute Cardiovascular/Vascular Causes	34 (4.0)	44 (5.1)	0.77	-1.2
Cerebrovascular Causes	10 (1.2)	6 (0.7)	1.67	0.5
Infectious Causes	17 (2.0)	18 (2.1)	0.95	-0.1

Deaths	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Renal/Electrolyte Disturbances Causes	17 (2.0)	21 (2.4)	0.81	-0.5
Acute Respiratory Causes	11 (1.3)	5 (0.6)	2.20	0.7
Oncological Causes	9 (1.1)	13 (1.5)	0.69	-0.5
Non-specific/Unknown Causes	35 (4.1)	27 (3.1)	1.30	0.9
Other Causes	6 (0.7)	5 (0.6)	1.20	0.1

Source: ADEM and SDTM datasets; Software: R and JMP
[1] Grouping definitions for causes of death can be found in section III.17.4.1.
Abbreviations: N, number of subjects in group; n, number of deaths.

Table 93. Characteristics of Subjects Experiencing Death During on-Study Period in the Safety Population, Trial 0015

Characteristic	Vadadustat N=139	Darbepoetin Alfa N=139
Age (years), mean (SD)	72.8 (12.5)	73.3 (11.3)
Male, n (%)	72 (52)	70 (50)
U.S. subjects, n (%)	63 (45)	69 (50)
Subjects in Developed Countries[1], n (%)	80 (58)	78 (56)
Maximal dose[2], median (25%-75% IQR)	450 (300 – 600)	0.52 (0.32 – 0.89)
Final dose[2], median (25%-75% IQR)	450 (300 – 600)	0.37 (0.19 – 0.66)
Duration of exposure (days), median (25%-75% IQR)	241 (117 – 419)	316 (141 – 568)
Study day of death, median (25%-75% IQR)	404 (247 – 609)	435 (239 – 781)

Source: SDTM datasets; Software: JMP
[1] Developed countries are defined by the availability and advancement of the practice of medicine, based on information collected by the world health organization. Listing of countries according to "developed" versus "developing" status can be found in section III.17.4.2.
[2] The dosage unit for subjects on vadadustat is mg. The dosage unit for patient on darbepoetin alfa is µg/kg/week.
Abbreviations: IQR, Interquartile range; N, total number of deaths in group; n, number of subjects

7.6.3.3. Serious Adverse Events, Trial 0015

There were 2,884 SAEs in 992 subjects in trial 0015, with 1,441 SAEs occurring in the vadadustat arm and 1,443 SAEs occurring in the darbepoetin alfa arm. Table 94 provides a frequency-based comparison of thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for trial 0015. There was a numerically higher occurrence of acute arterial thrombotic SAEs in the vadadustat arm, as observed in unadjudicated CV thrombosis (5.3% vs. 4.2%), unadjudicated CVA (2.4% vs. 1.7%), TIA (0.7% vs. 0.4%) and arterial thrombosis (0.5% vs. 0%). The occurrence of chronic/sub-acute thrombotic SAEs, such as atherosclerotic disease and AV connection stenosis, was also similar between study arms. In contrast, there was a numerical trend toward higher occurrence of acute venous thrombotic SAEs in the darbepoetin arm. There were no other concerning SAEs that occurred at an incidence of <2%.

Table 94. Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Trial 0015

Serious Adverse Event[1]	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Atherosclerotic disease	17 (2.0)	19 (2.2)	0.90	-0.2
Cardiac disorders (SOC)	123 (14.3)	145 (16.8)	0.85	-2.5
Unadjudicated cardiovascular thrombotic event	46 (5.3)	36 (4.2)	1.28	1.2
Unadjudicated cardiac life-threatening event	17 (2.0)	24 (2.8)	0.71	-0.8
Unadjudicated cardiac function failure	61 (7.1)	76 (8.8)	0.80	-1.7
Nervous system disorders (SOC)	58 (6.7)	46 (5.3)	1.26	1.4
Unadjudicated cerebrovascular accident	21 (2.4)	15 (1.7)	1.40	0.7
Transient ischemic attack	6 (0.7)	3 (0.4)	2.00	0.4
Product issues (SOC)	0 (0)	5 (0.6)	0	-0.6
AV connection stenosis	2 (0.2)	3 (0.4)	0.67	-0.1
AV fistula maturation failure	2 (0.2)	0 (0)	-	0.2
Respiratory, thoracic, and mediastinal disorders (SOC)	50 (5.8)	67 (7.8)	0.75	-2.0
Vascular disorders (SOC)	49 (5.7)	50 (5.8)	0.98	-0.1
VTE disease	9 (1.1)	21 (2.4)	0.43	-1.4
Arterial thrombosis	4 (0.5)	0 (0)	-	0.5

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class; MedDRA, Medical Dictionary for Regulatory Activities; AV, Arteriovenous; VTE, venous thromboembolism.

Table 95 provides a frequency-based comparison of non-thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for trial 0015. The following SAEs had a numerically higher occurrence in the vadadustat arm: GI bleeding (2.6% vs. 2.2%), GI acid-related disease (1.2% vs. 0.9%), diarrhea (0.5% vs. 0.3%), abdominal pain, hepatobiliary disorders – 1.9% vs. 1.3% (event rates of individual items of this SOC term were small, with no specific item accounting for the magnitude of this finding), fractures, acute kidney injury (4.0% vs. 3.6%) and hyperkalemia. The following SAEs had a numerical trend toward higher occurrence in the darbepoetin alfa arm: hypertension (0.9% vs. 1.3%), hypertension emergency, and falls. Infections and cancer were similar between study arms.

Table 95. Non-Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Trial 0015

Serious Adverse Event[1]	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Hypertension	8 (0.9)	11 (1.3)	0.73	-0.4
Hypertension emergency	9 (1.1)	17 (2.0)	0.53	-0.9
Seizures	3 (0.4)	2 (0.2)	1.50	0.1
Blood and lymphatic system disorders (SOC)	24 (2.8)	29 (3.4)	0.83	-0.6
Any bleeding adverse event	34 (4.0)	37 (4.3)	0.92	-0.3
GI bleeding	22 (2.6)	19 (2.2)	1.16	0.4

Serious Adverse Event[1]	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Gastrointestinal disorders (SOC)	56 (6.5)	48 (5.7)	1.15	0.8
GI acid-related disease	10 (1.2)	8 (0.9)	1.25	0.2
Any gastrointestinal symptoms	13 (1.5)	9 (1.0)	1.45	0.5
Diarrhea	4 (0.5)	2 (0.3)	2.00	0.2
Nausea	0 (0)	1 (0.1)	0	-0.1
Abdominal pain	5 (0.6)	1 (0.1)	5.01	0.4
Constipation	1 (0.1)	1 (0.1)	1.00	0
Hepatobiliary disorders (SOC)	16 (1.9)	11 (1.3)	1.45	0.6
Hepatotoxicity	15 (1.7)	20 (2.3)	0.75	-0.6
Infections and infestations (SOC)	155 (18.0)	154 (17.9)	1.01	0.1
Systemic infection	52 (6.0)	55 (6.4)	0.95	0.3
Localized infection	120 (13.9)	113 (13.1)	1.06	0.8
Injury, poisoning and procedural complications (SOC)	54 (6.3)	54 (6.3)	1.00	0
Falls	8 (0.9)	12 (1.4)	0.67	-0.5
Fractures	28 (3.3)	21 (2.4)	1.33	0.8
Metabolism and nutrition (SOC)	80 (9.3)	73 (8.5)	1.10	0.8
Neoplasm benign, malignant, and unspecified (SOC)	33 (3.8)	32 (3.7)	1.03	0.1
Cancer	31 (3.6)	32 (3.7)	0.97	-0.1
Renal and urinary disorders (SOC)	271 (31.5)	282 (32.7)	0.96	-1.2
Acute kidney injury	34 (4.0)	31 (3.6)	1.10	0.1
Hyperkalemia	13 (1.5)	9 (1.0)	1.45	0.5
Hyperphosphatemia	0 (0)	0 (0)	0	0

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class; MedDRA, Medical Dictionary for Regulatory Activities; GI, gastrointestinal.

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial 0015

In trial 0015, vadadustat is associated with higher rate of AEs leading to permanent discontinuation, compared to darbepoetin alfa (9.3% versus 5.1%). As shown in Table 96, the majority of this difference is attributable to the following AEs: GI symptoms (i.e., mainly abdominal pain, nausea, vomiting, and diarrhea), GI bleeding and hepatotoxicity. Exposure adjustment of the overall rate of AEs leading to permanent discontinuation and their specific etiologies resulted in similar conclusions (exposure-adjusted analyses).

Table 96. Adverse Events Leading to Discontinuation, Safety Population, Trial 0015

FDA Grouped PTs[1]	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Subjects with at least one AE leading to discontinuation	80 (9.3)	44 (5.1)	1.82	4.2
End stage renal disease	32 (3.7)	30 (3.5)	1.07	0.2
GI Symptoms	10 (1.2)	0 (0)	-	1.2
Hepatotoxicity	3 (0.4)	0 (0)	-	0.4
Cancer	5 (0.6)	4 (0.5)	1.26	0.1
GI bleeding	4 (0.5)	0 (0)	-	0.5
Localized Infection	2 (0.2)	0 (0)	-	0.2

FDA Grouped PTs[1]	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Cardiac Function Failure	3 (0.4)	1 (0.1)	2.92	0.2
Acute Kidney Injury	1 (0.1)	0 (0)	-	0.1
Systemic Infection	1 (0.1)	1 (0.1)	1.00	0.00
Unadjudicated cardiovascular thrombosis	1 (0.1)	1 (0.1)	1.00	0.00
Unadjudicated cerebrovascular accident	1 (0.1)	1 (0.1)	1.00	0.00
GI Acid Disease	1 (0.1)	0 (0)	-	0.1
Hyperkalemia	1 (0.1)	0 (0)	-	0.1
Hypertension	0 (0)	1 (0.1)	0.00	-0.1
Rhabdomyolysis	2 (0.2)	0 (0)	-	0.2
Adrenal Insufficiency	1 (0.1)	0 (0)	-	0.1
Seizure	1 (0.1)	0 (0)	-	0.1
Asthenia	2 (0.2)	0 (0)	-	0.2
Azotemia	1 (0.1)	1 (0.1)	1.00	0.00

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3. PTs were included if they were AEs of interest or if occur in >2 subjects in the vadadustat arm.
Abbreviations: AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term

7.6.3.5. Treatment-Emergent Adverse Events, Trial 0015

There were 12,023 TEAEs in 1,523 subjects in the NDD-CKD population, with 5,929 TEAEs occurring in the vadadustat arm and 6,094 TEAEs occurring in the darbepoetin alfa arm. Table 97 provides a frequency-based comparison of specific TEAE occurrence reported in the safety population during the on-study period for trial 0015, while Table 98 provides the exposure-adjusted analysis of the same data. The frequency-based analysis demonstrated that:

- The following TEAEs had a numerically higher occurrence in the vadadustat arm: unadjudicated CV thrombosis, AV fistula maturation failure, cerebrovascular atherosclerotic disease, GI acid-related disease, diarrhea, nausea, abdominal pain, hypoglycemia, and hyperphosphatemia.
- The following TEAEs had a numerically higher occurrence in the darbepoetin alfa arm: VTE, access-related VTE, access-unrelated VTE, AV connection stenosis, hypertensive-related AEs, fractures, and cancer.

There were no clinically significant differences between study arms in the remainder of the TEAEs. Adrenal disorders, as an AESI, were reported as an adrenal mass in one subject in the vadadustat arm vs. no subjects in the darbepoetin alpha arm (0.1% vs. 0%) in trial 0015. All adrenal function assessments using an ACTH stimulation test were normal. The results from the exposure-adjusted analysis were consistent with the results from the frequency-based analysis but subjects on vadadustat experienced a higher rate of the following additional TEAEs: any bleeding, and acute kidney injury.

Rhabdomyolysis occurred in 7 subjects in trial 0015 (6 subjects on vadadustat and 1 subject on darbepoetin alfa), with 2 of 7 subjects being severe, 2 of 7 subjects being moderate and 3 of 7 subjects being mild (2 subjects on vadadustat and 1 subject on darbepoetin alfa). Events were considered as a SAE in 3 of 7 subjects and 2 events led to permanent study drug discontinuation (all subjects being on vadadustat). There was no significant difference in CPK elevation observed between treatment arms. Overall, rhabdomyolysis is more prevalent in the vadadustat arm in trial 0015. However, given the rarity of these events and the presence of clinical risk

factors, obtained from review of the individual narratives, that may explain their occurrence, rhabdomyolysis may be unrelated to study drug in trial 0015.

The incidence of therapeutic phlebotomy in trial 0015, to treat excessive Hb response and avoid the risk of complications, was examined. Therapeutic phlebotomy was used in 6 patients, 3 patients on vadadustat and 3 patients on darbepoetin alfa. Overall, therapeutic phlebotomy was used infrequently and was balanced between the two treatment arms.

In assessing vitals signs for safety signals, there were no clinically significant differences between trial arms in relation to median, maximum and minimum values of SBP, DBP and heart rate, throughout the on-study period. In addition, there were no findings of outlier risk difference ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in maximum SBP, maximum DBP, occurrence of hypotension, and evaluation of HR.

Table 97. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects on Vadadustat and TEAEs of Special Interest, Safety Population, Trial 0015

FDA Grouped PTs[1]	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Unadjudicated cardiovascular thrombosis	49 (5.7)	41 (4.8)	1.20	0.9
Unadjudicated cardiac life-threatening event	17 (2.0)	24 (2.8)	0.71	-0.8
Unadjudicated cerebrovascular accident	21 (2.4)	20 (2.3)	1.05	0.1
Transient ischemic attack	6 (0.7)	4 (0.5)	1.5	0.2
Arterial thrombosis	4 (0.5)	2 (0.2)	2	0.2
VTE disease	25 (2.9)	37 (4.3)	0.68	-1.4
Access-related VTE	7 (0.8)	14 (1.6)	0.5	-0.8
Access unrelated VTE	20 (2.3)	25 (2.9)	0.8	-0.6
AV connection stenosis	7 (0.8)	14 (1.6)	0.5	-0.8
AV fistula maturation failure	4 (0.5)	0 (0)	-	0.5
Atherosclerotic disease	52 (6.0)	58 (6.7)	0.9	-0.7
Coronary disease	19 (2.2)	22 (2.6)	0.86	-0.4
Cerebrovascular disease	11 (1.3)	5 (0.6)	2.2	0.7
Vascular disease	26 (3.0)	32 (3.7)	0.81	-0.7
Unadjudicated cardiac function failure	76 (8.8)	93 (10.8)	0.82	-2.0
Hypertension	136 (15.8)	137 (15.9)	0.99	-0.1
Hypertension emergency	19 (2.2)	27 (3.1)	0.7	-0.9
Hypertension caused pathology	3 (0.4)	6 (0.7)	0.5	-0.4
Seizures	5 (0.6)	3 (0.4)	1.67	0.2
Hepatotoxicity	33 (3.8)	37 (4.3)	0.89	-0.5
Systemic infection	97 (11.3)	102 (11.8)	0.95	-0.6
Localized infection	312 (36.2)	317 (36.8)	0.99	-0.5
Any bleeding adverse event	120 (13.9)	110 (12.8)	1.09	1.2
GI bleeding	59 (6.9)	61 (7.1)	0.97	-0.2
Mucocutaneous bleeding	49 (5.7)	36 (4.2)	1.36	1.5
Visceral bleeding	11 (1.3)	16 (1.9)	0.69	-0.6
GU bleeding	12 (1.4)	13 (1.5)	0.92	-0.
GI acid-related disease	73 (8.5)	64 (7.4)	1.14	1.1
Any gastrointestinal symptoms	263 (30.6)	210 (24.4)	1.25	6.2
Diarrhea	119 (13.8)	76 (8.8)	1.57	5.0
Nausea	73 (8.5)	58 (6.7)	1.26	1.8
Abdominal pain	47 (5.5)	41 (4.8)	1.15	0.7
Constipation	44 (5.1)	39 (4.5)	1.13	0.6

FDA Grouped PTs[1]	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Relative Risk	Risk Difference (%)
Falls	69 (8.0)	65 (7.5)	1.06	0.5
Fractures	49 (5.7)	58 (6.7)	0.85	-1.0
Cancer	48 (5.6)	55 (6.4)	0.87	-0.8
Hypoglycemia	46 (5.3)	39 (4.5)	1.18	0.8
End stage renal disease	243 (28.2)	254 (29.5)	0.96	-1.2
Acute kidney injury	51 (5.9)	47 (5.5)	1.09	0.5
Peripheral edema	87 (10.1)	98 (11.4)	0.89	-1.3
Hyperkalemia	81 (9.4)	85 (9.9)	0.95	-0.5
Hyperphosphatemia	45 (5.2)	30 (3.5)	1.5	1.8
Hypotension	48 (5.6)	34 (4.0)	1.40	1.6
Arthralgia	45 (5.2)	48 (5.6)	0.93	-0.4
Bronchitis	50 (5.8)	34 (3.9)	1.49	-1.9

Source: SDTM datasets; Software: JMP
1 Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

Table 98. Exposure-Adjusted Treatment-Emergent Adverse Events, Safety Population, Trial 0015

FDA Grouped PTs[1]	Vadadustat N=1073 PY (/ 100 yrs)	Darbepoetin Alfa N=1176 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Unadjudicated cardiovascular thrombosis	4.57	3.49	1.31	1.08
Unadjudicated cardiac life-threatening event	1.58	2.04	0.78	-0.46
Unadjudicated cerebrovascular accident	1.96	1.70	1.15	0.26
Transient ischemic attack	0.56	0.34	1.65	0.22
Arterial thrombosis	0.37	0.17	2.18	0.2
VTE disease	2.33	3.15	0.74	-0.82
Access-related VTE	0.65	1.19	0.55	-0.54
Access unrelated VTE	1.86	2.13	0.87	-0.27
AV connection stenosis	0.65	1.19	0.55	-0.54
AV fistula maturation failure	0.37	0	-	0.37
Atherosclerotic disease	4.85	4.93	0.98	-0.08
Coronary disease	1.77	1.87	0.95	-0.1
Cerebrovascular disease	1.03	0.43	2.4	0.6
Vascular disease	2.42	2.72	0.89	-0.3
Unadjudicated cardiac function failure	7.08	7.91	0.9	-0.83
Hypertension	12.67	11.65	1.09	1.02
Hypertension emergency	1.77	2.3	0.77	-0.53
Hypertension caused pathology	0.28	0.51	0.55	-0.23
Seizures	0.47	0.26	1.81	0.21
Hepatotoxicity	3.08	3.15	0.98	-0.07
Systemic infection	9.04	8.67	1.04	0.37
Localized infection	29.08	26.96	1.08	2.12
Any bleeding adverse event	11.18	9.35	1.2	1.83
GI bleeding	5.5	5.19	1.06	0.31
Mucocutaneous bleeding	4.57	3.06	1.49	1.51
Visceral bleeding	1.03	1.36	0.76	-0.33
GU bleeding	1.12	1.11	1.01	0.01
GI acid-related disease	6.8	5.44	1.25	1.36
Any gastrointestinal symptoms	24.51	17.86	1.37	6.65
Diarrhea	11.09	6.46	1.72	4.63
Nausea	6.8	4.93	1.38	1.87

FDA Grouped PTs[1]	Vadadustat N=1073 PY (/ 100 yrs)	Darbepoetin Alfa N=1176 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Abdominal pain	4.38	3.49	1.26	0.89
Constipation	4.1	3.32	1.23	0.78
Falls	6.43	5.53	1.16	0.9
Fractures	4.57	4.93	0.93	-0.36
Cancer	4.47	4.68	0.96	-0.21
Hypoglycemia	4.29	3.32	1.29	0.97
End stage renal disease	22.65	21.6	1.05	1.05
Acute kidney injury	4.75	4	1.19	0.75
Peripheral edema	8.11	8.33	0.97	-0.22
Hyperkalemia	7.55	7.23	1.04	0.32
Hyperphosphatemia	4.19	2.55	1.64	1.64

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

7.6.3.6. Laboratory Findings, Trial 0015

Table 99 shows laboratory abnormalities that reached the outlier risk difference threshold of ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in trial 0015. It is important to note that elevation of creatinine and decrease in eGFR, of all severities, was higher in the darbepoetin arm, compared to the vadadustat arm, in trial 0015. There were no clinically significant differences between trial arms in relation to the change in mean values of laboratory parameters from baseline to end of treatment values.

Table 99. Subjects Meeting Laboratory Abnormality Criteria From Baseline to ≥ Week 36, Risk Difference ≥1% Higher in Vadadustat Arm, Safety Population, Trial 0015

Laboratory Analysis	Vadadustat N=861 n (%)	Darbepoetin Alfa N=862 n (%)	Risk Difference (%)
High Chloride (mEq/L)	N=782	N=796	
Mild[1]	204 (26.1)	185 (23.2)	2.8
Low Bicarbonate (mEq/L)	N=783	N=796	
Mild[2]	509 (65.0)	502 (63.1)	1.9
High Alkaline Phosphatase (mg/dL)	N=846	N=855	
Mild[3]	138 (16.3)	124 (14.5)	1.8
Moderate[4]	59 (7.0)	49 (5.7)	1.2
Low Platelets (cells/µL)	N=853	N=858	
Mild[5]	63 (7.4)	51 (5.9)	1.4

Source: ADEM datasets; Software: R.
[1] Mild high chloride defined as > 108 mEq/L.
[2] Mild low bicarbonate defined as < 20 mEq/L.
[3] Mild alkaline phosphatase defined as > 1.5x ULN.
[4] Moderate alkaline phosphatase defined as > 2x ULN.
[5] Mild low platelets defined as > 140,000 cells/µL.
Abbreviations: N, number of subjects; n, number of subjects with abnormality; ULN, upper limit of normal.

7.6.4. Safety Findings and Concerns, Pooled Trials 0016 and 0017

7.6.4.1. Overall Treatment-Emergent Adverse Event Summary, Pooled Trials 0016 and 0017

Table 100 provides a frequency-based overview of TEAEs reported in the safety population during the on-study period for the DD-CKD population obtained from the pooled trials 0016 and 0017, while Table 101 provides the exposure-adjusted analysis of the same data. Overall, there were no clinically significant differences between study arms in relation to TEAE occurrence, severe AEs occurrence, SAE occurrence and fatal SAE occurrence, based on the frequency-based analysis. However, subjects on vadadustat experienced a higher rate of TEAE, severe AEs, SAEs, and fatal SAEs, compared to subjects on darbepoetin alfa, when analysis was adjusted for exposure. Both frequency-based and exposure-adjusted analysis demonstrated that subjects on vadadustat experienced a higher rate of AEs leading to permanent treatment discontinuation and AEs leading to dose modification, such as interruption and dose reduction of study drug, when compared to subjects on darbepoetin alfa.

Table 100. Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Pooled Trials 0016 and 0017

Event	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Any treatment-emergent AE	1712 (87.9)	1739 (89.0)	0.99	-1.0
Severe AEs	767 (39.4)	812 (41.5)	0.95	-2.1
SAEs	1062 (54.6)	1137 (58.2)	0.94	-3.6
SAEs with fatal outcome	291 (15.0)	310 (15.9)	0.94	-0.9
AEs leading to permanent discontinuation of study drug	96 (4.9)	22 (1.1)	4.38	3.8
AEs leading to dosage modification of study drug	280 (14.4)	192 (9.8)	1.46	4.6
AEs leading to interruption of study drug	271 (13.9)	192 (9.8)	1.42	4.1
AEs leading to reduction of study drug	15 (0.8)	1 (0.1)	15.06	0.7
AEs leading to dosage delay of study drug	0 (0)	0 (0)	-	0

Source: ADEM and SDTM datasets; Software: R and JMP
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event;

Table 101. Exposure-Adjusted Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Pooled Trials 0016 and 0017

Event	Vadadustat N=1884 PY (/ 100 yrs)	Darbepoetin Alfa N=2272 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Any treatment-emergent AE	90.87	76.54	1.19	14.33
Severe AEs	40.71	35.74	1.14	4.97
SAEs	56.37	50.04	1.13	6.33
SAEs with fatal outcome	15.45	13.64	1.13	1.80
AEs leading to permanent discontinuation of study drug	5.10	0.97	5.26	4.13

Event	Vadadustat N=1884 PY (/ 100 yrs)	Darbepoetin Alfa N=2272 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
AEs leading to dosage modification of study drug	14.86	8.45	1.76	6.41
AEs leading to interruption of study drug	14.38	8.45	1.70	5.93
AEs leading to reduction of study drug	0.80	0.04	18.09	0.75
AEs leading to dosage delay of study drug	0	0	-	0

Source: SDTM datasets; Software: JMP
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; SAE, serious adverse event

Summary:

In the DD-CKD population, vadadustat is associated with higher rate of AEs leading to permanent discontinuation and AEs leading to dosage modification of study drug. In addition, vadadustat maybe associated with higher rates of any TEAEs, severe TEAEs, SAEs and fatal SAEs in the DD-CKD population.

7.6.4.2. Deaths, Pooled Trials 0016 and 0017

A total of 601 subjects died during the on-study period for the DD-CKD population obtained from the pooled trials 0016 and 0017, with 291 subjects on vadadustat and 310 subjects on darbepoetin alfa, as summarized in Table 102. The rates of all-cause mortality are comparable between the two treatment arms, with no clinically significant difference upon evaluation of specific causes of death. Table 103 summarizes key characteristics of subjects who died while on-study. There were no observed clinically significant differences in key demographic characteristics and study day of death but subjects on vadadustat had a shorter drug exposure duration prior to death.

Table 102. Deaths in Safety Population, on-Study Period, Pooled Trials 0016 and 0017

Deaths	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Treatment-emergent deaths[1]	291 (15.0)	310 (15.9)	0.94	-0.9
Acute cardiovascular/vascular causes	88 (4.5)	95 (4.9)	0.93	-0.3
Cerebrovascular causes	7 (0.4)	10 (0.5)	0.70	-0.2
Infectious causes	47 (2.4)	59 (3.0)	0.80	-0.6
Renal/electrolyte disturbances causes	24 (1.2)	20 (1.0)	1.20	0.2
Acute respiratory causes	12 (0.6)	17 (0.9)	0.71	-0.3
Oncological causes	4 (0.2)	13 (0.7)	0.31	-0.5
Non-specific/Unknown causes	85 (4.4)	77 (3.9)	1.11	0.4
Other causes	24 (1.2)	19 (1.0)	1.27	0.3

Source: ADEM and SDTM datasets; Software: R and JMP
[1] Grouping definitions for causes of death can be found in section III.17.4.1.
Abbreviations: N, number of subjects in group; n, number of deaths.

Table 103. Characteristics of Subjects Experiencing Death During on-Study Period in the Safety Population, Pooled Trials 0016 and 0017

Characteristics	Vadadustat N=291	Darbepoetin Alfa N=310
Age (years), mean (SD)	64.9 (12.1)	65.0 (11.8)
Male, n (%)	180 (61.9)	179 (57.7)
U.S. subject, n (%)	212 (72.9)	218 (70.3)
Subjects in developed countries[1], n (%)	227 (78.0)	239 (77.1)
Maximal dose[2], median (25% to 75% IQR)	450 (300 – 600)	0.72 (0.48 – 1.17)
Final dose[2], median (25% to 75% IQR)	450 (300 – 600)	0.53 (0.33 – 0.90)
Duration of exposure (days), median (25% to 75% IQR)	189 (98 – 357)	235 (113 – 384)
Study day of death, median (25% to 75% IQR)	350 (208 – 553)	347 (181 – 541)

Source: SDTM datasets; Software: JMP
[1] Developed countries are defined by the availability and advancement of the practice of medicine, based on information collected by the world health organization. Listing of countries according to "developed" versus "developing" status can be found in section III.17.4.2.
[2] The dosage unit for subjects on vadadustat is mg. The dosage unit for patient on darbepoetin alfa is µg/kg/week.
Abbreviations: IQR, Interquartile range; N, total number of deaths in group; n, number of subjects; U.S., United States

Summary:

In the DD-CKD population, the rates of all-cause mortality are comparable between the two treatment arms. However, patients on vadadustat had a shorter drug exposure duration prior to death.

7.6.4.3. Serious Adverse Events, Pooled Trials 0016 and 0017

There were 7,709 SAEs in 2,199 subjects in the DD-CKD population, with 3,718 SAEs occurring in the vadadustat arm and 3,991 SAEs occurring in the darbepoetin alfa arm. Table 104 provides a frequency-based comparison of thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for the DD-CKD population, obtained from the pooled trials 0016 and 0017. There was a numerically higher occurrence of acute venous thrombotic SAEs in the vadadustat arm. In contrast, with the exception of TIA, there was a numerically higher occurrence of acute arterial thrombotic SAEs in the darbepoetin arm, as observed in unadjudicated CV thrombotic events, and unadjudicated CVA. There was also a numerical trend toward higher occurrence of chronic/sub-acute thrombotic SAEs in the darbepoetin arm, as observed in atherosclerotic disease and AV connection stenosis. There were no other concerning SAEs that occurred at an incidence of <2%.

Table 104. Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Pooled Trial 0016 and 0017

Serious Adverse Event[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Atherosclerotic disease	93 (4.8)	103 (5.3)	0.91	-0.49
Cardiac disorders (SOC)	319 (16.4)	378 (19.3)	0.85	-2.95
Unadjudicated cardiovascular thrombotic event	107 (5.5)	119 (6.1)	0.90	-0.59
Unadjudicated cardiac life-threatening event	101 (5.2)	110 (5.6)	0.92	-0.44
Unadjudicated cardiac function failure	91 (4.7)	117 (6.0)	0.78	-1.31
Atrial fibrillation	47 (2.4)	41 (2.1)	1.15	0.31

Serious Adverse Event[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Nervous system disorders (SOC)	148 (7.6)	166 (8.5)	0.90	-0.89
Unadjudicated cerebrovascular accident	43 (2.2)	49 (2.5)	0.88	-0.30
Transient ischemic attack	16 (0.8)	7 (0.4)	2.30	0.46
Product issues (SOC)	14 (0.7)	11 (0.6)	1.28	0.16
AV connection stenosis	8 (0.4)	18 (0.9)	0.45	-0.51
Respiratory, thoracic, and mediastinal disorders (SOC)	194 (10.0)	201 (10.3)	0.97	-0.32
Acute respiratory failure	49 (2.5)	54 (2.8)	0.91	-0.24
Vascular disorders (SOC)	194 (10.0)	199 (10.2)	0.98	-0.21
VTE disease	123 (6.3)	116 (5.9)	1.06	0.38
Arterial thrombosis	4 (0.2)	6 (0.3)	0.67	-0.10

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: AV, arteriovenous; ;N, number of subjects in group; n, number of subjects with serious adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; VTE, venous thromboembolism.

Table 105 provides a frequency-based comparison of non-thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for the DD-CKD population, obtained from the pooled trials 0016 and 0017. The following SAEs had a numerically higher occurrence in the vadadustat arm: GI acid-related disease and hepatoxicity. The following SAEs had a numerically higher occurrence in the darbepoetin alfa arm: seizures, hypertension, any bleeding, GI bleeding, hyperkalemia, and cancer. GI symptoms, infections, falls, and fractures were similar between study arms.

Table 105. Non-Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Pooled Trial 0016 and 0017

Serious Adverse Event[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Hypertension	23 (1.2)	26 (1.3)	0.89	-0.15
Hypertension emergency	51 (2.6)	54 (2.8)	0.95	-0.14
Seizures	9 (0.5)	21 (1.1)	0.43	-0.61
Blood and lymphatic system disorders (SOC)	73 (3.8)	76 (3.9)	0.96	-0.14
Any bleeding adverse event	140 (7.2)	158 (8.1)	0.89	-0.89
GI bleeding	63 (3.2)	80 (4.1)	0.79	-0.86
Gastrointestinal disorders (SOC)	198 (10.2)	203 (10.4)	0.98	-0.21
GI acid-related disease	32 (1.6)	28 (1.4)	1.15	0.21
Any gastrointestinal symptoms	32 (1.6)	35 (1.8)	0.92	-0.15
Diarrhea	6 (0.3)	8 (0.4)	0.75	-0.10
Nausea	2 (0.1)	5 (0.3)	0.40	-0.15
Abdominal pain	14 (0.7)	15 (0.8)	0.94	-0.05
Constipation	6 (0.3)	2 (0.1)	3.01	0.21
Hepatobiliary disorders (SOC)	32 (1.6)	39 (2.0)	0.82	-0.35
Hepatotoxicity	42 (2.2)	32 (1.6)	1.32	0.52
Infections and infestations (SOC)	531 (27.3)	545 (27.9)	0.98	-0.60
Systemic infection	255 (13.1)	289 (14.8)	0.89	-1.69
Localized infection	302 (15.5)	305 (15.6)	0.99	-0.09
Injury, poisoning and procedural complications (SOC)	248 (12.7)	255 (13.0)	0.98	-0.31
Falls	18 (0.9)	19 (1.0)	0.95	-0.05
Fractures	57 (2.9)	68 (3.5)	0.84	-0.55

Serious Adverse Event[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Metabolism and nutrition (SOC)	209 (10.7)	219 (11.2)	0.96	-0.47
Neoplasm benign, malignant, and unspecified (SOC)	40 (2.1)	62 (3.2)	0.65	-1.12
Cancer	37 (1.9)	56 (2.9)	0.66	-0.96
Renal and urinary disorders (SOC)	53 (2.7)	36 (1.8)	1.48	0.88
Fluid overload	113 (5.8)	105 (5.4)	1.08	0.43
Hyperkalemia	60 (3.1)	80 (4.1)	0.75	-1.01
Hyperphosphatemia	0 (0)	1 (0.1)	0	-0.05

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class

Summary:

In the safety evaluation of thrombotic SAEs in the DD-CKD population, we detected a clinically significant pattern of higher occurrence of acute venous thrombotic SAEs in the vadadustat arm, compared to the darbepoetin alfa arm. This finding constitutes a major safety review issue. In relation to non-thrombotic SAEs, we detected a clinically significant pattern of higher occurrence of GI acid-related disease and hepatobiliary disorders in the vadadustat arm, compared to the darbepoetin alfa arm. These findings constitute major safety review issues. There was also a trend towards higher occurrence of TIA in the vadadustat arm, which warrants further investigation.

7.6.4.4. Dropouts and/or Discontinuations Due to Adverse Events, Pooled Trials 0016 and 0017

In the DD-CKD population, vadadustat is associated with higher rate of AEs leading to permanent discontinuation, compared to darbepoetin alfa (4.9% versus 1.1%). As shown in Table 106, the majority of this difference is attributable to the following AEs: GI symptoms (i.e., mainly nausea, vomiting, and diarrhea), GI acid disease, asthenia, hypertension-related events, and cardiac life-threatening events. Exposure adjustment of the overall rate of AEs leading to permanent discontinuation and their specific etiologies resulted in similar conclusions (exposure-adjusted analyses not shown).

Table 106. Adverse Events Leading to Discontinuation, Safety Population, Pooled Trial 0016 and 0017

FDA Grouped PTs[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Subjects with at least one AE leading to discontinuation	96 (4.9)	22 (1.1)	4.36	3.8
GI symptoms	35 (1.8)	1 (0.1)	35.14	1.8
Asthenia[2]	6 (0.3)	0 (0)	-	0.3
Rash[3]	6 (0.3)	4 (0.2)	1.51	0.1
Hypertension-related events	5 (0.3)	0 (0)	-	0.3
Any bleeding	5 (0.3)	2 (0.1)	2.51	0.2
Cardiac life-threatening event	4 (0.2)	0 (0)	-	0.2
Gastroduodenal acid disease	4 (0.2)	0 (0)	-	0.2

FDA Grouped PTs[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Localized infection	4 (0.2)	1 (0.1)	4.02	0.2
Cancer	4 (0.2)	2 (0.1)	2.01	0.1
Systemic infection	3 (0.2)	2 (0.1)	1.51	0.1
Unadjudicated cardiovascular thrombosis	3 (0.2)	2 (0.1)	1.51	0.1
Dyspnea	2 (0.1)	0 (0)	-	0.1
Cytopenia[4]	2 (0.1)	0 (0)	-	0.1
Headache	2 (0.1)	0 (0)	-	0.1
Hepatotoxicity	1 (0.1)	1 (0.1)	1.00	0
Unadjudicated cerebrovascular accident	0 (0)	1 (0.1)	0	-0.1

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3. PTs were included if they were AEs of interest or if occur in >2 subjects.
[2] PT Asthenia includes asthenia and muscle weakness.
[3] PT rash includes skin exfoliation, rash, urticaria, dermatitis and rash popular.
[4] PT Cytopenia includes bi-cytopenia and pancytopenia.
Abbreviations: AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term

Summary:

In the DD-CKD population, vadadustat is associated with higher rate of AEs leading to permanent discontinuation, with the most common etiologies being GI events and asthenia. These findings constitute minor safety review issues.

7.6.4.5. Treatment-Emergent Adverse Events, Pooled Trials 0016 and 0017

There were 29,728 TEAEs in 3,451 subjects in the NDD-CKD population, with 14,478 TEAEs occurring in the vadadustat arm and 15,250 TEAEs occurring in the darbepoetin alfa arm. Table 107 provides a frequency-based comparison of specific TEAE occurrence reported in the safety population during the on-study period for the DD-CKD population, obtained from the pooled trials 0016 and 0017, while Table 108 provides the exposure-adjusted analysis of the same data. The frequency-based analysis demonstrated that:

- The following TEAEs had a numerically higher occurrence in the vadadustat arm: TIA, Access-related VTE, GI acid-related disease, nausea and diarrhea.
- The following TEAEs had a numerically higher occurrence in the darbepoetin alfa arm: unadjudicated CVA, access-unrelated VTE, AV connection stenosis, most atherosclerotic diseases, hypertension, cancer, hyperkalemia, and hyperphosphatemia.

There were no clinically significant differences between study arms in the remainder of the TEAEs. Adrenal disorders, as an AESI, were reported as an adrenal mass in two subjects in each treatment arm (0.1% vs. 0.1%) in the DD-CKD population. The results from the exposure-adjusted analysis were consistent with the results from the frequency-based analysis but subjects on vadadustat experienced a higher rate of the following additional TEAEs: unadjudicated CV thrombosis, hepatotoxicity, most sub-types of bleeding, falls and fluid overload.

Rhabdomyolysis occurred in 8 subjects in the DD-CKD population (5 subjects on vadadustat and 3 subjects on darbepoetin alfa), with 1 of 8 subjects being severe (on vadadustat), 6 of 8 subjects being moderate (3 subjects on vadadustat and 3 subjects on darbepoetin alfa) and 1 of 8 subjects being mild (on vadadustat). Events were considered as a SAE in 1 of 8 subjects (on vadadustat)

and none of the events led to permanent study drug discontinuation. There was no significant difference in CPK elevation observed between treatment arms. Overall, the occurrence and severity of rhabdomyolysis in the DD-CKD population is balanced between treatment arms, is considered relatively rare and, after review of the individual narratives, may be due to the presence of clinical risk factors. Additional exploration of data was attempted to analyze whether drug interaction between vadadustat and statins could have led to the increased incidence of rhabdomyolysis in the vadadustat arm in the DD-CKD population. However, unlike with the NDD-CKD trials, the dose of concomitantly used drugs including statins was not captured in the patient narratives. This limited our ability to analyze the data further in the DD-CKD trials.

The incidence of therapeutic phlebotomy in DD-CKD population, to treat excessive Hb response and avoid the risk of complications, was examined. Therapeutic phlebotomy was used in 45 patients, 21 patients on vadadustat and 24 patients on darbepoetin alfa. Overall, therapeutic phlebotomy was used infrequently, occuring more in the dabepoetin alfa arm, as a treatment of excessive Hb response.

In assessing vitals signs for safety signals, there were no clinically significant differences between trial arms in relation to median, maximum and minimum values of SBP, DBP and HR, throughout the on-study period. In addition, there were no findings of outlier risk difference ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in maximum SBP, maximum DBP, and evaluation of heart rate. However, there was a small increase in the occurrence of hypotension due to SBP < 90 mm Hg (5.6% vs. 3.6%) but not due to DBP < 60 mm Hg.

Table 107. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects on Vadadustat and TEAEs of Special Interest, Safety Population, Pooled Trial 0016 and 0017

FDA Grouped PTs[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Unadjudicated cardiovascular thrombotic event	123 (6.3)	131 (6.7)	0.94	-0.4
Unadjudicated cardiac life-threatening event	101 (5.2)	112 (5.7)	0.91	-0.5
Unadjudicated cerebrovascular accident	46 (2.4)	56 (2.9)	0.82	-0.5
Transient ischemic attack	16 (0.8)	9 (0.5)	1.79	0.4
Arterial thrombosis	6 (0.3)	8 (0.4)	0.75	-0.1
VTE disease	230 (11.8)	229 (11.7)	1.01	0.1
Access-related VTE	195 (10.0)	176 (9.0)	1.11	1.0
Access unrelated VTE	50 (2.6)	75 (3.8)	0.67	-1.3
AV connection stenosis	84 (4.3)	111 (5.7)	0.76	-1.4
Atherosclerotic disease	190 (9.8)	213 (10.9)	0.90	-1.1
Coronary disease	65 (3.3)	88 (4.5)	0.74	-1.2
Cerebrovascular disease	16 (0.8)	22 (1.1)	0.73	-0.3
Vascular disease	129 (6.6)	126 (6.5)	1.03	0.2
Unadjudicated cardiac function failure	119 (6.1)	152 (7.8)	0.79	-1.7
Hypertension	236 (12.1)	298 (15.2)	0.80	-3.1
Hypertension emergency	86 (4.4)	91 (4.7)	0.95	-0.2
Hypertension caused pathology	4 (0.2)	6 (0.3)	0.67	-0.1

FDA Grouped PTs[1]	Vadadustat N=1947 n (%)	Darbepoetin Alfa N=1955 n (%)	Relative Risk	Risk Difference (%)
Seizures	31 (1.6)	29 (1.5)	1.07	0.1
Hepatotoxicity	75 (3.9)	80 (4.1)	0.94	-0.2
Systemic infection	349 (17.9)	382 (19.5)	0.92	-1.6
Localized infection	602 (30.9)	631 (32.3)	0.96	-1.4
Any bleeding adverse event	320 (16.4)	359 (18.4)	0.90	-1.9
GI bleeding	166 (8.5)	174 (8.9)	0.96	-0.4
Mucocutaneous bleeding	123 (6.3)	131 (6.7)	0.94	-0.4
Visceral bleeding	39 (2.0)	52 (2.7)	0.75	-0.7
GU bleeding	43 (2.2)	45 (2.3)	0.96	-0.1
GI acid-related disease	193 (9.9)	153 (7.8)	1.27	2.1
Any gastrointestinal symptoms	529 (27.2)	476 (24.4)	1.12	2.8
Diarrhea	248 (12.7)	196 (10.0)	1.27	2.7
Nausea	163 (8.4)	147 (7.5)	1.11	0.9
Vomiting	134 (6.9)	134 (6.9)	1.00	0.0
Abdominal pain	131 (6.7)	145 (7.4)	0.91	-0.7
Constipation	87 (4.5)	93 (4.8)	0.94	-0.3
Falls	162 (8.3)	168 (8.6)	0.97	-0.3
Fractures	111 (5.7)	123 (6.3)	0.91	-0.6
Cancer	75 (3.9)	98 (5.0)	0.77	-1.2
Fluid overload	180 (9.2)	188 (9.6)	0.96	-0.4
Hyperkalemia	168 (8.6)	201 (10.3)	0.84	-1.7
Hyperphosphatemia	33 (1.7)	64 (3.3)	0.52	-1.6
Hypoglycemia	97 (5.0)	87 (4.5)	1.11	0.5
Dialysis-related complications	106 (5.4)	133 (6.8)	0.79	-1.2
Hypotension	155 (8.0)	158 (8.1)	0.99	-0.1
Dyspnea	105 (5.4)	129 (6.6)	0.82	-1.2
Cough	119 (6.1)	147 (7.5)	0.81	-1.4
Pain in extremity	99 (5.1)	123 (6.3)	0.81	-1.2
Headache	175 (9.0)	153 (7.8)	1.15	1.2

Source: SDTM datasets; Software: JMP
1 Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

Table 108. Exposure-Adjusted Treatment-Emergent Adverse Events, Safety Population, Pooled Trial 0016 and 0017

FDA Grouped PTs[1]	Vadadustat N= 1884 PY (/ 100 yrs)	Darbepoetin Alfa N=2272 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Unadjudicated cardiovascular thrombosis	6.53	5.77	1.13	0.76
Unadjudicated cardiac life-threatening event	5.36	4.93	1.09	0.43
Unadjudicated cerebrovascular accident	2.44	2.46	0.99	-0.02
Transient ischemic attack	0.85	0.40	2.14	0.45
Arterial thrombosis	0.32	0.35	0.90	-0.03
VTE disease	12.21	10.08	1.21	2.13
Access-related VTE	10.35	7.75	1.34	2.60
Access unrelated VTE	2.65	3.30	0.80	-0.65
AV connection stenosis	4.46	4.89	0.91	-0.43
Atherosclerotic disease	10.08	9.38	1.08	0.71
Coronary disease	3.45	3.87	0.89	-0.42
Cerebrovascular disease	0.85	0.97	0.88	-0.12
Vascular disease	6.85	5.55	1.23	1.30

FDA Grouped PTs[1]	Vadadustat N= 1884 PY (/ 100 yrs)	Darbepoetin Alfa N=2272 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Unadjudicated cardiac function failure	6.32	6.69	0.94	-0.37
Hypertension	12.53	13.12	0.96	-0.59
Hypertension emergency	4.56	4.01	1.14	0.56
Hypertension caused pathology	0.21	0.26	0.80	-0.05
Seizures	1.65	1.28	1.29	0.37
Hepatotoxicity	3.98	3.52	1.13	0.46
Systemic infection	18.52	16.81	1.10	1.71
Localized infection	31.95	27.77	1.15	4.18
Any bleeding adverse event	16.99	15.80	1.07	1.18
GI bleeding	8.81	7.66	1.15	1.15
Mucocutaneous bleeding	6.53	5.77	1.13	0.76
Visceral bleeding	2.07	2.29	0.90	-0.22
GU bleeding	2.28	1.98	1.15	0.30
GI acid-related disease	10.24	6.73	1.52	3.51
Any gastrointestinal symptoms	28.08	20.95	1.34	7.13
Diarrhea	13.16	8.63	1.53	4.54
Nausea	8.65	6.47	1.34	2.18
Vomiting	7.11	5.90	1.21	1.21
Abdominal pain	6.95	6.38	1.09	0.57
Constipation	4.62	4.09	1.13	0.52
Falls	8.60	7.39	1.16	1.20
Fractures	5.89	5.41	1.09	0.48
Cancer	3.98	4.31	0.92	-0.33
Fluid overload	9.55	8.27	1.15	1.28
Hyperkalemia	8.92	8.85	1.01	0.07
Hyperphosphatemia	1.75	2.82	0.62	-1.07

Source: SDTM datasets; Software: JMP
1 Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

Summary:

In the safety evaluation of frequency-based and exposure-adjusted TEAEs in the DD-CKD population, we detected a clinically significant pattern of higher occurrence of access-related VTE, TIA, hepatotoxicity, GI acid-related disease, diarrhea and nausea. These findings constitute major safety review issues. Adrenal disorders, as an AESI, was assessed with no detected safety signal. Because the occurrence and severity of rhabdomyolysis was balanced between treatment arms, given the rarity of these events and the presence of appropriate clinical risk factors, the occurrence of rhabdomyolysis is most likely unrelated to study drug in the DD-CKD population.

7.6.4.1. Laboratory Findings, Pooled Trials 0016 and 0017

Clinically relevant laboratory abnormalities in the DD-CKD population are presented in sections pertaining to the safety review issues of the respective organ system. Specifically, liver biochemistries are presented in section II.7.7.3 and renal biochemistries are presented in section II.7.7.5. Table 109 shows other laboratory abnormalities that reached the outlier risk difference threshold of ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in the DD-CKD population. Elevation of potassium, elevation of WBCs, decrease in lymphocytes and decrease in

platelets, of all severities, was higher in the darbepoetin arm, compared to the vadadustat arm, in the DD-CKD population. There were no clinically significant differences between trial arms in relation to the change in mean values of laboratory parameters from baseline to end of treatment values.

Table 109. Subjects Meeting Laboratory Abnormality Criteria From Baseline to ≥ Week 36, Risk Difference ≥1% Higher in Vadadustat Arm, Safety Population, Pooled Trial 0016 and 0017

Laboratory Analysis	Vadadustat N=1947	Darbepoetin Alfa N=1955	Risk Difference (%)
Low bicarbonate (mEq/L)	N=1760	N=1801	
Severe[1], n (%)	235 (13.4)	214 (11.9)	1.5

Source: ADEM datasets; Software: R.
[1] Severe low bicarbonate defined as <15 mEq/L.
Abbreviations: N, number of subjects; n, number of subjects with abnormality.

7.6.4.2. Adverse Events of Special Interest

7.6.4.2.1. MACE and Other CV Outcomes

Table 110 presents the number (%) of subjects who had at least one adjudicated MACE event and the HR for MACE and other key secondary outcomes from the Applicant's pre-specified analyses. A total of 355 subjects (18.2%) in vadadustat arm had at least one adjudicated MACE event, whereas 377 subjects (19.3%) had an adjudicated MACE event in the darbepoetin arm. The estimated HR (95% CI) of MACE was 0.96 (0.83, 1.11), where the upper bound of the CI was lower than the pre-specified risk margin of 1.25. The estimated HRs and 95% CIs of all other key secondary outcomes did not indicate increased risks in the vadadustat arm (point estimates less than 1 and CIs included 1).

Table 110. Number (%) of Subjects and HRs (95% CI) of MACE and Key Secondary CV Outcomes in DD-CKD Population. Pre-Specified Analyses.

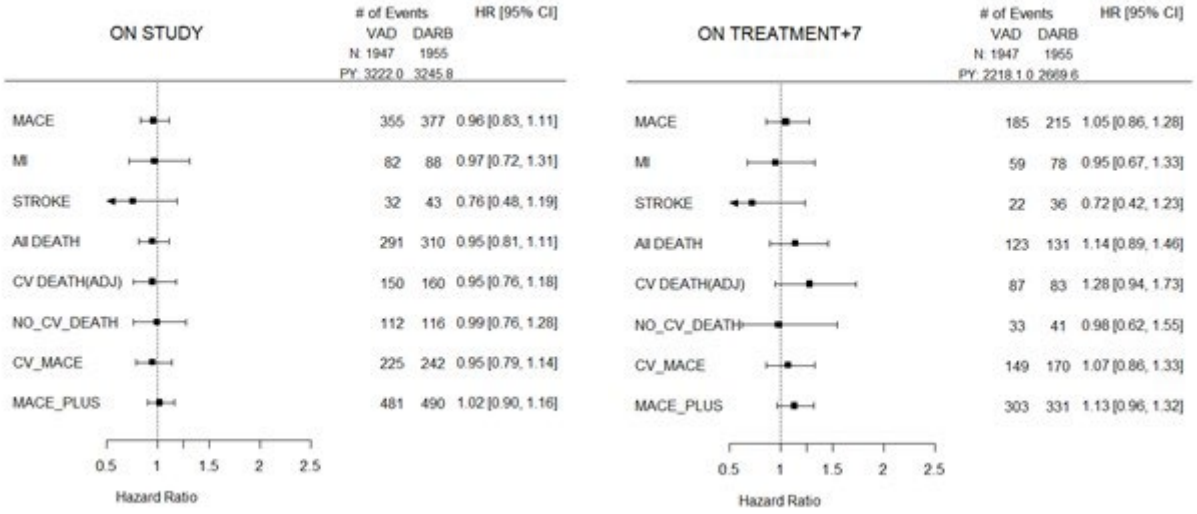
Outcomes	Vadadustat N=1947 n (%)	Darbepoetin N=1955 n (%)	HR (95% CI)
MACE	355 (18.2)	377 (19.3)	0.96, (0.83, 1.11)
MACE 2	420 (21.6)	449 (23.0)	0.96, (0.84, 1.10)
CV MACE	225 (11.6)	242 (12.4)	0.95, (0.80, 1.14)
CV death	150 (7.7)	160 (8.2)	0.96, (0.77, 1.20)
All death	291 (14.9)	310 (15.9)	0.95, (0.81, 1.12)

Source: Generated by statistical reviewer from adtte.xpt, adsl.xpt datasets from INNO2VATE program. Secondary outcomes did not indicate increased risks in the vadadustat arm (CIs included 1).
Abbreviations: CI, confidence interval; CV Death, cardiovascular death; CV MACE, composite outcome of cardiovascular death, non-fatal MI or non-fatal stroke; DD-CKD, dialysis dependent-chronic kidney disease; HR, hazard ratio; MACE 2, MACE plus hospitalization for heart failure or thromboembolic event excluding vascular access thrombosis; N, number of subjects in group; n, number of subjects with serious adverse event

Our analysis produced similar results (Figure 28). The estimated HR (95% CI) of MACE was the same as the pre-specified analysis result (HR, 0.96; 95% CI, 0.83, 1.11). The result from the sensitivity meta-analysis using inverse variance (on-study analysis) was also the same (HR, 0.96; 95% CI, 0.83, 1.11). However, the OT +7 analysis that took the difference in duration of drug exposure into consideration, showed an increased risk of CV death, CV MACE and all-cause mortality, with a 95% CI that includes 1. In addition, the estimated risk of MACE+ (which includes thrombotic events) was slightly higher in the vadadustat arm compared to the darbepoetin arm in the OT +7 analysis (HR, 1.13; 95% CI, 0.96, 1.32). The OT+7 analysis is an

informative sensitivity analysis that is not diluted by events off treatment that may not be related to the treatment. However, it has limitations that events off treatment may be related to the treatment and the OT+7 analysis is not a strictly randomized comparison because stopping treatment may be related to adverse events or other factors.

Figure 28. Risk of MACE, Death and Other CV Outcomes: DD-CKD Population



Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from INNO2VATE program.
Abbreviations: MACE, major adverse cardiovascular event; MI, non-fatal myocardial infarction; CV DEATH(ADJ), death caused by cardiovascular events; NO_CV_DEATH, death unrelated to cardiovascular events; CV_MACE, composite outcome of non-fatal MI, non-fatal stroke and CV death; MACE_PLUS, composite outcome of non-fatal MI, non-fatal stroke, all-cause mortality and thromboembolic event; HR, hazard ratio; CI, confidence interval; VAD, vadadustat; DARB, darbepoetin alfa; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25) for on-treatment analysis.

Regarding deaths, 291 subjects in the vadadustat arm died (14.9%), whereas 310 subjects (15.9%) in the darbepoetin arm died during the study period. (Table 111). The estimated HR (95% CI) of all-cause mortality was 0.96 (0.83, 1.11). However, when accounting for the difference in duration of drug exposure (OT +7 analysis), the estimated HR (95% CI) of all-cause mortality was greater than 1 (HR, 1.14; 95% CI, 0.89, 1.46).

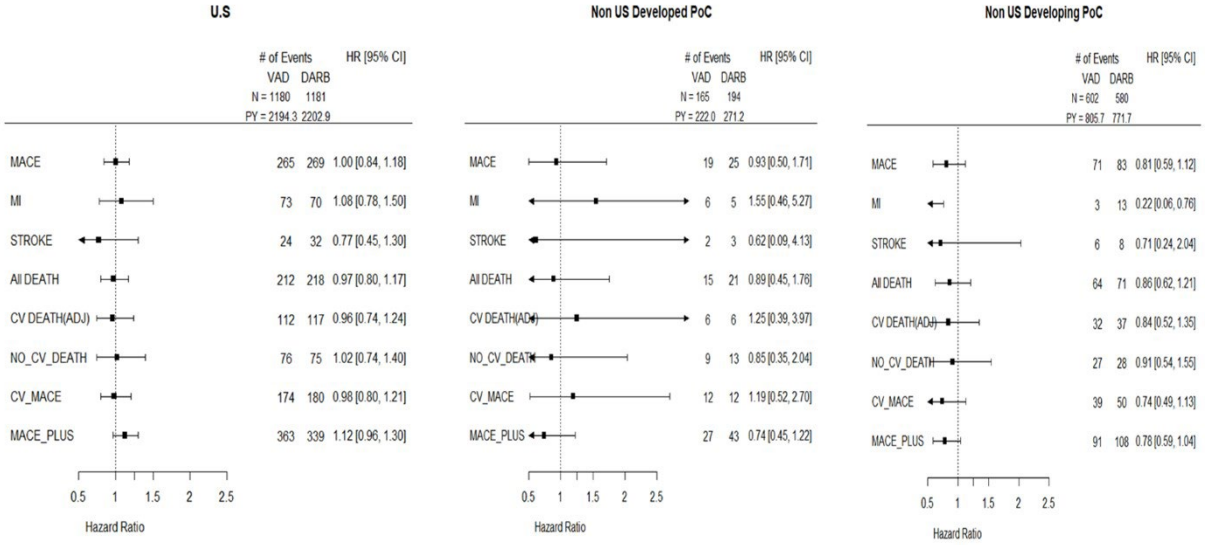
Table 111. Number (%) of Subjects Who Died During Study Period: DD-CKD Population

Types of Death	Vadadustat N=1947	Darbepoetin N=1955
All death	291 (14.9%)	310 (15.9%)
CV death	150 (7.7%)	160 (8.2%)
Non-CV death	112 (5.8%)	116 (5.9%)
Unknown	29 (1.5%)	34 (1.7%)

Source: Generated statistical reviewer from adtte.xpt, adadj.xpt datasets from INNOVATE program.
Abbreviations: CV, cardiovascular; DD-CKD, dialysis dependent-chronic kidney disease; N, number of subjects in group

When looking at the data by region (Agency's definition), the majority of CV outcomes occurred in the United States (Figure 29). On study analysis showed that the estimated HRs of MACE were 1.0 (0.84, 1.18), 0.93 (0.50, 1.71) and 0.81 (0.59, 1.12) for the United States, non-U.S. developed PoC regions and non-U.S. developing PoC regions, respectively. Most CV risks were comparable between the two arms in the United States in the on-study analysis.

Figure 29. Risk of MACE, Death and Other CV Outcomes by Region: DD-CKD Population, on Study Analyses



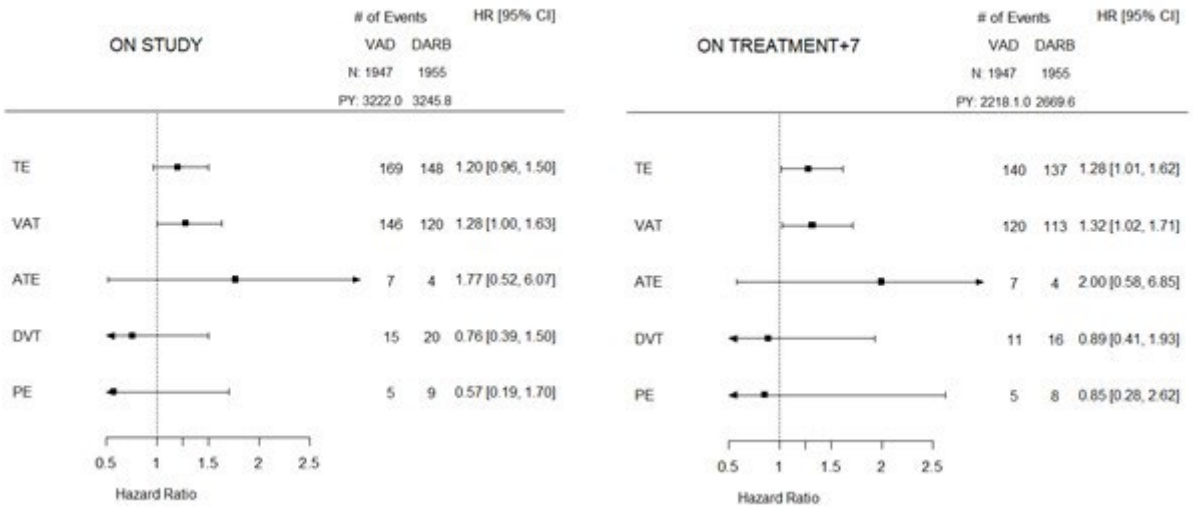
Source: The reviewer's independent analyses. Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from INNO2VATE program.
Abbreviations: MACE, major adverse cardiovascular event; MI, non-fatal myocardial infarction; CV DEATH(ADJ), death caused by cardiovascular events; NO_CV_DEATH, death unrelated to cardiovascular events; CV_MACE, composite outcome of non-fatal MI, non-fatal stroke and CV death; MACE_PLUS, composite outcome of non-fatal MI, non-fatal stroke, all-cause mortality and thromboembolic event; HR, hazard ratio; CI, confidence interval; VAD, vadadustat; DARB, darbepoetin alfa; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25)for on-treatment analysis.

Subgroup analyses of MACE by other baseline variables are presented in section III.17.6.

7.6.4.2.2. Thromboembolic Events

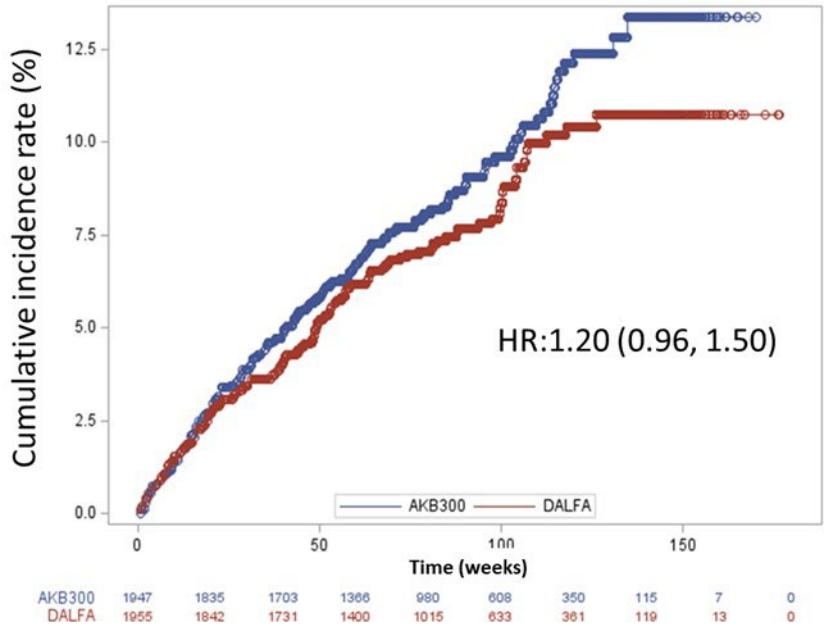
Figure 30 the forest plot which summarizes the results of thromboembolic events from the Applicant's adjudicated data. The analysis results of the adjudicated data showed that a greater number of subjects in the vadadustat arm had a thromboembolic event compared to those in the darbepoetin arm:169 (8.7%) versus 149 (7.6%). The estimated HR (95% CI) was 1.20 (0.96, 1.50). The cumulative incidence rate plot also indicated a consistently higher risk of thromboembolic events over time in the vadadustat arm (Figure 31). More than 80% of the thromboembolic events were vascular access thrombosis events. The estimated HR (95% CI) of vascular access thrombosis events was 1.28 (1.00, 1.63). The OT +7 analysis results showed a similar risk profile to the on-study analysis results, but with the associated 95% CIs excluding 1.0 for thromboembolic events and vascular access thrombosis events.

Figure 30. Risk of Thromboembolic Event and Sub-Outcomes Based on Adjudicated Data in DD-CKD Population



Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from INNO2VATE program.
Abbreviations: ATE, arterial thrombosis; CI, confidence interval; DD-CKD, dialysis dependent-chronic kidney disease; DARB, darbepoetin alfa; DVT, deep vein thrombosis; HR, hazard ratio; N, number of subjects in group; PE, pulmonary embolism; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25)for on-treatment analysis; TE, applicant's adjudicated thromboembolic events including arterial thrombosis, deep vein thrombosis, pulmonary embolism and vascular access thrombosis; VAD, vadadustat; VAT, vascular access thrombosis

Figure 31. Cumulative Incidence Rate of Thromboembolic Events (Adjudicated Data): DD-CKD Population; on-Study Analysis

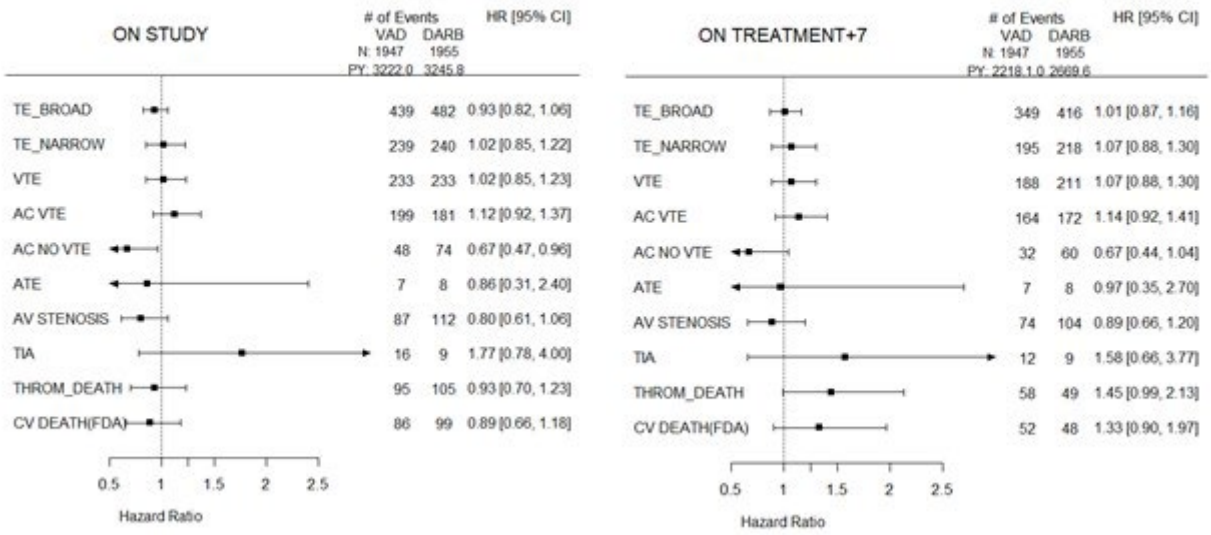


Source: The reviewer's independent analyses. Generated by Joo-Yeon Lee, statistical reviewer from ae.xpt, adsl.xpt datasets from INNOVATE program.
Abbreviations: DD-CKD, dialysis-dependent chronic kidney disease; HR hazard ratio

Compared to the adjudicated data, using the Agency's TE definition (see section II.7.4 for details of definition) a greater number of thromboembolic events were identified (Figure 32). However, the magnitude of the HR (95% CI) was diminished to 1.02 (0.85, 1.22) and 0.93 (0.82, 1.06),

using the narrow and broad definitions, respectively. Among the sub-components of thromboembolic events, the HR for access-related VTE was increased in the vadadustat arm (HR, 1.12; 95% CI, 0.92, 1.37). The HR for transient ischemic attack was also higher in the vadadustat arm (HR, 1.77; 95% CI, 0.78, 4.00), but number of events was small. The OT +7 analysis results of the Agency's defined TE events were similar, apart from thrombosis related death, which had a HR (95% CI) of 1.45 (0.99, 2.13).

Figure 32. Risk of Thromboembolic Event and Sub-Outcomes Using the Agency's Definition: DD-CKD Population



Source: Generated by statistical reviewer from ae.xpt, adsl.xpt datasets from INNO2VATE program.
Abbreviations: AC VTE, access-related venous thrombosis; AC NO VTE, access unrelated venous thrombosis; AV STENOSIS, arteriovenous connection stenosis; CI, confidence interval; CV DEATH(FDA), FDA's own definition of cardiovascular death; DARB, darbepoetin alfa; DD-CKD, dialysis dependent-chronic kidney disease; HR, hazard ratio; N, number of subjects in group; PY, follow-up time ((last contact date-date of first dose-1)/365.25) for on-study analysis and duration of drug exposure ((date of last dose-date of first dose-1)/365.25) for on-treatment analysis; TE_BROAD, FDA's broad definition of TE; TE_NARROW, FDA's narrow definition including venous thrombosis and arterial thrombosis only; VTE, venous thrombosis; TIA, transient ischemic attack; THROM_DEATH, thrombosis-related death; VAD, vadadustat

Table 112 shows adjudicated TE results by region. The risk of thromboembolic events was much more apparent in the U.S. population. In the United States, 11.6% of the vadadustat arm subjects experienced a thromboembolic event compared to 8.4% of the darbepoetin arm subjects. The estimated HR in the U.S. population was higher (HR, 1.46; 95% CI, 1.13, 1.89) than other regions. Similar to all non-U.S. regions, vascular access thrombosis was a major driver for the increased risk of thromboembolic events in the U.S. population. OT +7 analysis results were consistent with the results from the on-study analyses (data not shown). No increased risk of TE was observed in regions outside the United States. The results based on the Agency's narrow definition also showed an increased HR for thromboembolic events in the vadadustat arm in the United States (HR, 1.14; 95% CI, 0.92, 1.42).

Table 112. Number of Subjects with Thromboembolic Events and HR Based on Adjudicated Data: DD-CKD Population

		United States		Non-U.S. Developed PoC		Non-U.S. Developing PoC	
Events		**Vadadustat N=1180**	**Darbepoetin N=1181**	**Vadadustat N=165**	**Darbepoetin N=194**	**Vadadustat N=602**	**Darbepoetin N=580**
TE (ADJ)	n (%)	137 (11.6)	99 (8.4)	10 (6.1)	19 (9.8)	22 (3.7)	30 (5.2)
	HR (95% CI)	1.46 (1.13-1.89)		0.55 (0.25-1.21)		0.71 (0.41-1.23)	
VAT	n (%)	119 (10.1)	79 (6.7)	9 (5.5)	17 (8.8)	18 (3.0)	24 (4.1)
	HR (95% CI)	1.58 (1.19-2.1)		0.58 (0.25-1.34)		0.72 (0.39-1.33)	
ATE	n (%)	4 (0.3)	0	1 (0.6)	0	2 (0.3)	4 (0.7)
	HR (95% CI)	——		——		0.43 (0.08-2.39)	
DVT	n (%)	13 (1.1)	15 (1.3)	0	2 (1.0)	2 (0.3)	3 (0.5)
	HR (95% CI)	0.87 (0.41-1.83)		——		0.64 (0.1-4.07)	
PE	n (%)	4 (0.3)	8 (0.7)	0	1 (0.5)	1 (0.2)	0
	HR (95% CI)	0.51 (0.15-1.7)		——		——	
TE_NARROW	n (%)	174	158	9	21	56	61
	HR (95% CI)	1.14 (0.92-1.42)		0.43 (0.19-0.97)		0.86 (0.60-1.24)	
AC_VTE	n (%)	144	119	9	17	46	45
	HR (95% CI)	1.25 (0.98-1.59)		0.55 (0.24-1.28)		0.98 (0.65-1.47)	

Source: Generated by statistical reviewer from adtte.xpt, adadj.xpt, adsl.xpt datasets from INNO2VATE program.
Abbreviation: AC_VTE, access-related venous thrombosis; ATE, arterial thrombosis; CI, confidence interval; DD-CKD, dialysis dependent-chronic kidney disease; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; PoC, practice of care; TE (ADJ), adjudicated thromboembolic event; TE_NARROW, thromboembolic event based on the Agency's narrow definition; VAT, vascular access thrombosis.

7.6.5. Safety Findings and Concerns, Trial 0016

7.6.5.1. Overall Treatment-Emergent Adverse Event Summary, Trial 0016

Table 113 provides a frequency-based overview of TEAEs reported in the safety population during the on-study period for trial 0016, while Table 114 provides the exposure-adjusted analysis of the same data. Based on frequency-based and exposure-adjusted analysis, there were no clinically significant differences between study arms in relation to TEAE occurrence, severe AEs occurrence, SAE occurrence and fatal SAE occurrence. Both frequency-based and exposure-adjusted analysis demonstrated that subjects on vadadustat experienced a higher rate of AEs leading to permanent treatment discontinuation and AEs leading to dose interruption, when compared to subjects on darbepoetin alfa.

Table 113. Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0016

Event	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Any treatment-emergent AE	150 (83.8)	159 (85.5)	0.98	-1.7
Severe AEs	60 (33.5)	64 (34.4)	0.97	-0.9
SAEs	89 (49.7)	105 (56.5)	0.88	-6.7
SAEs with fatal outcome	15 (8.4)	20 (10.8)	0.78	-2.4
AEs leading to permanent discontinuation of study drug	5 (2.8)	2 (1.1)	2.60	1.7
AEs leading to dosage modification of study drug	23 (12.8)	17 (9.1)	1.41	3.7
AEs leading to interruption of study drug	23 (12.8)	17 (9.1)	1.41	3.7
AEs leading to reduction of study drug	0 (0)	0 (0)	-	0
AEs leading to dosage delay of study drug	0 (0)	0 (0)	-	0

Source: ADEM and SDTM datasets; Software: R and JMP
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

Table 114. Exposure-Adjusted Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0016

Event	Vadadustat N=158 PY (/ 100 yrs)	Darbepoetin Alfa N=182 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Any treatment-emergent AE	94.94	87.36	1.09	7.57
Severe AEs	37.97	35.16	1.08	2.81
SAEs	56.33	57.69	0.98	-1.36
SAEs with fatal outcome	9.49	10.99	0.86	-1.50

Event	Vadadustat N=158 PY (/ 100 yrs)	Darbepoetin Alfa N=182 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
AEs leading to permanent discontinuation of study drug	3.16	1.10	2.88	2.07
AEs leading to dosage modification of study drug	14.56	9.34	1.56	5.22
AEs leading to interruption of study drug	14.56	9.34	1.56	5.22
AEs leading to reduction of study drug	0	0	-	0
AEs leading to dosage delay of study drug	0	0	-	0

Source: SDTM datasets; Software: JMP
Abbreviations: AE, adverse event; SAE, serious adverse event; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; N, number of subjects in group; n, number of subjects with at least one event

7.6.5.2. Deaths, Trial 0016

A total of 35 subjects died during the on-study period of trial 0016, with 15 subjects on vadadustat and 20 subjects on darbepoetin alfa, as summarized in Table 115. The rates of all-cause mortality are lower in the vadadustat arm. Table 116 summarizes key characteristics of subjects who died while on-study. Conclusions are limited given the small number of events.

Table 115. Deaths in Safety Population, on-Study Period, Trial 0016

Deaths	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Treatment-emergent deaths[1]	15 (8.4)	20 (10.8)	0.78	-2.4
Acute cardiovascular/vascular causes	5 (2.8)	8 (4.3)	0.65	-1.5
Cerebrovascular causes	0 (0)	0 (0)	-	0
Infectious causes	3 (1.7)	2 (1.1)	1.56	0.6
Renal/Electrolyte disturbances causes	1 (0.6)	4 (2.2)	0.26	-1.6
Acute respiratory causes	0 (0)	0 (0)	-	0
Oncological causes	1 (0.6)	0 (0)	-	0.6
Non-specific/Unknown causes	3 (1.7)	5 (2.7)	0.62	-1.0
Other causes	2 (1.1)	1 (0.5)	2.08	0.6

Source: ADEM and SDTM datasets; Software: R and JMP
[1] Grouping definitions for causes of death can be found in section III.17.4.1.
Abbreviations: N, number of subjects in group; n, number of deaths.

Table 116. Characteristics of Subjects Experiencing Death During On-Study Period in The Safety Population, Trial 0016

Characteristic	Vadadustat N=15	Darbepoetin Alfa N=20
Age (years), mean (SD)	63.8 (17.3)	64.1 (12.7)
Male, n (%)	8 (53)	12 (60)
U.S. subjects, n (%)	6 (40)	11 (55)
Subjects in developed countries[1], n (%)	7 (47)	12 (60)
Maximal dose[2], median (25% to 75% IQR)	600 (450 – 600)	0.66 (0.48 – 1.13)
Final dose[2], median (25% to 75% IQR)	600 (450 – 600)	0.50 (0.35 – 0.60)
Duration of exposure (days), median (25% to 75% IQR)	213 (88 – 366)	169 (60 - 343)
Study day of death, median (25% to 75% IQR)	222 (96 – 434)	318 (150 - 408)

Source: SDTM datasets; Software: JMP
[1] Developed countries are defined by the availability and advancement of the practice of medicine, based on information collected by the world health organization. Listing of countries according to "developed" versus "developing" status can be found in section III.17.4.2.
[2] The dosage unit for subjects on vadadustat is mg. The dosage unit for patient on darbepoetin alfa is µg/kg/week.
Abbreviations: IQR, Interquartile range; N, total number of deaths in group; n, number of subjects; U.S., United States.

7.6.5.3. Serious Adverse Events, Trial 0016

There were 554 SAEs in 194 subjects in trial 0016, with 270 SAEs occurring in the vadadustat arm and 284 SAEs occurring in the darbepoetin alfa arm. Table 117 provides a frequency-based comparison of thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for trial 0016. Given the relatively small number of individual thrombotic SAEs, there were no clear differences between study arms. However, VTE had a numerical trend toward higher occurrence in the darbepoetin alfa arm. There were no other concerning SAEs that occurred at an incidence of <2%.

Table 117. Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Trial 0016

Serious Adverse Event[1]	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Atherosclerotic disease	8 (4.5)	8 (4.3)	1.04	0.2
Cardiac disorders (SOC)	23 (12.9)	25 (13.4)	0.96	-0.6
Unadjudicated cardiovascular thrombotic event	6 (3.4)	6 (3.2)	1.04	0.1
Unadjudicated cardiac life-threatening event	8 (4.5)	5 (2.7)	1.66	1.8
Unadjudicated cardiac failure	3 (1.7)	10 (5.4)	0.31	-3.7
Nervous system disorders (SOC)	8 (4.5)	9 (4.8)	0.92	-0.4
Unadjudicated cerebrovascular accident	5 (2.8)	3 (1.6)	1.73	1.2
Transient ischemic attack	1 (0.6)	2 (1.1)	0.52	-0.5
Product issues (SOC)	0 (0)	0 (0)	-	0
AV connection stenosis	0 (0)	0 (0)	-	0
Respiratory, thoracic, and mediastinal disorders (SOC)	15 (8.4)	10 (5.4)	1.56	3.0
Acute respiratory failure	5 (2.8)	4 (2.2)	1.30	0.6
Pulmonary edema	6 (3.4)	5 (2.7)	1.25	0.7

Serious Adverse Event[1]	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Vascular disorders (SOC)	16 (8.9)	20 (10.8)	0.83	-1.8
VTE disease	6 (3.4)	13 (7.0)	0.48	-3.6
Arterial thrombosis	0 (0)	1 (0.5)	0	-0.5

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: AV, Arteriovenous; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class; VTE, venous thromboembolism

Table 118 provides a frequency-based comparison of non-thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for trial 0016. The following SAEs had a numerically higher occurrence in the vadadustat arm: hypertensive emergency (5.0% vs. 2.7%), fractures (3.4% vs. 2.2%), and fluid overload. The following SAEs had a numerically higher occurrence in the darbepoetin alfa arm: any bleeding, GI bleeding, GI acid-related disease (1.7% vs. 3.2%) systemic infections, and cancer. Hypertension, GI symptoms, hepatotoxicity, and falls were similar between study arms.

Table 118. Non-Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Trial 0016

Serious Adverse Event[1]	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Hypertension	3 (1.7)	3 (1.6)	1.04	0.1
Hypertension emergency	9 (5.0)	5 (2.8)	1.87	2.3
Seizures	0 (0)	1 (0.5)	0	-0.5
Blood and lymphatic system disorders (SOC)	3 (1.7)	5 (2.7)	0.63	-1.0
Any bleeding adverse event	6 (3.4)	10 (5.4)	0.62	-2.0
GI bleeding	2 (1.1)	8 (4.3)	0.26	-3.2
Gastrointestinal disorders (SOC)	11 (6.2)	22 (11.8)	0.52	-5.7
GI acid-related disease	3 (1.7)	6 (3.2)	0.52	-1.6
Any gastrointestinal symptoms	1 (0.6)	3 (1.6)	0.35	-1.1
Diarrhea	0 (0)	1 (0.5)	0	-0.5
Nausea	0 (0)	0 (0)	-	0
Abdominal pain	1 (0.6)	1 (0.5)	1.04	0
Constipation	0 (0)	0 (0)	-	0
Hepatobiliary disorders (SOC)	2 (1.1)	4 (2.2)	0.52	-1.0
Hepatotoxicity	4 (2.2)	5 (2.7)	0.83	-0.5
Infections and infestations (SOC)	40 (22.4)	46 (24.7)	0.90	-2.4
Systemic infection	18 (10.1)	24 (12.9)	0.78	-2.9
Localized infection	23 (12.9)	23 (12.4)	1.04	0.5
Injury, poisoning and procedural complications (SOC)	18 (10.1)	18 (9.7)	1.04	0.4
Falls	1 (0.6)	1 (0.5)	1.04	0
Fractures	6 (3.4)	4 (2.2)	1.56	1.2
Metabolism and nutrition (SOC)	14 (7.8)	11 (5.9)	1.32	1.9
Neoplasm benign, malignant, and unspecified (SOC)	2 (1.1)	4 (2.2)	0.52	-1.0
Cancer	2 (1.1)	4 (2.2)	0.52	-1.0
Renal and urinary disorders (SOC)	2 (1.1)	3 (1.6)	0.70	-0.5
Fluid overload	10 (5.6)	2 (1.1)	5.20	4.5
Hyperkalemia	5 (2.8)	4 (2.2)	1.30	0.7
Hyperphosphatemia	0 (0)	0 (0)	-	0

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; SOC, system organ class

7.6.5.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial 0016

In trial 0016, vadadustat is associated with a higher rate of AEs leading to permanent discontinuation, compared to darbepoetin alfa (2.8% versus 1.1%). As shown in Table 119, the majority of this difference is attributable to the following AEs: asthenia, cardiovascular thrombosis, GI symptoms (i.e., mainly nausea, vomiting, and diarrhea) and acute pulmonary edema. Exposure adjustment of the overall rate of AEs leading to permanent discontinuation and their specific etiologies resulted in similar conclusions (exposure-adjusted analyses not shown).

Table 119. Adverse Events Leading to Discontinuation, Safety Population, Trial 0016

FDA Grouped PTs[1]	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Subjects with at least one AE leading to discontinuation	5 (2.8)	2 (1.1)	2.60	1.7
Asthenia[2]	6 (3.4)	0 (0)	-	3.4
Unadjudicated cardiovascular thrombosis	4 (2.2)	0 (0)	-	2.2
GI symptoms	5 (2.8)	0 (0)	-	2.8
Localized infection	5 (2.8)	2 (1.1)	-	1.7
Cytopenia[3]	2 (1.1)	0 (0)	-	1.1
Rash[4]	5 (2.8)	4 (2.2)	0	0.6
Acute pulmonary edema	4 (2.2)	0 (0)	0	2.2
Alopecia	4 (2.2)	1 (0.5)	0	1.7

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3. PTs were included if they were AEs of interest or if occur in >2 subjects.
[2] PT Asthenia includes asthenia and muscle weakness.
[3] PT Cytopenia includes bi-cytopenia and pancytopenia.
[4] PT rash includes skin exfoliation, rash, urticaria, dermatitis and rash popular.
Abbreviations: AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term

7.6.5.5. Treatment-Emergent Adverse Events, Trial 0016

There were 2,273 TEAEs in 309 subjects in the NDD-CKD population, with 1,074 TEAEs occurring in the vadadustat arm and 1,199 TEAEs occurring in the darbepoetin alfa arm. Table 120 provides a frequency-based comparison of specific TEAE occurrence reported in the safety population during the on-study period for trial 0016, while Table 121 provides the exposure-adjusted analysis of the same data. The frequency-based analysis demonstrated that:

- The following TEAEs had a numerically higher occurrence in the vadadustat arm: and hypertensive emergency, vomiting, and fluid overload.
- The following TEAEs had a numerically higher occurrence in the darbepoetin alfa arm: VTE, access-related VTE, access-unrelated VTE, infection, cancer.

There were no other notable differences between study arms in the remainder of the TEAEs, many of which had low event rates, limiting conclusions. There were no adrenal disorders, as an AESI, reported in any subjects in trial 0016. There were no identified cases of rhabdomyolysis

and no significant difference in CPK elevation observed between treatment arms in trial 0016. The results from the exposure-adjusted analysis were consistent with the results from the frequency-based analysis.

The incidence of therapeutic phlebotomy in trial 0016, to treat excessive Hb response and avoid the risk of complications, was examined. Therapeutic phlebotomy was used in 7 patients: 4 patients on vadadustat and 3 patients on darbepoetin alfa. Overall, therapeutic phlebotomy was used infrequently and was balanced between the two treatment arms.

In assessing vitals signs for safety signals, there were no clinically significant differences between trial arms in relation to median, maximum and minimum values of SBP, DBP and HR, throughout the on-study period. In addition, there were no findings of outlier risk difference ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in maximum DBP and evaluation of HR. However, there was a small increase in the occurrence of SBP ≥ 160 mm Hg (64.8% vs. 62.4%), SBP ≥ 180 mm Hg (37.4% vs. 31.2%), and hypotension (SBP < 90 mm Hg: 4.5% vs. 2.7% and DBP < 60 mm Hg: 40.8% vs. 34.9%).

Table 120. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects on Vadadustat and TEAEs of Special Interest, Safety Population, Trial 0016

FDA Grouped PTs[1]	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Unadjudicated cardiovascular thrombotic event	6 (3.4)	7 (3.8)	0.89	-0.4
Unadjudicated cardiac life-threatening event	8 (4.5)	5 (2.7)	1.66	1.8
Unadjudicated cerebrovascular accident	6 (3.4)	4 (2.2)	1.56	1.2
Transient ischemic attack	1 (0.6)	3 (1.6)	0.35	-1.1
Arterial thrombosis	0 (0)	1 (0.5)	0	-0.5
VTE disease	15 (8.4)	26 (14.0)	0.60	-5.6
Access-related VTE	13 (7.3)	20 (10.8)	0.68	-3.5
Access unrelated VTE	2 (1.1)	9 (4.8)	0.23	-3.7
AV connection stenosis	7 (3.9)	7 (3.8)	1.04	0.2
Atherosclerotic disease	15 (8.4)	15 (8.1)	1.04	0.3
Coronary disease	8 (4.5)	12 (6.5)	0.69	-2.0
Cerebrovascular disease	0 (0)	3 (1.6)	0	-1.6
Vascular disease	8 (4.5)	4 (2.2)	2.08	2.3
Unadjudicated cardiac function failure	6 (3.4)	11 (5.9)	0.57	-2.6
Hypertension	30 (16.8)	27 (14.5)	1.15	2.2
Hypertension emergency	12 (6.7)	7 (3.8)	1.78	2.9
Hypertension caused pathology	0 (0)	0 (0)	-	0
Seizures	2 (1.1)	2 (1.1)	1.04	0
Hepatotoxicity	6 (3.4)	9 (4.8)	0.69	-1.5
Systemic infection	24 (13.4)	35 (18.8)	0.71	-5.4
Localized infection	55 (30.7)	70 (37.6)	0.82	-6.9
Any bleeding adverse event	19 (10.6)	26 (14.0)	0.76	-3.4
GI bleeding	6 (3.4)	9 (4.8)	0.69	-1.5
Mucocutaneous bleeding	11 (6.2)	12 (6.5)	0.95	-0.3
Visceral bleeding	2 (1.1)	3 (1.6)	0.69	-0.5
GU bleeding	4 (2.2)	5 (2.7)	0.83	-0.5
GI acid-related disease	20 (11.2)	18 (9.7)	1.15	1.5
Any gastrointestinal symptoms	39 (21.8)	39 (21.0)	1.04	0.8
Diarrhea	18 (10.1)	18 (9.7)	1.04	0.4
Nausea	14 (7.8)	13 (7.0)	1.12	0.8
Vomiting	14 (7.8)	10 (5.4)	1.45	2.4

FDA Grouped PTs[1]	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Relative Risk	Risk Difference (%)
Abdominal pain	10 (5.6)	14 (7.5)	0.74	-1.9
Constipation	3 (1.7)	13 (7.0)	0.24	-5.3
Falls	11 (6.2)	9 (4.8)	1.27	1.3
Fractures	5 (2.8)	6 (3.2)	0.87	-0.4
Cancer	4 (2.2)	10 (5.4)	0.42	-3.1
Fluid overload	13 (7.3)	6 (3.2)	2.25	4.0
Hyperkalemia	8 (4.5)	10 (5.4)	0.83	-0.9
Hyperphosphatemia	5 (2.8)	8 (4.3)	0.65	-1.5
Dyspnea	13 (7.3%)	10 (5.4%)	1.35	1.9
Procedural hypotension	11 (6.3%)	12 (6.5%)	0.97	-0.2
Cough	11 (6.2%)	6 (3.2%)	1.94	3.0

Source: SDTM datasets; Software: JMP
1, Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

Table 121. Exposure-Adjusted Treatment-Emergent Adverse Events, Safety Population, Trial 0016

FDA Grouped PTs[1]	Vadadustat N= 158 PY (/ 100 yrs)	Darbepoetin Alfa N=182 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Unadjudicated cardiovascular thrombosis	3.80	3.85	0.99	-0.05
Unadjudicated cardiac life-threatening event	5.06	2.75	1.84	2.32
Unadjudicated cerebrovascular accident	3.80	2.20	1.73	1.60
Transient ischemic attack	0.63	1.65	0.38	-1.02
Arterial thrombosis	0	0.55	0	-0.55
VTE disease	9.49	14.29	0.66	-4.79
Access-related VTE	8.23	10.99	0.75	-2.76
Access unrelated VTE	1.27	4.95	0.26	-3.68
AV connection stenosis	4.43	3.85	1.15	0.58
Atherosclerotic disease	9.49	8.24	1.15	1.25
Coronary disease	5.06	6.59	0.77	-1.53
Cerebrovascular disease	0	1.65	0	-1.65
Vascular disease	5.06	2.20	2.30	2.87
Unadjudicated cardiac function failure	3.80	6.04	0.63	-2.25
Hypertension	18.99	14.84	1.28	4.15
Hypertension emergency	7.59	3.85	1.97	3.75
Hypertension caused pathology	0	0	-	0.00
Seizures	1.27	1.10	1.15	0.17
Hepatotoxicity	3.80	4.95	0.77	-1.15
Systemic infection	15.19	19.23	0.79	-4.04
Localized infection	34.81	38.46	0.91	-3.65
Any bleeding adverse event	12.03	14.29	0.84	-2.26
GI bleeding	3.80	4.95	0.77	-1.15
Mucocutaneous bleeding	6.96	6.59	1.06	0.37
Visceral bleeding	1.27	1.65	0.77	-0.38
GU bleeding	2.53	2.75	0.92	-0.22
GI acid-related disease	12.66	9.89	1.28	2.77
Any gastrointestinal symptoms	24.68	21.43	1.15	3.25
Diarrhea	11.39	9.89	1.15	1.50
Nausea	8.86	7.14	1.24	1.72
Vomiting	8.86	5.50	1.61	3.36
Abdominal pain	6.33	7.69	0.82	-1.36

FDA Grouped PTs[1]	Vadadustat N= 158 PY (/ 100 yrs)	Darbepoetin Alfa N=182 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Constipation	1.90	7.14	0.27	-5.24
Falls	6.96	4.95	1.41	2.02
Fractures	3.16	3.30	0.96	-0.13
Cancer	2.53	5.49	0.46	-2.96
Fluid overload	8.23	3.30	2.50	4.93
Hyperkalemia	5.06	5.49	0.92	-0.43
Hyperphosphatemia	3.16	4.40	0.72	-1.23

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

7.6.5.6. Laboratory Findings, Trial 0016

Table 122 shows laboratory abnormalities that reached the outlier risk difference threshold of ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in trial 0016. Elevation of potassium and decrease in platelets, of all severities, was higher in the darbepoetin arm, compared to the vadadustat arm, in trial 0016. There were no clinically significant differences between trial arms in relation to the change in mean values of laboratory parameters from baseline to end of treatment values.

Table 122. Subjects Meeting Laboratory Abnormality Criteria From Baseline to ≥ Week 36, Risk Difference ≥1% Higher in Vadadustat Arm, Safety Population, Trial 0016

Laboratory Analysis	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Risk Difference (%)
Low sodium (mEq/L)	N=161	N=171	
Moderate[1]	10 (6.2)	7 (4.1)	2.1
Low chloride (mEq/L)	N=161	N=171	
Mild[2]	64 (39.8)	66 (38.6)	1.2
Moderate[3]	7 (4.3)	5 (2.9)	1.4
High glucose (mg/dL)	N=161	N=171	
Mild[4]	42 (26.1)	37 (21.6)	4.4
Moderate[5]	7 (16.8)	20 (11.7)	5.1
Low bicarbonate (mEq/L)	N=162	N=172	
Mild[6]	96 (59.3)	96 (55.8)	3.4
Low phosphate (mg/dL)	N=161	N=171	
Mild[7]	20 (12.4)	19 (11.1)	1.3
Moderate[8]	12 (7.5)	9 (5.3)	2.2
High BUN (mg/dL)	N=161	N=171	
Mild[9]	160 (99.4)	168 (98.2)	1.1
High creatinine (mg/dL)	N=161	N=171	
Moderate[10]	20 (12.4)	18 (10.5)	1.9
Severe[11]	4 (2.5)	2 (1.2)	1.3

Laboratory Analysis	Vadadustat N=179 n (%)	Darbepoetin Alfa N=186 n (%)	Risk Difference (%)
High eosinophils (cells/µL)	N=156	N=168	
Mild[12]	15 (9.6)	13 (7.7)	1.9

Source: ADEM datasets; Software: R.
[1] Mild low sodium defined as <132 mEq/L.
[2] Mild low chloride defined as <95 mEq/L.
[3] Moderate low chloride defined as <88 mEq/L.
[4] Mild high glucose defined as >200 mg/dL.
[5] Moderate high glucose defined as >250 mg/dL
[6] Mild low bicarbonate defined as <20 mEq/L.
[7] Mild low phosphate defined as <2.5 mg/dL.
[8] Moderate low phosphate defined as <2 mg/dL
[9] Mild high BUN defined as >23 mg/dL.
[10] Moderate high creatinine defined as ≥2x baseline.
[11] Severe high creatinine defined as ≥3x baseline.
[12] Mild high eosinophils defined as >650 cells/µL.
Abbreviations: BUN, blood urea nitrogen; N, number of subjects; n, number of subjects with abnormality; ULN, upper limit of normal

7.6.6. Safety Findings and Concerns, Trial 0017

7.6.6.1. Overall Adverse Event Summary, Trial 0017

Table 123 provides a frequency-based overview of TEAEs reported in the safety population during the on-study period for trial 0017, while Table 124 provides the exposure-adjusted analysis of the same data. Overall, there were no clinically significant differences between study arms in relation to TEAE occurrence, severe AEs occurrence, SAE occurrence and fatal SAE occurrence, based on the frequency-based analysis. However, subjects on vadadustat experienced a higher rate of TEAE, severe AEs, SAEs, and fatal SAEs, compared to subjects on darbepoetin alfa, when analysis was adjusted for exposure. Both frequency-based and exposure-adjusted analysis demonstrated that subjects on vadadustat experienced a higher rate of AEs leading to permanent treatment discontinuation and AEs leading to dose modification, such as interruption and dose reduction of study drug, when compared to subjects on darbepoetin alfa.

Table 123. Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0017

Event	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Any treatment-emergent AE	1562 (88.4)	1580 (89.3)	0.99	-1.0
Severe AEs	707 (40.0)	748 (42.3)	0.95	-2.3
SAEs	973 (55.0)	1032 (58.3)	0.94	-3.3
SAEs with fatal outcome	276 (15.6)	290 (16.4)	0.95	-0.8
AEs leading to permanent discontinuation of study drug	91 (5.2)	20 (1.1)	4.56	4.0

Event	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
AEs leading to dosage modification of study drug	257 (14.5)	175 (9.9)	1.47	4.7
AEs leading to interruption of study drug	248 (14.0)	175 (9.9)	1.42	4.1
AEs leading to reduction of study drug	15 (0.9)	1 (0.1)	14.17	0.8
AEs leading to dosage delay of study drug	0 (0)	0 (0)	-	0

Source: ADEM and SDTM datasets; Software: R and JMP
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

Table 124. Exposure-Adjusted Overview of Treatment-Emergent Adverse Events, Safety Population, on-Study Period, Trial 0017

Event	Vadadustat N=1726 PY (/ 100 yrs)	Darbepoetin Alfa N=2090 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Any treatment-emergent AE	90.50	75.60	1.20	14.90
Severe AEs	40.96	35.79	1.14	5.17
SAEs	56.37	49.38	1.14	7.00
SAEs with fatal outcome	15.99	13.88	1.15	2.12
AEs leading to permanent discontinuation of study drug	5.27	0.96	5.51	4.32
AEs leading to dosage modification of study drug	14.89	8.37	1.78	6.52
AEs leading to interruption of study drug	14.37	8.37	1.72	6.00
AEs leading to reduction of study drug	0.87	0.05	18.16	0.82
AEs leading to dosage delay of study drug	0	0	-	0

Source: SDTM datasets; Software: JMP
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with at least one event; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; SAE, serious adverse event.

7.6.6.2. Deaths, Trial 0017

A total of 566 subjects died during the on-study period of trial 0017, with 276 subjects on vadadustat and 290 subjects on darbepoetin alfa, as summarized in Table 125. The rates of all-cause mortality are comparable between the two treatment arms, with no clinically significant difference upon evaluation of specific causes of death. Table 126 summarizes key characteristics of subjects who died while on-study. There were no observed clinically significant differences in key demographic characteristics and study day of death but subjects on vadadustat had a shorter drug exposure duration prior to death.

Table 125. Deaths in Safety Population, on-Study Period, Trial 0017

Deaths	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Treatment-emergent deaths[1]	276 (15.6)	290 (16.4)	0.95	-0.8
Acute cardiovascular/vascular causes	83 (4.7)	87 (4.9)	0.95	-0.2
Cerebrovascular causes	7 (0.4)	10 (0.6)	0.70	-0.2
Infectious causes	44 (2.5)	57 (3.2)	0.77	-0.7
Renal/Electrolyte disturbances causes	23 (1.3)	16 (0.9)	1.44	0.4
Acute respiratory causes	12 (0.7)	17 (1.0)	0.71	-0.3
Oncological causes	3 (0.2)	13 (0.7)	0.23	-0.6
Non-specific/Unknown causes	82 (4.6)	72 (4.1)	1.14	0.6
Other causes	22 (1.2)	18 (1.0)	1.22	0.2

Source: ADEM and SDTM datasets; Software: R and JMP
[1] Grouping definitions for causes of death can be found in section III.17.4.1.
Abbreviations: N, number of subjects in group; n, number of deaths.

Table 126. Characteristics of Subjects Experiencing Death During On-Study Period in The Safety Population, Trial 0017

Characteristic	Vadadustat N=276	Darbepoetin Alfa N=290
Age (years), mean (SD)	65.0 (11.8)	65.1 (11.7)
Male, n (%)	172 (62.3)	167 (57.6)
U.S. subjects, n (%)	206 (74.6)	207 (71.4)
Subjects in developed countries[1], n (%)	220 (79.7)	227 (78.3)
Maximal dose[2], median (25% to 75% IQR)	450 (300 – 600)	0.72 (0.48 – 1.17)
Final dose[2], median (25% to 75% IQR)	450 (300 – 600)	0.55 (0.32 – 0.9)
Duration of exposure (days), median (25% to 75% IQR)	188 (99 – 356)	242 (113 – 393)
Study day of death, median (25% to 75% IQR)	356 (212 – 566)	353 (183 – 552)

Source: SDTM datasets; Software: JMP
[1] Developed countries are defined by the availability and advancement of the practice of medicine, based on information collected by the world health organization. Listing of countries according to "developed" versus "developing" status can be found in section III.17.4.2.
[2] The dosage unit for subjects on vadadustat is mg. The dosage unit for patient on darbepoetin alfa is µg/kg/week.
Abbreviations: N, total number of deaths in group; n, number of subjects; U.S., United States; IQR, Interquartile range.

7.6.6.3. Serious Adverse Events, Trial 0017

There were 7,155 SAEs in 2005 subjects in trial 0017, with 3,448 SAEs occurring in the vadadustat arm and 3,707 SAEs occurring in the darbepoetin alfa arm. Table 127 provides a frequency-based comparison of thrombotic SAE occurrence, by system organ class (SOC) and FDA groupings, reported in the safety population during the on-study period for trial 0017. There was a numerical trend toward higher occurrence of acute venous thrombotic SAEs in the vadadustat arm. In contrast, with the exception of TIA, there was a numerical trend toward higher occurrence of acute arterial thrombotic SAEs in the darbepoetin arm, as observed in unadjudicated CV thrombotic event and unadjudicated CVA. There was also a numerical trend toward higher occurrence of chronic/sub-acute thrombotic SAEs in the darbepoetin arm, as observed in atherosclerotic disease and AV connection stenosis. There were no other concerning SAEs that occurred at an incidence of <2%.

Table 127. Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Trial 0017

Serious Adverse Event[1]	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Atherosclerotic disease	85 (4.8)	95 (5.4)	0.90	-0.6
Cardiac disorders (SOC)	296 (16.7)	353 (20.0)	0.84	-3.2
Unadjudicated cardiovascular thrombotic event	101 (5.7)	113 (6.4)	0.89	-0.7
Unadjudicated cardiac life-threatening event	93 (5.3)	105 (5.9)	0.89	-0.7
Unadjudicated cardiac failure	88 (5.0)	107 (6.1)	0.82	-1.1
Atrial fibrillation	44 (2.5)	37 (2.1)	1.19	0.4
Nervous system disorders (SOC)	140 (7.9)	157 (8.9)	0.89	-1.0
Unadjudicated cerebrovascular accident	38 (2.2)	46 (2.6)	0.83	-0.5
Transient ischemic attack	15 (0.9)	5 (0.3)	3.00	0.6
Product issues (SOC)	14 (0.8)	11 (0.6)	1.27	0.2
AV connection stenosis	8 (0.5)	18 (1.0)	0.44	-0.6
Respiratory, thoracic, and mediastinal disorders (SOC)	179 (10.1)	191 (10.8)	0.94	-0.7
Acute respiratory failure	44 (2.5)	50 (2.8)	0.88	-0.3
Vascular disorders (SOC)	178 (10.1)	179 (10.1)	1.00	-0.1
VTE disease	117 (6.6)	103 (5.8)	1.14	0.8
Arterial thrombosis	4 (0.2)	5 (0.3)	0.80	-0.1

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: AV, Arteriovenous; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; SAE, serious adverse events; SOC, system organ class; VTE, venous thromboembolism.

Table 128 provides a frequency-based comparison of non-thrombotic SAE occurrence, by system organ class and FDA groupings, reported in the safety population during the on-study period for trial 0017. The following SAEs had a numerically higher occurrence in the vadadustat arm: GI acid-related disease and hepatoxicity. The following SAEs had a numerically higher occurrence in the darbepoetin alfa arm: seizures, hypertensive emergency, GI bleeding, fractures, hyperkalemia, and cancer. GI symptoms, infections, and falls were similar between study arms.

Table 128. Non-Thrombotic Serious Adverse Events by System Organ Class and FDA Groupings, Safety Population, Trial 0017

Serious Adverse Event[1]	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Hypertension	20 (1.13)	23 (1.30)	0.87	-0.17
Hypertension emergency	42 (2.38)	49 (2.77)	0.86	-0.39
Seizures	9 (0.51)	20 (1.13)	0.45	-0.62
Blood and lymphatic system disorders (SOC)	70 (3.96)	71 (4.01)	0.99	-0.05
Any bleeding adverse event	134 (7.58)	146 (8.25)	0.92	-0.67
GI bleeding	61 (3.45)	72 (4.07)	0.85	-0.62
Gastrointestinal disorders (SOC)	187 (10.58)	181 (10.23)	1.03	0.35
GI acid-related disease	29 (1.64)	22 (1.24)	1.32	0.40
Any gastrointestinal symptoms	31 (1.75)	32 (1.81)	0.97	-0.06
Diarrhea	6 (0.34)	7 (0.40)	0.86	-0.06
Nausea	2 (0.11)	5 (0.28)	0.40	-0.17
Abdominal pain	13 (0.74)	14 (0.79)	0.93	-0.06

Serious Adverse Event[1]	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Hypertension	20 (1.13)	23 (1.30)	0.87	-0.17
Hypertension emergency	42 (2.38)	49 (2.77)	0.86	-0.39
Constipation	6 (0.34)	2 (0.11)	3.00	0.23
Hepatobiliary disorders (SOC)	30 (1.70)	35 (1.98)	0.86	-0.28
Hepatotoxicity	38 (2.15)	27 (1.53)	1.41	0.62
Infections and infestations (SOC)	491 (27.72)	499 (28.21)	0.98	-0.49
Systemic infection	237 (13.40)	265 (14.98)	0.89	-1.58
Localized infection	279 (15.78)	282 (15.94)	0.99	-0.16
Injury, poisoning and procedural complications (SOC)	230 (13.01)	237 (13.40)	0.97	-0.39
Falls	17 (0.96)	18 (1.02)	0.94	-0.06
Fractures	53 (3.00)	64 (3.62)	0.83	-0.62
Metabolism and nutrition (SOC)	195 (11.03)	208 (11.76)	0.94	-0.73
Neoplasm benign, malignant, and unspecified (SOC)	38 (2.15)	58 (3.28)	0.66	-1.13
Cancer	35 (1.98)	52 (2.94)	0.67	-0.96
Renal and urinary disorders (SOC)	51 (2.89)	33 (1.87)	1.55	1.02
Fluid overload	103 (5.83)	103 (5.82)	1.00	0.01
Hyperkalemia	55 (3.11)	76 (4.30)	0.72	-1.19
Hyperphosphatemia	0 (0)	1 (0.06)	0	-0.06

Source: ADEM and SDTM datasets; Software: R and JMP
[1] MedDRA PTs that occurred at ≥2% in the vadadustat versus darbepoetin alfa arm are considered SAEs of interest. There PTs were coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3.
Abbreviations: GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; SAE, serious adverse events; SOC, system organ class

7.6.6.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial 0017

In trial 0017, vadadustat is associated with a higher rate of AEs leading to permanent discontinuation, compared to darbepoetin alfa (5.2% versus 1.1%). As shown in Table 129, the majority of this difference is attributable to the following AEs: GI symptoms (i.e., mainly nausea, vomiting, and diarrhea), hypertension-related events, GI acid disease, asthenia, and cardiac life-threatening events. Exposure adjustment of the overall rate of AEs leading to permanent discontinuation and their specific etiologies resulted in similar conclusions (exposure-adjusted analyses not shown).

Table 129. Adverse Events Leading to Discontinuation, Safety Population, Trial 0017

FDA Grouped PTs[1]	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Subjects with at least one AE leading to discontinuation	91 (5.15)	20 (1.13)	4.56	4.02
GI symptoms	35 (1.98)	1 (0.06)	35.02	1.92
Rash[2]	6 (0.34)	3 (0.17)	2.00	0.17
Hypertension-related events	5 (0.28)	0 (0.00)	-	0.28
Any bleeding	5 (0.28)	2 (0.11)	2.50	0.17
Asthenia[3]	4 (0.23)	0 (0.00)	-	0.23
Cardiac life-threatening event	4 (0.23)	0 (0.00)	-	0.23
Gastroduodenal acid disease	4 (0.23)	0 (0.00)	-	0.23
Cancer	4 (0.23)	2 (0.11)	2.00	0.11
Localized infection	3 (0.17)	1 (0.06)	3.00	0.11

FDA Grouped PTs[1]	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Systemic infection	3 (0.17)	2 (0.11)	1.50	0.06
Dyspnea	2 (0.11)	0 (0.00)	-	0.11
Headache	2 (0.11)	0 (0.00)	-	0.11
Cytopenia[4]	1 (0.06)	0 (0.00)	-	0.06
Unadjudicated cardiovascular thrombosis	1 (0.06)	2 (0.11)	0.50	-0.06
Hepatotoxicity	1 (0.06)	1 (0.06)	1.00	0.00
Unadjudicated cerebrovascular accident	0 (0)	1 (0.06)	0	-0.06

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3. PTs were included if they were AEs of interest or if occur in >2 subjects.
[2] PT rash includes skin exfoliation, rash, urticaria, dermatitis and rash popular.
[3] PT Asthenia includes asthenia and muscle weakness.
[4] PT Cytopenia includes bi-cytopenia and pancytopenia.
Abbreviations: AE, adverse event; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term

7.6.6.5. Treatment-Emergent Adverse Events, Trial 0017

There were 27,455 TEAEs in 3,142 subjects in the NDD-CKD population, with 13,404 TEAEs occurring in the vadadustat arm and 14,051 TEAEs occurring in the darbepoetin alfa arm. Table 130 provides a frequency-based comparison of specific TEAE occurrence reported in the safety population during the on-study period for trial 0017, while Table 131 provides the exposure-adjusted analysis of the same data. The frequency-based analysis demonstrated that:

- The following TEAEs had a numerically higher occurrence in the vadadustat arm: TIA, Access-related VTE, GI acid-related disease, diarrhea and nausea.
- The following TEAEs had a numerically higher occurrence in the darbepoetin alfa arm: unadjudicated CVA, access-unrelated VTE, AV connection stenosis, hypertension and hypertensive-related AEs, cancer, hyperkalemia, and hyperphosphatemia.

There were no clinically significant differences between study arms in the remainder of the TEAEs. Adrenal disorders, as an AESI, were reported as an adrenal mass in two subjects in each treatment arm (0.1% vs. 0.1%) in trial 0017. The results from the exposure-adjusted analysis were consistent with the results from the frequency-based analysis but subjects on vadadustat experienced a higher rate of the following additional TEAEs: unadjudicated CV thrombosis, VTE, most sub-types of bleeding, falls, fractures, and fluid overload.

Rhabdomyolysis occurred in 8 subjects in trial 0017 (5 subjects on vadadustat and 3 subjects on darbepoetin alfa), with 1 of 8 subjects being severe (on vadadustat), 6 of 8 subjects being moderate (3 subjects on vadadustat and 3 subjects on darbepoetin alfa) and 1 of 8 subjects being mild (on vadadustat). Events were considered as a SAE in 1 of 8 subjects (on vadadustat) and none of the events ledi to permanent study drug discontinuation. There was no significant difference in CPK elevation observed between treatment arms. Overall, the occurrence and severity of rhabdomyolysis is balanced between treatment arms, is considered relatively rare and, after review of the individual narratives, may be due to the presence of clinical risk factors.

The incidence of therapeutic phlebotomy in trial 0017, to treat excessive Hb response and avoid the risk of complications, was examined. Therapeutic phlebotomy was used in 38 patients: 17 patients on vadadustat and 21 patients on darbepoetin alfa. Overall, therapeutic phlebotomy was used infrequently, occuring more in the dabepoetin alfa arm, as a treatment of excessive Hb response.

In assessing vitals signs for safety signals, there were no clinically significant differences between trial arms in relation to median, maximum and minimum values of SBP, DBP and HR, throughout the on-study period. In addition, there were no findings of outlier risk difference ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in maximum SBP, maximum DBP, and evaluation of HR. However, there was a small increase in the occurrence hypotension due to SBP < 90 mm Hg (5.8% vs. 3.7%) but not due to DBP < 60 mm Hg.

Table 130. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects on Vadadustat and TEAEs of Special Interest, Safety Population, Trial 0017

FDA Grouped PTs[1]	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Unadjudicated cardiovascular thrombotic event	117 (6.6)	124 (7.0)	0.94	-0.4
Unadjudicated cardiac life-threatening event	93 (5.3)	107 (6.1)	0.87	-0.8
Unadjudicated cerebrovascular accident	40 (2.3)	52 (2.9)	0.77	-0.7
Transient ischemic attack	15 (0.9)	6 (0.3)	2.50	0.5
Arterial thrombosis	6 (0.3)	7 (0.4)	0.86	-0.1
VTE disease	215 (12.2)	203 (11.5)	1.06	0.7
Access-related VTE	182 (10.3)	156 (8.8)	1.17	1.5
Access unrelated VTE	48 (2.7)	66 (3.7)	0.73	-1.0
AV connection stenosis	77 (4.4)	104 (5.9)	0.74	-1.5
Atherosclerotic disease	175 (9.9)	198 (11.2)	0.88	-1.3
Coronary disease	57 (3.2)	76 (4.3)	0.75	-1.1
Cerebrovascular disease	16 (0.9)	19 (1.1)	0.84	-0.2
Vascular disease	121 (6.8)	122 (6.9)	0.99	-0.1
Unadjudicated cardiac function failure	113 (6.4)	141 (8.0)	0.80	-1.6
Hypertension	206 (11.7)	271 (15.3)	0.76	-3.8
Hypertension emergency	74 (4.2)	84 (4.8)	0.88	-0.6
Hypertension caused pathology	4 (0.2)	6 (0.3)	0.67	-0.1
Seizures	29 (1.6)	27 (1.5)	1.07	0.1
Hepatotoxicity	69 (3.9)	71 (4.0)	0.97	-0.1
Systemic infection	325 (18.4)	347 (19.6)	0.94	-1.2
Localized infection	547 (31.0)	561 (31.7)	0.98	-0.8
Any bleeding adverse event	301 (17.0)	333 (18.8)	0.90	-1.8
GI bleeding	117 (6.6)	122 (6.9)	0.96	-0.3
Mucocutaneous bleeding	155 (8.8)	162 (9.2)	0.96	-0.4
Visceral bleeding	37 (2.1)	49 (2.8)	0.76	-0.7
GU bleeding	39 (2.2)	40 (2.3)	0.98	-0.1
GI acid-related disease	173 (9.8)	135 (7.6)	1.28	2.2
Any gastrointestinal symptoms	490 (27.7)	437 (24.7)	1.12	3.0
Diarrhea	230 (13.0)	178 (10.1)	1.29	3.0
Nausea	149 (8.4)	134 (7.6)	1.11	0.9
Vomiting	120 (6.8)	124 (7.0)	0.97	-0.2
Abdominal pain	121 (6.8)	131 (7.4)	0.92	-0.6
Constipation	84 (4.8)	80 (4.5)	1.05	0.2

FDA Grouped PTs[1]	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Relative Risk	Risk Difference (%)
Falls	151 (8.5)	159 (9.0)	0.95	-0.5
Fractures	106 (6.0)	117 (6.6)	0.91	-0.6
Cancer	71 (4.0)	88 (5.0)	0.81	-1.0
Fluid overload	167 (9.5)	182 (10.3)	0.92	-0.8
Hyperkalemia	160 (9.1)	191 (10.8)	0.84	-1.8
Hyperphosphatemia	28 (1.6)	56 (3.2)	0.50	-1.6
Hypoglycemia	92 (5.2)	78 (4.4)	1.18	0.8
Dialysis-related complication	98 (5.5)	123 (7.0)	0.79	-1.5
Hypotension	148 (8.4)	142 (8.0)	1.05	0.4
Dyspnea	92 (5.2)	119 (6.7)	0.78	-1.5
Cough	108 (6.1)	141 (8.0)	0.76	-1.9
Asthenia	88 (5.0)	61 (3.5)	1.43	1.5
Headache	167 (9.5)	142 (8.0)	1.19	1.5

Source: SDTM datasets; Software: JMP
1, Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

Table 131. Exposure-Adjusted Treatment-Emergent Adverse Events, Safety Population, Trial 0017

FDA Grouped PTs[1]	Vadadustat N=1726 PY (/ 100 yrs)	Darbepoetin Alfa N=2090 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Unadjudicated cardiovascular thrombosis	6.78	5.93	1.14	0.85
Unadjudicated cardiac life-threatening event	5.39	5.12	1.05	0.27
Unadjudicated cerebrovascular accident	2.32	2.49	0.93	-0.17
Transient ischemic attack	0.87	0.29	3.03	0.58
Arterial thrombosis	0.35	0.33	1.04	0.01
VTE disease	12.46	9.71	1.28	2.74
Access-related VTE	10.54	7.46	1.41	3.08
Access unrelated VTE	2.78	3.16	0.88	-0.38
AV connection stenosis	4.46	4.98	0.90	-0.51
Atherosclerotic disease	10.14	9.47	1.07	0.67
Coronary disease	3.30	3.64	0.91	-0.33
Cerebrovascular disease	0.93	0.91	1.02	0.02
Vascular disease	7.01	5.84	1.20	1.17
Unadjudicated cardiac function failure	6.55	6.75	0.97	-0.20
Hypertension	11.94	12.97	0.92	-1.03
Hypertension emergency	4.29	4.02	1.07	0.27
Hypertension caused pathology	0.23	0.29	0.81	-0.06
Seizures	1.68	1.29	1.30	0.39
Hepatotoxicity	4.00	3.40	1.18	0.60
Systemic infection	18.83	16.60	1.13	2.23
Localized infection	31.69	26.84	1.18	4.85
Any bleeding adverse event	17.44	15.93	1.09	1.51
GI bleeding	6.78	5.84	1.16	0.94
Mucocutaneous bleeding	8.98	7.75	1.16	1.23
Visceral bleeding	2.14	2.34	0.91	-0.20
GU bleeding	2.26	1.91	1.18	0.35
GI acid-related disease	10.02	6.46	1.55	3.56
Any gastrointestinal symptoms	28.39	20.91	1.36	7.48
Diarrhea	13.33	8.52	1.56	4.81
Nausea	8.63	6.41	1.35	2.22

FDA Grouped PTs[1]	Vadadustat N=1726 PY (/ 100 yrs)	Darbepoetin Alfa N=2090 PY (/ 100 yrs)	Relative Risk	Risk Difference (/ 100 yrs)
Vomiting	6.95	5.93	1.17	1.02
Abdominal pain	7.01	6.27	1.12	0.74
Constipation	4.87	3.83	1.27	1.04
Falls	8.75	7.61	1.15	1.14
Fractures	6.14	5.60	1.10	0.54
Cancer	4.11	4.21	0.98	-0.10
Fluid overload	9.68	8.71	1.11	0.97
Hyperkalemia	9.27	9.14	1.01	0.13
Hyperphosphatemia	1.62	2.68	0.61	-1.06

Source: SDTM datasets; Software: JMP
[1] Coded as MedDRA preferred term that are grouped according to definitions found in section III.17.4.3
Abbreviations: AV, Arteriovenous; GI, gastrointestinal; GU, genital-urinary; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with serious adverse event; PTs, preferred term; PY, drug exposure time calculated as follows: ([date of last dose – date of first dose] + 1)/365.25) - total period of drug interruption from the standard duration of treatment; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism

7.6.6.6. Laboratory Findings, Trial 0017

Table 132 shows other laboratory abnormalities that reached the outlier risk difference threshold of ≥1% in the vadadustat arm, compared to the darbepoetin alfa arm, in trial 0017. Elevation of potassium, elevation of WBCs, decrease in lymphocytes, and decrease in platelets, of all severities, was higher in the darbepoetin arm, compared to the vadadustat arm, in trial 0017. There were no clinically significant differences between trial arms in relation to the change in mean values of laboratory parameters from baseline to end of treatment values.

Table 132. Subjects Meeting Laboratory Abnormality Criteria From Baseline to ≥ Week 36, Risk Difference ≥1% Higher in Vadadustat Arm, Safety Population, Pooled Trial 0017

Laboratory Analysis	Vadadustat N=1768 n (%)	Darbepoetin Alfa N=1769 n (%)	Risk Difference (%)
Low bicarbonate (mEq/L)	N=1598	N=1629	
Severe[1]	207 (13.0)	182 (11.2)	1.8

Source: ADEM datasets; Software: R.
[1] Severe low bicarbonate defined as <15 mEq/L.
Abbreviations: N, number of subjects; n, number of subjects with abnormality.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Failure to Demonstrate Non-Inferiority of MACE Risk in the NDD-CKD population

Issue

The Applicant failed to demonstrate non-inferiority of vadadustat, compared to darbepoetin, regarding the risk of MACE in the NDD-CKD population.

Background

The PRO2TECT program in the NDD-CKD population was designed to pool the two pivotal trials (CI-0014 and CI-0015) and rule out a risk margin of 1.25 with 80% power and 2.5% one-sided type I error. The Applicant estimated a total of 631 MACE events (only the first event of a subject) to be sufficient. The Applicant observed a total of 726 MACE events, which was 95 more events than planned. However, the Applicant failed to demonstrate the non-inferiority of vadadustat compared to darbepoetin regarding the risk of MACE in the primary analysis. The Applicant reasoned that they failed to meet the risk margin of 1.25 mainly because of the large variability in the estimates between regions and stated that vadadustat is safe to be used in the U.S. population.

Assessment

The pre-specified primary analysis for adjudicated MACE showed that the estimated HR and corresponding 95% CI was 1.17 (1.01, 1.36) indicating that the upper bound of the 95% CI exceeded the risk margin of 1.25 with lower bound of the 95% CI exceeding 1. Our analysis using the modified region variable in the Cox proportional hazard model also resulted in the same conclusion (HR, 1.17; 95% CI, 1.01, 1.35). The components of MACE – non-fatal MI, non-fatal stroke and all-cause mortality – all had unfavorable HRs; the estimated HRs and 95% CIs were 1.42 (0.98, 2.07) for non-fatal MI, 1.24 (0.75, 2.04) for non-fatal stroke and 1.08 (0.93, 1.27) for all-cause mortality. When taking the different duration of drug exposure into consideration (OT +7 analysis), the magnitude of the estimated risk of MACE became larger (HR 1.50; 95% CI, 1.22, 1.85). Subgroup analysis of MACE and its subcomponents by region did not support the Applicant's reasoning that vadadustat is safe to be used in the U.S. population. In the U.S. population, the estimated hazard ratio for adjudicated MACE was 1.06 (95% CI, 0.87, 1.29). Although the study was not powered to rule out a risk margin of 1.25 for MACE occurrence in the U.S. population only, the upper bound of 1.29 does not provide reassurance of an absent safety signal for MACE occurrence. Furthermore, there was an increased hazard ratio for non-fatal MI in the vadadustat arm in the U.S. population (HR, 1.49, 95% CI, 0.97, 2.30). Exploratory analysis of the impact of post-baseline covariates, such as occurrence of maximum Hb value above Hb target and excessive rate of rise of Hb, was performed. The results did not show a clear association between presence of these post-baseline factors and the risk of occurrence of MACE in the NDD-CKD population. However, these results are inconclusive due to the post-baseline nature of these factors and the exploratory nature of the analysis.

Conclusion

The Applicant did not demonstrate non-inferiority of vadadustat compared to darbepoetin alfa for the primary safety endpoint, adjudicated MACE, with the 95% CI excluding the value of no effect. The associated risk of MACE observed with vadadustat was shown in comparison to darbepoetin, an ESA active comparator with an established increased risk of non-fatal MI, non-fatal stroke, and all-cause mortality. The results were consistent when duration of drug exposure was taken into account using the OT +7 analysis. In addition, all the components of MACE (adjudicated non-fatal myocardial infarction, adjudicated non-fatal stroke and adjudicated all-cause mortality) showed a numerically unfavorable hazard ratio for vadadustat. Results from additional sensitivity analyses that assessed MACE and cardiovascular death supported the same conclusion. In addition, the Applicant's statement that vadadustat is safe in the U.S. population

was not supported by our analysis that observed an increased risk of non-fatal MI in the U.S. population similar to that seen in the overall population. In addition, although the study was not powered to rule out a risk margin of 1.25 for MACE occurrence in the U.S. population, the upper bound of 1.29 does not provide reassurance of an absent safety signal for MACE occurrence.

7.7.2. Increased Risk of Thromboembolic Events in the DD-CKD Population

Issue

The risk of thromboembolic events was higher in the vadadustat arm, compared to the darbepoetin arm, in the DD-CKD population. The magnitude of risk was larger in the U.S.-only population compared to pooled region.

Background

Thromboembolic events (TE) were assessed in two ways – based on the Applicant's pre-specified adjudication data and the Agency's definition using PT terms. The Applicant defined TE as arterial thrombosis (ATE), deep vein thrombosis (DVT), pulmonary embolism (PE) and vascular access thrombosis (VAT), where potential cases were adjudicated by the adjudication committee. The Agency independently defined TE using PT terms relevant to venous thrombosis (VTE) and ATE**.**

Assessment

Results using the Applicant's adjudicated data and the Agency-defined access-related VTE both indicated an increased risk of TE in the vadadustat arm, compared to the darbepoetin arm, in the DD-CKD population (i.e., the pooled analysis of trial CI-0016 and CI-0017).

The analysis of the Applicant's adjudicated data for TE events resulted in an estimated HR (95% CI) of 1.20 (0.96, 1.50). This increased risk of the Applicant's adjudicated TE was more apparent in the U.S.-only population, with an estimated HR of adjudicated TE of 1.46 (1.13, 1.89). More than 80% of the Applicant's adjudicated TE events were vascular access thrombosis events. The estimated HR (95% CI) of the Applicant's adjudicated vascular access thrombosis events was 1.28 (1.00, 1.63).

The analysis using the Agency-defined TE events showed no apparent signal (HR, 1.02; 95% CI, 0.85, 1.22). However, the risk of access-related VTE was higher in the vadadustat arm (HR, 1.12; 95% CI, 0.92, 1.37), consistent with results obtained from the analysis of the adjudicated TE data.

Exploratory analysis of the impact of post-baseline covariates, such as occurrence of maximum Hb value above Hb target and excessive rate of rise of Hb, was performed. The results did not show a clear association between presence of these post-baseline factors and the risk of occurrence of VTE in the DD-CKD population, with the exception of the occurrence of maximum erythropoietin levels above the upper limit of normal. However, these results are inconclusive due to the post-baseline nature of these factors and the exploratory nature of the analysis.

In relation to the Applicant's assessment of this safety signal, the Applicant agrees with the presence of an increased signal for vascular-access thrombosis in patients on vadadustat, but

states that its impact is not clinically significant because vascular access was salvaged in the majority of patients who experienced vascular-access thrombosis and this risk can be addressed with appropriate content in the Warning and Precautions of the label. The FDA disagrees with this assessment, as the impact of vascular-access thrombosis in dialysis-dependent patients can potentially result in significant morbidity and mortality, thus negatively affecting the benefit-risk assessment of vadadustat in this patient population.

Conclusion

There is a concerning signal for adjudicated TE events in the vadadustat arm, compared to darbepoetin arm, in the DD-CKD population. The same conclusion was reached when examining VTE, which was mainly driven by access-related VTE. In addition, the magnitude of TE risk was higher in the U.S.-only population.

7.7.3. Hepatotoxicity in the NDD-CKD population and the DD-CKD population

Issue

There is a clinically significant hepatocellular injury risk with the use of vadadustat in subjects with CKD, as evident by the presence of one Hy's Law case and at least seven cases of probable DILI in Temple's Corollary.

Background

There was a significant hepatotoxicity signal identified by the Applicant during the drug development program of vadadustat. As a result, FDA required the Applicant to submit quarterly hepatic safety reports during the conduct of the phase 3 global trials and to amend the protocols and other documents to include hepatic criteria for permanent discontinuation and sufficient warnings of the hepatic risk. During the safety review, the clinical team identified a similar signal during the preliminary analysis, in both the DD-CKD and the NDD-CKD populations. As a result, the division consulted the DILI team to evaluate the hepatotoxicity signal (see section III.17.7 for more details).

Assessment

The clinical review team, with the help of the DILI team, identified one probable Hy's Law case attributable to vadadustat. The Applicant did not agree with our assessment due to the presence of elevation of alkaline phosphatase (AP), with peak value >2x ULN. However, because the ALT and AST were both over 1000 U/L and the total bilirubin was 17.3 mg/dL (severe jaundice), there is sufficient evidence indicating the hepatocellular nature of the injury and meeting Hy's Law. Hy's Law and the 2009 FDA Guidance on DILI (July 2009) do not specify a firm cut-off of AP elevation.

In cases where there is concomitant AP elevation, the R-value is useful. The R-value equals [ALT/ULN] ÷ [AP/ULN]. It is an internationally recognized and routinely used means of categorizing DILI into hepatocellular and cholestatic injury (R-value $\geq$ 5 defines hepatocellular injury) (Aithal et al. 2011; Council for International Organizations of Medical Sciences (CIOMS) 2020). A validated new Hy's Law criteria uses a new R-value (nR value) based on peak ALT or AST, whichever is higher (Bessone et al. 2019). In subjects with jaundice, an nR >

5 improves identification of patients at risk of poor outcome, compared to a Hy's Law that uses an AP limit of <2x ULN (Robles-Diaz et al. 2014). By nR-value criterion, this subject had hepatocellular DILI with at least 10% mortality risk, thus fulfilling Hy's Law.

There were another seven cases of probable DILI due to vadadustat without jaundice, but with ALT levels >5x ULN, and with five cases having ALT levels >10x ULN. Thus, these cases fell under Temple's Corollary, which suggests studies with Hy's Law cases will often have several other cases with significant ALT elevation without jaundice where study drug is discontinued in time, preventing further hepatocyte loss and hyperbilirubinemia. There were no cases of significant cholestasis (i.e., alkaline phosphatase >3x ULN with bilirubin >2x ULN, in the absence of high transaminases).

In these eight probable DILI cases, the injury had a median latency of 56 days (range 9-168). Overall, the injury pattern was mostly compatible with hepatocellular injury (median R-value 7.1, range 4.1 to 19.2). When using a category counts approach (i.e., 3-5 x ULN, 5-10 x ULN, etc.), transaminase elevations were similar between the two study arms. However, when specific cut-off values were considered (i.e., >3x ULN, >5x ULN, etc.), there were more cases detected in the higher ALT categories in the vadadustat arm, compared to the darbepoetin alfa arm. For example, there were 42 vadadustat arm subjects with peak ALT >5x ULN versus 31 darbepoetin alfa subjects.

To further evaluate the hepatic safety signal, the Applicant instituted two hepatology assessment committees, to adjudicate AEs for drug-related hepatic disorders. The first committee was unblinded and found increased attribution to vadadustat in the treatment arm compared to control. The second committee was blinded and did not find increase attribution to vadadustat in the treatment arm compared to control. It is important to note that knowledge of medications taken is core to DILI causality accuracy, particularly when the control medication has known, low DILI potential. As a result, blinding fundamentally eroded the accuracy of causality assessment since it introduced another bias, DILI causality misclassification from lack of necessary data. Such non-differential, misclassification biases toward the null. Therefore, the blinded committee increase in possible and probable cases in the control arm led to a null finding, which did not dismiss the findings of the prior unblinded committee or the FDA review team assessments and did not sufficiently address our concerns for DILI with the use of vadadustat. Please see section III.17.7 for more details of the DILI assessment.

Conclusion

Given the identification of one probable Hy's Law case, at least seven cases of probable DILI in Temple's Corollary, and a higher incidence of cases detected in the higher ALT categories in the vadadustat arm, compared to the darbepoetin alfa arm, there is a clinically significant hepatocellular injury risk with the use of vadadustat in patients with CKD. These findings were confirmed by both an Applicant-driven independent unblinded hepatology assessment and an FDA DILI team assessment.

7.7.4. Increased Risk of Seizures in the DD-CKD Population

Issue

There is a comparable risk of seizures with vadadustat, compared to darbepoetin alfa, in the NDD-CKD and DD-CKD populations.

Background

An increased risk of seizures in patients with anemia associated with CKD treated with ESAs, is an established adverse reaction that is documented in the Warning and Precautions section of the USPI of all approved ESAs. Furthermore, a safety signal of increased risk of seizures, in both the NDD-CKD population and the DD-CKD population, was detected during the safety evaluation of roxadustat, the first-in-class HIF-PH inhibitor. As a result, the clinical review team conducted a safety analysis of the occurrence of seizures in the pooled NDD-CKD population (i.e., trial 0014 and trial 0015) and the pooled DD-CKD population (i.e., trial 0016 and 0017), using a comprehensive grouping approach listed in section III.17.4.3.

Assessment

In the NDD-CKD population, seizures, as an SAE, were reported with a frequency-based occurrence of 0.4% (7/1739) in the vadadustat arm versus 0.3% (5/1732) in the darbepoetin alfa arm (see section II.7.6.1.3). Seizures, as an AE leading to permanent discontinuation, occurred in two subjects in the vadadustat arm, versus no patient in the darbepoetin alfa arm (see section II.7.6.1.4). The frequency-based occurrence of seizure AEs in the two treatment arms was the same (i.e., 12 subjects in each arm, with an incidence of 0.7%). The exposure-adjusted relative risk was 1.07, with 0.58/100 years in the vadadustat arm versus 0.54/100 years in the darbepoetin alfa arm (see section II.7.6.1.5). Overall, our assessment did not reveal a clinically significant increase in risk of seizures with vadadustat, compared to darbepoetin alfa, in the NDD-CKD population.

In the DD-CKD population, the relative risk of seizures, as an SAE, was 0.43, with a frequency-based occurrence of 0.5% (9/1947) in the vadadustat arm versus 1.1% (21/1955) in the darbepoetin alfa arm (see section II.7.6.4.3). There was no occurrence of seizures, as an AE leading to permanent discontinuation, in either treatment arm (see section II.7.6.4.4). The frequency-based occurrence of seizure AEs was 1.6% (31/1947) in the vadadustat arm versus 1.5% (29/1955) in the darbepoetin alfa arm, with a relative risk of 1.07. When adjusting for differential drug exposure between treatment arms, the relative risk increased to 1.29, with 1.65/100 yrs in the vadadustat arm versus 1.28/100 yrs in the darbepoetin alfa arm (see section II.7.6.4.5). However, this analysis is limited because of only a 2-event difference in seizures between treatment groups. Overall, our assessment revealed a lower risk of seizure SAEs but a comparable or slightly higher risk of seizure AEs with vadadustat compared to darbepoetin alfa in the DD-CKD population.

The Applicant conducted additional analyses that did not utilize the on-study period and did not correct for differential drug exposure. Based on their analyses, they concluded that vadadustat does not increase seizure risk in the DD-CKD population. We conclude that vadadustat has a risk of seizures that is comparable to the increased risk of seizures seen with darbepoetin alfa in the

NDD and DD CKD populations. We consider this review issue a minor review issue, which can be addressed with appropriate content in the Warning and Precautions of the label.

Conclusion

During the safety analysis of the clinical review team, we identified a clinically significant increase in the overall risk of seizures in the DD-CKD population, which was better appreciated when analysis was adjusted for differential drug exposure. Overall, we consider this review issue a minor review issue, which can be addressed with appropriate content in the Warning and Precautions of the label.

7.7.5. Increased Risk of Gastrointestinal Adverse Reactions in the CKD Population

Issue

There is a higher incidence of gastrointestinal (GI) adverse reactions with vadadustat, compared to darbepoetin alfa, in the NDD-CKD population and DD-CKD populations.

Background

Currently, there are no approved oral treatments for patients with anemia associated with CKD. Vadadustat is the second oral HIF-PH inhibitor to be considered for approval for treatment of this condition. During the safety evaluation of roxadustat, the first-in-class oral HIF-PH inhibitor, there was a higher rate of GI AEs occurrences associated with roxadustat, resulting in it being the second most common organ system affected. Given its route of administration and previous occurrence of GI AEs in the drug class, the clinical review team conducted a safety analysis of the occurrence of GI adverse reactions in the pooled NDD-CKD population (i.e., trial 0014 and trial 0015) and the pooled DD-CKD population (i.e., trial 0016 and 0017), using a comprehensive grouping approach listed in section III.17.4.3.

Assessment

In the NDD-CKD population, the relative risk of GI disorders, as an SAE, was 1.18, with a frequency-based occurrence of 7.1% (123/1739) in the vadadustat arm versus 6.0% (104/1732) in the darbepoetin alfa arm. Similarly, the relative risk of any GI symptom occurrence as an SAE was 1.82, with the relative risk of diarrhea and abdominal pain at or above 2.0 (see section II.7.6.1.3). GI symptoms (i.e., mainly abdominal pain, nausea, vomiting, and diarrhea), as an AE leading to permanent discontinuation, were the second most common cause, with a relative risk of 24.0 and a frequency-based occurrence of 1.4% (25/1739) in the vadadustat arm versus 0.1% (1/1732) in the darbepoetin alfa arm (see section II.7.6.1.4). Overall, the relative risks of the frequency-based occurrence of GI acid-related disease and any GI symptoms were 1.11 and 1.28, respectively. Individual GI symptoms (i.e., abdominal pain, nausea, vomiting, diarrhea, and constipation) showed a relative risk >1.0, with the largest risk difference observed in the occurrence of diarrhea (4.5%) and nausea (1.8%). Exposure-adjusted analysis of GI AEs showed even higher relative risks of occurrence, demonstrating the increased risk of GI adverse reactions with vadadustat in the NDD-CKD population, compared to darbepoetin alfa (see section II.7.6.1.5).

In the DD-CKD population, the relative risk of GI acid-related disease, as an SAE, was 1.15, with a frequency-based occurrence of 1.6% (32/1947) in the vadadustat arm versus 1.4% (28/1955) in the darbepoetin alfa arm (see section II.7.6.1.3). GI symptoms (i.e., mainly nausea, vomiting, and diarrhea), as an AE leading to permanent discontinuation, were the most common cause, with a relative risk of 35.1 and a frequency-based occurrence of 1.8% (35/1947) in the vadadustat arm versus 0.1% (1/1955) in the darbepoetin alfa arm (see section II.7.6.1.4). Overall, the relative risks of the frequency-based occurrence of GI acid-related disease and any GI symptoms were 1.27 and 1.12, respectively. Of the individual GI symptoms evaluated, diarrhea and nausea are the main GI symptoms, with relative risks of 1.27 and 1.11, respectively. Exposure-adjusted analysis of GI AEs showed even higher relative risks of occurrence, demonstrating the increased risk of GI adverse reactions with vadadustat in in the DD-CKD population (see section II.7.6.1.5).

The Applicant-conducted analyses agreed with our results and conclusions and proposed appropriate labeling to inform of this risk. Overall, we consider this review issue a minor review issue, which can be addressed with appropriate content in the label.

Conclusion

During the safety analysis, we identified a clinically significant increase in the overall risk of gastrointestinal adverse reactions in the NDD-CKD population and DD-CKD populations. Overall, we consider this review issue a minor review issue, which can be addressed with appropriate content in the label.

7.8. Risk and Evaluation Mitigation Strategy

REMS Proposed by Applicant

The Applicant proposed a Risk and Evaluation Mitigation Strategy (REMS) comprised of a communication plan to mitigate the risk of serious and fatal cardiac adverse events. The REMS would inform healthcare providers of the greater risks in patients with NDD-CKD if dosing with vadadustat results in hemoglobin levels greater than 11 g/dL, and the need to monitor hemoglobin levels. The proposed REMS includes a REMS Letter, Fact Sheet, and Journal Information Piece that would be disseminated up to 12 months following approval to healthcare providers who are likely to prescribe vadadustat to manage anemia associated with NDD-CKD.

REMS Considerations

The review team does not believe that the proposed REMS is sufficient to mitigate the risk of MACE in the NDD-CKD population. The proposed strategy relies on informing healthcare providers of the risks associated when patient hemoglobin levels surpass 11 g/dL and thereby would prevent MACE through drug titration and monitoring of hemoglobin. There are concerns with the proposed strategy. First, dosing of vadadustat in clinical trials was guided by a treatment algorithm that sought to titrate the medication without surpassing hemoglobin thresholds of 11g/dL or 12 g/dL depending on where the trial was taking place. Despite this careful approach to dosing, the Applicant failed to rule out the pre-specified risk margin of 1.25 for the primary safety endpoint of the adjudicated MACE outcome. Further, the same conclusions were reached when evaluating the US population separately and despite a lower hemoglobin target (10-11g/dL) for this population and appropriate implementation of the treatment algorithm. Thus, there is not sufficient evidence to suggest that limiting hemoglobin levels less than 11 g/dL will

mitigate the risk of MACE at this time. Therefore, the proposed REMS would not ensure the benefits of vadadustat outweigh its risk of MACE in the NDD-CKD population.

Other risk mitigation elements, such as narrowing the indicated population, minimizing the risk by early detection and reducing the negative impact of the risk once it occurred, and informed decision making were considered as possible strategies to address the risks of MACE in the NDD-CKD population and TE events in the DD-CKD population. For the risk of MACE in the NDD-CKD population, the review team has not identified a sub-population of patients where the benefits may outweigh the risk. For the risk of TE events in the DD-CKD population, there is no evidence in the clinical development program to suggest that the risk may be avoided or detected early to prevent progression. The risk of TE is difficult to avoid in the DD-CKD patient population, given the presence of multiple TE risk factors at baseline and the general ineffectiveness of TE screening strategies. While there are anticoagulation therapies available to treat TE events, the increased risk of TE seen in the DD-CKD cohorts is especially problematic. Access-related thrombosis could impact patients' ability to receive life-sustaining dialysis. Even though patients can be treated for a thrombus, they can potentially experience significant morbidity and mortality, associated with the occurrence of the TE event. Further, the convenience of an oral agent is diminished since patients with DD-CKD can still get their ESAs with dialysis. A strategy to ensure that healthcare providers and patients are informed of the risk of vadadustat was also considered. However, the benefit of treatment with vadadustat does not outweigh the potentially life-threatening risk of losing dialysis access or other clot-related sequelae.

REMS Conclusions

A REMS will not ensure the benefits of vadadustat outweigh the risks of MACE in the NDD-CKD population. The review team has not identified a subpopulation where benefits may be favorable and outweigh the risk of MACE in the NDD-CKD population. Given the diminished benefit of vadadustat in the DD-CKD population who can receive ESAs with dialysis, the risk of thromboembolic events in the DD-CKD population cannot be adequately mitigated to ensure the benefits outweigh the risks. Additionally, other therapies are available to treat CKD and an informed benefit-risk decision between healthcare providers and patients would not ensure that the benefits outweigh the risk. Overall, at this time, the review team has not identified a risk management strategy that would ensure the benefits of vadadustat outweigh the risks of MACE in the NDD-CKD population and thromboembolic risks in the DD-CKD population.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

Vadadustat and its metabolites were excreted in urine (58.9%) and in feces (26.9%) with a total recovery of 85.9% determined in the human mass balance study. Of the 26.9% radioactivity in feces, unchanged vadadustat accounted for 35% of fecal radioactivity or approximately 10% of the administered dose, which is likely unabsorbed drug in feces. In urine, most of the radioactivity was associated with vadadustat-O-glucuronide and less than 1% of unchanged vadadustat was accounted for in human urine. Based on comparison between studies, exposures

to vadadustat in healthy subjects and subjects with Stage 3 or Stage 4 CKD or on dialysis were similar when extrapolated to 600 mg based on non-compartmental analyses. Based on the population PK analysis across studies, eGFR is a significant covariate for vadadustat PK in subjects with NDD-CKD and exposures in subjects on dialysis were higher (~2-fold) compared to healthy subjects. The PK outcome differences for renal impairment between non-compartmental and population PK analyses are attributed to integration of covariates (age, sex, body weight, etc.).

In subjects with Stage 5 CKD on dialysis, no significant differences in PK (maximum plasma concentration [C_{max}], AUC, or t½) were observed when vadadustat was administered 4 hours before dialysis or 2 hours after dialysis. The target population with renal impairment, both NDD-CKD and DD-CKD was studied in the pivotal trials. Therefore, dose-adjustments as such for renal impairment are not warranted.

Hepatic Impairment

A dedicated hepatic impairment study was conducted where participants with normal hepatic function and moderate hepatic impairment (Child Pugh B) were given a single 450 mg dose of vadadustat (study CI-0024). Results are shown below in Table 133 and they show that moderate hepatic impairment did not appear to significantly affect systemic exposure of vadadustat.

The mean $C_{max\ unbound}$, $AUC_{last\ unbound}$, and $AUC_{inf\ unbound}$ values of the moderate hepatic impairment group were slightly higher than those of the normal group, however, the total plasma mean C_{max}, AUC_{last}, and AUC_{inf} values were similar. Following treatment with vadadustat, point estimates of the Geometric LSM ratios of the primary parameters C_{max}, AUC_{last}, and AUCinf plasma total were 1.02, 1.05, and 1.06 respectively. Therefore, hepatic impairment has minimal effect on the PK of vadadustat. Based on these results of this adaptive design study, it is not necessary to study vadadustat in subjects with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of vadadustat is unknown.

Table 133. Point Estimates and 90% Confidence Intervals for Geometric LSM Ratios of PK Parameters of Total and Unbound Vadadustat

	Geometric LS Mean			
Parameter	Moderate	Normal	Ratio (Moderate/Normal)	90% CI
C_{max}, µg/mL	51.6	50.3	1.02	(0.79, 1.32)
AUC_{last}, µg·h/mL	410	389	1.05	(0.82, 1.35)
AUC_{inf}, µg·h/mL	414	391	1.06	(0.82, 1.36)
$C_{max\ unbound}$, µg/mL	0.433	0.360	1.20	(0.90, 1.61)
$AUC_{last\ unbound}$, µg·h/mL	3.44	2.78	1.24	(0.89, 1.72)
$AUC_{inf\ unbound}$, µg·h/mL	3.47	2.79	1.24	(0.89, 1.73)

Source: Tables 14.2.3.1 and 14.2.3.2 of study report AKB-6548-CI-0024
Abbreviations: AUC_{inf}, area under the curve to infinity; $AUC_{inf\ unbound}$, area under the curve to infinity of unbound drug; AUC_{last}, area under the curve to the last quantifiable time point; $AUC_{last\ unbound}$, area under the curve to the last quantifiable time point of unbound drug; CI: confidence interval; C_{max}, maximum plasma concentration; C_{max}, maximum plasma concentration of unbound drug; LS mean: least squares mean; PK: pharmacokinetic

The review team agrees that no dose adjustment is required in patients with mild and moderate hepatic impairment.

Race

A multiple ascending dose (MAD) study was conducted in healthy adult Japanese and White subjects. Three cohorts, each of which consisted of 8 Japanese and 8 White subjects, were randomly assigned in a 3:1 ratio to receive vadadustat or placebo (N=6 vadadustat Japanese and White subjects, N=2 placebo Japanese and White subjects). The daily tablet doses of vadadustat were 150, 300, and 600 mg QD for cohorts 1, 2, and 3 respectively. Doses were administered QD for 10 days after at least a 10-hour fast.

Vadadustat was absorbed with a median time to maximum concentration (T_{max}) of 0.75 to 2.28 hours on Days 1 and 10. Vadadustat C_{max} and AUC_{tau} increased in a dose proportional manner for Japanese and White subjects across the dose range studied (150, 300, and 600 mg) following single and multiple dose administration. A comparison between White and Japanese subject dose normalized PK parameters for vadadustat is provided in Table 134. Analysis of variance (ANCOVA) after PK parameters were normalized by dose for Japanese and White subjects showed that the ratio of the geometric mean values was almost 1 regardless of the first dose or following multiple doses.

Table 134: Point Estimates and 90% Confidence Intervals for Geometric LSM Ratios of Dose-Normalized PK Parameters for Vadadustat Between Healthy Japanese and White Subjects

		Japanese Subjects			White Subjects			Japanese/White Subjects	
Regimen	Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Single Dose Day 1	AUC_{tau} (µg·h/mL)	18	0.704	0.63, 0.787	18	0.796	0.705, 0.899	0.884	0.788, 0.993
	C_{max} (µg/mL)	18	0.118	0.104, 0.135	18	0.133	0.115, 0.154	0.892	0.776, 1.024
Multiple Dose Day 10	AUC_{tau} (µg·h/mL)	18	0.891	0.764, 1.04	18	0.916	0.774, 1.08	0.973	0.830, 1.142
	C_{max} (µg/mL)	18	0.156	0.14, 0.173	18	0.147	0.131, 0.166	1.055	0.943, 1.181

Source: Tables 14.2.4.1 and 14.2.4.2 of study report AKB-6548-CI-0020
Abbreviations: AUC_{tau}, area under the curve during a dosing interval; C_{max}, maximum plasma concentration; GMR, geometric means ratio; LS mean: least squares mean

Based on these results, the review team agrees that there was no clinically significant difference in the PK of vadadustat based on race.

Age and Sex

The effect of both age and sex on the PK of vadadustat was evaluated by popPK analysis and neither was found to be a statistically significant covariate.

Body Weight

Increasing body weight was associated with decreasing AUC of vadadustat. The body weights of subjects with DD-CKD included in the popPK analysis ranged from 47 to 118 kg (at 5th and 95th percentile), and the estimated AUC_{ss} ranged from +34.2% to -24.8% of the AUC of subjects with the median body weight (75 kg) of subjects with DD-CKD. The body weights of subjects with NDD-CKD included in the popPK analysis ranged from 49 to 118 kg (at 5th and 95th percentile), and the estimated AUC_{ss} ranged from +30.5% to -24.7% of the AUC of subjects with the median body weight (75 kg) of subjects with NDD-CKD. The changes in AUC with body

weight are modest and not clinically significant. No dose adjustments are needed based on body weight.

8.2. Drug Interactions

Metabolic and Disposition Pathway

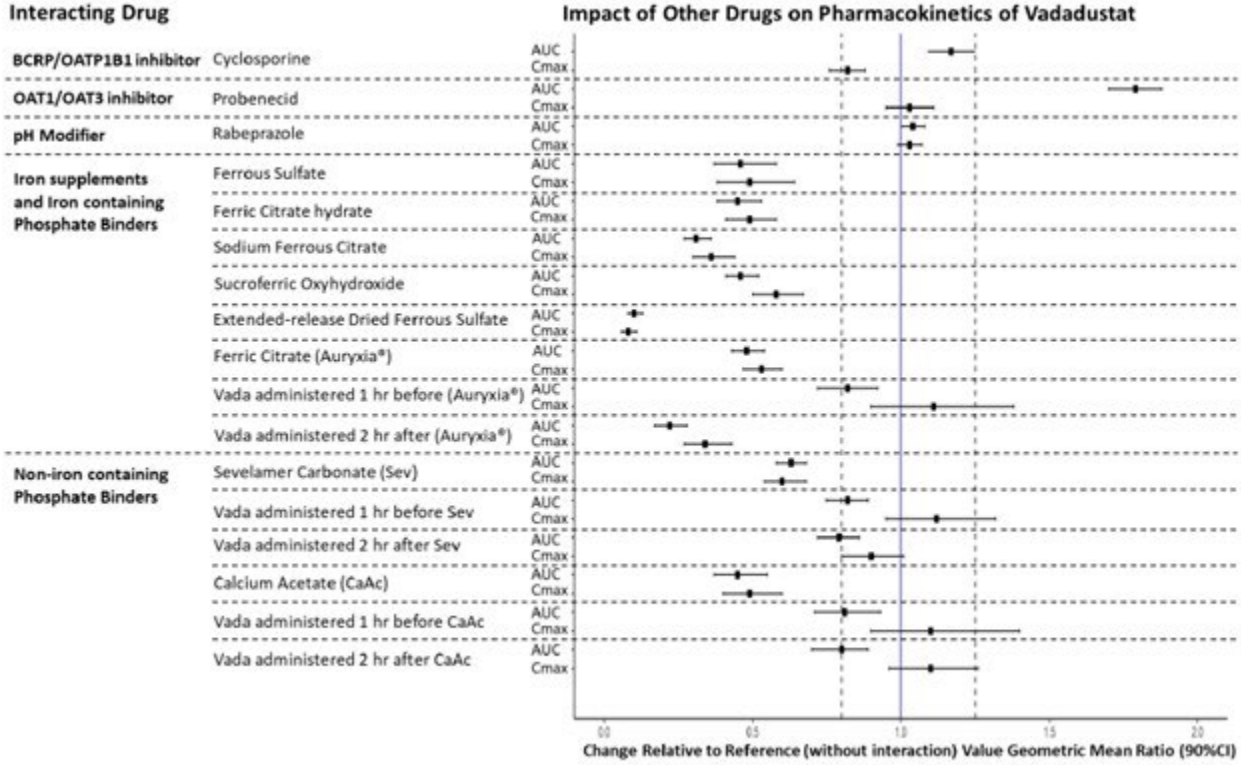
Vadadustat was metabolically stable in vitro and contribution of cytochrome P450 isoenzymes (CYPs) was minimal for the metabolism of vadadustat. The metabolic pathways involved were oxidation and mainly glucuronidation. The major circulating metabolite vadadustat-O-glucuronide formation was catalyzed by multiple uridine diphosphate glucuronosyltransferase (UGTs) (UGT1A1, 1A7, 1A8 and 1A9) and the minor metabolite acyl-glucuronide was formed by UGT1A1 and UGT2B7. Vadadustat, in vitro, was shown to be a substrate of BCRP, OATP1B1, OAT1/OAT3, and multiple UGTs. Vadadustat-O-glucuronide has also been shown to be an in vitro substrate of OAT3 and MRP2 and a possible substrate of OATP1B3. Clinical drug-drug interaction (DDI) (CI-0029, CI-0030, and CI-0031) studies were therefore conducted to evaluate the potential of vadadustat to mediate DDI via these enzymes and transporters.

Effect of Other Drugs on Vadadustat

As the solubility of vadadustat increases with increasing pH, an in vivo clinical DDI study was conducted to evaluate the co-administration of vadadustat with rabeprazole, a proton-pump inhibitor (CI-0033). It is expected that oral iron agents, iron-containing phosphate binders and non-iron-containing phosphate binders will be used in patients with CKD. The clinical DDI study (CI-0012, CI-0037, and J05) was conducted to assess the effect of oral iron agents, iron-containing phosphate binders and non-iron-containing phosphate binders on vadadustat PK.

A forest plot showing the drug-drug interactions (DDI) is provided in Figure 33.

Figure 33. Effect of Co-Administered Drugs on PK of Vadadustat



Source: Figure 1 of Module 2.7.2 Summary of Clinical Pharmacology Studies
The solid vertical line represents geometric mean ratio of 1 and dotted vertical lines represent the 0.80 to 1.25 boundary.
Abbreviations: BCRP: breast cancer resistance protein; CI: confidence interval; OAT: organic anion transporter; OATP: organic anion-transporting polypeptide; PK, pharmacokinetic

Drug Interaction Study With Cyclosporine (BCRP, P-gp, and OATP1B1 inhibitor)

The effect of a single dose of oral cyclosporine 500 mg was evaluated on a single dose of vadadustat 300 mg. Systemic exposure to vadadustat was not significantly altered when co-administered with cyclosporine with an approximate increase of 17% in vadadustat AUC and decrease of 18% in vadadustat C_{max} in healthy subjects (Figure 33).

Drug Interaction Study With Probenecid (UGT and OAT1/OAT3 inhibitor)

After dosing probenecid to steady state (500 mg Q12 hours from days 3 to 6), a single dose of vadadustat 300 mg was administered with the morning dose of probenecid on day 5. Statistical analysis of vadadustat C_{max} and AUC values showed that there was an almost 2-fold increase in total exposures of vadadustat and vadadustat-O-glucuronide while C_{max} did not change (Figure 33). Urinary excretion decreased for both vadadustat and vadadustat-O-glucuronide. As the AUC values for both vadadustat and vadadustat-O-glucuronide increased similarly (i.e., parent to metabolite ratio unchanged), it suggests that contribution of UGT inhibition is minimal and interaction is primarily due to OAT1/3 inhibition.

The Applicant's proposed labeling recommendation is that patients should be managed cautiously and evaluated for excessive effects of vadadustat. An information request was sent to the Applicant seeking justification for not proposing a dose adjustment for the starting dose of vadadustat when co-administered with OAT1/3 inhibitors, despite the ~2-fold increase in the total exposure of vadadustat when co-administered with probenecid. The Applicant's rationale for not proposing a dose adjustment when co-administered with probenecid is based upon the

following: (1) Most (13/18) subjects in Study AKB-6548-CI-0029 had <2-fold increase in vadadustat exposure when co-administered with probenecid. A dose reduction by half may result in some patients to be at risk of being underdosed; (2) The rise in hemoglobin with initiation of vadadustat treatment is gradual. In clinical practice vadadustat will be titrated to effect based upon frequent hemoglobin measurements which will mitigate the risk of overdose when vadadustat is given with OAT1/OAT3 inhibitors; (3) The expression of OAT1/OAT3 mRNA in kidney disease is lower compared to the expression in healthy subjects, thus the impact of co-administration of vadadustat with OAT1/OAT3 inhibitors would likely be less in magnitude in subjects with kidney disease compared to healthy volunteers; and (4) based upon an exposure-response analysis there was no significant relationship between vadadustat concentrations and MACE, non-fatal myocardial infarction, selected safety endpoints (SSEs) including diarrhea, vomiting, nausea, gastrointestinal disorders (defined as nausea, vomiting, abdominal pain, and diarrhea; all grades), hepatotoxicity, and hyperkalemia.

The evidence for the lower expression of renal transporters in patients with renal disease suggesting that probenecid's effect to inhibit OAT1/OAT3 and increase vadadustat total exposure may be less in magnitude in patients with renal disease compared to healthy volunteers was verified by the review team. We agree with the Applicant's rationale and agree to the proposed labeling recommendations with minor edits to reflect close monitoring for large increase in hemoglobin response.

Drug Interaction Study With Rabeprazole (Proton Pump Inhibitor)

The effect of multiple oral doses of rabeprazole (20 mg Q12 hours from days 2 to 6) was evaluated on the PK of a single dose of vadadustat 300 mg in healthy subjects. Results indicate that the systemic exposure to vadadustat and vadadustat-O-glucuronide is unchanged when vadadustat is administered with rabeprazole compared to when vadadustat is administered alone (Figure 33). These results suggest that the vadadustat exposure is not affected when vadadustat is given with gastric acid reducing agents.

Drug Interaction Study With Iron Supplements and Iron-containing Phosphate Binders

A single-dose, open-label, randomized crossover study to evaluate the impact of oral iron and iron-containing phosphate binders on the PK and safety of vadadustat 150 mg in healthy Japanese adult males was conducted (study MT-6548-J05). In cohort 1, the effect of sodium ferrous citrate (200 mg of iron in total) or ferric citrate hydrate (496 mg of iron in a 2000 mg dose) on the PK of vadadustat was evaluated in the fed condition. In cohort 2, the effect of sucroferric oxyhydroxide (1000 mg of iron in total) on the PK of vadadustat was evaluated in the preprandial condition. In cohort 3, the effect of dried ferrous sulfate (210 mg of iron in total, extended-release tablet) on the PK of vadadustat was evaluated in the fasted condition. The coadministration of each oral iron-based drug reduced the bioavailability of vadadustat by approximately 50%, with the greatest reduction occurring when co-administered with dried ferrous sulfate as an extended-release (Figure 33).

Part 3 of study CI-0037 evaluated the interaction of vadadustat with ferric citrate (Auryxia®) in healthy male and female subjects. Vadadustat administered 2 hours after ferric citrate exhibited greater DDI compared to vadadustat and ferric citrate administered concomitantly. The separation of vadadustat dosing one hour before ferric citrate was able to overcome the drug interaction. This effect may be due to vadadustat forming a complex with iron or the phosphate binder in the gastrointestinal tract leading to reduced absorption.

The Applicant's proposed dosing recommendation is that vadadustat should be administered at least one hour before oral iron supplements, products containing iron or iron-containing phosphate binders, which is acceptable to the review team based on the DDI results.

Drug Interaction Study With Non-Iron containing Phosphate Binders

A Phase 1, open-label, 3-part study to evaluate the interaction of vadadustat with sevelamer carbonate, calcium acetate, and ferric citrate (Auryxia®) was conducted in healthy male and female subjects (CI-0037). Part 1 assessed the effect of a single oral dose of sevelamer carbonate (1600 mg) on the PK of a single oral dose of vadadustat (300 mg). Part 2 assessed the effect of a single oral dose of calcium acetate (1334 mg) on the PK of a single oral dose of vadadustat (300 mg). The co-administration of non-iron-containing phosphate binders (sevelamer carbonate and calcium acetate) reduced the bioavailability of vadadustat up to 55% (Figure 33). The separation of vadadustat dosing one hour before or two hours after non-iron phosphate binder was able to overcome the drug interactions. Based on these results, the Applicant's proposed dosing recommendation that vadadustat should be administered at least one hour before or two hours after non-iron-containing phosphate binders is acceptable.

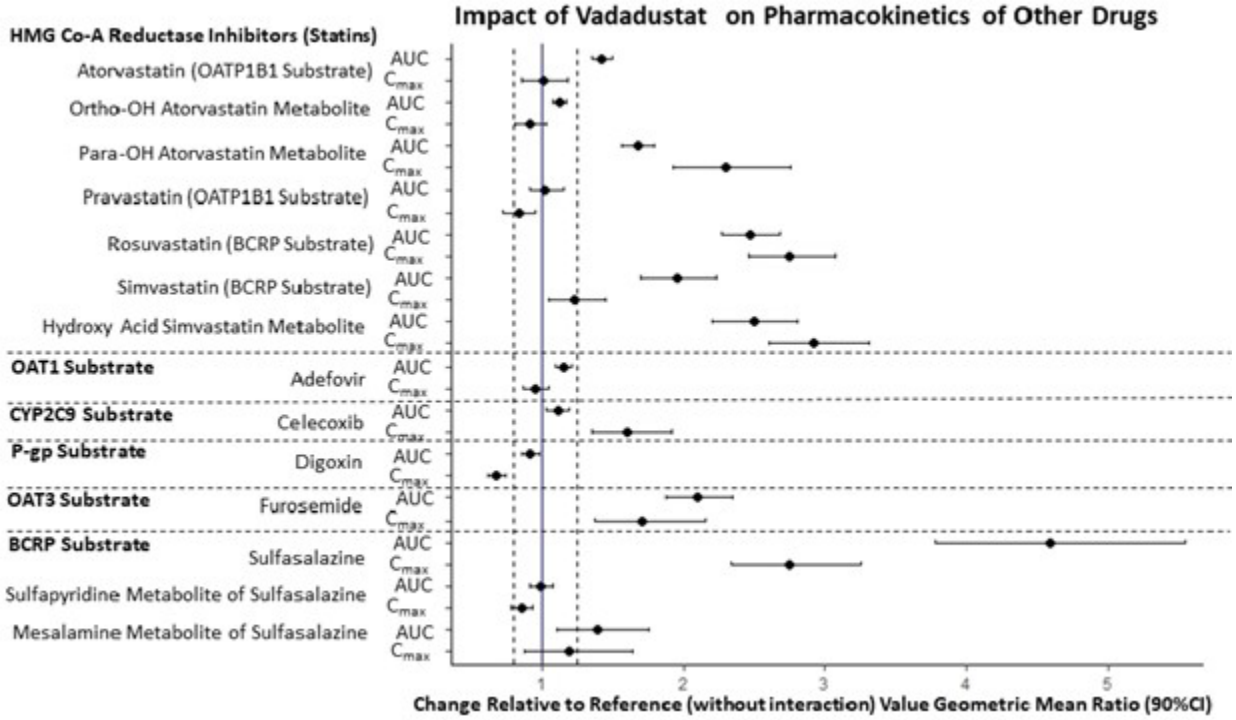
Effect of Vadadustat on Other Drugs

When AUC ratios of CYP substrates were calculated based on a mechanistic static PK model to evaluate the DDI risk of vadadustat as a perpetrator, the AUC ratios of all CYP substrates were <1.25. Thus, in vivo clinical DDI studies with substrates of CYPs were not considered necessary. However, a clinical DDI study with celecoxib (CYP2C9 substrate) was conducted.

Vadadustat was shown to have inhibition potential for P-gp, BCRP, OATP1B1, OAT1 and OAT3 in vitro. In addition, the I_{gut}/IC_{50} for BCRP, the R value for OATP1B1 and the $I_{max,unbound}$ / IC_{50} ratios for OAT1 and OAT3 exceeded the criteria specified in the DDI guideline. Thus, clinical DDI studies with statins (BCRP and OATP1B1 substrates) and sulfasalazine (BCRP substrate) were conducted to evaluate the DDI risk of vadadustat as a perpetrator of these transporters following administration of vadadustat 600 mg QD dose. Vadadustat-O-glucuronide was also shown to have inhibition potential for OAT1 and OAT3. The clinical DDI studies with OAT1 and/or OAT3 substrates (adefovir and furosemide) evaluated the effect of both vadadustat and vadadustat-O-glucuronide. Vadadustat showed weak inhibition potential for P-gp in vitro. A clinical DDI study with a P-gp substrate (digoxin) was conducted to evaluate the DDI risk.

Forest plot of the DDI interactions is presented in Figure 34.

Figure 34. Effect of Vadadustat on the PK of Other Drugs



Source: Figure 2 of Module 2.7.2 Summary of Clinical Pharmacology Studies
The solid vertical line represents geometric mean ratio of 1 and dotted vertical lines represent the 0.80 to 1.25 boundary.
Abbreviations: BCRP: breast cancer resistance protein; CI: confidence interval; CYP: cytochrome; OAT: organic anion transporter; OATP: organic anion-transporting polypeptide; P-gp: P-glycoprotein.

Drug Interaction Study With Digoxin (P-gp Substrate)

Vadadustat (600 mg) QD was dosed to steady state for 4 days followed by a single dose of digoxin (0.5 mg) to evaluate the effect of vadadustat on the PK of digoxin. The total exposure (AUC_{last} and AUC_{inf}) to digoxin was unchanged when digoxin (0.5 mg) was administered following multiple doses of vadadustat (600 mg QD) compared to when digoxin (0.5 mg) was administered alone. The digoxin C_{max} was decreased by about 35% when digoxin (0.5 mg) was administered with vadadustat (600 mg QD) compared to when digoxin (0.5 mg) was administered alone (Figure 34). Vadadustat is unlikely to cause DDI with substrates of P-gp.

Drug Interaction Study With Adefovir (OAT1 Substrate) and Furosemide (OAT1/3 Substrate)

Average peak (C_{max}) and total exposures (AUC) of adefovir were similar when adefovir (10 mg) was administered following multiple doses of vadadustat (600 mg QD) and when adefovir (10 mg) was given alone. The systemic exposure to furosemide was increased by approximately 2-fold when furosemide (40 mg) was administered with vadadustat (600 mg QD) compared to when furosemide (40 mg) was administered alone (Figure 34). As vadadustat did not affect adefovir (an OAT1 substrate) PK, the increased exposure to furosemide is possibly caused by OAT3 inhibition of vadadustat.

The Applicant's proposed labeling recommendation for OAT3 substrates is to "monitor for signs of excessive effects of the co-administered OAT3 substrates". When vadadustat can be approved, the review team recommends also noting in labeling the potential need for dose adjustment due to adverse events with co-administered OAT3 substrates.

Drug Interaction Study With Celecoxib (CYP2C9 Substrate)

Vadadustat (600 mg) QD was dosed to steady state followed by a single dose of celecoxib (200 mg) to evaluate the effect of vadadustat on the PK of celecoxib. Co-administration with vadadustat resulted in a 60% increase in the C_{max} of celecoxib while corresponding AUC values increased <25% (Figure 34). Thus, dose adjustments for celecoxib are not recommended in patients with CKD on vadadustat.

Drug Interaction Study With Sulfasalazine (BCRP Substrate)

The effect of repeated oral doses of vadadustat (600 mg QD) on the PK of a single oral dose of sulfasalazine (500 mg) was evaluated. Co-administration with vadadustat resulted in up to 4.5-fold increase in AUC and 2.8-fold increase in C_{max} of sulfasalazine. The drug sulfasalazine is structurally one molecule of mesalamine linked to one molecule of sulfapyridine with an azo chemical linker. The metabolism of sulfasalazine results in the release of sulfapyridine and mesalamine. Exposures to sulfapyridine did not alter considerably in the presence of vadadustat and exposure to mesalamine was increased about 40% (Figure 34**).**

This result suggests that vadadustat is an inhibitor of BCRP and vadadustat may cause drug interaction when administered with other substrates of BCRP. However, for sulfasalazine, because there was minimal to no change in the exposure to the active metabolites (i.e., mesalamine (5-ASA) and sulfapyridine) no dose adjustments for sulfasalazine are needed in patients with CKD on vadadustat.

Drug Interaction Study With Statins

HMG-CoA reductase inhibitor (statins) are commonly prescribed to patients with CKD for the treatment of dyslipidemia. OATP1B1 and BCRP are important in absorption and/or elimination of statins. OATP1B1 is involved in the uptake of all statins, with simvastatin acid (metabolite of simvastatin) being a highly sensitive substrate. Simvastatin and atorvastatin are probe clinical substrates of OATP1B1. Rosuvastatin is a probe clinical substrate of BCRP. The effect of repeated oral doses of vadadustat (600 mg QD) on the PK of a single oral dose of pravastatin (40 mg), atorvastatin (40 mg), rosuvastatin (20 mg), and simvastatin (40 mg) were evaluated in study CI-0030.

Pravastatin and Atorvastatin

The systemic exposure to pravastatin (an OATP1B1 substrate) was unchanged when pravastatin was administered following multiple doses of vadadustat (Figure 34). Atorvastatin C_{max} was unchanged but total exposure (AUC) was increased about 40% when atorvastatin was administered with vadadustat compared to when atorvastatin was administered alone. There were minimal changes in the C_{max}, and AUC of the active metabolite o-hydroxy atorvastatin. Although P-hydroxy atorvastatin C_{max} and AUC increased 2.3-fold and 1.7-fold in the presence of vadadustat, respectively, the metabolite to parent ratio is 1/10th of atorvastatin (Figure 34). Therefore, dose adjustments for atorvastatin are not proposed in patients with CKD on vadadustat, which is acceptable.

Simvastatin

Average total (AUC) exposures of simvastatin (BCRP substrate) were about 2-fold higher when simvastatin was administered with vadadustat than when simvastatin was given alone. The exposure (AUC and C_{max}) to simvastatin hydroxy acid (active metabolite) was increased

approximately 2.5- to 3-fold when simvastatin was administered with vadadustat compared to when simvastatin was administered alone (Figure 34). Based on these results, the Applicant proposed to consider limiting the dose of simvastatin to 20 mg daily in patients with CKD on vadadustat and monitor for signs of adverse effects of simvastatin.

The approved adult dose range of simvastatin is 5 to 40 mg/day. The recommended starting dose is 10 mg to 20 mg to be taken once daily in the evening. Simvastatin does not undergo significant renal excretion, therefore, modification of dosage for patients with mild to moderate renal impairment is not recommended in its product label. For severe renal impairment, due to the risk of statin-related adverse events, a starting daily dose of 5 mg and close monitoring is recommended in the simvastatin product label. Considering the drug-drug interaction and simvastatin's product label for renal impairment, for patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and patients with end-stage renal disease on dialysis when coadministered simvastatin with vadadustat, a simvastatin starting dose of 5 mg/day in the evening is recommended. Monitoring for possible statin-related adverse reactions and to avoid exceeding the daily dose of simvastatin 20 mg is recommended for vadadustat-treated patients regardless of renal function status (Table 135).

Rosuvastatin

Systemic exposure (AUC and C_{max}) to rosuvastatin (BCRP substrate) was increased by approximately 2- to 3-fold when rosuvastatin was administered with vadadustat compared to when rosuvastatin was administered alone (Figure 34). Based on these results, the Applicant proposed to consider limiting the dose of rosuvastatin to 10 mg daily in patients with CKD on vadadustat and monitor for signs of adverse effects of rosuvastatin.

The dose range for rosuvastatin in adults is 5 to 40 mg orally once daily. The usual starting dose is 10 to 20 mg once daily. Rosuvastatin exposure is not influenced by mild to moderate renal impairment. To account for the ~3-fold increase in systemic exposure, a starting dose of 5 mg once daily and a maximum rosuvastatin daily dose of 10 mg, i.e., close to 3-fold lower than maximum daily dose of 40 mg, is recommended for patients with eGFR ≥30 mL/min/1.73m^2 when taken concomitantly with vadadustat. For patients with severe renal impairment not on hemodialysis, the rosuvastatin product label recommends that the dose be started at 5 mg once daily and not to exceed 10 mg once daily. Because exposure to rosuvastatin is increased by ~3-fold in patients with severe renal impairment who are not on hemodialysis, a dose not to exceed 5 mg once daily is recommended in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) when taking vadadustat concomitantly (Table 135).

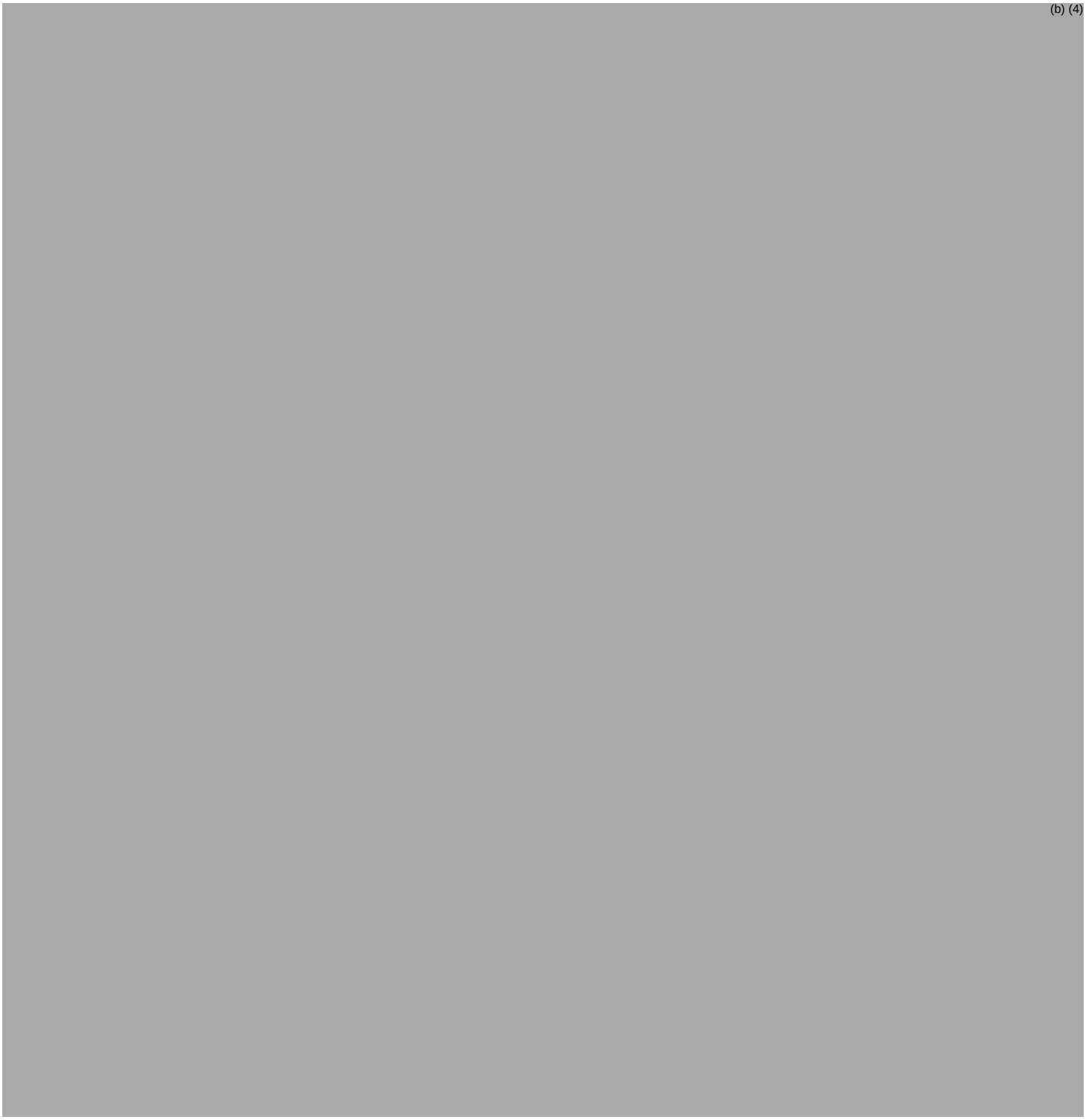
Table 135. Dosing Recommendations for Statins When Administered Concomitantly With Vadadustat

Concomitant Drug Name	Renal Consideration	Recommendation
Atorvastatin*	-	No dose adjustments
Simvastatin*	eGFR ≥30 mL/min/1.73m^2	Maximum daily dose not to exceed 20 mg
	eGFR <30 mL/min/1.73m^2 ESRD on dialysis	Starting dose should be 5 mg/day Maximum daily dose not to exceed 20 mg

Concomitant Drug Name	Renal Consideration	Recommendation
Rosuvastatin*	eGFR ≥30 mL/min/1.73m^2	Starting dose should be 5 mg/day Maximum daily dose not to exceed 10 mg
	eGFR <30 mL/min/1.73m^2 ESRD on dialysis	Maximum daily dose not to exceed 5 mg

Source: Reviewer's table
*Monitor for possible statin-related adverse reactions.
Abbreviations: eGFR, estimated glomerular filtration rate

(b) (4)



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8.4. Pregnancy and Lactation

A standard battery of reproductive toxicology studies was conducted. Results and conclusions of animal studies assessing reproductive function can be found in section III.13.1.4.4.

Fertility and early embryonic development studies were conducted in rats at doses of 0, 40, 80 or 120 mg/kg/day, where males were treated from 4 weeks prior to pairing until euthanasia and females from 2 weeks prior to paring to gestation Day 6. Vadadustat-related decreases in body weight gain and food consumption in 120 mg/kg/day males and mortality related to polycythemia in ≥80 mg/kg/day males were observed. No vadadustat-related effects were observed in females. Male and female fertility, reproductive indices and sperm parameters were not affected by vadadustat administration. The NOAEL for fertility and early embryo-development was 120 mg/kg/day.

In the embryo-fetal development studies, vadadustat was administered to rats at 0, 40, 80 or 160 mg/kg and to rabbits at 0, 10, 25, or 50 mg/kg/day throughout organogenesis. There were no adverse effects on fetal development observed in rats or rabbits. Reduced fetal weights (-7%) and increased incidence of reduced fetal skeletal ossification in rats at 160 mg/kg/day were both attributable to a decline of gestational body weight gain (-36%) and food consumption (-20%) in the pregnant dams. Post-implantation loss was also observed in the dose-range finding study in rats. The NOAELs for fetal development were 80 mg/kg (AUC 1007 µg.h/mL) in rats and 50 mg/kg/day (AUC 99.5 µg.h/mL) in rabbits, based on reduced fetal body weights at the dose of 160 mg/kg/day which caused maternal toxicity in rats and on the lack of remarkable fetal findings at 50 mg/kg/day in rabbits, respectively.

In the pre- and post-natal development study, vadadustat was administered to rats at 0, 20, 40, or 80 mg/kg/day from gestation day 6 to lactation day 20. There were no remarkable maternal toxicities noted. Reduced F1 pup body weight (-5% to -11%) that persisted and extended into growth phase was observed at 80 mg/kg/day. There were no vadadustat-related findings in F0 females during gestation, parturition and through to weaning the F1 litters, and for F1 offspring's growth, sexual maturation, behavior and fertility and reproductive function. The NOAEL for pre- and post-natal development was 40 mg/kg/day based on the reduced pup body weight finding at 80 mg/kg/day.

Table 137. Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (µg.hr/mL)	Exposure Margins[1] (Multiples)
Fertility rat	120	657[2]	1.00x
EFD rat	80	1007	1.53x
EFD rabbit	50	100	0.15x
PPND rat	40	214[2]	0.33x

Source: Reviewer constructed summary table of reproductive toxicology studies submitted to the new drug application.
[1] Exposure multiples were based on population pharmacokinetics analysis where a 600 mg QD clinical dose resulted in systemic exposures of $AUC_{0\text{-}24hr}$ = 654.9 µg•hr/mL
[2] data obtained from the 3-month toxicology study in rats
Abbreviations: EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

Table 138. Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In embryofetal development studies in rats and rabbits, vadadustat was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. No adverse effects on fetal development were observed in either species. A slightly reduced body weight (-7%) and an increased incidence of a reduction in skeletal ossification in fetuses were noted in rats at 160 mg/kg, both of which were attributable to the decline in body weight and food consumption in the pregnant dams. The NOAELs for the development toxicity were 80 mg/kg/day in the rat and 50 mg/kg/day in the rabbit, corresponding to 1.5x and 0.15x the clinical dose of 600 mg, respectively, based on AUC comparisons. In a pre- and post-natal development study, vadadustat was administered to maternal rats from gestation day 6 throughout lactation day 20 at doses of 20, 40 or 80 mg/kg/day, and pups were indirectly exposed in utero and through milk during lactation. Mild reduction of F1 pup body weights (-5% to -11%) was observed in rats administered 80 mg/kg/day in the absence of maternal toxicity findings. The reduced pup weights persisted and extended into the growth phase. The NOAEL for the prenatal and postnatal development was 40 mg/kg/day which is 0.3x the clinical dose of 600 mg, based on an AUC comparison.
8.2 Lactation	Vadadustat related compounds were detected in the milk of lactating rats after a single oral administration of radiolabeled vadadustat at 50 mg/kg. The maximum ratio of milk to plasma concentration in rats was 14.5 at 8 hours postdose and the ratio of milk to plasma AUC was 6.00.

(b) (4)

Labeling Section	Nonclinical Data
13.1 Carcinogenesis, mutagenesis, impairment of fertility	Carcinogenesis: The carcinogenic potential of vadadustat was evaluated in a 6-month RasH2 transgenic mouse study and in a 2-year rat study. Vadadustat was not carcinogenic in RasH2 transgenic mice and was not carcinogenic in Sprague Dawley rats administered vadadustat up to approximately 0.3-fold the clinical dose of 600 mg, based on AUC. Mutagenesis: Vadadustat was negative for mutagenicity in the Ames assay. Vadadustat yielded clastogenic activity from two in vitro assays but was negative for genotoxic activity when administered to Sprague Dawley rats in an in vivo COMET and chromosomal aberration study. Impairment of fertility: Vadadustat had no effects on mating, fertility, or early embryonic development in treated male or female rats up to the high dose of 120 mg/kg/day (approximately 1.0 times the 600 mg clinical dose, based on AUC).

Source: Reviewer constructed summary table
Abbreviations: AUC, area under the concentration-time curve; COMET, Computerized Molecular Evaluation of Toxicity; NOAEL, no observed adverse effect level

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed this NDA with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective. The drug product consists of film-coated, immediate release tablets at 150 mg, 300 mg, and 450 mg strengths that are adequately differentiated by color, size, shape, and debossing. Based on the stability data submitted to date, the expiry dating period for vadadustat tablets shall be 36 months from the date of manufacture when stored at 25 °C.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Good Clinical Practice Compliance

In relation to good clinical practice (GCP) compliance, the Applicant stated that the clinical trial protocol, informed consent form (ICF), and printed patient information materials were reviewed and approved by the independent ethics committee (IEC) and/or institutional review boards (IRB) for each site before any trial procedures were performed. Any subsequent informed consent revisions were approved by the IRB or IEC before any changes were initiated. The Applicant also stated that all trials were conducted according to International Conferences on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (International Conference on Harmonization) guidelines concerning GCP, the European Union

Clinical Trials Directive (2001/20/EC), Title 21 of the U.S. Code of Federal Regulations (21 CFR), and the practices and regulations of each participating nation. Written informed consent to participate in the study was obtained from each subject (or the subject's guardian) before any trial-specific procedures were performed. Periodic monitoring visits at all sites and quality assurance audits at selected sites were performed to ensure adherence to the protocol and GCP guidelines.

Significant protocol deviations were noted and are summarized by trial in section III.16.1. For the NDD-CKD population, the Applicant identified quality and non-compliance issues from site 10047, which enrolled subjects in Trials 0014 and 0015. The non-compliance issues were identified in the areas of investigator oversight, subject consent process, source documentation requirements, SAE reporting, and investigational product management. The Applicant notified the FDA promptly, terminated the site and evaluated the data provided by the site, which identified data integrity issues resulting in exclusion of the site's data from the database. The review team agrees with the Applicant's assessment and action. Otherwise, there were no other issues that had significant impact on the GCP compliance. Sensitivity analyses were performed when appropriate, such as with the exclusion of site 10047, with no significant differences to report and no impact on the interpretation of the safety or efficacy results of the trials.

Data Quality Assessment

Data quality was ensured by the Applicant through periodic monitoring with primary source verification of trial data at all trial sites. In addition, quality assurance audits were performed to further ensure data quality. Throughout the application review period, data quality was evaluated by the clinical review team using several approaches:

- Using the FDA CDER Clinical Investigator Site Selection Tool (v.2.9.05) and the Applicant-provided BIMO dataset for the four phase 3 global trials, we suggested the following sites for inspection to the FDA Office of Scientific Investigations: trial 0014 – site 10013 and site 10006; trial 0015 – site 10006; and trial 0017 – site 10008, site 10506, and site 10304. Given the limitation of travel and access to sites outside of the United States due to the COVID-19 Pandemic, these sites were limited in location to the United States. Our selection was based on several factors, with the following factors having stronger contribution to the site ranking: 1) Total number of subjects per site, 2) Treatment efficacy results and site-specific treatment effect, 3) Serious adverse event (SAE) ratio and 4) Principal Investigator and site regulatory history. The inspections of all sites were unremarkable, resulting in No Action Indicated letters.
- The Office of Computational Science provided data quality evaluation reports using the FDA Validator tool, which were reviewed by the clinical reviewer to assess the validity of any data quality findings and no data quality issues were identified.
- The clinical review team independently reviewed the provided datasets and noted no anomalies in enrollment characteristics, patterns of protocol violations reported, patterns of efficacy reporting, or patterns of SAE reporting. Sensitivity analyses were performed when appropriate, with no significant differences to report.

Financial Disclosure

The four global phase 3 trials (i.e., trial 0014, trial 0015, trial 0016 and trial 0017) were covered trials included in the submission for NDA 215192. In accordance with 21 CFR 54, the Applicant submitted financial disclosure certification documents for these trials. In addition, the Applicant

stated that there were no Investigators/Sub-investigators participating in either trials that were a part-time or full-time employee of Akebia Therapeutics, Inc.

For trial 0014, 1514 Investigators/Sub-investigators reported no financial arrangements or interests to disclose but 8 Investigators/Sub-investigators were lacking the financial disclosure questionnaire (FDQ). Of those lacking a completed FDQ, six individuals had missing forms after inquiry and two individuals had incorrectly completed the form. For trial 0015, 1623 Investigators/Sub-investigators reported no financial arrangements or interests to disclose but 12 Investigators/Sub-investigators were lacking the financial disclosure questionnaire. Of those lacking a completed FDQ, all 12 individuals had missing forms after inquiry.

For trial 0016, 546 Investigators/Sub-investigators reported no financial arrangements or interests to disclose but 8 Investigators/Sub-investigators were lacking the financial disclosure questionnaire. Of those lacking a completed FDQ, three individuals had missing forms after inquiry and two individuals had incorrectly completed the form. Of those lacking a completed FDQ, all three individuals had missing forms after inquiry. For trial 0017, 1366 Investigators/Sub-investigators reported no financial arrangements or interests to disclose but 4 Investigators/Sub-investigators were lacking the financial disclosure questionnaire. Of those lacking a completed FDQ, three individuals had missing forms after inquiry and one individual did not complete the form and is no longer working at the site. Financial disclosure tables are listed in section III.23.

11. Advisory Committee Summary

An Advisory Committee meeting was not held during this marketing application review because we did not identify any efficacy or safety issues requiring public discussion with outside experts.

III. Appendices

12. Summary of Regulatory History

Table 139. Summary of Regulatory History

Date	Activity	Key Outcome(s)
August 7, 2008	Type B Pre-IND meeting to discuss the development of AKB-6548 (code name for vadadustat), and oral erythropoietic agent.	FDA advised the Applicant of the preclinical requirements for the "first in human" protocol as well as the need to describe the amount of drug substance in each capsule and details on how the capsule is filled.
July 20, 2009	IND 102465 was submitted for AKB-6548 for the treatment of anemia associated with CKD and chronic renal failure.	IND 102465 was deemed safe to proceed on August 25, 2009.
August 14, 2009	Type A meeting to discuss the study's cohort population and dosage scheduling.	The Applicant stated that subjects will be monitored for 18-24 hours after drug administration, with follow-up the next day. FDA recommended patient monitoring should be at least 24 hours after drug administration and plan for follow-up of subjects after discharge. FDA also recommended the Applicant to develop a more detailed protocol for the food effect portion of the study. The Applicant agreed to submit an amendment detailing the protocol for the food effect portion of the study prior to starting the study.
February 3, 2011	Type B, End-of-Phase 1 meeting to discuss the phase 2 development program for AKB-6548 and reach agreement on the design of the phase 2 controlled clinical trials.	Details on the primary and secondary endpoints to be collected in the phase 2a study were discussed. FDA noted the study appears reasonable and provided recommendations on adding erythropoietin as one of the secondary endpoints, including a detailed plan on how transfusion during the trial will be handled, requested justification for using the 350 mg dose, and including details of the frequency of laboratory and clinical monitoring in the study protocol.
May 1, 2012	Type B meeting to discuss and reach agreement on the design of the pivotal phase 2b controlled clinical trials.	FDA did not agree with the Applicant's proposed clinical study design for a phase 2b study. FDA recommended the Applicant revise the design, eligibility criteria and endpoints of the study.

Date	Activity	Key Outcome(s)
July 11, 2014	Type C meeting to discuss a proposal to enrich the population studied for the initial marketing application and reach agreement on primary endpoints.	FDA noted the Applicant did not have any long-term phase 2 studies in either dialysis-dependent subjects or non-dialysis dependent subjects. FDA recommended the Applicant conduct two adequate and well-controlled trials to support each indication.
October 16, 2014	SPA Assessment, 2-year Carcinogenicity Study	FDA recommended doses of 0 (water or saline), 0 (vehicle), 2, 7, and 20 mg/kg/day by oral gavage with high dose based on deaths at 60 mg/kg/day for the 104-week carcinogenicity study in Sprague-Dawley Crl:CD (SD) rats.
March 3, 2015	Type C meeting to discuss the proposed phase 3 program.	FDA did not agree with the proposed phase 3 development plan and recommended the Applicant use an active comparator arm and not a placebo-controlled arm in a non-inferiority trial. FDA also recommended the primary efficacy endpoint be the mean change in Hemoglobin between baseline and the evaluation period which should be at least 12 weeks in duration and include assessments up to Week 52. FDA noted the secondary safety endpoint should include each component of the MACE endpoint to confirm that the result is not dependent on only one of the components.
July 7, 2015	Type B, End-of-Phase 2 meeting to discuss the design of the two phase 3 studies, the clinical pharmacology/biopharmaceutics plan, and the nonclinical development plan.	FDA noted the nonclinical program appears adequate to support an NDA. FDA did not agree with the non-inferiority margin for the phase 2 studies and recommended the Applicant submit the results from the phase 3 studies for both dialysis dependent and non-dialysis dependent CKD populations. FDA also recommended to add the mean change of hemoglobin between weeks 40-52 as a key secondary endpoint and to include a PK sample at Week 2 or Week 4.
July 16, 2015	Type B, End-of-Phase 2 meeting to discuss the starting materials, specifications for registration stability batches for drug substance and drug product, and elements of the drug product manufacturing process.	FDA agreed with (b) (4) (b) (4) vadadustat drug substance. FDA also agreed with the Applicant's plan to qualify impurity (b) (4) in a 28-day bridging study using rats. FDA recommended the Applicant provide data to support the absence of microbial testing.

Date	Activity	Key Outcome(s)
October 1, 2015	Type C WRO to obtain feedback on the non-inferiority margin for the primary endpoint.	FDA noted the proposed approach to assess the comparative cardiovascular safety of vadadustat, including the proposed MACE non-inferiority margin appeared reasonable. FDA reiterated that the efficacy and safety results of the phase 3 studies in both the DD-CKD and NDD-CKD populations should be submitted at the same time. FDA also noted the proposed starting dose at 300 mg for the phase 3 studies appeared reasonable.
January 6, 2016	Type B, End-of-Phase 2 meeting to discuss key elements of the phase 3 clinical protocols for the use of vadadustat in treatment of subjects with anemia secondary to DD-CKD.	FDA informed the Applicant to meet both the primary efficacy and primary safety endpoints to conclude success of vadadustat. FDA did not agree with the key secondary endpoint and recommended the evaluation of mean change in hemoglobin between weeks 40-52 as the key secondary endpoint. FDA also did not agree with the proposed inclusion criteria of subjects with CKD who do not receive adequate iron supplementation prior to study enrollment.
July 12, 2016	SPA Assessment, 6-month Carcinogenicity Study	FDA recommended doses of water or saline control, vehicle control [(0.25% (w/v) hydroxypropyl methyl cellulose/0.1%(w/v) Tween® 80 in reverse osmosis deionized water], 5, 15, or 50 mg/kg/day by oral gavage for the 6-month carcinogenicity study in CB6B6F1/Tg rasH2 mice.
January 31, 2018	Type C meeting to discuss the key elements of the CMC development of vadadustat.	FDA recommended a minimum of 3 batches be manufactured by the second supplier in order to qualify the supplier. FDA also recommended that the first commercial batch manufactured be placed on stability. Recommendations on the in vitro dissolution test were also provided.
May 23, 2018	Type C WRO to obtain feedback on the clinical pharmacology plans for vadadustat.	The Applicant outlined their plan to collect PK data from drug-drug interaction studies and the FDA did not agree that the PK data would adequately characterize the clinical drug interactions of vadadustat. FDA recommended the Applicant conduct a clinical study to investigate the effect of concomitant gastric acid-reducing agents on the pharmacokinetics of the drug, as vadadustat exhibits pH-dependent solubility.

Date	Activity	Key Outcome(s)
June 5, 2018	Type C meeting to discuss the SAPs for the phase 3 studies.	FDA agreed with the Applicant's approach of conducting multiple sensitivity and subgroup analyses. FDA emphasized the importance of demonstrating durability of efficacy with analysis of week 40-52 and week 24-52 evaluation periods.
February 11, 2020	Type C meeting to obtain guidance on the NDA submission.	FDA did not agree with the Applicant's plan for (b) (4) (b) (4) (b) (4) FDA informed the Applicant that an NDA submission (b) (4) was expected and recommended to submit a pre-NDA meeting request once the topline results of the phase 3 studies became available.
June 17, 2020	Type C WRO to obtain feedback on the CMC development and biopharmaceutic strategy for vadadustat.	FDA recommended the starting materials to be used for the drug substance and noted required CMC information the Applicant should include in the NDA submission.
October 29, 2020	Type B, Pre-NDA meeting to discuss the planned content of the NDA submission as well as review the phase 3 study data.	FDA noted not all subgroup analysis were post-hoc in nature and that some analyses were not conducted in the 'not on dialysis' population. FDA recommended the Applicant conduct key analyses for individual studies based on the intent-to-treat population and Per-Protocol population regardless of whether the patient was on or off study treatment. The Applicant stated they will submit the NDA at the end of Q1 2021 with no late submissions.

Source: Regulatory Project Manager
Abbreviations: AKB-6548, vadadustat; CKD, Chronic Kidney Disease; CMC, Chemistry, Manufacturing and Controls; DD-CKD, Dialysis-Dependent Chronic Kidney Disease; MACE, Major Adverse Cardiovascular Events; SAP, Statistical Analysis Plan; SPA, Special Protocol Assessment; WRO, Written Responses Only

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Primary Primary/Secondary Pharmacology

Vadadustat is a small molecule inhibitor of prolyl hydroxylase domain-containing proteins (PHD) indicated for treatment of anemia associated with chronic kidney disease. The mechanism of action is that inhibition of PHD results in increased stability of hypoxia-inducible factor alpha (HIFα) which initiates a transcriptional program that increases expression of genes related to erythropoiesis, including most notably erythropoietin.

A summary is presented in section II.5.1. The following provides additional characteristics of the pharmacological effects of vadadustat.

Vadadustat transcriptionally increases erythropoietin rapidly and transiently following a single dose. Serum erythropoietin (EPO) increased by 3 hours, peaked at 6 hours, and returned to baseline by 72 hours postdose (Table 140).

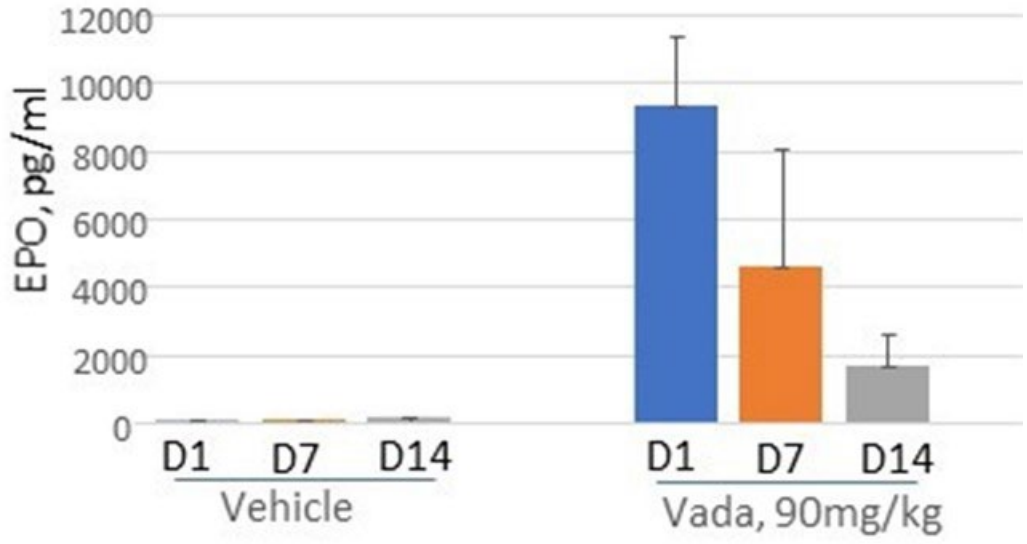
Table 140. Time Course of Rise in Serum Erythropoietin Following a Single Oral Dose of Vadadustat to Normoxic Rats

Time (h)	Mean (SD) EPO pg/mL	
	50 mg/kg	150 mg/kg
0	61.57 (13.10)	54.74 (8.65)
1	63.39 (9.72)	71.51 (11.00)
3	1439.49 (867.40)	4840.91 (1581.44)
6	2568.93 (835.85)	19395.94 (8674.15)
24	209.24 (115.29)	2653.93 (530.52)
72	83.52 (16.43)	55.44 (7.92)

EPO: erythropoietin; SD: standard deviation
Lower Limit of Quantitation (LLOQ) = 20.00 pg/mL.
Source: Applicant-derived table, NDA 215192, Study 6901490

The EPO response induced by vadadustat is blunted upon repeated dosing in rats (Figure 36).

Figure 36. Peak Serum Erythropoietin Measured 6hrs Post-Dose in Response to Vadadustat After 1, 7, and 14 Days of Oral Administration to Sprague Dawley Rats



Source: Reviewer-constructed Figure, Study 6901490
Data are mean ± SD.
Abbreviations: EPO, erythropoietin; Vehicle, 0.25% HPMC/0.1% w/v Tween 80; Vada, vadadustat

Secondary Pharmacology Effects

In vitro, among 112 receptor binding assays and 42 enzyme assays, vadadustat at 10 µM showed one major (>50% inhibition of ligand binding) receptor and one major enzyme interaction, peripheral benzodiazepine (BZD) and angiotensin converting enzyme (ACE), respectively. Based on a clinical maximum plasma concentration (C_{max}) of ~30µg/ml and correcting for ~99.5% protein binding, the estimated free concentration of ~0.5µM does not raise concern for off-target interactions assessed in this assay.

Table 141. Vadadustat off-Target Effects

Receptor	% Inhibition	Ligand	Comment
Peripheral Benzodiazepine (BZD)	70	PK 11195	Major interaction (>50%)
Kainate	34	Kainic acid	
Glycine (strychnine insensitive)	23	Glycine	
Tumor Necrosis Factor alpha (TNFα)	30	TNFα	
CCR3	20	Eotaxin	
Glucocorticoid	28	Dexamethasone	
Sodium Channel – site 2	26	Batrachotoxinin	

Enzyme	% Inhibition	Reference Compound	Comment
Angiotensin converting enzyme (ACE)	60	Captopril	Major interaction (>50%) – however the compound demonstrated some interference with the detection method.
Lyn A kinase	29	Staurosporine	
Metallo-matrix-protease 1 (MMP-1)	22	GM6001	The compound demonstrated some interference with the detection method.

Source: Applicant submission, NDA215192, Study 14651

13.1.2. Safety Pharmacology

Vadadustat showed no significant toxicities to the central nervous system (CNS), cardiovascular, or respiratory systems as assessed in good laboratory practice (GLP) safety pharmacology studies.

Table 142. Safety Pharmacology

Study Title (Study No.): Doses	Finding	Exposure Multiple[1]
Evaluation of the Effect of AKB-6548 on the Delayed Rectifier Current Using HEK 293 Cells Transfected with the Human Ether-a-go-go Related Gene (hERG) (Study No. 701205-2): 10, 30, 100, or 300 µM	No remarkable findings	NA
Cardiovascular Safety Pharmacology Study Using Radiotelemetry in Conscious Male Beagle Dogs Following Oral Gavage Administration (Study No.AKB-6548-PC-0002): 0, 60, 120 or 360 mg/kg in a cross-over study with 5 days washout period between doses	P-QRS-T complexes were not affected. Mean heart rate was increased (20-40%) at 2 hours postdose that remained elevated in mid and high dose animals until 7 and 17 hours postdose, respectively. Mean arterial blood pressure was also decreased (5-24%) in treated animals beginning at approximately 3 hours postdose that remained decreased in high dose animals until 8 hours postdose. NOAEL=60 mg/kg	3.3x
Respiratory Assessment in Male Sprague-Dawley Rats Following a Single Oral Gavage (Study No. 1008-23271): 0, 120, 180, 360 mg/kg	Increased tidal volume (up to 52%) and minute volume (up to 19%), but not respiratory rate was observed in high dose animals compared to control at 8–9 hours postdose. NOAEL=360 mg/kg	5.8x
A Functional Observational Battery (FOB) Neurological Assessment in Male Sprague-Dawley Rats Following a Single Oral Gavage (Study No. 1008-2361): 0, 120, 180 or 360 mg/kg)	No treatment-related observations. NOAEL=360 mg/kg	5.8x

Source: Reviewer generated table
[1] relative to MRHD 600 mg/day, on a mg/m2 basis
Abbreviations: AKB-6548, vadadustat; FOB, Functional Observational Battery; hERG, Human Ether-a-go-go Related Gene; NOAEL, no observed adverse effect level

13.1.3. Pharmacokinetics/Absorption, Distribution, Metabolism, Excretion/Toxicokinetic

In rats and dogs, orally administered vadadustat is quickly and almost completely absorbed, with highest distribution to the gastrointestinal (GI) tract/content, followed by the liver and kidney. The parent drug accounted for 71-86% of drug-related material in the circulation of rats, dogs, and humans. The major elimination pathway in rats and dogs is fecal via hepatobiliary secretion, whereas urine excretion of vadadustat-O-glucuronide is the primary route of elimination in humans. Terminal $T_{1/2}$ was shorter in nonclinical species (rats, 0.5-2 hours; dogs, 2-5 hours) relative to humans (~5 to 8 hours).

Administered to pregnant rats and lactating rats, vadadustat related compounds were detected in the fetal tissues and the milk, demonstrating that vadadustat can cross placental tissues and can be delivered to newborns via nursing.

Absorption

Vadadustat has low aqueous solubility. An oral suspension formulation (0.25% HPMC/0.1% Tween-80 in water) was used in the animal studies.

Following single oral doses, vadadustat was rapidly absorbed with time to maximum concentration (T_{max}) value of 0.5 hours and bioavailability ≥91% in rats and dogs. In repeat dose studies, the T_{max} value was in a range of 1-4 hours for rats and 1-1.6 hours for dogs.

Plasma elimination half-life was 3.3 hours in mice, 2.1 hours in rats, and 4 hours in dogs.

Distribution

In vitro, vadadustat exhibited high protein binding in plasma across all species tested (≥93.2% bound), with the highest extent in humans (≥99.5% bound), whereas vadadustat-O-glucuronide exhibited moderate binding to human plasma proteins (~88% bound).

Upon [^{14}C]-vadadustat administration to rats and dogs, highest radioactivity was found in the GI tract and contents (31-73% and 33-47% of administered dose in rats and dogs, respectively, in the first 8 hours postdose), followed by the liver (at 2-hour, 6.9% in rats, and 5.3% in dog) and kidney (at 2-hour, 2.9% in rats and 0.9% in dogs). Blood-to-plasma ratio was ≤0.66 in both species, suggesting a lack of partitioning to red blood cells.

Fetal-placenta transfer of [^{14}C]-vadadustat was observed in a study in pregnant rats on GD18 where drug-related radioactivity was detected in fetal blood (0.23x maternal plasma concentration at 1-hour postdose) and fetal tissues (0.01-0.09x maternal plasma concentration for liver, lung, heart, kidney, and brain at 1-hour postdose).

Additionally, a study in lactating rats showed active secretion of [^{14}C]-vadadustat into milk with a maternal plasma to milk ratio of ~6, based on area under the concentration-time curve (AUC).

Metabolism

Vadadustat was metabolically stable after incubation in vitro with mouse, rat, dog, monkey, or human liver microsomes, suggesting that metabolism via cytochrome P450s is minimal. Rather, vadadustat is glucuronidated via UDP-glucuronosyltransferase enzymes.

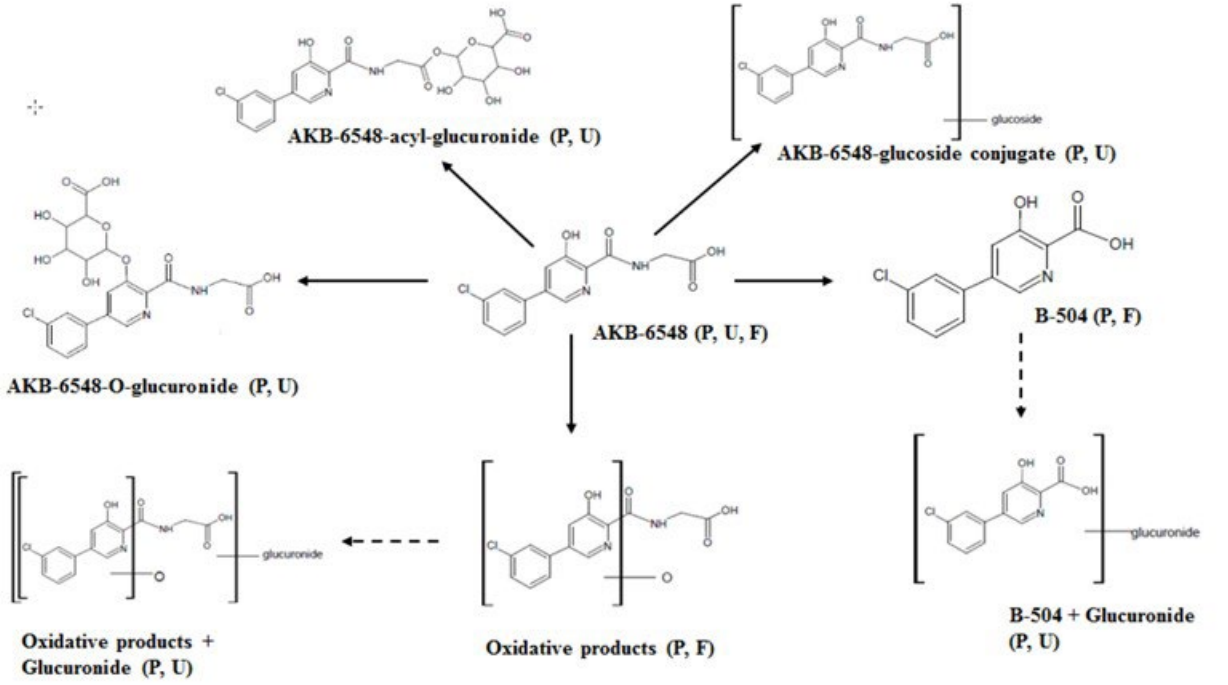
Vadadustat is not extensively metabolized in animals or humans. After an oral dose of [^{14}C]-vadadustat, the parent was the most abundant component in plasma. Metabolites including the glycine-cleaved form of vadadustat, B-504, and vadadustat conjugated with an O-glucuronide and acyl-glucuronide were observed in animals and/or humans. There were no human unique metabolites. See the table below for details.

Table 143. Metabolites Observed in Animals and Humans

Metabolites	Rats[1]	Dogs[1]	Mice[2]	Humans[3]
Vadadustat	86%	71%		75%
B504	9.6%-11.6%	18.1%-38%		
Vadadustat-O-glucuronide		7.1-11.4%	11%	15%
Vadadustat-acyl-glucuronide			0.5%	0.05%

Source: Reviewer generated table
[1] radioactivity% at 8-h postdose
[2] AUC% of parent drug
[3] radioactivity AUC_{inf} %

Figure 37. Proposed Vadadustat Metabolic Pathways in Animals and Humans



The solid line indicates the principal metabolic pathway; dotted lines indicate minor metabolic pathway. Oxidative products are not the major components of vadadustat biotransformation. Additionally, some other minor metabolites are observed but are not included in the figure.
F: Feces; P: Plasma; U: Urine.

Source: Applicant-derived figure, NDA 215192, Study 6901490

In human hepatocyte incubations, vadadustat induced CYP2B6, but not CYP1A2 or CYP3A4.

Excretion

The major elimination pathway in rats and dogs was hepatobiliary elimination into feces in the form of parent drug. The glycine-cleaved metabolite, B-504, was the most abundant metabolite in rat feces. In humans, urine is the major elimination route of conjugated parent, accounting for approximately 63% of an administered dose.

Table 144. Vadadustat-Related Compound Excretion (% of Dose in 24-H Urine/Bile, and 72-H Feces)

	Rats			Dogs		Humans	
Compound	**Feces**	**Bile**	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**
Unchanged parent	16.2%	3.5%	1.5%	65.0%	<1%	24.2%	0.37%
B-504	12%		<0.5%				
Vadadustat-O-glucuronide		30%	3.5%		9.4%		62.7%
Vadadustat-O-glucoside			1.0%		3%		
Vadadustat-acyl-glucuronide							0.59%

Source: Reviewer generated table

Terminal $T_{1/2}$ values of vadadustat following oral administration are 0.5-2 hours in rats and 2-5 hours in dogs.

Toxicokinetic Data

Systemic exposures in rats and dogs following repeat dosing appear to be dose proportional in general. There was no exposure accumulation over the treatment duration (3 months, 6 months, or 9 months). There was no consistent pattern of sex-specific differences in pharmacokinetics.

Note, AUC values in the 9-month dog study were approximately 2-3-fold lower than observed in the 3-month dog study despite administration of similar doses; the cause of this variability is unclear, but it does not change the interpretation or conclusions from these studies.

Table 145. Toxicokinetic Data - 3-Month Rat Study

Group	Dose (mg/kg)	Sex	Tmax (h)	Cmax (ng/mL)	AUC(0-last) (h*ng/mL)
Day 1					
2	40	M	1	44240	137600[a]
		F	1	70410	227700
3	80	M	1	71420	423700
		F	1	91300	522800
4	120	M	2	77220	557400
		F	1	179500	756600
Day 90					
2	40	M	1	39000	183100
		F	1	62860	244500
3	70	M	1	48560	261300
		F	1	75610	490900
4	90	M	1	42740	409000
		F	2	65790	622600

[a] AUC(0-8): C_{last} was at 8 hours for this group and at 24 hours for all other groups.

Source: Reviewer generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Table 146. Toxicokinetic Data - 6-Month Rat Study

Group	Dose (mg/kg)	Sex	T_{max} (h)	C_{max} (ng/mL)	$AUC_{(last)}$ (h•ng/mL)
Day 1					
2	20	M	1	12590	52000
		F	1	16770	54590
3	40	M	1	36120	160100
		F	1	46770	144600
4	60	M	1	50400	301000
		F	1	66180	242300
Day 182					
2	20	M	1	28180	118000
		F	1	36510	130800
3	40	M	1	42140	285300
		F	2	57450	250500
4	60	M	2	37040	231800
		F	1	55590	422600

Source: Reviewer generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Table 147. Toxicokinetic Data - 3-Month Dog Study

Group No.	Dose Level (mg/kg/day)	Sex	Tmax (h)	Cmax (ng/mL)	AUC(0-last) (h*ng/mL)
Day 1					
2	25	Male	1.2	29340	68540
		Female	1.0	35080	62310
3	45	Male	1.0	74920	165000
		Female	1.0	83580	165600
4	90/65	Male[a]	1.3	152800	385700
		Female	1.0	169600	486300
Day 90					
2	25	Male	1.0	35240	63440
		Female	1.0	45720	83980
3	45	Male	1.0	87770	178000
		Female	1.0	107900	253600
4	90/65	Male	1.2	106700	277500
		Female	1.0	105300	328700

[a] Values for Dog No. D4358 (Day 1) were excluded from Mean (±SD) calculations: plasma concentration *vs* time profile was considered anomalous.

Source: Reviewer generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

Table 148. Toxicokinetic Data - 9-Month Dog Study

Group No.	Dose Level (mg/kg/day)	Sex	Tmax (h)	Cmax (ng/mL)	AUC(last) (h*ng/mL)
Day 1					
2	10	Male	1.0	6081	10560
		Female	1.0	2474	6513
3	25	Male	1.0	34700	64800
		Female	1.0	6714	12170
4	50	Male	1.0	73820	139200
		Female	1.0	29120	51360
Day 204 (females)/205 (males)					
2	10	Male	1.0	2458	4646
		Female	1.0	4262	8625
3	25	Male	1.0	17730	28020
		Female	1.0	25760	36570
4	50	Male	1.0	35420	74000
		Female	1.0	39140	97410
Day 274					
2	10	Male	1.0	2563	4563
		Female	1.0	3850	8019
3	25	Male	1.0	24060	39780
		Female	1.0	30580	46270
4	50	Male	1.0	47870	76960
		Female	1.0	68170	119800

Source: Reviewer generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration

13.1.4. Toxicology

13.1.4.1. General Toxicology

General toxicology studies were conducted in mice (3-month), rats (4-week, 3-month, 6-month), and dogs (4-week, 3-month, 9-month) using the oral route of administration and with a formulation of 0.25% w/v HPMC 4000cp/0.1% w/v Tween® 80 in reverse-osmosis deionized water. All studies summarized here are GLP complaint. At beginning of dosing, the animal ages were approximately 7 weeks, 8 weeks, and 6 months for mice, rats, and dogs, respectively.

The study title and designs are presented below.

Table 149. a 3-Month Oral Gavage Toxicity and Toxicokinetic Study in CD-1 Mice (Study No.20035235)

Experimental Design

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Animals Main Study	
					Males	Females
1	Control Article	0	10	0	10	10
2	AKB-6548	25	10	2.5	10	10
3	AKB-6548	50	10	5	10	10
4	AKB-6548	100	10	10	10	10
5	AKB-6548	150	10	15	10	10
6	AKB-6548	200	10	20	10	10

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Animals Toxicokinetic Study		Hematology Study	
					Males	Females	Males	Females
1	Control Article	0	10	0	8	8	6	6
2	AKB-6548	25	10	2.5	38	38	6	6
3	AKB-6548	50	10	5	38	38	6	6
4	AKB-6548	100	10	10	38	38	6	6
5	AKB-6548	150	10	15	38	38	6	6
6	AKB-6548	200	10	20	38	38	6	6

Source: Reviewer generated table

Table 150. a 3-Month Oral Toxicity and Toxicokinetic Study With a 3-Month Recovery in Sprague-Dawley Rats (Study No. 20002194)

Group Number	Number of Main (Recovery) Study Animals		Number of Toxicokinetic Animals [a]		Test Material	Dose Level (mg/kg)	Concentration (mg/mL)	Dose Volume (mL/kg)
	Males	Females	Males	Females				
1	10 (5)	10 (5)	7	7	Control Article	0	0	10
2	10 (5)	10 (5)	7	7	AKB-6548	40	4	10
3	10 (5)	10 (5)	7	7	AKB-6548	80/70[b]	8/7 [b]	10
4	10 (5)	10 (5)	7	7	AKB-6548	120/90[b]	12/9 [b]	10

[a] Toxicokinetic animals were also used for interim hematology sample collection.

[b] Beginning on Day 47, the Group 3 and 4 dose levels were reduced due to test article-related mortality in Group 4 and the Week 7 hematology results.

Source: Reviewer generated table

Table 151. a 6-Month Oral Gavage Toxicity and Toxicokinetic Study With a 3-Month Recovery in Sprague-Dawley Rats (Study No. 20008611)

Group No.	No. of Animals				Test Material	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
	Main (Recovery)		Toxicokinetics[a]					
	Male	Female	Male	Female				
1	15 (5)	15 (5)	3	3	Control Article[b]	0	0	10
2	15 (5)	15 (5)	6	6	AKB-6548	20	2	10
3	15 (5)	15 (5)	6	6	AKB-6548	40	4	10
4	15 (5)	15 (5)	6	6	AKB-6548	60	6	10

[a] Toxicokinetic animals were also used for interim hematology sample collection.
[b] The control article was 0.25% (w/v) Hydroxypropyl Methyl Cellulose (HPMC; 3500-5600 cP)/0.1% (w/v) TWEEN® 80 in Reverse Osmosis Deionized Water.

Source: Reviewer generated table

Table 152. AKB-6548: a 3-Month Oral Toxicity and Toxicokinetic Study With a 3-Month Recovery in Dogs (Study No. 20002195)

Group No.	No. of Main (Recovery) Animals		Test Material	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
	Male	Female				
1	3 (2)	3 (2)	Control Article[a]	0	0	5
2	3 (2)	3 (2)	AKB-6548	25	5	5
3	3 (2)	3 (2)	AKB-6548	45	9	5
4	3 (2)	3 (2)	AKB-6548	90/65[b]	18/13[b]	5

[a] The vehicle control article was 0.25% (w/v) hydroxypropyl methyl cellulose (HPMC; 3500-5600 cP)/0.1% (w/v) TWEEN® 80 in reverse osmosis deionized water.
[b] The Group 4 dose level was decreased beginning on Day 43 throughout the remainder of the study in order to lower the risk of sustained polycythemia-related toxicity, including sudden mortality.

Source: Reviewer generated table
Abbreviations: AKB-6548, vadadustat

Table 153. a 9-Month Oral Toxicity and Toxicokinetic Study With a 3-Month Recovery in Dogs (Study No. 20008612)

Group No.	No. of Main (Recovery) Animals		Dose Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)
	Males	Females				
1	5 (2)	5 (2)	Control Article	0	5	0
2	5 (2)	5 (2)	AKB-6548	10	5	2
3	5 (2)	5 (2)	AKB-6548	25	5	5
4	5 (2)	5 (2)	AKB-6548	50	5	10

Source: Reviewer generated table

Dose-related increases in reticulocytes and red blood cell indices (blood cell count, hemoglobulin, hematocrit) were predominate observations. Microscopically, bone marrow hypercellularity and increased splenic erythropoiesis in mice and rats, and secondary effects of blood hyperviscosity including thrombosis, tissue infarction/necrosis in multiple organs and/or mortalities were also observed in all animal species. The dose levels that produced polycythemia and related toxicities in these toxicology studies are similar to or below clinically relevant exposures. However, the toxicology studies are conducted in non-anemic test species where polycythemia would be produced by an erythropoiesis-simulating agent such as vadadustat, whereas the clinical context is treatment of patients with anemia.

Findings that were unique to a specific species:

(1) The 3-month study in CD1 mice exhibited minimal to moderate lacrimal gland atrophy in males administered ≥100 mg/kg. The hematocrit levels at ≥100 mg/kg were ≥1.7x that of controls. Similar findings were also observed in a previous 8-week study in CByC6F1mice, where the findings were accompanied by single cell necrosis, with higher incidence for males, and correlated with ≥1.54x increased hematocrit. The lacrimal gland atrophy is likely related to increased blood viscosity and altered blood flow.
(2) Rat studies displayed decreased platelet counts in a dose-related manner (3-month study, 0.41x, 6-month study, 0.29x). However, there were no associated findings in prothrombin time or APTT. There was no similar finding in recovery animals after three months of a non-dosing recovery period.
(3) Dog studies displayed adrenal cortex infiltration of hypertrophied cells (single or aggregated, occasionally with multiple nucleated cells) and mononuclear cells in the 3-month and 9-month studies. Note, the hypertrophied cells in the 9-month study were reported as histiocytes in the 3-month dog study. The occurrence of the adrenal findings was independent of increases in red blood cell indices. In the 9-month dog study, the expected pharmacologic effects were not observed in most treated animals except one high dose animal that was prematurely euthanized (hematocrit was 1.9x that of control). This adrenal finding was not fully reversible upon treatment cessation. There were no correlative changes in clinical chemistry (levels of sodium, chloride, or potassium) nor clinical signs indicative of adrenal insufficiency; as such, this finding appears to be confined to a histological change without clinical consequence.

There was no evidence that toxicities progressed with dosing duration when subchronic studies were compared with chronic studies (rats: 3-month versus 6-month; dogs, 3-month versus 9-month).

Key findings from selected pivotal toxicology studies are presented below.

Table 154. Key Findings From Toxicology Studies

Study (Study No.): Doses	NOAEL, mg/kg (AUC)	Key Study Findings
Mouse 3-month study (20035235): 25, 50, 100, 150, 200 mg/kg/day	150 mg/kg (310 µg.h/mL)	Mortalities in 200 mg/kg females due to thrombosis, infarction/necrosis, and tissue hemorrhage Lacrimal gland atrophy in males at ≥ 100 mg/kg Increases in circulating red blood cell mass, spleen erythropoiesis and bone marrow cellularity and decreases in platelet counts (up to -91%) at ≥50 mg/kg
Rat 3-month (20002194): 40, 80/70, 120/90 mg/kg/day	40 mg/kg (213.8 µg.h/mL)	Mortalities at ≥80/70 mg/kg. Dose reductions were made on Day 47 for the 120 mg/kg and the 80 mg/kg groups. Thrombosis and necrosis in multiple organs (heart, kidney, lung, skeletal muscle, and glandular stomach mucosa) at ≥80/70 mg/kg Adrenal hypertrophy, increased cellularity in the bone marrow and the spleen at ≥80/70 mg/kg Increased red blood cell indices, and decreased platelet counts (up to -59%) at ≥40 mg/kg

Study (Study No.): Doses	NOAEL, mg/kg (AUC)	Key Study Findings
Rat 6-month (20008611): 20, 40, 60 mg/kg	20 mg/kg (124 µg.h/mL)	Mortalities at 60 mg/kg due to polycythemia related complications
		Fibrin thrombosis and necrosis in the stomach mucosa at 40 mg/kg and in multiple organs (heart, kidney, lung, ileum/cecum, and glandular stomach mucosa) at 60 mg/kg
		Adrenal hypertrophy at 60 mg/kg
		Increased cellularity in the bone marrow and the spleen at ≥40 mg/kg
		Increased red blood cell indices and decreased platelet counts (up to -71%) at ≥40 mg/kg
Dog 3-month (20002195): 25, 45, 90/65 mg/kg/day	45 mg/kg (AUC, 216 µg.h/mL at Day 90)	The high dose of 90 mg/kg dose was reduced to 65 mg/kg on Day 43 due to a potential of polycythemia development.
		Increases in red blood cell indices, primarily at 90/65 mg/kg
		Dose related increases in Creatine Kinase BB, Lactate Dehydrogenase (LDH), LDH5, potassium and alterations in iron related parameters (decreased serum iron and increased unsaturated iron-binding capacity).
		Bone marrow erythroid hypercellularity in 90/65 mg/kg males and ≥45 mg/kg females
		Adrenal cortex mononuclear/multinuclear cell infiltrations at ≥25 mg/kg in the main study and recovery animals
Dog 9-month (Study No. 20008612): 10, 25, 50 mg/kg)	25 mg/kg (AUC, 32.3 µg.h/mL)	Exposures limited to <0.2x MRHD (AUC) to limit polycythemia-related toxicity.
		Mortality occurred in one 50 mg/kg female due to polycythemia (hematocrit increased 1.9x); minimal hematological changes observed for all other surviving animals.
		Adrenal cortex infiltration with hypertrophied cells (grades 1-2, mainly at ≥25 mg/kg) and mononuclear cells (grade ~1.0, ≥25mg/kg)
		Accumulation of brownish pigment in the centrilobular hepatocytes and sinusoidal macrophages in 50 mg/kg males and ≥25mg/kg females.

Source: Reviewer generated table
Abbreviations: LDH, lactate dehydrogenase, MRHD maximum recommended human dose

13.1.4.2. Genotoxicity

Genotoxicity of AKB-6548 was negative based on the totality of the findings described below.

The following is a summary of GLP-compliant genotoxicity studies.

Table 155. Genotoxicity Studies

Study Title (Study No.)	Positive/ Negative/ Equivocal	Notes
Ames (PC-0007)	Negative	
In Vitro Mammalian Chromosomal Aberration Test (PC-0008)	Positive	Dose-related increase of chromosomal structural aberration in CHO cells in absence of metabolic activation in 20-hour treatment condition
Chromosome Aberration Assay in Peripheral Blood Lymphocytes from Male Sprague Dawley Rats Administered AKB-6548 Orally for Five Consecutive Days (as19sx 139m-btl)	Negative	Only one dose (60 mg/kg/day) was evaluated due to excessive reduction in mitotic index at higher doses
In Vivo Comet Assay: An Alkaline Single Cell Gel Electrophoresis Assay of Liver Cells from Male Sprague-Dawley Rats Administered a Single Dose ofiAKB-6548 by Oral Gavage (8220896)	Negative	Rats were given single oral doses of 500, 1000, or 2000 mg/kg

Source: Reviewer generated table
Abbreviations: AKB-6548, vadadustat; CHO, Chinese hamster ovary; GLP, good laboratory practice

13.1.4.3. Carcinogenicity

The carcinogenic potential of vadadustat was evaluated in a 2-year rat study and a 6-month transgenic mouse study, both under GLP compliance. In both studies, double control groups (water and vehicle control) were employed and vadadustat was formulated in 0.25% hydroxypropyl methyl cellulose, 0.1% TWEEN® 80, in reverse osmosis deionized water.

The 2-year oral carcinogenicity study in rats (Study No. 20057392) was conducted with AKB-6548 (code for vadadustat) at doses of 2, 7, and 20 mg/kg/day. Treatment did not affect animal survival or cause body weight loss. There were no treatment related tumor findings at any dose tested. Non-neoplastic findings were related to increased erythropoiesis including increased splenic hematopoiesis with pigmented macrophages, and stomach findings of erosion, inflammation, and necrosis in the glandular region. The maximum recommended human dosage (NOAEL) for the neoplastic findings was 20 mg/kg/day (AUC 216 µg.h/mL) which provides a 0.32x multiple of the maximum recommended human dosage $(MRHD)_{AUC}$ (654.9 µg.h/mL at 600 mg once daily [QD]).

The 6-month oral carcinogenicity study in transgenic Ras H2 mice (Study No. 20092949) used AKB-6548 doses of 5, 15 and 50 mg/kg/day. Treatment did not affect animal survival or body weights. There were no treatment related tumor findings in male or female mice. The positive control, N-Nitrosomethylurea, showed a mortality rate of 87% for both sexes, primarily due to malignant lymphoma. Non-neoplastic findings in AKB-6548 treatment group were limited to increased splenic hematopoiesis. NOAEL for AKB-6548 related neoplastic findings was 50 mg/kg/day (AUC 131 µg.h/mL), which provides a 0.2x multiple of the maximum recommended human dosage $(MRHD)_{AUC}$.

Of some note, the drug labels for marketed erythropoiesis stimulating agents (ESAs) contain a boxed warning for an increased risk of tumor progression based on clinical observations.

Vadadustat increases erythropoietin as part of its mechanism of action. Whether vadadustat and other hypoxia inducible factor-prolyl hydroxylase (HIF-PH) inhibitors share this risk of ESA products is uncertain. However, the increase in erythropoietin is more moderate and consistent with HIF-PHD inhibitors than with periodic infusion of ESA products, which may indicate an overall lower level of concern.

13.1.4.4. Reproductive Toxicology

A battery of standard reproductive toxicology studies was conducted using oral route of administration with formulation in 0.25% w/v hydroxypropyl methylcellulose (HPMC; 4000cp)/0.1% w/v Tween® 80 in reverse-osmosis deionized water. All studies were GLP compliant except dose ranging studies. The study designs are presented below.

AKB-6548: An Oral Study of Fertility and Early Embryonic Development to Implantation in Male and Female Rats (Study No. 1817-022)

Males were dosed starting 28 days prior to pairing, and females starting 14 days prior to pairing. Dosing for males continued through the mating and post-mating period until euthanasia on Day 63 or 64, while dosing of the females continued through the mating period to gestation day (GD) 7. Females were euthanized on GD 13. Females with no evidence of mating were cohabited with a second male from the same dosing group for up to 7 additional days.

Table 156. Dosing for AKB-6548

		NUMBER OF ANIMALS			
	DOSE LEVEL	INITIAL		NECROPSY	
GROUP	mg/kg/day	M	F	M	F
1	0	25	25	25	25
2	40	25	25	25	25
3	80	25	25	25	25
4	120	25	25	25	25

Source: Reviewer generated table

Reviewer's Comment:

There were no hematology data collected in this study. Previous studies reported that rats given AKB-6548 for 7 days orally resulted in hematocrit increases of 27% and 16% at 200 mg/kg/day and 120 mg/kg/day, respectively (sw08-0195, kgi00016).

An Oral Dose Range-Finding Developmental Toxicity Study in Rats (Study No. 1817-006)

Animals were dosed at gestation days (GD) 6-17 and sacrificed on GD 20.

Table 157. Dosing Range

Group Assignments			
Group Number	Dose Level (mg/kg/day)	Number of Time-mated Females	Animal Numbers
1	0	5	101-105
2	40	5	106-110
3	120	5	111-115
4	240	5	116-120

Source: Reviewer generated table

AKB-6548: An Oral Study for Effects on Embryo-Fetal Development in Rats With a Toxicokinetic Evaluation (Study No. 1817-008)

Animals were dosed at gestation days (GD) 6-17 and sacrificed on GD 20

Table 158. Animal Dosing for Study 1817-008

		NUMBER OF ANIMALS		
GROUP	DOSE LEVEL mg/kg/day	INITIAL F	CESAREAN SECTION/ NECROPSY F	TOXICO-KINETICS F
1	0	25	25	-
2	40	25	25	-
3	80	25	25	-
4	160	25	25	-
5	0	3	-	3
6	40	8	-	8
7	80	8	-	8
8	160	8	-	8

Source: Reviewer generated table

Reviewer's Comment:

There were no hematology data collected in this study. However, the doses tested are expected to exert pharmacodynamic activity based on previous studies in rats that resulted in hematocrit increases of 27% and 16% at 200 mg/kg/day and 120 mg/kg/day, respectively (sw08-0195, kgi00016).

AKB-6548: An Oral Dose Range-Finding Developmental Toxicity Study in Rabbits (No. 1817-007)

Table 159. Phase A. Dose Tolerance Phase in Non-Pregant Rabbits

Group Assignments – Phase A			
Group Number	Dose Level (mg/kg/day)	Number of Females	Animal Numbers
1	60	2	101-102
2	360	2	103-104
3	120	2	105-106
4	240	2	107-108

Source: Reviewer generated table

Table 160. Phase B. Developmental Range-Finding Phase

Group Assignments – Phase B			
Group Number	Dose Level (mg/kg/day)	Number of Time-mated Females	Animal Numbers
Main Study			
5	0	6	201-206
6	30	6	207-212
7	90	6	213-218
8	150	6	219-224
Toxicokinetic			
9	30	3	225-227
10	90	3	228-230
11	150	3	231-233

Source: Reviewer generated table

In Phase B, animals were dosed at gestation days (GD) 6-18 and sacrificed on GD 29.

AKB-6548: An Oral Study for Effects on Embryo-Fetal Development in Rabbits With a Toxicokinetic Evaluation (Study No. 1817-009)

Animals were dosed at gestation days (GD) 6-18 and sacrificed on GD 29.

Table 161. Animal Dosing for Study 1817-009

GROUP	DOSE LEVEL mg/kg/day	INITIAL F	CESAREAN SECTION/ NECROPSY F	TOXICO-KINETICS F
1	0	23	23	-
2	10	23	23	-
3	25	23	23	-
4	50	23	23	-
5	0	3	-	3
6	10	5	-	5
7	25	5	-	5
8	50	5	-	5

Source: Reviewer generated table
Note: Hematology data were not collected in the rabbit study.

AKB-6548: An Oral Study for Effects on Pre- and Postnatal Development including Maternal Function in Rats (Study No. 1817-037)

F0 females were dosed from GD 6 to Lactation Day (LD) 20. F1 offspring were potentially exposed to the test article in utero and through milk during the lactation period but were not dosed directly.

Table 162. Study Design for Study 1817-037

Table A: Study Design				
		Number of Animals		
			Selected F_1 Litters[a]	
Group Number	Dose Level (mg/kg/day)	F_0 Females	Male	Female
1	0	25	16	16
2	20	25	21	21
3	40	25	19	19
4	80	25	19	19
[a]Number of males and females are reflective of the number of litters available for evaluation in the F_1 generation.				

Source: Reviewer generated table

Reviewer's Comments

Red blood cell indices and toxicokinetic data were not collected. However, a 52% increase of hematocrit at Day 45 in rats given 80 mg/kg/day was noted in a previous 3-month study. Also, a study with radiolabeled AKB-6548 in pregnant rats showed a plasma to milk concentration ratio of 6-fold, suggesting that the pups were likely exposed to vadadustat via lactation.

Table 163. Key Findings

Study/ Dose	NOAEL (AUC); exposure multiple[1]	Key Study Findings
FEED in rats (Study No.1807-022): 0, 40, 80, or 120 mg/kg/day	120 mg/kg/day (657 µg.h/mL); 1x MRHD	Decreased body weight and/or food consumption in 120 mg/kg males Mortalities in ≥80 mg/kg males secondary to polycythemia No clinical pathology data collected No vadadustat-related effects in the male and female reproductive and fertility indices or sperm parameters were observed.
Dose-ranging EFD study in rats (Study No. 1817-006): 0, 40, 120, or 240		Decreased maternal body weight and food consumption at 240 mg/kg Increased post-implantation loss at 120 mg/kg (19.9% vs. 9.5%) and 240 mg/kg (26.1% vs. 9.5%) Decreased fetal body weight at 240 mg/kg (-14%) No systemic exposure data collected No teratology findings
EFD study in rats (Study No. 1817-008): 0, 40, 80, or 160 mg/kg/day	80 mg/kg/day (1007 µg.h/mL); 1.5x	Decreases in maternal body weight gains and food consumptions at ≥80 mg/kg/day Reduced fetal body weights (-7%) Increased fetal incidence of reduced skeletal ossification at 160 mg/kg/day No post-implantation loss No teratology findings

Study/ Dose	NOAEL (AUC); exposure multiple[1]	Key Study Findings
Dose-ranging EFD in rabbits (Study No. 1817-007): 0, 30, 90, or 150 mg/kg/day		Mortalities at ≥ 90 mg/kg (150 mg/kg, 100%; 90 mg/kg, 67%) Decreased fetal weights at 90 mg/kg (-19.8%). No systemic exposure data collected No teratogenic effects
EFD study in rabbits (Study No. 1817-009): 0, 10, 25, 50 mg/kg/day	50 mg/kg/day (99.5 µg.h/mL); 0.15x	Decreases in gestation body weight gain and food consumptions at 50 mg/kg/day No fetal toxicities
PPND study in rats (Study No. 1817-037): 0, 20, 40, 80 mg/kg/day	40 mg/kg/day (214 µg.h/mL)[2]; 0.33x	No maternal toxicities F1 pup body weights were reduced in 80 mg/kg/day group (-5% to -11%)

Source: Reviewer generated table
[1] $MRHD_{AUC}$ = 654.9 µg.h/mL
[2] obtained from a 3-month rat study
Abbreviations: FEED, fertility and early fetal developmental study; EFD, Embryo-fetal developmental study; PPND, pre- and post-natal developmental study

13.1.4.5. Juvenile Animal Study

A 10-Week Study of AKB-6548 by Oral Gavage in Juvenile Rats With a 6-Week Recovery Period (Study No. 9001442, GLP compliant)

Vadadustat was formulated in 0.25% (w/v) hydroxypropyl methyl cellulose/0.1% (w/w) Tween® 80 in water

Table 164. Study Design of AKB-6548 (Study No. 9001442)

Experimental Design – Main and Recovery Subsets

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	No. of Animals					
					Main Study		Recovery Study		Dosed Spares[d,f]	
					Males	Females	Males	Females	Males	Females
1	Reference Item/ Vehicle Control	0	10	0	12	12	12	12	2	2
2	AKB-6548	5[b] / 10[c]	10	0.5[b] / 1.0[c]	12	12	12	12	2	2
3	AKB-6548	15[b] / 30[c]	10	1.5[b] / 3.0[c]	12	12	12	12	2	2
4	AKB-6548	40[b] / 80[c]	10	4.0[b] / 8.0[c]	16[e]	12	13[e]	12	2	2

[a] Based on the most recent body weight measurement.
[b] Dose Level and Dose Concentration of dose formulation administered from PND 7 to 27
[c] Dose Level and Dose Concentration of dose formulation administered from PND 28 to 76
[d] Dosed spare pups from these litters may be assigned as Main, Recovery or TK subset animals, if necessary. Any dosed spare animals remaining unassigned to a subset will be released from the study on PND 77, as applicable.
[e] Due to mortality observed at 40/80 mg/kg/day, two male dosed spare and three male PND 28 TK subset animals will be reassigned to the Main and Recovery subsets.
[f] As applicable, animals in the PND 28 TK cohort will be reassigned to the dose spare animals on PND 35.

Source: Reviewer generated table
Vadadustat was formulated in 0.25% (w/v) hydroxypropyl methyl cellulose/0.1% (w/w) Tween® 80 in water
Abbreviations: AKB-6548, vadadustat; GLP, good laboratory practice

The high dose of 40/80 mg/kg/day was selected based on a dose ranging study in juvenile rats and a 13-week toxicity study in adolescent/adult rats. In the juvenile dose ranging study, mortalities occurred at ≥50 mg/kg during the first 7 days. Additionally, systemic exposures on day 7 were 7.1-11.8 fold higher than Day 34, which is attributable to the maturation of hepatic metabolism that occurs around the time of weaning in rats. Selection of high dose for the postweaning phase was based on mortalities observed at ≥80/70 mg/kg in the 13-week rat toxicity study.

Key Findings

Juvenile rats were given vadadustat orally for 10 weeks at doses of 0 (vehicle), 5, 15 or 40 mg from PND 7-27 and at doses of 0 (vehicle), 10, 30 or 80 mg/kg/day from PND 28-76. Toxicity findings were similar to those observed in adult rats and included increases in red blood cell indices, polycythemia-related thrombosis, tissue infarction/necrosis, hemorrhage and/or septicemia, and resulting mortalities. Also, treatments resulted in mild decreases in body weight gain and food consumption. Based on the mortality and polycythemia related histopathological findings at 40/80 mg/kg/day, the NOAEL was defined as 15/30 mg/kg (PNDs 7-27, 15 mg/kg; PNDs 28-76, 30 mg/kg). See tabulated summary data below.

Table 165. Juvenile Rat Study Summary

Dose	NOAEL, (AUC)	Key Study Findings
PND 7-27: 0, 5, 15 or 40 mg/kg/day PND 28-76: 0, 10, 30 or 80 mg/kg/day	15/30 mg/kg/day (229 µg.h/mL)	Mortality at 40/80 mg/kg secondary to polycythemia Dose-related lower body weight gain during first 5 weeks and lower food consumption after weaning, more prominently in 40/80 mg/kg/day animals Elevated red blood cell indices (Hb, HCT, Retic) and decreased platelet counts at ≥ 15/30 mg/kg/day Histopathological findings, primarily at 40/80 mg/kg/day including organ hemorrhage, erosion and/or inflammation (lung stomach, thymus), kidney nephropathy (tubular basophilic or mineralization, cortex necrotic cells, vascular/perivascular inflammation), heart valve stromal proliferation and epicardial inflammation; increased hematopoiesis in the spleen and bone marrow

Source: Reviewer generated table
Abbreviations: AUC, area under the concentration-time curve; HCT, hematocrit; NOAEL, no observed adverse effect level; PND, postnatal development

13.1.4.6. Special Studies

Key Findings

In vitro hemolysis (Study No. cyp0385-r1-r2)

AKB-6548 at concentrations up to 1 mM did not induce hemolysis in rat, mouse, or dog whole blood, in vitro.

Phototoxicity (Study No. 20055304)

In vitro phototoxicity screening assays suggested a potential for photosensitization with vadadustat; however, in vivo, pigmented rats (Long-Evans) administered AKB-6548 at doses up to 400 mg/kg/day for three days followed by ultraviolet (UV) radiation (UVA +UVB, with UVA dose 10.3-11.3 J/cm^2) for up to 120 minutes showed no evidence of ocular or cutaneous phototoxicity elicited by AKB-6548.

The negative in vivo findings might be due to limited skin distribution of the orally administered test article. Thus, the potential of human phototoxicity is likely insignificant.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

In vitro Assessment of Vadadustat Protein Binding in Mouse, Rat, Dog, Rabbit, and Human Plasma (XS-1137)

The objective of this study was to assess the in vitro protein binding of vadadustat in mouse, rat, dog, rabbit, and human plasma by the rapid equilibrium dialysis method. Dialysis time to reach

equilibrium, non-specific binding, and plasma stability were evaluated. Nominal vadadustat concentrations in plasma were 3, 10, 30, 100, and 300 µg/mL. Warfarin administered at 10 µM served as a positive control.

The in vitro plasma protein binding of vadadustat is summarized in Table 166. Table 167 shows the plasma protein bindings of warfarin.

Table 166. Plasma Protein Binding of Vadadustat in Mouse, Rat, Dog, Rabbit and Human Plasma

Species	Time (hr)	Concentration (µg/mL)	Unbound (% Free)	Protein binding (% Binding)	Recovery (%)
Mouse	4	3	3.5 ± 0.1	96.5 ± 0.1	87.8 ± 2.7
		10	3.4 ± 0.1	96.6 ± 0.1	86.5 ± 0.5
		30	4.3 ± 0.2	95.7 ± 0.2	84.3 ± 2.8
		100	4.9 ± 0.1	95.1 ± 0.1	90.4 ± 0.5
		300	6.8 ± 0.6	93.2 ± 0.6	90.4 ± 0.9
Rat	4	3	0.9 ± 0.1	99.1 ± 0.1	97.6 ± 1.9
		10	0.8 ± 0.0	99.2 ± 0.0	99.6 ± 0.9
		30	0.9 ± 0.0	99.1 ± 0.0	92.6 ± 1.0
		100	1.4 ± 0.1	98.6 ± 0.1	93.4 ± 4.4
		300	3.6 ± 0.3	96.4 ± 0.3	97.1 ± 2.1
Dog	4	3	1.8 ± 0.1	98.2 ± 0.1	88.6 ± 0.7
		10	1.8 ± 0.1	98.2 ± 0.1	100.3 ± 3.4
		30	1.9 ± 0.2	98.1 ± 0.2	92.0 ± 6.7
		100	2.8 ± 0.1	97.2 ± 0.1	91.5 ± 4.5
		300	4.4 ± 0.2	95.6 ± 0.2	104.0 ± 2.0
Rabbit	4	3	0.7 ± 0.1	99.3 ± 0.1	102.7 ± 1.3
		10	0.7 ± 0.1	99.3 ± 0.1	105.2 ± 1.2
		30	0.8 ± 0.1	99.2 ± 0.1	99.7 ± 1.1
		100	1.1 ± 0.0	98.9 ± 0.0	97.6 ± 0.7
		300	1.9 ± 0.1	98.1 ± 0.1	96.0 ± 1.8
Human	4	3	0.2 ± 0.0	99.8 ± 0.0	95.6 ± 3.5
		10	0.2 ± 0.0	99.8 ± 0.0	95.4 ± 1.6
		30	0.2 ± 0.0	99.8 ± 0.0	96.1 ± 0.5
		100	0.3 ± 0.0	99.7 ± 0.0	99.4 ± 2.5
		300	0.5 ± 0.1	99.5 ± 0.1	92.6 ± 2.3

Source: Table 9 of study report XS-1137
Data are expressed as the mean ± SD of three samples.

Table 167. Plasma Protein Binding of Positive Control (Warfarin) in Human Plasma

Species	Warfarin concentration (µM)	Unbound (% Free)	Protein binding (% Binding)
Human	10	0.8 ± 0.1	99.2 ± 0.1
		0.8 ± 0.1	99.2 ± 0.1

Source: Table 10 of study report XS-1137

In human plasma, warfarin exhibited high plasma protein binding (99.2% bound), consistent with historical in-house data. Under the conditions of this assay and over the investigated concentration range, vadadustat exhibited high protein binding in plasma across all species tested (≥93.2% bound), with the highest extent of binding observed in human plasma (≥99.5% bound).

In Vitro Assessment of Vadadustat-O-glucuronide Protein Binding in Human Plasma (XS-1159)

The objective of this study was to assess the in vitro protein binding of vadadustat-O-glucuronide in human plasma by the rapid equilibrium dialysis method. Nominal vadadustat-O-glucuronide concentrations in plasma were 5, 15, 50, and 100 µg/mL. The in vitro plasma protein binding of vadadustat-O-glucuronide is summarized in Table 168. Table 169 shows the plasma protein bindings of warfarin.

Table 168. Plasma Protein Binding of Vadadustat-O-Glucuronide in Human Plasma

Species	Time (hr)	Concentration (µg/mL)	Unbound (% Free)	Protein binding (% Binding)	Recovery (%)
Human	24	5	12.2 ± 1.4	87.8 ± 1.4	93.1 ± 1.6
		15	12.9 ± 0.8	87.1 ± 0.8	89.3 ± 2.9
		50	12.9 ± 0.8	87.1 ± 0.8	111.0 ± 2.1
		100	13.5 ± 1.4	86.5 ± 1.4	92.5 ± 2.6

Source: Table 8 of study report XS-1159

Table 169. Plasma Protein Binding of Positive Control (Warfarin) in Human Plasma

Species	Time (hr)	Warfarin concentration (µM)	Unbound (% Free)	Protein binding (% Binding)
Human	24	10	0.6 ± 0.1	99.4 ± 0.1

Source: Table 9 of study report XS-1159

Under the conditions of this assay and over the investigated concentration range of 5 to 100 µg/mL, vadadustat-O-glucuronide exhibited moderate binding to human plasma proteins (% bound ranging from 86.5% to 87.8%). There were no notable changes in fu,p of vadadustat-O-glucuronide in human plasma over the concentration range tested of 5 to 100 µg/mL. The positive control, warfarin (10 µM) was 99.4% bound to human plasma proteins.

In Vitro Phase I Metabolism of Vadadustat (XT134105)

The aim of this study was to investigate the Phase I metabolism of vadadustat (0.1, 1, and 10 μM) in human liver microsomes. Little to no loss of vadadustat was observed in incubations with human liver microsomes in the presence or absence of NADPH (a cofactor required to support cytochrome P450 and flavin monooxygenase reactions). The results from these studies indicate that CYP-mediated metabolism of vadadustat was minor.

Incubation of Vadadustat With Human Intestine, Kidney, and Liver Microsomes (MC17M-0103)

The objective of this study was to determine the potential metabolic stability and formation of glucuronide conjugates of vadadustat during in vitro incubations with microsomes from human intestine, human kidney, and human liver. Vadadustat was incubated at 10 μM, and the microsomal protein concentration was 1.0 mg/mL. The reaction was supplemented with both NADPH and uridine diphosphate glucuronic acid (UDPGA). Metabolites were tentatively identified by liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Formation of 3 glucuronide metabolites was observed. One of the glucuronides formed in the incubations with human kidney and liver microsomes was confirmed to be vadadustat-O-glucuronide using reference standard, with a retention time of 4.12 min. When vadadustat was incubated with human intestinal microsomes, 2 additional glucuronides were observed at retention times of 5.22 and 5.42 min; however, they were not vadadustat-O-glucuronide.

In Vitro UDP-Glucuronosyltransferase Reaction Phenotyping of Vadadustat

The aim of this study was to identify the human UDP-glucuronosyltransferase (UGT) enzymes responsible for converting vadadustat to vadadustat-acyl-glucuronide and vadadustat-O glucuronide. Vadadustat (100 μM, or 20,000 pmol) was incubated with a panel of recombinant UGT enzymes (rUGT1A1, rUGT1A3, rUGT1A4, rUGT1A6, rUGT1A7, rUGT1A8, rUGT1A9, rUGT1A10, rUGT2B4, rUGT2B7, rUGT2B10, rUGT2B15 and rUGT2B17, 0.25 mg protein/mL) for 45 minutes to evaluate the involvement of UGT enzymes in the conversion of vadadustat to vadadustat-acyl-glucuronide and vadadustat-O-glucuronide. Positive control incubations (4-methylumbelliferone, imipramine and 1-naphthol) were included in the experiment to demonstrate the metabolic competency of each recombinant human UGT enzyme used in the experiment.

Vadadustat-acyl-glucuronide formation was observed in the vadadustat incubations with rUGT1A1 and rUGT2B7 (with percent conversions of 0.015 and 0.012%, respectively; with a cumulative vadadustat percent conversion of 0.027%). Vadadustat-O-glucuronide formation was observed in vadadustat incubations with rUGT1A1, rUGT1A7, rUGT1A8 and rUGT1A9 (with percent conversions of 0.40, 0.28, 0.074 and 0.87%, respectively; with a cumulative vadadustat percent conversion of 1.3%). No other recombinant UGT enzymes were found to form vadadustat-acyl-glucuronide or vadadustat-O-glucuronide at quantifiable levels.

Inhibitory Potential of Vadadustat Towards Human Hepatic Microsomal Cytochrome P450 Isoenzymes (8275722)

The objective of this study was to characterize the in vitro inhibitory potential of vadadustat on the activities of the following human hepatic cytochrome P450 (CYP) isoenzymes: CYP1A2,

CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The potential for vadadustat to inhibit major human drug metabolizing CYP isozymes was evaluated in pooled human liver microsomes with vadadustat concentrations up to 1300 µM. The above CYP isozymes were evaluated for direct, time-, and metabolism-dependent inhibition.

Vadadustat inhibited CYP2B6, CYP2C8, and CYP2C9 in a mixed manner (competitive and uncompetitive) with affinity constant for enzyme inactivation (K_i) values of 110, 25.1, and 48.6 µM, respectively. The concentration required to produce 50% inhibition (IC_{50}) values for inhibition of other CYP isoforms was ≥344 µM (Table 170). In a metabolism-dependent inhibition study, when vadadustat (33.3, 208, and 1300 µM) was pre-incubated with human liver microsomes for 30 minutes in the presence or absence of the NADPH, the remaining activities of CYP2B6 and CYP3A4/5 (midazolam 1'-hydroxylase and testosterone 6β-hydroxylase) in the presence of NADPH were slightly reduced than those in the absence of NADPH at 1300 µM. Only weak metabolism-dependent inhibition was observed at 1300 µM. Based on the results above, the potential for vadadustat to be a perpetrator of a CYP-mediated drug interaction via metabolism-dependent inhibition is unlikely at clinically relevant exposures in humans.

A mechanism-based static pharmacokinetic (PK) model was applied to the data for direct CYP inhibition and showed that the computed area under the plasma concentration time curve ratio (AUCR) values for all the CYP isoforms evaluated were <1.25 at vadadustat oral doses of 600 mg (Table 170). It should be noted that this assessment utilized a total mean plasma C_{max} value of 84.8 µg/mL observed in healthy subjects, which is higher than the mean total C_{max} values seen in non-dialysis dependent (NDD) and dialysis dependent (DD) subjects. Based on this assessment, vadadustat is unlikely to cause a clinically relevant drug interaction via direct CYP inhibition in the intended patient populations.

Table 170. Vadadustat IC50 and Ki Values for Inhibition of Human CYPs and Mechanistic Static Approach to CYP Inhibition Assessment

P450	Assay	IC_{50} (µM)	K_i (µM)	AUCR[a] (600 mg)
CYP1A2	Phenacetin O-deethylase	344	ND	1.01
CYP2B6	Bupropion hydroxylase	129	110	1.01
CYP2C8	Amodiaquine N-deethylase	42.7	25.1	1.17
CYP2C9	Diclofenac 4′-hydroxylase	119	48.6	1.04[b]
CYP2C19	S-Mephenytoin 4′-hydroxylase	459	ND	1.01
CYP2D6	Bufuralol 1′-hydroxylase	580	ND	1.01
CYP3A4/5	Testosterone 6β-hydroxylase	861	ND	ND
CYP3A4/5	Midazolam 1′-hydroxylase	764	ND	1.08

a. AUCR was calculated as $R = \left(\frac{1}{[Ag \times Bg \times Cg] \times (1 - Fg) + Fg}\right) \times \left(\frac{1}{[Ah \times Bh \times Ch] \times fm + (1 - fm)}\right)$, as described by Fahmi et al., 2009 and DDI guidance. The highest reported C_{max} value of 84.8 µg/mL (277 µM), obtained following the dosing of 600 mg QD in CI-0020, was used in the calculation.
b. Using warfarin as in vivo substrate for the AUCR calculations.

Source: Pharmacokinetics Tabulated Summary 2.6.5.16.A, study report 8275722
Abbreviations: AUCR, area under the concentration time curve ratio; CYP; cytochrome P450 isoenzymes; IC_{50}, half maximal inhibitory concentration; K_i, inhibitory constant

Vadadustat: Screening In Vitro Human UGT Enzyme Inhibition Assay (XT11A028)

The objective of this study was to evaluate the ability of vadadustat to inhibit the major UGT enzymes in human liver microsomes (namely UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) following in vitro incubation. Pooled human liver microsomes were incubated with UGT-specific marker substrates, at concentrations approximately equal to their apparent K_m, in the presence or absence of vadadustat. UGT enzyme inhibition was measured by evaluating a decrease in substrate glucuronidation relative to control.

Table 171. Vadadustat Percent Inhibition of Human UGT Enzyme-Mediated Substrate Glucuronidation

Enzyme	Enzyme reaction	AKB-6548 Direct inhibition [a]						
		Percent inhibition at 0.4 µM	Percent inhibition at 1.2 µM	Percent inhibition at 4 µM	Percent inhibition at 12 µM	Percent inhibition at 40 µM	Percent inhibition at 120 µM	Percent inhibition at 400 µM
UGT1A1	17β-Estradiol 3-glucuronidation	11	5.6	11	13	23	51	77
UGT1A4	Trifluoperazine glucuronidation	NA	2.9	2.2	16	6.5	4.0	19
UGT1A6	1-Naphthol glucuronidation	9.8	6.8	NA	NA	NA	NA	22
UGT1A9	Propofol glucuronidation	4.2	4.5	2.6	3.9	13	19	29
UGT2B7	Morphine 3-glucuronidation	3.0	5.7	7.0	NA	4.7	16	21

NA Not applicable: no value was obtained as the area ratio at the indicated concentration of AKB-6548 was higher than the control area ratio.

a Percent inhibition was calculated using the mean area ratio of duplicate determinations.

Source: Table 2 of study report XT11A028

Abbreviations: AKB-6548: Vadadustat; UGT, uridine diphosphate-glucuronosyltransferase

Under the experimental conditions examined, vadadustat was a direct inhibitor of UGT1A1 with an IC_{50} value of 110 µM. Vadadustat was also found to directly inhibit UGT1A9 and UGT2B7 with approximately 29% and 21% inhibition, respectively, in incubations containing the highest dose concentration of 400 µM vadadustat (Table 171). The IC_{50} values for UGT1A9 and UGT2B7 were >400 µM. A complex response was observed on UGT1A6, with a concentration-dependent increase in UGT1A6 activity at concentrations up to 120 µM vadadustat, and a decrease in activity at 400 µM vadadustat. There was no evidence that vadadustat directly inhibited UGT1A4.

A mechanism-based static PK model was applied and showed that the area under the plasma concentration time curve ratio value for UGT1A1 was <1.25 at the vadadustat by mouth (PO) dose of 600 mg. Based on this assessment, vadadustat is unlikely to cause a clinically relevant drug interaction via UGT1A1 inhibition in the intended patient populations.

Evaluation of Cytochrome P450 and UGT1A1 Induction Following Exposure of Vadadustat to Primary Cultures of Human Hepatocytes (8273558)

The objective of this study was to measure the extent of induction of specific human cytochrome P450 (CYP450) enzymes (CYP1A2, CYP2B6, CYP3A4), and uridine diphosphate glycosyltransferase 1A1 (UGT1A1) following exposure of human hepatocytes to vadadustat.

Vadadustat showed induction of CYP2B6 but not of CYP1A2, CYP3A4, or UGT1A1 under the study conditions (Table 172 through Table 175). The fold induction of CYP2B6 mRNA levels by vadadustat over the solvent control was ≥4.19 in hepatocytes from three donors. The fold induction of CYP2B6 activity by vadadustat was ≥2.23 in hepatocytes from two donors and only <10% of that induced by phenobarbital indicating vadadustat did not consistently increase activity of CYP2B6. Based on this assessment, the risk of drug-drug interactions with co-administration of vadadustat with substrates of the CYPs evaluated in the study is minimal.

Table 172. Fold Increase in CYP1A2 mRNA and Activity Following Exposure of Vadadustat in Primary Human Hepatocytes

Tabulated Results:	Test Concentration (µM)	CYP1A2 mRNA (Fold Increase[a])			CYP1A2 Activity (Fold Increase[a])		
		Donor 2	Donor 3	Donor 4	Donor 2	Donor 3	Donor 4
Flumazenil	20	3.70	6.57	3.95	1.51	1.61	1.85
Omeprazole	25	33.7	20.8	87.6	58.4	22.2	3.05
Vadadustat	1.12	0.500	1.48	0.651	ND	ND	ND
	2.03	1.84	1.70	0.847	ND	ND	ND
	4.06	0.616	1.77	0.451	ND	ND	ND
	8.13	0.758	1.60	0.253	1.27	1.24	1.09
	16.25	1.78	3.81	0.774	ND	ND	ND
	32.5	1.26	1.15	0.417	0.387	0.645	0.427
	65	0.445	0.548	0.548	ND	ND	ND
	130	1.00	1.23	1.28	0.186	0.446	0.329

Source: Pharmacokinetics Tabulated Summary 2.6.5.16.B, 8273558
Abbreviations: CYP cytochrome P450 isoenzyme

Table 173. Fold Increase in CYP2B6 mRNA and Activity Following Exposure of Vadadustat in Primary Human Hepatocytes

Tabulated Results:	Test Concentration (µM)	CYP2B6 mRNA (Fold Increase[a])			CYP2B6 Activity (Fold Increase[a])		
		Donor 2	Donor 3	Donor 4	Donor 2	Donor 3	Donor 4
Flumazenil	20	0.471	2.96	1.43	1.36	1.55	1.10
Phenobarbital	1000	3.99	5.63	9.94	13.4	17.0	6.32
Vadadustat	1.12	0.548	1.90	1.36	ND	ND	ND
	2.03	1.42	2.83	1.95	ND	ND	ND
	4.06	1.27	3.07	2.20	ND	ND	ND
	8.13	2.67	2.49	4.80	2.23	1.94	1.61
	16.25	3.28	7.64	7.96	ND	ND	ND
	32.5	3.07	3.22	6.08	1.41	1.08	1.04
	65	2.40	8.53	3.54	ND	ND	ND
	130	4.19	14.6	7.98	1.65	2.47	1.16

Source: Pharmacokinetics Tabulated Summary 2.6.5.16.C, 8273558
Abbreviations: CYP cytochrome P450 isoenzyme

Table 174. Fold Increase in CYP3A4 mRNA and Activity Following Exposure of Vadadustat in Primary Human Hepatocytes

Tabulated Results:	Test Concentration (µM)	CYP3A4 mRNA (Fold Increase[a])			CYP3A4 Activity (Fold Increase[a])		
		Donor 2	Donor 3	Donor 4	Donor 2	Donor 3	Donor 4
Flumazenil	20	1.44	2.75	1.55	1.15	1.33	1.31
Rifampicin	50	5.31	42.3	50.4	5.64	24.1	16.1
Vadadustat	1.12	0.532	1.16	0.964	ND	ND	ND
	2.03	1.32	0.851	2.10	ND	ND	ND
	4.06	0.683	0.694	0.599	ND	ND	ND
	8.13	0.378	0.621	0.664	0.511	0.500	0.683
	16.25	0.600	0.959	0.927	ND	ND	ND
	32.5	0.205	0.600	0.372	0.103	0.283	0.261
	65	0.0569	0.384	0.234	ND	ND	ND
	130	0.0800	0.476	0.339	0.0555	0.277	0.155

Source: Pharmacokinetics Tabulated Summary 2.6.5.16.D, 8273558
Abbreviations: CYP cytochrome P450 isoenzyme

Table 175. Fold Increase in UGT1A1 mRNA and Activity Following Exposure of Vadadustat in Primary Human Hepatocytes

Tabulated Results:	Test Concentration (µM)	UGT1A1 mRNA (Fold Increase[a])			UGT1A1 Activity (Fold Increase[a])		
		Donor 2	Donor 3	Donor 4	Donor 2	Donor 3	Donor 4
Flumazenil	20	0.719	1.12	0.873	0.933	1.30	0.941
Rifampicin	50	2.54	3.29	1.43	0.875	1.27	0.624
3-Methylcholanthrene	5	6.74	11.3	5.88	1.74	1.28	1.17
Vadadustat	1.12	0.607	1.64	1.00	ND	ND	ND
	2.03	1.23	2.22	0.948	ND	ND	ND
	4.06	1.10	1.34	0.855	ND	ND	ND
	8.13	0.593	1.07	1.10	1.18	0.824	0.814
	16.25	0.685	2.31	1.60	ND	ND	ND
	32.5	1.05	1.56	1.42	1.15	0.452	0.887
	65	0.651	1.64	1.32	ND	ND	ND
	130	1.68	5.48	2.43	1.16	0.870	0.892

Source: Pharmacokinetics Tabulated Summary 2.6.5.16.E, 8273558
Abbreviations: UGT, uridine diphosphate glycosyltransferase

In Vitro Evaluation of Vadadustat and Vadadustat-O-glucuronide as Inhibitors and Substrates of Human BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2K Transporters (XT138057)

The objective of this study was to evaluate vadadustat and vadadustat-O-glucuronide as inhibitors and substrates of human transporters.

Inhibition Methods

The ability of vadadustat (0.3, 1, 3, 10, 30 and 50 µg/mL) to inhibit the human efflux transporter BCRP (ABCG2) was evaluated by measuring the bidirectional permeability of a probe substrate (prazosin) across a monolayer of MDCKII-BCRP cells in the presence of vadadustat. The ability of vadadustat-O-glucuronide (0.3, 1, 3, 10, 30 and 50 µg/mL) to inhibit human efflux transporters, namely, P-gp (MDR1/ABCB1) and BCRP, was evaluated by measuring the

bidirectional permeability of a probe substrate (digoxin or prazosin, respectively) across a monolayer of Caco-2 and MDCKII-BCRP cells, respectively, in the presence of vadadustat-O-glucuronide. The ability of vadadustat and vadadustat-O-glucuronide (0.03, 0.1, 0.3, 1, 3, 10 and 30 µg/mL) to inhibit human uptake transporters, namely, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 was evaluated by measuring the accumulation of probe substrates (estradiol-17β-glucuronide [OATP1B1 and OATP1B3], metformin [OCT2], p-aminohippurate [OAT1] or estrone-3-sulfate [OAT3]) in transporter-expressing and control HEK293 cells in the presence of vadadustat and vadadustat-O-glucuronide respectively. In addition, the ability of vadadustat and vadadustat-O-glucuronide to inhibit human MATE1 and MATE2K was evaluated by accumulation of probe substrates into transporter-expressing and control cells.

Substrate Methods

To determine if vadadustat (0.3 and 1 µg/mL) is a substrate of the human efflux transporter BCRP, the bidirectional permeability of vadadustat across MDCKII-BCRP cells was measured. To determine if vadadustat (0.3, 1, 3 and 30 µg/mL) and vadadustat-O-glucuronide (1, 3 and 30 µg/mL) is a substrate of human uptake transporters (namely, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3), the accumulation of vadadustat (0.3, 1, 3 and 30 µg/mL) and vadadustat-O-glucuronide (1, 3 and 30 µg/mL) respectively, in transporter-expressing and control HEK293 cells was measured. To determine if vadadustat-O-glucuronide (1, 3 and 30 µg/mL) is a substrate of MRP2, the accumulation of vadadustat-O-glucuronide in transporter-expressing vesicles in the presence and absence of ATP was measured. Additionally, to determine if vadadustat and vadadustat-O-glucuronide are substrates of human MATE1 and MATE2K, the accumulation of vadadustat and vadadustat-O-glucuronide in transporter-expressing and control cells was measured.

Results

Vadadustat and vadadustat-O-glucuronide as an inhibitor of transporters

The potential of vadadustat or vadadustat-O-glucuronide to inhibit several transporters is summarized in Table 176.

Table 176. Summary of In Vitro Transporter Inhibition Potential of Vadadustat and Vadadustat-O-Glucuronide

Transporter	Substrate	Vadadustat		Vadadustat-O-Glucuronide	
		IC_{50} (µg/mL)	R-value	IC_{50} (µg/mL)	R-value
P-gp	Digoxin	>80	ND	>50	ND
BCRP	Prazosin	10.4	231 (>10)	>50	ND
OATP1B1	[^{3}H]-Estradiol-17β-glucuronide	4.02	1.2 (>1.1)	>30	ND
OATP1B3	[^{3}H]-Estradiol-17β-glucuronide	>30	ND	>30	ND
OCT2	[^{14}C]-Metformin	>30	ND	>30	ND
OAT1	[^{3}H]-Aminohippurate	3.76	0.12 (>0.1)	5.93	0.29 (>0.1)
OAT3	[^{3}H]-Estrone-3-sulfate	0.336	1.3 (>0.1)	9.10	0.19 (>0.1)
MATE1	[^{14}C]-Metformin	>30	ND	>30	ND
MATE2-K	[^{14}C]-Metformin	>30	ND	>30	ND
BSEP	[^{3}H]-taurocholic acid	>500	ND	NC	ND

For P-gp and BCRP inhibition, R-value = I_{gut}/IC_{50}, where I_{gut} is dose/250 mL (600 mg/250 mL = 2400 µg/mL). It should be noted that the I_{gut} concentration calculated as per guideline recommendations far exceeds the measured aqueous solubility at 37°C at pH 4.3 of 0.053 mg/mL (53 µg/mL) (Module 3.2.S.1 Drug Substance General Information).

For OATP1B1 inhibition, R-value = $1+((f_{u,p} \times I_{in,max})/IC_{50})$, where $I_{in,max} = (I_{max} + (f_a f_g \times k_a \times dose)/Q_h$, and k_a is assumed to be 0.1 min^{-1} and $f_a f_g = 1$.

For OAT inhibition, R-value = $I_{max,u}/IC_{50}$, where $I_{max,u}$ is the mean unbound human C_{max} at an oral dose of 600 mg (see Table 5).

BCRP: breast cancer resistance protein; BSEP: bile salt export pump; IC_{50}: concentration at which 50% inhibition is observed; MATE1 and 2-K: multidrug and toxin extrusion 1 and 2-K; NC: not calculated; ND: not determined; OAT1 and 3: organic anion transporter 1 and 3; OATP1B1 and 1B3: organic anion-transporting polypeptide 1B1 and 1B3; OCT2: organic cation transporter 2; P-gp: P-glycoprotein.

Source: Reviewer generated table

Vadadustat inhibited BCRP with an IC_{50} value of 10.4 µg/mL. The R-value was estimated at >10 (Table 176), suggesting that inhibition of BCRP may lead to a clinically relevant drug interaction upon co-administration of vadadustat and BCRP substrates in subjects. At 50 µg/mL, vadadustat-O-glucuronide (75.6% of control) did not inhibit prazosin transport by >50% in MDCK-II-BCRP cells.

Vadadustat inhibited OATP1B1 with an IC_{50} value of 4.02 µg/mL. The R-value was estimated at >1.1 (Table 176), suggesting that co-administration of vadadustat at a PO dose of 600 mg in subjects may result in a clinically relevant drug interaction with drugs that are sensitive substrates of OATP1B1. Vadadustat did not inhibit OATP1B3 (IC_{50}>30 µg/mL) at the concentrations evaluated. Vadadustat-O-glucuronide did not inhibit OATP1B1 and OATP1B3 at the concentrations evaluated (IC_{50}>30 µg/mL).

Vadadustat inhibited OAT1 and OAT3 with IC_{50} values of 3.76 µg/mL and 0.336 µg/mL, respectively. The R-values for OAT1 and OAT3 inhibition were estimated at 0.12 and 1.3, respectively (Table 176), suggesting that inhibition of OAT may result in a clinically relevant DDI at vadadustat exposures in subjects at the 600 mg PO dose upon co-administration with

drugs that are sensitive OAT substrates. Vadadustat-O-glucuronide inhibited OAT1 and OAT3 with IC_{50} values of 5.93 and 9.10 µg/mL, respectively. The R-values ($I_{max,u}/IC_{50}$) for OAT1 and OAT3 inhibition were estimated at 0.29 and 0.19, respectively (Table 176), suggesting that inhibition of OAT may result in a clinically relevant DDI at vadadustat exposures in subjects at the 600 mg PO dose upon co-administration with drugs that are sensitive OAT substrates. Vadadustat and vadadustat-O-glucuronide did not inhibit OCT2 at the concentrations evaluated (IC_{50}>30 µg/mL).

Vadadustat and vadadustat-O-glucuronide at concentrations ranging from 0.03 to 30 µg/mL did not inhibit the transport of [^{14}C]-metformin (10 µM) by MATE1 and MATE2-K in transporter-expressing and control cells.

Vadadustat and vadadustat-O-glucuronide as a substrate of transporters

A summary of the in vitro transporter substrate assays conducted with vadadustat and vadadustat-O-glucuronide is summarized in Table 177. Vadadustat and its major metabolite, vadadustat-O-glucuronide, were classified as a substrate when net uptake or efflux ratios were ≥2-fold and the uptake or flux is inhibited by ≥50% in the presence of a specific inhibitor.

Table 177. Summary of In Vitro Transporter Substrate Identification Studies of Vadadustat and Vadadustat-O-Glucuronide

Transporter	Positive Control	Vadadustat	Vadadustat-O-glucuronide
P-gp	Digoxin	Not a substrate	NC
BCRP	Prazosin	Substrate	NC
OATP1B1	[^{3}H]-Estradiol-17β-glucuronide	Substrate	Substrate
OATP1B3	[^{3}H]-Estradiol-17β-glucuronide	Not a substrate	Substrate
OCT2	[^{14}C]-Metformin	Not a substrate	Not a substrate
OAT1	[^{3}H]-*p*-Aminohippurate	Substrate	Not a substrate
OAT3	[^{3}H]-Estrone-3-sulfate	Substrate	Substrate
MATE1	[^{14}C]-Metformin	Not a substrate	Not a substrate
MATE2-K	[^{14}C]-Metformin	Not a substrate	Not a substrate
MRP2	Estradiol-17β-glucuronide	NC	Substrate

Source: Table 8 of Pharmacokinetics Written Summary, Module 2.6.4
Abbreviations: BCRP; breast cancer resistance protein; MATE1 and 2-K; multidrug and toxin extrusion 1 and 2-K; MRP2, multidrug resistance associated protein 2; NC, not calculated; OAT1 and 3, organic anion transporter 1 and 3; OATP1B1 and 1B3, organic anion-transporting polypeptide 1B1 and 1B3; P-gp, p-glycoprotein

The transcellular transport of vadadustat at concentrations up to 30 µg/mL was evaluated in BCRP-expressing cells. The net efflux ratios at 0.3, 1, 3, and 30 µg/mL vadadustat were >2 at all concentrations tested, suggesting that vadadustat is likely a BCRP substrate.

The accumulation of vadadustat into OATP1B1- and OATP1B3-expressing cells was evaluated at concentrations from 0.03 to 30 µg/mL. The uptake ratio of vadadustat into OATP1B1- and OATP1B3-expressing cells compared to control cells was >2 at concentrations up to 3 µg/mL. The uptake ratio for vadadustat at 30 µg/mL was <2 for both OATP1B1- and OATP1B3-expressing cells compared to control cells, which may indicate that saturation had occurred.

The uptake ratio of vadadustat into OAT1- and OAT3-expressing cells was evaluated at concentrations from 0.03 to 30 µg/mL. The uptake ratio of vadadustat into OAT1- and OAT3-expressing cells was >2 at concentrations up to 3 µg/mL. The uptake ratio for vadadustat at 30 µg/mL was <2 for both OAT1- and OAT3-expressing cells compared to control cells, which may indicate that saturation had occurred.

The uptake ratio of vadadustat into organic cation transporter 2 (OCT2)-expressing cells was evaluated at concentrations of 0.3 to 50 µg/mL. In 1 study, the uptake ratio for vadadustat at 30 µg/mL was >2 for OCT2-expressing cells compared to control cells.

The accumulation of vadadustat into MATE1- and MATE2-K-expressing cells was evaluated at concentrations from 0.3 to 30 µg/mL. The uptake of vadadustat into MATE1- and MATE2-K-expressing cells was <2 compared to controls cells. These data support that vadadustat is a not a substrate of MATE1 and MATE2-K.

The accumulation of vadadustat-O-glucuronide into OATP1B1- and OATP1B3-expressing cells was evaluated at concentrations up to 30 µg/mL. The uptake ratio of vadadustat-O-glucuronide into OATP1B1-expressing cells was <2, indicating that vadadustat-O-glucuronide is not a substrate of OATP1B1. The uptake ratio of vadadustat-O-glucuronide into OATP1B3 expressing cells compared to control cells was above 2 at 1 µg/mL at 1, 3 and 10 min, and at 3 µg/mL at 3 min, and was reduced to below 2 in the presence of the positive control inhibitor rifampin (10 µM). However, the uptake ratio was below 2 at all other concentrations. Overall, the results suggest that vadadustat-O-glucuronide is not a substrate of OATP1B3 and the uptake ratio above 2 is an artifact possibly due to low uptake of the compound into the OATP1B3- expressing cells.

In vitro studies evaluating the uptake of vadadustat-O-glucuronide at concentrations 1, 3, and 30 µg/mL in OCT2-, OAT1-, and OAT3-expressing cells indicate that vadadustat-O-glucuronide is transported by OAT3 with uptake ratios ranging from 9.66 to 20.7. The OAT3-mediated vadadustat-O-glucuronide uptake was inhibited by the positive control probenecid (100 µM). These data indicate vadadustat-O-glucuronide is a substrate of OAT3. The accumulation of vadadustat-O-glucuronide into OCT2 and OAT1 cells was similar to control cells, indicating that vadadustat-O-glucuronide is not a substrate of OCT2 and OAT1.

The accumulation of vadadustat-O-glucuronide into MATE1- and MATE2-K-expressing cells was evaluated at concentrations up to 30 µg/mL. At 30 µg/mL, the cleared volume of vadadustat-O-glucuronide into the MATE1- and MATE2K-expressing cells was higher than that into the control cells; however, there was no inhibitory effect of cimetidine towards vadadustat-O-glucuronide uptake. These results indicate that the uptake of vadadustat-O-glucuronide is not considered to be active uptake by the MATE1 and MATE2K transporters.

The accumulation of vadadustat-O-glucuronide at 1, 3, and 30 µg/mL into MRP2 vesicles was represented by an adenosine triphosphate (ATP)/adenosine monophosphate (AMP) ratio of >2 and was reduced significantly in the presence of positive control inhibitor benzbromarone (100 µM). These results suggest that vadadustat-O-glucuronide is a substrate of MRP2.

In Vitro Evaluation of Vadadustat as an Inhibitor and a Substrate of Human ABC and SLC Transporters (XT178101)

The objective of this study was to evaluate vadadustat as an inhibitor of human transporters P-gp and BSEP and a substrate of human transporters BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2.

Results

Table 178. Evaluation of Vadadustat as an Inhibitor of P-Gp and BSEP

Transporter	Test system	Substrate	Test article concentration	IC_{50}
P-gp	Caco-2	Digoxin (10 µM)	1, 3, 10, 30, 60 and 80 µg/mL	> 80 µg/mL
BSEP	Vesicles	[^{3}H]-Taurocholic acid (0.4 µM)	1, 5, 10, 20, 50, 200 and 500 µM	> 500 µM

Source: Study report XT178101
Abbreviations: BSEP, bile salt export pump; IC_{50}, half maximal inhibitory concentration; P-gp, p-glycoprotein

Under the conditions examined vadadustat was not an inhibitor of P-gp or BSEP with IC_{50} values of >80 µg/mL and >500 µM, respectively (Table 178).

The efflux ratio of vadadustat (1 to 50 µg/mL) across MDCKII-BCRP cells was greater than 2 for all vadadustat concentrations tested except 5 µg/mL. Furthermore, the efflux was reduced by >50% in the presence of the inhibitor Ko143 (1 µM). This suggests that vadadustat is a substrate of BCRP.

Vadadustat transport into OATP1B1- and OATP1B3-expressing cells was inhibited in the presence of the OATP1B1- and OATP1B3-specific inhibitor, rifampin (10 µM) to values that were nearly <50% of the uptake ratio in absence of an inhibitor for OATP1B1; however, uptake was not inhibited by >50% for OATP1B3. Under the experimental conditions of this assay, these results support that vadadustat is a substrate of OATP1B1, but not a substrate of OATP1B3.

Vadadustat transport into OAT1- and OAT3-expressing cells was shown to be inhibited in the presence of the OAT1- and OAT3-specific inhibitor, probenecid (100 µM) to values that were <50% of the uptake ratio in absence of inhibitor. These results support that vadadustat is a substrate of OAT1 and OAT3. The ratios of vadadustat into OCT2-expressing cells were <2 in the presence and absence of the prototypical inhibitor, quinidine (300 µM). These data support that vadadustat is not a substrate of OCT2.

In Vitro Evaluation of Vadadustat as an Inhibitor or a Substrate for the P-gp (XS-0236)

The objective of this study was to examine the inhibitory effect of vadadustat on the transport of P-gp, and to determine if vadadustat is a P-gp substrate. The bi-directional transcellular transport of vadadustat at concentrations of 0.3, 3, and 30 µg/mL was examined in human MDR1 expressing LLC-PK1 cells.

The efflux ratios were 1.0, 0.9, and 1.0 at vadadustat concentrations of 0.3, 3.0, and 30 µg/mL in the mock untransfected LLC-PK1 cells. The efflux ratios were 2.7, 2.9, and 1.6 at vadadustat concentrations of 0.3, 3.0, and 30 µg/mL in MDR1-expressing cells. The net efflux ratios were not reduced by >50% in the presence of the P-gp inhibitors GF120918 (10 µM) or verapamil (30 µM). As the net efflux ratio of vadadustat was not reduced in the presence of two P-gp inhibitors, these results indicate that vadadustat is not a substrate of P-gp.

Vadadustat was shown to inhibit digoxin transport up to 69.0% at a concentration of 30 µg/mL. Upon escalation of vadadustat concentrations, the inhibition by vadadustat of [^{3}H]-digoxin transport was 50.0%, 42.5%, and 69.2% at concentrations of 30, 100, and 400 µg/mL, respectively. However, at concentrations of 100 and 400 µg/mL, vadadustat solutions were not clear and gave precipitate after centrifugation. Therefore, the solubility limit of vadadustat was between 30 and 100 µg/mL in this assay. These results indicate that vadadustat is a P-gp inhibitor with an IC_{50} value between 30 and 100 µg/mL.

14.2. In Vivo Studies

A Double-Blind, Randomized, Placebo-Controlled, Oral, Single- Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Vadadustat in Healthy Male Volunteers (AKB-6548-CI-0001)

Study Design

The primary objective of this study was to assess the safety and tolerability of ascending dose levels of vadadustat after a single dose administered orally as vadadustat capsules to healthy male subjects. The secondary objectives of this study were to assess the PK, change in serum erythropoietin (EPO), change in a series of exploratory biomarkers, and to conduct a pilot evaluation of PK when a single oral dose is administered with a standard meal (exploratory food-effect). A total of 6 cohorts (n=8 per cohort) were enrolled. Subjects in each cohort were randomized to receive either vadadustat (n=6 per dose group) at 80, 160, 300, 600, 900, and 1200 mg as 40 or 300 mg capsules, or placebo orally under fasted conditions. For the food effect evaluation, a total of 5 subjects who were administered vadadustat (300 mg) under fasted conditions, returned to the unit and were administered a second dose of 300 mg vadadustat immediately after a standard meal.

Results

Summary statistics for vadadustat plasma PK parameters for vadadustat are shown in Table 179. The plasma C_{max}, AUC_{last}, and AUC_{inf} of vadadustat increased proportionally to dose over the entire dose range studied. A power analysis of dose proportionality showed the slope (95% confidence interval [CI]) of the regression model for C_{max}, AUC_{last}, and AUC_{inf} to be 0.96 (0.86, 1.07), 1.06 (0.97, 1.15), and 1.07 (0.98, 1.17), respectively. The median time to maximal concentrations (T_{max}) ranged between 3.0 and 4.0 hours for the dosages evaluated. The terminal half-life for vadadustat was short, ranging from 4.3 to 5.4 hours over the dose range evaluated. When vadadustat was administered as a single oral dose following a standard meal, the geometric least squares (LS) mean for C_{max} in the fasting cohorts was 15% more than in the fed cohort. The geometric LS means for AUC_{0-t} and AUC_{0-inf} were both 5% higher in the fed cohort than in the fasted cohorts (Table 180).

Table 179. Mean (CV%) [SD] Pharmacokinetic Parameters of Vadadustat After a Single Oral Dose of 80, 160, 300, 600, 900, or 1200 mg Under Fasted Conditions and 300 mg in the Fed Conditions to Healthy Subjects

	Vadadustat						
Parameter	80 mg Fasted N=6	160 mg Fasted N=6	300 mg Fasted N=6	600 mg Fasted N=6	900 mg Fasted N=6	1200 mg Fasted N=6	300 mg Fed N=5
T_{max}, h	3.02 (1.50, 4.00)	3.00 (1.50, 4.03)	3.00 (1.50, 4.05)	3.50 (3.00, 4.00)	3.50 (2.00, 4.00)	4.00 (3.00, 4.00)	3.00 (1.50, 6.00)
C_{max}, µg/mL	9.10 (25.9) [2.36]	15.5 (41.6) [6.45]	27.9 (27.5) [7.67]	65.3 (38.0) [24.8]	85.60 (28.8) [24.7]	114 (25.1) [28.7]	27.1 (26.7) [7.24]
AUC_{last}, µg·h/mL	59.5 (25.5) [15.2]	108 (22.3) [24.0]	184 (14.6) [26.8]	537 (32.9) [177]	674 (36.6) [247]	1010 (18.2) [184]	195 (17.9) [35.0]
AUC_{inf}, µg·h/mL	60.7 (25.9) [15.7]	110 (22.2) [24.5]	190 (14.8) [28.0]	561 (39.3) [220]	747 (37.7) [282]	1063 (19.0) [202]	201 (18.0) [36.1]
t½, h	4.32 (12.6) [0.546]	4.39 (13.4) [0.588]	4.66 (10.1) [0.469]	4.92 (16.4) [0.807]	5.40 (15.0) [0.813]	5.12 (19.2) [0.981]	4.55 (12.3) [0.560]
CL/F, L/h	1.39 (25.3) [0.353]	1.52 (26.4) [0.401]	1.61 (15.4) [0.247]	1.17 (27.7) [0.324]	1.37 (41.2) [0.565]	1.17 (20.7) [0.241]	1.54 (21.9) [0.337]
Vd/F, L	8.58 (23.2) [1.99]	9.56 (24.7) [2.36]	10.8 (15.3) [1.65]	8.03 (19.9) [1.60]	10.4 (37.5) [3.92]	8.41 (16.6) [1.40]	10.1 (24.4) [2.48]

Source: Tables 4.2.1 and 4.2.2. of study report AKB-6548-CI-0001
T_{max} is expressed as median (minimum, maximum)
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; CI/F, apparent clearance, C_{max}, maximum plasma concentration; CV: coefficient of variation; SD: standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration

Table 180. Statistical Analysis of Pharmacokinetic Parameters Following Administration of Vadadustat Capsules (300 mg) in Fed and Fasted Conditions to Healthy Subjects

	Geometric LS Mean[a]			
Parameter	Fasted	Fed	Ratio	90% CI[b]
AUC_{last}, µg·h/mL	183	192	105	84.5, 130
AUC_{inf}, µg·h/mL	188	198	105	84.6, 131
C_{max}, µg/mL	30.9	26.3	85.1	67.8, 107

Source: Post-text Table 4.4. of study report AKB-6548-CI-0001
Abbreviations: ANOVA, analysis of variance; AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variance; LS mean, least squares mean

The effects of single dose vadadustat on EPO, reticulocytes, and hemoglobin (Hb) were also assessed. The concentrations of EPO increased maximally by 76%, 165%, and 322% from baseline after administration of 600, 900, and 1200 mg, respectively. Peak EPO concentrations were observed at about 18 hours after dosing. No consistent dose related change was observed in reticulocyte counts and Hb at 4-, 8-, and 24-hours post-dose.

Conclusions

Vadadustat appeared to be safe and well tolerated at dose levels ranging from 80 mg to 1200 mg. The PK data demonstrated that pharmacokinetics of vadadustat across the studied dose ranges were dose proportional. The administration of vadadustat (300 mg) with food resulted in a 15% decrease in C_{max} and 5% increase in AUC, which was deemed not clinically relevant. The pharmacodynamic (PD) data demonstrated that at the two highest doses tested, 900 mg and 1200 mg, there was an approximately 3- to 4-fold increase in mean plasma EPO concentrations at 18 hours post-dose, compared with the approximately 2-fold diurnal increase in mean EPO concentration at the same time point in the placebo.

A Phase 1b Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Cohort Trial to Assess the Safety, Tolerability and Pharmacodynamic Response of Vadadustat in Healthy Male Volunteers (AKB-6548-CI-0002)

Study Design

The primary objectives of this study were to assess the safety and tolerability of oral vadadustat during repeat dosing for 10 days at 3 different dose levels and to assess the change from baseline in reticulocyte count. The secondary objectives of this study were to assess the PK, change from baseline in morning EPO, hemoglobin, and exploratory biomarkers. Subjects in each cohort were randomized to receive either 500 mg, 700 mg, and 900 mg of vadadustat capsule (n=8 planned) or placebo (n=3 planned) orally QD for 10 consecutive days.

Results

Summary statistics for vadadustat plasma PK parameters are shown in Table 181. Plasma C_{max}, AUC_{last}, and AUC_{inf} for vadadustat increased approximately proportional to dose over the dose range of 500 to 900 mg. CL/F values did not show consistent increases or decreases with increasing dose. The median time to maximal concentrations (T_{max}) was 2 to 3 hours. The terminal half-life for vadadustat ranged approximately from 4.14 to 4.43 hours over the dose range tested and was not dose or time dependent. A modest (1.3- to 1.4-fold) increase in C_{max} was observed with repeated dosing. There was minimal accumulation of vadadustat AUC with repeated dosing, as accumulation index (R_{ac}) values ranged from 0.99 to 1.18 for the 3 doses studied.

Table 181. Mean (CV%) [SD] Pharmacokinetic Parameters of Vadadustat Daily Oral Doses of 500, 700, or 900 mg Vadadustat for 10 Consecutive Days in Healthy Subjects

	Vadadustat 500 mg		Vadadustat 700 mg		Vadadustat 900 mg	
Parameter	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
N	8	8	8	8	8	7
T_{max}, h	2.00 (1.00, 4.00)	2.00 (1.00, 4.07)	2.00 (1.00, 4.00)	2.00 (2.00, 2.00)	3.00 (2.00, 8.00)	2.00 (1.00, 4.00)
C_{max}, µg/mL	47.2 (26.9) [12.7]	52.8 (35.4) [18.7]	69.1 (23.6) [16.3]	72.8 (15.0) [10.9]	59.6 (21.2) [12.6]	84.1 (22.2) [18.7]
AUC_{tau}, µg·h/mL	358 (11.4) [40.7]	353 (13.4) [47.1]	473 (16.2) [76.4]	487 (13.4) [65.1]	574 (23.8) [137]	658 (24.0) [158]
AUC_{inf}, µg·h/mL	366 (11.8) [43.4]	359 (13.3) [47.8]	483 (16.7) [80.9]	497 (14.2) [70.7]	556 (21.4) [119]	677 (24.9) [168]
t½, h	4.24 (12.9) [0.545]	4.12 (10.4) [0.430]	4.18 (11.1) [0.462]	4.19 (12.4) [0.518]	4.59 (13.2) [0.606]	4.45 (14.5) [0.645]
CL/F, L/h	1.38 (11.2) [0.154]	1.41 (12.4) [0.175]	1.48 (14.9) [0.221]	1.43 (13.9) [0.198]	1.70 (28.0) [0.476]	1.41 (27.9) [0.394]
Vd/F, L	8.41 (12.7) [1.07]	8.38 (15.2) [1.28]	8.85 (13.7) [1.22]	8.55 (8.55) [0.731]	11.5 (42.8) [4.9]	8.99 (28.6) [2.57]
Rac_{Cmax}	NA	1.28 (63.5) [0.812]	NA	1.13 (34.8) [0.393]	NA	1.45 (21.0) [0.304]
$Rac_{AUClast}$	NA	0.997 (18.8) [0.187]	NA	1.038 (10.4) [0.108]	NA	1.16 (10.1) [0.118]
Rac_{AUCinf}	NA	0.994 (18.4) [0.183]	NA	1.04 (10.3) [0.107]	NA	1.18 (9.74) [0.115]

Source: Tables 4.2a and 4.3. of study report AKB-6548-CI-0002
T_{max} is expressed as median (minimum, maximum)
AUC_{tau} represents a dosing interval of 24 hours
Abbreviations: AUC_{inf}, area under the curve to infinity; $AUC_{0\text{-}tau}$, area under the curve to the last quantifiable time point; Cl/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; Rac_{Cmax}, accumulation ratio based on maximum plasma concentration; $Rac_{AUClast}$, accumulation ratio base on area under the curve until the last quantifiable time point; Rac_{AUCinf}, accumulation ratio based on area under the curve to infinity; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration; Vd/F, volume of distribution;

The mean EPO levels showed an increase from baseline at all 3 dose levels on Day 1 and Day 7 of dosing, and the increase in EPO levels ranged from 48% to 110% on Day 1 and 31% to 106% on Day 7.

Conclusions

Vadadustat appeared to be safe and well tolerated at all doses tested. There was no consistent drug accumulation from Day 1 to Day 7 across the 3 cohorts. The mean per cohort T_{max} ranged between 2 and 4 hours in all 3 cohorts at Days 1 and 7. The mean per cohort elimination half-life

was consistently in the 4.0 to 4.5-hour range in all cohorts at Days 1 and 7. The greatest mean per cohort percent change from baseline in EPO levels was seen in the 2 highest dose cohorts.

An Open-Label, Single-Dose, Single-Centre, Phase 1 Study To Assess The Absorption, Metabolism, Excretion, And Pharmacokinetics Of [14-C]Akb-6548 In Healthy Male Volunteers (AKB-6548-CI-0008)

Study Design

Study AKB-6548-CI-0008 was an open-label, single-dose, single center study in healthy male subjects designed to evaluate the absorption, distribution, metabolism, excretion of orally administered [^{14}C]-vadadustat in capsule form. A total of 6 male subjects were administered a single, 650 mg dose of [14C]-vadadustat (100 μCi) on the morning of day 1. Subjects were confined to the clinical site for the duration of the study. Serial blood, urine and fecal samples were collected until subjects were discharged. Subjects were discharged once radioactivity recovery criteria were met (i.e., greater than 90% of the administered radioactivity dose had been recovered or <1% of the radioactivity dose was recovered in 2 consecutive 24-hour urine and fecal collections).

Results

A mean total of 85.9% of the [^{14}C] vadadustat dose was recovered in urine and feces by 72 hours after dosing with 58.9% of the dose recovered in urine and 26.9% of the dose recovered in feces. Vadadustat and vadadustat acyl glucuronide, represented <1% of the [^{14}C]vadadustat dose excreted in urine. Urinary excretion of vadadustat- O-glucuronide represented the majority of the dose. Vadadustat, vadadustat-O-glucuronide, and vadadustat-acyl-glucuronide represented 75.0%, 14.9%, and 0.047% of the total circulating radioactivity in plasma, respectively. Thus, about 90% of the total radioactivity in plasma is accounted for by vadadustat and vadadustat-O-glucuronide. Blood to plasma ratio data ranged from 0.504 to 0.546, which indicated that vadadustat and its metabolite do not penetrate into red blood cells (RBCs).

Conclusions

The mean cumulative urinary excretion of total radioactivity was 58.9% of the total dose, which was comprised predominately of the vadadustat-O-glucuronide. These data indicate that vadadustat is eliminated primarily via glucuronidation to form vadadustat-O-glucuronide, which is eliminated through renal excretion. Approximately 27% of the radioactivity in feces was excreted within 144 hr after dosing, which represented either unabsorbed vadadustat, or vadadustat and its metabolites excreted in the feces. The majority of the drug-related radioactivity in plasma was associated with vadadustat.

A Double-Blind, Multiple Ascending Dose Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Vadadustat in Healthy Japanese and Caucasian Subjects (AKB-6548-CI-0020)

Study Design

This was a randomized, double-blinded, placebo-controlled, single-site, dose escalation study to evaluate the safety, tolerability, PK and PD of multiple oral doses of vadadustat in healthy adult Japanese and healthy adult Caucasian subjects. Three sequential dose level cohorts were enrolled

with daily doses of 150 mg, 300 mg, and 600 mg of vadadustat for 10 days in Cohorts 1 through 3, respectively. Within each dose cohort, 8 Japanese subjects and 8 Caucasian subjects were randomly assigned in a 3:1 ratio to receive vadadustat or placebo (i.e., 6 active and 2 placebo Japanese subjects and 6 active and 2 placebo Caucasian subjects within each dose cohort).

Results

Summary statistics for vadadustat plasma PK parameters on Day 1 and Day 10 are shown in Table 182 and Table 183, respectively. Vadadustat was absorbed with a median T_{max} of 0.75 to 2.28 hours on Days 1 and 10. Vadadustat C_{max} and AUC_{tau} increased in a dose proportional manner for Japanese and White subjects across the dose range studied (150, 300, and 600 mg) following single and multiple dose administration. Compared to White subjects, Japanese subjects tended to show slightly higher exposure across all dose levels. A comparison between White and Japanese subject dose normalized PK parameters for vadadustat is provided in Table 184. There was minimal accumulation of vadadustat with multiple dose administration, as the mean AUC_{tau} R_{ac} values for White subjects and Japanese subjects were 1.10 and 1.18, respectively. The mean R_{ac} for C_{max} was slightly higher for Japanese (1.30) compared to White subjects (1.08), but still small. These results suggest that steady state is reached earlier than Day 10. Overall, PK parameters were similar between White and Japanese subjects.

Table 182. Mean (CV%) [SD] Pharmacokinetic Parameters of Vadadustat After a Single Oral Dose of 150 mg, 300 mg, and 600 mg Vadadustat on Day 1 in Japanese and White Healthy Subjects

Ethnicity	Dose (mg)	n	AUC_{tau} (h·µg/mL)	C_{max} (µg/mL)	T_{max} (h)	MR Vadadustat-O-Glucuronide	MR Vadadustat Acyl Glucuronide
White	150	6	94.8 (14.4) [13.6]	17.0 (5.27) [0.89]	2.00 (1.00, 4.03)	0.0779 (17.5) [0.0137]	NC
	300	6	199 (21.5) [42.7]	35.1 (24.3) [8.55]	1.95 (1.00, 4.02)	0.106 (24.1) [0.0254]	NC
	600	6	526 (22.5) [118]	83.1 (17.9) [14.9]	1.98 (0.97, 5.93)	0.0854 (21.8) [0.0186]	NC
Japanese	150	6	113 (33.9) [38.2]	17.9 (28.8) [5.16]	1.52 (1.00, 6.12)	0.0821 (28.6) [0.0234]	NC
	300	6	241 (12.4) [29.8]	39.6 (17.5) [6.94]	2.28 (0.97, 3.95)	0.0838 (17.6) [0.0148]	NC
	600	6	513 (19.8) [101]	69.0 (16.3) [11.2]	2.00 (1.98, 4.02)	0.0863 (10.0) [0.00865]	0.0006 (26.8) [0.0002]

Source: Tables 14.2.2.1 and 14.2.2.7 of study report AKB-6548-CI-0020
T_{max} is expressed as median (minimum, maximum)
Abbreviations: AUC_{tau}, area under the curve during a dosing interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; NC, not calculable; T_{max}, time to maximum plasma concentration

Table 183. Mean (CV%) [SD] Pharmacokinetic Parameters of Vadadustat After a Multiple Oral Daily Doses of 150, 300, and 600 mg Vadadustat on Day 10 in Japanese and White Healthy Subjects

Ethnicity	Dose (mg)	n	AUC_{tau} (h·µg/mL)	$C_{max,ss}$ (µg/mL)	T_{max} (h)	$t_{1/2,ss}$ (h)	CL/F, ss (L/h)	Vz/F, ss (L)	MR Vadadustat-O-Glucuronide	MR Vadadustat Acyl Glucuronide
White	150	6	102 (22.0) [22.3]	18.0 (9.29) [1.67]	2.0 (1.0, 4.03)	6.05 (14.0) [0.848]	1.54 (24.1) [0.372]	13.6 (29.1) [3.95]	0.0704 (14.4) [0.0102]	NC
	300	6	226 (21.0) [47.3]	40.4 (13.5) [5.46]	2.02 (1.95, 2.05)	5.55 (13.2) [0.735]	1.39 (23.7) [0.328]	11.0 (22.5) [2.48]	0.105 (22.4) [0.0235]	NC
	600	6	556 (27.7) [154]	79.0 (18.2) [14.4]	1.53 (0.970, 4.02)	5.64 (15.3) [0.863]	1.16 (31.0) [0.360]	9.23 (23.7) [2.18]	0.0845 (22.5) [0.0190]	0.000627 (15.3) (0.0000961)
Japanese	150	6	123 (24.8) [30.5]	24.2 (20.6) [4.99]	0.750 (0.450, 3.93)	5.96 (15.4) [0.914]	1.29 (27.4) [0.355]	10.8 (19.2) [2.09]	0.0803 (23.2) [0.0186]	NC
	300	6	289 (26.1) [75.3]	44.3 (24.5) [10.8]	1.99 (1.95, 4.00)	6.14 (12.4) [0.763]	1.10 (26.6) [0.293]	9.73 (26.0) [2.53]	0.0779 (20.4) [0.0159]	NC
	600	6	624 (32.9) [205]	84.8 (26.3) [22.3]	1.98 (0.98, 4.00)	6.07 (6.90) [0.419]	1.04 (28.3) [0.294]	9.16 (30.3) [2.78]	0.0829 (26.1) [0.0217]	0.000775 (no %CV or SD reported)

Source: Tables 14.2.2.4 and 14.2.28 of study report AKB-6548-CI-0020
Abbreviations: AUC_{tau}, area under the curve during a dosing interval; CL/F,ss, apparent clearance at steady state; C_{maxss}, maximum plasma concentration at steady state; $t_{1/2ss}$, half-life at steady state; T_{max}, time to maximum plasma concentration; V/F,ss, apparent volume of distribution during steady state

Table 184. Comparison of Dose-Normalized Pharmacokinetic Parameter Values for Vadadustat Between Healthy Japanese and White Subjects Following Administration of Single and Repeated Doses Once Daily for 10 Days

		Japanese Subjects			White Subjects			Japanese/White Subjects	
Regimen	Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
Single Dose Day 1	AUC_{tau} (µg·h/mL)	18	0.704	0.63, 0.787	18	0.796	0.705, 0.899	0.884	0.788, 0.993
	C_{max} (µg/mL)	18	0.118	0.104, 0.135	18	0.133	0.115, 0.154	0.892	0.776, 1.024
Multiple Dose Day 10	AUC_{tau} (µg·h/mL)	18	0.891	0.764, 1.04	18	0.916	0.774, 1.08	0.973	0.830, 1.142
	C_{max} (µg/mL)	18	0.156	0.14, 0.173	18	0.147	0.131, 0.166	1.055	0.943, 1.181

Source: Tables 14.2.4.1 and 14.2.4.2 of study report AKB-6548-CI-0020
ANCOVA, analysis of covariance; CI, confidence interval; GM, geometric mean; GMR, geometric mean ratio

EPO exposure (AUC) and peak EPO levels (C_{max}) in Japanese and Caucasian subjects were similar in the 150 mg and 300 mg dose groups. In the 600 mg dose groups, EPO exposure was higher in Japanese compared with Caucasian subjects by 40% overall and by 21-27% after exclusion of a single outlier, a low-weight female subject. Peak EPO levels were higher in Japanese compared with Caucasian subjects by 24% overall and by 20% after exclusion of the single outlier.

Conclusions

Vadadustat was quickly absorbed with a median T_{max} of 0.75 – 2.28 hours. C_{max} and $AUC_{0-\tau}$ appeared to increase in a dose proportional manner for Japanese and Caucasian subjects across the dose range studied (150, 300, and 600 mg) following single and multiple dose administration. Following multiple dose administration, Japanese subjects showed slightly higher exposure across all dose levels compared with Caucasian subjects; however, these differences are not considered to be clinically significant. EPO exposure was higher in Japanese compared with Caucasian subjects by 40% overall and by 21-27% after exclusion of a single outlier in the 600 mg dose group.

A Randomized, Open-Label, Single-Dose, Three-Period Six-Sequence Crossover Study In Healthy Adults To Assess Bioequivalence Between Test And Reference Vadadustat 450 mg And 150 mg Tablets And To Determine Food Effect On The 450 mg Vadadustat Tablet (AKB-6548-CI-0028)

Study Design

The primary objective of this study was to assess the relative bioavailability of formulation F 1 × 450 mg (test) and formulation E2 3 × 150 mg (reference) and to evaluate the food effect for formulation F (450 mg). A total of 54 eligible subjects were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA). Each sequence was comprised of 3 treatments listed below:

- Treatment A: Vadadustat Reference Formulation E2 3 × 150 mg tablets (phase 3 formulation) with PVA-based film-coating under fasting conditions (overnight fast of at least 10 hours)

- Treatment B: Vadadustat Test Formulation F 1 × 450 mg tablet (to-be-marketed formulation) with PVA-based film-coating under fasting conditions (overnight fast of at least 10 hours)
- Treatment C: Vadadustat Test Formulation F 1 × 450 mg tablet with PVA-based film-coating under fed conditions (overnight fast of at least 10 hours, followed by a standardized FDA high-fat breakfast 30 minutes before dosing)

Results

The statistical analysis comparing the exposure to vadadustat under fasting conditions following administration of the Test formulation F (1 × 450 mg) and Reference formulation E2 (3 × 150 mg) tablet formulation is in Table 185. Formulation F was bioequivalent to formulation E2 under fasting conditions as the GMRs for the primary PK parameters AUC_{all}, AUC_{inf}, AUC_{last}, and C_{max} were 110.12%, 110.07%, 110.12%, and 111.06%, respectively, and the 90% CIs were fully contained within the 80.00% to 125.00% bioequivalence limits.

Table 185. Summary Statistics of Ratio [Test (Treatment B)/Reference (Treatment A)] of Plasma Vadadustat Primary PK Parameters (ANOVA) (BE Analysis Population)

Comparison	Pharmacokinetic Parameter (Unit)	N	Least Squares Means		% Ratio (Test/Reference)	90% Confidence Interval of (Test/Reference) Ratio	Intra CV (%)
			Treatment B (Test)	Treatment A (Reference)			
Treatment B (Test) vs. Treatment A (Reference)	AUC_{all} (h*µg/mL)	52	359	326	110.12	(104.50, 116.04)	16.0
	AUC_{inf} (h*µg/mL)	52	361	328	110.07	(104.44, 116.01)	16.1
	AUC_{last} (h*µg/mL)	52	359	326	110.12	(104.47, 116.07)	16.1
	C_{max} (µg/mL)	52	61.5	55.4	111.06	(103.56, 119.11)	21.5

Source: Table 14.2.8.1 of CSR AKB-6548-CI-0028
Abbreviations: CV, coefficient of variation; PK, pharmacokinetics

A comparison of the exposure to vadadustat following administration of the test formulation F (450 mg) tablet under fed and fasting conditions is provided in Table 186. The point estimates for the primary PK parameters AUC_{inf}, AUC_{last}, and C_{max} were 94.3%, 94.3%, and 73.1%, respectively. The median T_{max} value significantly increased in the presence of a high fat meal from 2 hours to 3.52 hours.

Table 186. Summary Statistics of Ratio [Fed (Treatment C)/Fasted (Treatment B)] of Plasma Vadadustat Primary PK Parameters (ANOVA) (Food Effect Analysis Population)

Comparison	Pharmacokinetic Parameter (Unit)	N	Least Squares Means		% Ratio (Test/Reference)	90% Confidence Interval of (Test/Reference) Ratio	Intra CV (%)
			Treatment C (Fed)	Treatment B (Fasted)			
Treatment C (Fed) vs. Treatment B (Fasted)	AUC_{inf} (h*µg/mL)	52	339	359	94.30	(90.30, 98.49)	13.3
	AUC_{last} (h*µg/mL)	52	337	357	94.31	(90.29, 98.50)	13.3
	C_{max} (µg/mL)	52	44.9	61.5	73.07	(67.92, 78.61)	22.5

Source: Table 14.2.8.2 of CSR AKB-6548-CI-0028
Abbreviations: CV, coefficient of variation; PK, pharmacokinetics

Conclusions:

The test tablet formulation F was found to be bioequivalent to the reference tablet formulation E2 based on the 90% CI for the geometric LS mean ratios for AUC and C_{max} values, that were within 80% to 125%. The food effect evaluation of Formulation F showed a small decrease in C_{max} with a geometric LS mean ratio (90% CI) of 73.1 (67.9, 78.6). The 90% CIs for the geometric LS mean ratios for the AUC values were within the 80% to 125% limit, indicating that administration of vadadustat with food had minimal effect on its PK profile and that vadadustat can be administered with or without food.

Phase 1, Open-Label, Parallel-Group, Pharmacokinetic Single Dose Study of Oral Vadadustat in Subjects with Normal and Impaired Hepatic Function (AKB-6548-CI-0024)

Study Design

The primary objective of this study was to evaluate the PK profile of vadadustat and the secondary objective was to assess the safety and tolerability following a single oral 450 mg dose in subjects with hepatic impairment relative to control subjects with normal hepatic function. The study population consisted of male and female subjects who were ≥18 to ≤70 years, with moderate hepatic impairment (Group 1; 8 subjects) and normal hepatic function (Group 2; 8 subjects). Subjects with normal hepatic function were to be matched by race, age (±5 years), weight (±15%), body mass index (BMI; ±15%), and sex to subjects with moderate hepatic impairment (Group 1). The study employed an adaptive study design wherein 8 subjects with mild hepatic impairment (Group 3) would be enrolled, if deemed necessary, after reviewing the safety and PK data from Groups 1 and 2. As moderate hepatic impairment did not appear to significantly affect the systemic exposure to vadadustat, further evaluation of subjects with mild hepatic impairment was not warranted.

A summary of the groups is below:

- Group 1: 8 subjects with moderate hepatic impairment (Child-Pugh Class B)
- Group 2: 8 subjects with normal hepatic function
- Group 3: 8 subjects with mild hepatic impairment (Child-Pugh Class A)

Results

Following treatment with vadadustat, point estimates of the geometric LSM ratios of the primary parameters AUC and C_{max} unbound and plasma total are presented in Table 187. The point estimates of the test/reference (i.e., moderate hepatic impairment/normal hepatic function) mean ratios of the primary parameters AUC_{last}, AUC_{inf}, and C_{max} for vadadustat were 105%, 106%, and 102%, respectively. The point estimates of the test/reference mean ratios of the primary parameters AUC_{last}, AUC_{inf}, and C_{max} for vadadustat unbound were 124%, 124%, and 120%, respectively. These data indicated that moderate hepatic impairment did not appear to significantly affect systemic exposure to vadadustat.

Table 187. Plasma Vadadustat C_{max} and AUC Values Following 450 mg Vadadustat Dose in Subjects With Moderate Hepatic Function Compared to Subjects With Normal Hepatic Function

	Geometric LS Mean			
Parameter	Moderate	Normal	Ratio (Moderate/Normal)	90% CI
C_{max}, µg/mL	51.6	50.3	1.02	(0.79, 1.32)
AUC_{last}, µg·h/mL	410	389	1.05	(0.82, 1.35)
AUC_{inf}, µg·h/mL	414	391	1.06	(0.82, 1.36)
$C_{max\ unbound}$, µg/mL	0.433	0.360	1.20	(0.90, 1.61)
$AUC_{last\ unbound}$, µg·h/mL	3.44	2.78	1.24	(0.89, 1.72)
$AUC_{inf\ unbound}$, µg·h/mL	3.47	2.79	1.24	(0.89, 1.73)

Source: Tables 14.2.3.1 and 14.2.3.2 of CSR AKB-6548-CI-0024
Abbreviations: AUC_{inf}, area under the curve to infinity; $AUC_{inf\ unbound}$, area under the curve to infinity of unbound drug; AUC_{last}, area under the curve to the last quantifiable time point; $AUC_{last\ unbound}$, area under the curve to the last quantifiable time point of unbound drug; CI, confidence interval; C_{max}, maximum plasma concentration; $C_{max\ unbound}$, maximum plasma concentration of unbound drug; LS mean, least squares mean

Conclusions

Plasma total and unbound vadadustat C_{max} and AUC values were comparable for subjects with normal hepatic function and subjects with moderate hepatic impairment. As moderate hepatic impairment did not appear to significantly affect the systemic exposure to vadadustat, further evaluation of subjects with mild hepatic impairment was not warranted. The half-life and CL/F values for vadadustat were comparable between subjects with normal hepatic function and subjects with moderate hepatic impairment.

A Phase 1, Two-Part, Open-Label Study In Healthy Adult Volunteers To Assess A Single Dose Of Vadadustat As A Victim In Drug-Drug Interactions With Cyclosporine, Probenecid (AKB-6548-CI-0029)

Study Design

This was a Phase 1, open-label study to evaluate the potential for interaction of cyclosporine (BCRP, OATP1B1 inhibitor) and probenecid (OAT1/OAT3 inhibitor) with vadadustat in healthy male and female subjects. The primary objectives of this study were to assess the effect of a single oral dose of cyclosporine 500 mg on the plasma PK profile of a single oral dose of vadadustat 300 mg and to assess the effect of repeated oral doses of probenecid 500 mg twice daily every 12 hours (Q12h) on the plasma PK profile of a single dose of oral vadadustat 300 mg.

Results

Systemic exposure to vadadustat was not altered when co-administered with cyclosporine. Statistical analysis of vadadustat C_{max} and AUC values after administration of a single dose of vadadustat 300 mg given alone and with a single oral dose of cyclosporine 500 mg are shown in Table 188.

Table 188. Statistical Analysis for Vadadustat PK Parameters for the Comparison of 300 mg Vadadustat Alone and 300 mg Vadadustat in Combination With 500 mg Oral Cyclosporine in Healthy Subjects

	Geometric LS Mean		Ratio (V+C)/V[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment V+C	Treatment V	(%)	Lower (%)	Upper (%)
AUC_{last}, h·µg/mL	292	249	117	109	125
AUC_{inf}, h·µg/mL	293	251	117	109	125
C_{max}, µg/mL	37.1	45.4	81.8	76.0	87.9

Source: Table 14.2.1-4 of CSR AKB-6548-CI-0029
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Following multiple doses of probenecid (500 mg Q12 hours) when vadadustat was co-administered (300 mg QD), there was an almost 2-fold increase in total exposures of vadadustat while C_{max} did not change. Statistical analysis of vadadustat C_{max} and AUC values after administration of a single dose of vadadustat 300 mg alone and after multiple doses of probenecid (500 mg Q12h) are shown in Table 189.

Table 189. Statistical Analysis for Vadadustat PK Parameters for the Comparison of 300 mg Vadadustat Alone and 300 mg Vadadustat in Combination With 500 mg Q12 Hours Probenecid in Healthy Subjects

	Geometric LS Mean		Ratio (V+P)/V[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment V+P	Treatment V	(%)	Lower (%)	Upper (%)
AUC_{last}, h·µg/mL	417	233	179	170	188
AUC_{inf}, h·µg/mL	427	234	182	171	194
C_{max}, µg/mL	48.8	47.5	103	95.0	111

Source: Table 14.2.1-12 of CSR AKB-6548-CI-0029
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

The results for vadadustat-O-glucuronide were similar to vadadustat with a just over 2-fold increase in total exposure of vadadustat-O-glucuronide when vadadustat (300 mg) was administered concomitantly with probenecid (500 mg Q12h) compared to when vadadustat (300 mg) was given alone, whereas C_{max} was unchanged. Statistical analysis of vadadustat-O-glucuronide C_{max} and AUC values after administration of a single dose of vadadustat 300 mg alone and with probenecid (500 mg Q12 hours) are shown in Table 190.

Table 190. Statistical Analysis for Vadadustat-O-Glucuronide PK Parameters for the Comparison of 300 mg Vadadustat Alone and in Combination With 500 mg Q12 Hours Probenecid in Healthy Subjects

	Geometric LS Mean		Ratio (V+P)/V[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment V+P	Treatment V	(%)	Lower (%)	Upper (%)
AUC_{last}, h·µg/mL	83.8	37.4	224	208	242
AUC_{inf}, h·µg/mL	86.6	38.2	226	209	245
C_{max}, µg/mL	6.17	5.59	110	105	116

Source: Table 14.2.1-19 of CSR AKB-6548-CI-0029
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Conclusions

When vadadustat was administered in combination with cyclosporine, an OATP1B1 and BCRP inhibitor, there were no clinically relevant changes in the C_{max} and AUC values of vadadustat. When vadadustat was administered in combination with probenecid (a UGT and OAT3 inhibitor), the AUC values for both vadadustat and vadadustat-O-glucuronide increased about 2-fold whereas, the C_{max} values were relatively unchanged. Urinary excretion decreased for both vadadustat and vadadustat-O-glucuronide. As the AUC values for both vadadustat and vadadustat-O-glucuronide were increased similarly (i.e., parent to metabolite ratio unchanged), this suggests that the increase in vadadustat AUC was primarily due to OAT1/3 inhibition and contribution of UGT inhibition is minimal.

A Phase 1, Fixed Sequence, Open-Label Study in Healthy Adult Subjects to Evaluate the Effect of Multiple Doses of Rabeprazole on the Pharmacokinetics of a Single Dose of Vadadustat (AKB-6548-CI-0033)

Study Design

This was a Phase 1, fixed-sequence, open-label study in healthy subjects to evaluate the effect of multiple oral doses of rabeprazole (20 mg Q12 hours) on the PK of a single dose of vadadustat 300 mg in 19 healthy male and female subjects. On the morning of Day 1 subjects received a single oral dose of vadadustat 300 mg followed by a 1-day washout period. On Days 2, 3, 4, and 5, subjects received oral rabeprazole 20 mg Q12 hours. On Day 6 subjects received a single oral dose of rabeprazole 20 mg followed by a single oral dose of vadadustat 300 mg.

Results

Systemic exposure to vadadustat and vadadustat-O-glucuronide is unchanged when vadadustat is administered with rabeprazole compared to when vadadustat is administered alone. Statistical analysis of vadadustat C_{max} and AUC values after administration of vadadustat (300 mg) alone and with rabeprazole (20 mg Q12h) are shown in Table 191. The C_{max}, AUC_{last}, and AUC_{inf} geometric LS mean ratios (90% CI) for vadadustat-O-glucuronide were 108 (103, 114), 106 (102, 111), and 106 (102, 111), respectively.

Table 191. Statistical Analysis for Vadadustat PK Parameters for the Comparison of 300 mg Single Dose Vadadustat Alone and in Combination With 20 mg Q12h Rabeprazole in Healthy Subjects

	Geometric LS Mean		Ratio (R+V)/R[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment R+V	Treatment R	(%)	Lower (%)	Upper (%)
AUC_{last}, h·µg/mL	243	252	104	100	108
AUC_{inf}, h·µg/mL	245	254	104	100	107
C_{max}, µg/mL	45.8	47.1	103	98.8	107

Source: Table 14.2.1-4 of CSR AKB-6548-CI-0033
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Conclusions

When vadadustat was administered in combination with rabeprazole, a proton-pump inhibitor, there were no clinically relevant changes in the C_{max} and AUC values of vadadustat or vadadustat-O-glucuronide. Since co-administration of vadadustat after treatment with

rabeprazole did not affect exposure of vadadustat, it is likely that other gastric acid reducing agents (proton pump inhibitors and H2 antagonists) will not affect the absorption of vadadustat.

An Open-Label, Randomized, Single-Dose Study to Evaluate the Effects of 325 mg Ferrous Sulfate Tablet (65 mg Iron) on the Pharmacokinetics of 450 mg Dose of Vadadustat in Healthy Male Volunteers (AKB-6548-CI-0012)

Study Design

The primary objective of this study was to assess the single-dose bioavailability of vadadustat (450 mg) co-administered with 325 mg ferrous sulfate (65 mg elemental iron) relative to vadadustat (450 mg) alone in healthy volunteers. Each subject was randomized to 1 of 2 treatment sequences: (1) vadadustat alone followed by vadadustat + iron or (2) vadadustat + iron followed by vadadustat alone. There was at least a 3-day washout period between the 2 treatments. All subjects were fasted (other than water) overnight for at least 10 hours prior to dosing. Fasting continued for 4 hours after dosing.

Results

Statistical analyses of vadadustat PK exposure parameters after administration of 450 mg vadadustat with and without ferrous sulfate are shown in Table 192. The C_{max} and AUC values for vadadustat were reduced by approximately 50% when dosed concurrently with ferrous sulfate (equivalent to 65 mg elemental iron).

Table 192. Statistical Analysis for Vadadustat PK Parameters for the Comparison of Vadadustat 450 mg in Combination With Ferrous Sulfate 325 mg (65 mg Elemental Iron) to Vadadustat Alone in Healthy Subjects

	Least Squares Geometric Means		Geometric	
Parameter	Vadadustat Alone	Vadadustat + Iron	Mean Ratio (%)	90% CI
AUC_{last}, µg·h/mL	253	117	46.0	36.7, 57.6
AUC_{inf}, µg·h/mL	263	122	46.3	37.1, 57.8
C_{max}, µg/mL	45.3	22.3	49.3	37.8, 64.4

Source: Table 14.2.7 through Table 14.2.12 of CSR AKB-6548-CI-0012
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Conclusions

The bioavailability of vadadustat, as measured by vadadustat AUC and C_{max}, was significantly reduced when a single 450 mg oral dose of vadadustat was administered with a single 325-mg oral dose of ferrous sulfate tablets (65 mg elemental iron). Vadadustat mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were reduced by 54% and mean C_{max} was reduced by 51% following concomitant administration of vadadustat with ferrous sulfate (iron) versus vadadustat alone.

A Clinical Pharmacological Study to Evaluate the Effects of Oral Irons and Iron-Containing Phosphate Binders on the Pharmacokinetics of MT-6548 in Healthy Male Volunteers (MT-6548-J05)

This is a single-dose, open-label, randomized crossover study to evaluate the impact of oral iron and iron-containing phosphate binders on the PK and safety of vadadustat 150 mg in healthy Japanese adult males.

In cohort 1, the effect of sodium ferrous citrate (200 mg of iron in total) or ferric citrate hydrate (496 mg of iron in a 2000 mg dose) on the PK of vadadustat was evaluated in the fed conditions. Cohort 1 was a 3-period, 3-sequence crossover design. Subjects received vadadustat (i) alone, (ii) in combination with sodium ferrous citrate, and (iii) in combination with ferric citrate hydrate, according to the sequences specified for the individual treatment groups. These treatments were separated by 3-day washout periods.

In cohort 2, the effect of sucroferric oxyhydroxide (1000 mg of iron in total) on the PK of vadadustat was evaluated in the preprandial condition. Cohort 2 was a 2-period, 2-sequence crossover design. Subjects received vadadustat (i) alone and (ii) in combination with sucroferric oxyhydroxide, according to the sequences specified for the individual treatment groups. These treatments were separated by a 3-day washout period.

In cohort 3, the effect of dried ferrous sulfate (210 mg of iron in total, extended-release tablet) on the PK of vadadustat was evaluated in the fasted condition. Cohort 3 was a 2-period, 2-sequence crossover design. Subjects received vadadustat (i) alone and (ii) in combination with dried ferrous sulfate, according to the sequences specified for the individual treatment groups. These treatments were separated by a 3-day washout period.

Results

Statistical analysis of vadadustat PK exposure parameters after administration of 150 mg vadadustat with and without each iron are shown in Table 193 through Table 196.

Table 193. Statistical Analysis for Vadadustat PK Parameters for Vadadustat Administered Alone and in Combination With Sodium Ferrous Citrate in Cohort 1 in Healthy Japanese Subjects

	Geometric LS Mean		Geometric LS Mean Ratio for Vadadustat + Sodium Ferrous Citrate to Vadadustat Alone	
Vadadustat PK Parameter	Vadadustat Alone (N=21)	Vadadustat + Sodium Ferrous Citrate (N=20)	Point Estimate (%)	90% CI (%)
$AUC_{0\text{-last}}$, µg·h/mL	99.2	44.4	44.8	38.0, 52.7
$AUC_{0\text{-inf}}$, µg·h/mL	104	46.6	44.8	38.1, 52.6
C_{max}, µg/mL	14.3	6.96	48.7	40.6, 58.4

Source: Table 11-5 of CSR MT-6548-J05
Abbreviations: $AUC_{0\text{-inf}}$, area under the curve from zero to infinity; $AUC_{0\text{-last}}$, area under the curve from zero to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Table 194. Statistical Analysis for Vadadustat PK Parameters for Vadadustat Administered Alone and in Combination With Ferric Citrate Hydrate in Cohort One in Healthy Japanese Subjects

	Geometric LS Mean		Geometric LS Mean Ratio for Vadadustat + Ferric Citrate Hydrate to Vadadustat Alone	
Vadadustat PK Parameter	Vadadustat Alone (N=21)	Vadadustat + Ferric Citrate Hydrate (N=20)	Point Estimate (%)	90% CI (%)
$AUC_{0\text{-last}}$, µg·h/mL	99.2	31.1	31.4	26.6, 37.0
$AUC_{0\text{-inf}}$, µg·h/mL	104	32.4	31.1	26.5, 36.5
C_{max}, µg/mL	14.3	5.18	36.3	30.2, 43.5

Source: Table 11-7 of CSR MT-6548-J05
Abbreviations: $AUC_{0\text{-inf}}$, area under the curve from zero to infinity; $AUC_{0\text{-last}}$, area under the curve from zero to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Table 195. Statistical Analysis for Vadadustat PK Parameters for Vadadustat Administered Alone and in Combination With Sucroferric Oxyhydroxide in Cohort 2 in Healthy Japanese Subjects

	Geometric LS Mean		Geometric LS Mean Ratio for MT-6548 + Sucroferric Oxyhydroxide to MT-6548 Alone	
Vadadustat PK Parameter	Vadadustat Alone (N=20)	Vadadustat + Sucroferric Oxyhydroxide (N=20)	Point Estimate (%)	90% CI (%)
$AUC_{0\text{-last}}$, µg·h/mL	95.7	44.5	46.6	41.2–52.6
$AUC_{0\text{-inf}}$, µg·h/mL	99.5	45.7	46.0	40.8–51.9
C_{max}, µg/mL	15.2	8.81	58.0	49.9–67.3

Source: Table 11-9 of CSR MT-6548-J05
Abbreviations: $AUC_{0\text{-inf}}$, area under the curve from zero to infinity; $AUC_{0\text{-last}}$, area under the curve from zero to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Table 196. Statistical Analysis for Vadadustat PK Parameters for Vadadustat Administered Alone and in Combination With Dried Ferrous Sulfate in Cohort 3 in Healthy Japanese Subjects

	Geometric LS Mean		Geometric LS Mean Ratio for MT-6548 + Dried Ferrous Sulfate to MT-6548 Alone	
Vadadustat PK Parameter	Vadadustat Alone (N=20)	Vadadustat + Dried Ferrous Sulfate (N=20)	Point Estimate (%)	90% CI (%)
$AUC_{0\text{-last}}$, µg·h/mL	124	12.0	9.72	7.46–12.7
$AUC_{0\text{-inf}}$, µg·h/mL	128	13.2	10.3	8.03–13.3
C_{max}, µg/mL	26.5	2.14	8.09	6.20–10.6

Source: Table 11-11 of CSR MT-6548-J05
Abbreviations: $AUC_{0\text{-inf}}$, area under the curve from zero to infinity; $AUC_{0\text{-last}}$, area under the curve from zero to the last quantifiable time point; C_{max}, maximum plasma concentration; LS mean, least squares mean; PK, pharmacokinetics

Conclusions

The coadministration of each oral iron-based drug reduced the bioavailability of vadadustat, with the greatest reduction occurring when co-administered with dried ferrous sulfate as an extended-release.

A Phase 1, 3-part, Open-label Study in Healthy Adult Subjects to Assess the Effect of Phosphate Binders on the PK of a Single Dose of Vadadustat (AKB-6548-CI-0037)

Study Design

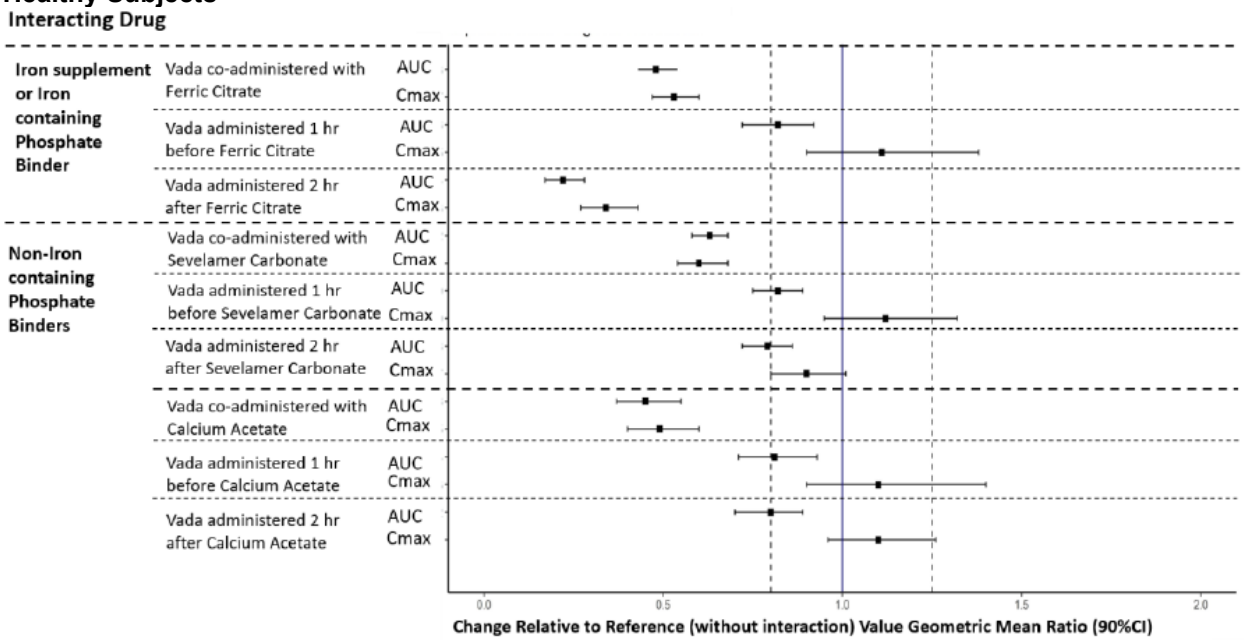
This study is conducted to evaluate the interaction of vadadustat with sevelamer carbonate, calcium acetate, and ferric citrate (Auryxia®) in healthy male and female subjects. Part 1 assessed the effect of a single oral dose of sevelamer carbonate (1600 mg) on the PK of a single oral dose of vadadustat (300 mg). Part 2 assessed the effect of a single oral dose of calcium acetate (1334 mg) on the PK of a single oral dose of vadadustat (300 mg), and Part 3 assessed the effect of a single oral dose of ferric citrate (2 g) on the PK of a single oral dose of vadadustat (300 mg). On day 1, vadadustat was administered alone immediately after breakfast. On day 3, vadadustat was administered under fasting condition followed by the phosphate binder and breakfast 1 hour later. On day 7, the phosphate binder was administered immediately after breakfast and vadadustat was administered 2 hours later.

Results

The mean AUC_{last}, AUC_{inf}, and C_{max} values were lower when vadadustat and sevelamer carbonate were co-administered compared to when vadadustat was administered alone. When vadadustat administration was 1 hour prior to or 2 hours after sevelamer carbonate administration, exposures (AUC) were lower than vadadustat was administered alone, but the reductions were small and not clinically significant. Similar results were obtained for calcium acetate. Administration of vadadustat 1 hour prior to ferric citrate reduced the interaction; although vadadustat exposure was still reduced, the change was small and not clinically relevant. However, for ferric citrate, administration of vadadustat 2 hours after ferric citrate reduced vadadustat exposure to a greater extent than observed with co-administration.

Statistical analysis of vadadustat PK exposure parameters after administration of a single oral dose (300 mg) vadadustat with a single oral dose of sevelamer carbonate, calcium acetate, and ferric citrate are shown in Table 197 through Table 199, respectively, and summarized in Figure 38.

Figure 38. Impact of Co-Administered Oral Iron or Phosphate Binders on Vadadustat Exposure in Healthy Subjects



Source: Applicant's analysis from Tables 11.4.2.3-2, 11.4.2.3-6 and 11.4.2.3-10 of CSR AKB-6548-CI-0037

Table 197. Statistical Analysis for Vadadustat PK Parameters: Comparison of Vadadustat-Part 1 (300 mg Single Dose) Alone and in Combination With Sevelamer Carbonate (1600 mg Single Dose) in Healthy Subjects

Comparison (T vs R)	Parameter (unit)	Geometric LS Mean		90% Geometric CI[b]			Intra-subject CV (%)[c]
		Treatment T (N=18)	Treatment R (N=18)	Ratio(T/R)[a] (%)	Lower (%)	Upper (%)	
V+S Day 3 vs V Day 1	AUC_{last}, h·µg/mL	111.21	177.27	62.73	57.79	68.10	14.22
	AUC_{inf}, h·µg/mL	113.98	181.35	62.85	57.96	68.16	14.05
	C_{max}, µg/mL	15.72	26.00	60.45	53.89	67.81	20.01
V+S Day 5 vs V Day 1	AUC_{last}, h·µg/mL	144.89	177.27	81.73	74.87	89.22	15.20
	AUC_{inf}, h·µg/mL	148.26	181.35	81.75	74.98	89.14	15.00
	C_{max}, µg/mL	29.18	26.00	112.23	95.12	132.42	29.12
V+S Day 7 vs V Day 1	AUC_{last}, h·µg/mL	139.88	177.27	78.91	71.84	86.68	16.30
	AUC_{inf}, h·µg/mL	142.63	181.35	78.65	71.84	86.10	15.71
	C_{max}, µg/mL	23.52	26.00	90.45	80.59	101.52	20.11

Source: Table 11.4.2.3-2 of CSR AKB-6548-CI-0037
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; CV, coefficient of variation; LS mean, least squares mean; PK, pharmacokinetics

Table 198. Statistical Analysis for Vadadustat PK Parameters: Comparison of Vadadustat-Part 2 (300 mg Single Dose) Alone and in Combination With Calcium Acetate (1334 mg Single Dose) in Healthy Subjects

Comparison (T vs R)	Parameter (unit)	Geometric LS Mean		90% Geometric CI[b]			Intra-subject CV (%)[c]
		Treatment T (N=18)	Treatment R (N=18)	Ratio(T/R)[a] (%)	Lower (%)	Upper (%)	
V+C Day 3 vs V Day 1	AUC_{last}, h·µg/mL	70.37	157.76	44.61	36.25	54.90	36.97
	AUC_{inf}, h·µg/mL	72.44	160.97	45.00	36.67	55.24	36.47
	C_{max}, µg/mL	10.39	21.24	48.92	39.70	60.29	37.23
V+C Day 5 vs V Day 1	AUC_{last}, h·µg/mL	128.57	157.76	81.49	70.95	93.61	23.45
	AUC_{inf}, h·µg/mL	131.06	160.97	81.42	70.97	93.40	23.23
	C_{max}, µg/mL	23.55	21.24	110.85	89.97	136.58	35.94
V+C Day 7 vs V Day 1	AUC_{last}, h·µg/mL	124.29	157.76	78.78	69.54	89.26	21.78
	AUC_{inf}, h·µg/mL	127.35	160.97	79.11	69.94	89.49	21.51
	C_{max}, µg/mL	23.39	21.24	110.09	95.76	126.56	24.40

Source: Table 11.4.2.3-6 of CSR AKB-6548-CI-0037
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; CV, coefficient of variation; LS mean, least squares mean; PK, pharmacokinetics

Table 199. Statistical Analysis for Vadadustat PK Parameters: Comparison of Vadadustat-Part 3 (300 mg Single Dose) Alone and in Combination With Ferric Citrate (2 G Single Dose) in Healthy Subjects

Comparison (T versus R)	Parameter (unit)	Geometric LSM		Ratio (T/R)[a] (%)	90% Geometric CI[b]		Intrasubject CV (%)[c]
		Treatment T (N=18)	Treatment R (N=18)		Lower (%)	Upper (%)	
V+F Day 3 vs V Day 1	AUC_{last}, h·µg/mL	78.74	164.83	47.77	42.55	53.64	20.17
	AUC_{inf}, h·µg/mL	80.90	168.78	47.93	42.75	53.75	19.94
	C_{max}, µg/mL	11.45	21.58	53.06	46.93	59.98	21.40
V+F Day 5 vs V Day 1	AUC_{last}, h·µg/mL	134.86	164.83	81.82	72.02	92.94	21.53
	AUC_{inf}, h·µg/mL	138.00	168.78	81.76	72.23	92.55	20.92
	C_{max}, µg/mL	24.06	21.58	111.49	90.27	137.71	36.39
V+F Day 7 vs V Day 1	AUC_{last}, h·µg/mL	35.94	164.83	21.81	17.13	27.76	43.49
	AUC_{inf}, h·µg/mL	37.47	168.78	22.20	17.54	28.10	42.39
	C_{max}, µg/mL	7.39	21.58	34.24	27.09	43.28	42.09

Source: Table 11.4.2.3-10 of CSR AKB-6548-CI-0037
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; CV, coefficient of variation; LS mean, least squares mean; PK, pharmacokinetics

Conclusions

Systemic exposure to vadadustat was decreased when vadadustat is given concomitantly with sevelamer carbonate, calcium acetate, and ferric citrate. When vadadustat administration was 1 hour prior to or 2 hours after sevelamer carbonate or calcium acetate administration, the decrease in vadadustat exposure was less than that when they were co-administered with vadadustat. This suggests that the DDI can be reduced when vadadustat and sevelamer carbonate or calcium acetate doses are staggered. When vadadustat administration was 1 hour prior to ferric citrate administration, the decrease in systemic exposure to vadadustat was less than that when the drugs were administered concomitantly. However, when vadadustat was administered 2 hours after ferric citrate, systemic exposure to vadadustat was reduced to a greater extent than when the two drugs are administered concomitantly. This suggests that the DDI can be reduced only when vadadustat was administered 1 hour prior to ferric citrate.

An Open-Label Study in Healthy Subjects to Assess the Effect of Once-Daily Multiple Dosing of Vadadustat on the Pharmacokinetics of the CYP2C9 Substrate Celecoxib (AKB-6548-CI-0019)

Study Design

The primary objective of this study is to assess the single dose plasma PK of celecoxib 200 mg in healthy subjects with CYP2C9 extensive metabolizer (EM) genotype when administered alone (Day 1) and following multiple daily doses of 600 mg of vadadustat (Day 8). A single dose of celecoxib (200 mg) was administered on Day 1 followed by once-daily administration of vadadustat (600 mg, 4 x 150 mg capsule) on Days 3 to 9. A single dose of celecoxib (200 mg) was administered with the vadadustat dose on the morning of Day 8.

Results

Statistical analysis of celecoxib PK exposure parameters after administration celecoxib (200 mg) with vadadustat (600 mg) are shown in Table 200. Based on the ratio of geometric means for celecoxib + vadadustat/celecoxib alone, co-administration of vadadustat (600 mg daily) and celecoxib (200 mg) resulted in a 12% and 11% increase in celecoxib AUC_{0-t} and AUC_{0-inf}, respectively. Celecoxib C_{max} for the combination treatment was approximately 60% higher than C_{max} for celecoxib administered alone.

Table 200. Statistical Analysis for Primary Celecoxib PK Parameters for the Comparison of Vadadustat (600 mg) in Combination With Celecoxib (200 mg) to Vadadustat Alone in Healthy Subjects

Parameter	Geometric Mean Ratio (%)	90% CI (%)
AUC_{last}, µg·h/mL	112	103, 122
AUC_{inf}, µg·h/mL	111	103, 119
C_{max}, µg/mL	160	135, 191

Source: Table 14.2.3 of CSR AKB-6548-CI-0019
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Conclusions

Although celecoxib AUC was similar, C_{max} was increased by 60% (1.6-fold), when a single 200-mg dose of celecoxib was administered following multiple daily doses of vadadustat for 6 days, compared to celecoxib administered alone. The similarity in celecoxib AUC when dosed with and without vadadustat does not support the potential for an interaction between vadadustat and CYP2C9 substrates.

A Phase 1 Open-Label, Three Arm Study In Healthy Adult Volunteers To Assess Vadadustat As A Perpetrator In Drug-Drug Interactions With Digoxin, Adefovir And Furosemide (AKB-6548-CI-0031)

Study Design

This is a Phase 1, open-label, 3-arm study in healthy subjects to evaluate vadadustat as a perpetrator of DDIs with digoxin (a P-gp substrate), adefovir (an OAT1 substrate), and furosemide (an OAT1/OAT3 substrate) in healthy male and female subjects. The primary objectives of this study were to assess the effect of repeated oral doses of vadadustat (600 mg QD) on the PK of a single oral dose of 0.5 mg digoxin (arm 1), single oral dose of 10 mg adefovir (arm 2), and single oral dose of 40 mg furosemide (arm 3). In arm 1, on the morning of Day 1, subjects received a single oral 0.5 mg dose of digoxin alone followed by a washout period (Days 2 to 12). On Days 13 to 19, subjects received vadadustat 600 mg QD. A single dose of digoxin (0.5 mg) was administered with vadadustat on the morning of Day 16. In arm 2, on the morning of Day 1, subjects received a single oral 10 mg dose of adefovir alone followed by a washout period (Days 2 to 3). On Days 4 to 8, subjects received vadadustat 600 mg QD. A single oral dose of adefovir (10 mg) was administered with vadadustat on the morning of Day 7. In arm 3, on the morning of Day 1, subjects received a single oral 40 mg oral dose of furosemide alone followed by a 2-day washout period. On Days 3 to 6, subjects received vadadustat 600 mg QD. A single oral dose of furosemide 40 mg was administered with vadadustat on the morning of Day 6.

Results

The total exposure (AUC_{last} and AUC_{inf}) to digoxin was unchanged, while the C_{max} was decreased by about 35% when digoxin (0.5 mg) was administered following multiple doses of vadadustat (600 mg QD) compared to when digoxin (0.5 mg) was administered alone. Statistical analysis of digoxin C_{max} and AUC values after administration of digoxin alone and with vadadustat are shown in Table 201.

Table 201. Statistical Analysis for Digoxin PK Parameters for the Comparison of 0.5 mg Single Dose Digoxin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (D+V)/D[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment D+V	Treatment D	(%)	Lower (%)	Upper (%)
AUC_{last}, h·ng/mL	31.7	34.6	91.5	85.4	98.0
AUC_{inf}, h·ng/mL	33.2	36.3	91.4	85.2	98.0
C_{max}, ng/mL	1.64	2.46	66.9	60.5	74.0

Source: Table 14.2.1-8 of CSR AKB-6548-CI-0031
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Average peak (C_{max}) and total exposures (AUC) of adefovir were similar when adefovir (10 mg) was administered following multiple doses of vadadustat (600 mg QD) and when adefovir (10 mg) was given alone. Statistical analysis of adefovir C_{max} and AUC values after administration of adefovir alone and with vadadustat are shown in Table 202.

Table 202. Statistical Analysis for Adefovir PK Parameters for the Comparison of 10 mg Single Dose Adefovir Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (A+V)/A[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment A+V	Treatment A	(%)	Lower (%)	Upper (%)
AUC_{last}, h·ng/mL	227	198	115	109	121
AUC_{inf}, h·ng/mL	230	201	115	109	121
C_{max}, ng/mL	17.1	17.9	95.2	86.3	105

Source: Table 14.2.1-8 of CSR AKB-6548-CI-0031
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

The systemic exposure (AUC and C_{max}) to furosemide was increased by approximately 2-fold when furosemide (40 mg) was administered with vadadustat (600 mg QD) compared to when furosemide (40 mg) was administered alone. Statistical analysis of furosemide C_{max} and AUC values after administration of furosemide alone and following multiple doses of vadadustat are shown in Table 203.

Table 203. Statistical Analysis for Furosemide PK Parameters for the Comparison of 40 mg Single Dose Furosemide Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (F+V)/F[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment F+V	Treatment F	(%)	Lower (%)	Upper (%)
AUC_{last}, h·ng/mL	5390	2490	217	192	244
AUC_{inf}, h·ng/mL	5440	2600	209	187	234
C_{max}, ng/mL	1460	855	171	137	215

Source: Table 14.2.1-8 of CSR AKB-6548-CI-0031
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Conclusions

When vadadustat was administered in combination with digoxin, a p-gp substrate, total exposure to digoxin was unchanged, suggesting that vadadustat would likely have minimal interaction with other P-gp substrates. Systemic exposure to adefovir (OAT1 substrate) was relatively unchanged when vadadustat was administered in combination with adefovir, suggesting that vadadustat would likely have minimal interaction with other OAT1 substrates. Total systemic

exposure (AUC) to furosemide (OAT1/OAT3 substrate) was increased by approximately 2-fold and peak exposure (C_{max}) was increased by <2- fold, when vadadustat was administered in combination with furosemide. As vadadustat did not affect adefovir (an OAT1 substrate) PK, the increased exposure to furosemide is possibly caused by OAT3 inhibition of vadadustat. Based on these results, we recommended dose adjustment for OAT3 substrates and proposed the labeling recommendation as "monitor for signs of adverse events based on which a dose adjustment may be needed for co-administered OAT3 substrates".

A Phase 1, Three-Part, Open-Label Study in Healthy Adult Volunteers to Assess Vadadustat as a Perpetrator in Drug-Drug Interactions With Rosuvastatin, Sulfasalazine, Pravastatin, Atorvastatin and Simvastatin (AKB-6548-CI-0030)

Study Design

This is a Phase 1, open-label, three-part study to evaluate DDIs of vadadustat with rosuvastatin (a BCRP and OATP1B1 substrate), sulfasalazine (a BCRP substrate), pravastatin (an OATP1B1 substrate), atorvastatin (OATP1B1 substrate), and simvastatin (BCRP substrate) in healthy male and female subjects. The primary objectives of this study were to assess the effect of repeated oral doses of vadadustat (600 mg QD) on the PK of a single oral dose of 20 mg rosuvastatin (part 1), single oral dose of 500 mg sulfasalazine (part 2, arm 1), single oral dose of 40 mg pravastatin (part 2, arm 2), single oral dose of 40 mg atorvastatin (part 3, arm 1), and single oral dose of 40 mg simvastatin (part 3, arm 2). In part 1, subjects received a single 20 mg dose of rosuvastatin alone on Day 1. Following a 6-day washout (Days 1 to 6) period, starting on Day 7 subjects received 600 mg QD vadadustat for 8 days (Days 7 to 14) and a single dose of rosuvastatin (20 mg) on Day 10. In part 2 (arm 1), subjects received a single 500 mg dose of sulfasalazine alone on Day 1. Following a 5-day washout (Days 1 to 5) period, starting on Day 6 subjects received 600 mg QD vadadustat for 7 days (Days 6 to 12) and a single dose of sulfasalazine (500 mg) on Day 9. In part 2 (arm 2), subjects received a single 40 mg dose of pravastatin alone on Day 1. Following a 2-day washout (Days 1 to 2) period, starting on Day 3 subjects received 600 mg QD vadadustat for 4 days (Days 3 to 6) and a single dose of pravastatin (40 mg) on Day 6. In part 3 (arm 1), subjects received 40 mg atorvastatin QD for 4 days (Days 1 to 4). Beginning on Day 5, subjects received atorvastatin 40 mg QD and vadadustat 600 mg QD for 4 days (Days 5 to 8). In part 3 (arm 2), subjects received a single 40 mg dose of simvastatin on Day 1. Following a 1-day washout period subjects received vadadustat 600 mg beginning on Day 2 for 3 days (Day 2 to 4). On Day 5, subjects received a single dose of simvastatin 40 mg and a morning dose of vadadustat 600 mg QD.

Results

Systemic exposure to rosuvastatin was increased by approximately 2- to 3-fold when rosuvastatin (20 mg) was administered with vadadustat (600 mg QD) compared to when rosuvastatin (20 mg) was administered alone. Statistical analysis of rosuvastatin PK exposure parameters after administration of rosuvastatin alone and with vadadustat are shown in Table 204.

Table 204. Statistical Analysis for Rosuvastatin PK Parameters for the Comparison of 20 mg Single Dose Rosuvastatin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (R+V)/R[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment R+V	Treatment R	(%)	Lower (%)	Upper (%)
AUC_{last}, h·ng/mL	249	98.4	253	232	276
AUC_{inf}, h·ng/mL	254	103	247	227	268
C_{max}, ng/mL	27.9	10.2	275	246	307

Source: Table 11.4.2.3-2 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

The total systemic exposure (AUC) to sulfasalazine was increased up to 4.5-fold and peak exposure (Cmax) was increased up to 2.8-fold when sulfasalazine (500 mg) was administered with vadadustat (600 mg QD) compared to when sulfasalazine (500 mg) was administered alone. Statistical analysis of sulfasalazine PK exposure parameters after administration of sulfasalazine alone and with vadadustat are shown in Table 205.

Table 205. Statistical Analysis for Sulfasalazine PK Parameters for the Comparison of 500 mg Single Dose Sulfasalazine Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (S+V)/S[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment S+V	Treatment S	(%)	Lower (%)	Upper (%)
AUC_{last}, h·µg/mL	373	82.1	454	376	549
AUC_{inf}, h·µg/mL	379	82.7	458	378	554
C_{max}, µg/mL	26.7	9.70	275	233	325

Source: Table 11.4.2.3-4 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

The drug sulfasalazine is structurally one molecule of mesalamine linked to one molecule of sulfapyridine with an azo chemical linker. The metabolism of sulfasalazine results in the release of sulfapyridine and mesalamine.

Exposures to sulfapyridine did not alter considerably in the presence of vadadustat and exposure to mesalamine was increased about 40% when sulfasalazine (500 mg) was given following multiple doses of vadadustat (600 mg QD) compared to when sulfasalazine (500 mg) was given alone. Statistical analysis of sulfapyridine and mesalamine PK exposure parameters after administration of sulfasalazine alone and with vadadustat are shown in Table 206 and Table 207, respectively.

Table 206. Statistical Analysis for Sulfapyridine PK Parameters for the Comparison of 500 mg Single Dose Sulfasalazine Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (S+V)/S[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment S+V	Treatment S	(%)	Lower (%)	Upper (%)
AUC_{last}, h·µg/mL	41.5	42.4	97.9	90.0	106
AUC_{inf}, h·µg/mL	42.2	42.8	98.5	90.8	107
C_{max}, µg/mL	2.19	2.58	84.8	77.5	92.8

Source: Table 11.4.2.3-6 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Table 207. Statistical Analysis for Mesalamine PK Parameters for the Comparison of 500 mg Single Dose Sulfasalazine Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (S+V)/S[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment S+V	Treatment S	(%)	Lower (%)	Upper (%)
AUC_{last}, h·µg/mL	0.318	0.220	144	116	181
AUC_{inf}, h·µg/mL	0.343	0.247	139	110	176
C_{max}, µg/mL	0.027	0.022	119	86.7	164

Source: Table 11.4.2.3-8 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Systemic exposure to pravastatin was unchanged when pravastatin (40 mg) was administered following multiple doses of vadadustat (600 mg QD) compared to when pravastatin (40 mg) was administered alone. Statistical analysis of pravastatin PK exposure parameters after administration of pravastatin alone and with vadadustat is shown in Table 208.

Table 208. Statistical Analysis for Pravastatin PK Parameters for the Comparison of 40 mg Single Dose Pravastatin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (P+V)/P[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment P+V	Treatment P	(%)	Lower (%)	Upper (%)
AUC_{last}, h·ng/mL	134	130	103	92.8	114
AUC_{inf}, h·ng/mL	137	134	102	90.9	115
C_{max}, ng/mL	44.0	53.2	82.7	72.3	94.7

Source: Table 11.4.2.3-10 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Atorvastatin C_{max} was unchanged but total exposure (AUC) was increased about 40% when atorvastatin was administered with vadadustat compared to when atorvastatin was administered alone. There were minimal changes in the exposure (AUC and C_{max}) of the active metabolite o-hydroxy atorvastatin. Total exposure (AUC) of another active metabolite p-hydroxy atorvastatin was increased by 1.7-fold while the peak exposure (C_{max}) was increased by 2.3-fold. Statistical analysis of atorvastatin PK exposure parameters after administration of atorvastatin alone and with vadadustat are shown in Table 209. Statistical analysis of o-hydroxy atorvastatin and p-hydroxy atorvastatin PK exposure parameters after administration of atorvastatin alone and with vadadustat is shown in Table 210 and Table 211, respectively.

Table 209. Statistical Analysis for Atorvastatin PK Parameters for the Comparison of 40 mg Single Dose Atorvastatin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (A+V)/A[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment A+V	Treatment A	(%)	Lower (%)	Upper (%)
AUC_{tau}, h·ng/mL	99.5	69.7	143	136	150
AUC_{inf}, h·ng/mL	104	73.0	142	135	149
C_{max}, ng/mL	18.1	18.0	100	85.3	118

Source: Table 11.4.2.3-12 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{last}, area under the curve to the last quantifiable time point; AUC_{tau}, area under the curve during a dosing interval; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Table 210. Statistical Analysis for O-Hydroxy Atorvastatin PK Parameters for the Comparison of 40 mg Single Dose Atorvastatin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (A+V)/A[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment A+V	Treatment A	(%)	Lower (%)	Upper (%)
AUC_{tau}, h·ng/mL	107	96.0	111	106	117
AUC_{inf}, h·ng/mL	114	102	112	107	117
C_{max}, ng/mL	13.7	15.0	91.2	80.5	103

Source: Table 11.4.2.3-14 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{last}, area under the curve to the last quantifiable time point; AUC_{tau}, area under the curve during a dosing interval; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Table 211. Statistical Analysis for P-Hydroxy Atorvastatin PK Parameters for the Comparison of 40 mg Single Dose Atorvastatin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (A+V)/A[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment A+V	Treatment A	(%)	Lower (%)	Upper (%)
AUC_{tau}, h·ng/mL	15.7	8.92	176	163	190
AUC_{inf}, h·ng/mL	19.2	11.5	168	156	180
C_{max}, ng/mL	1.44	0.62	230	192	276

Source: Table 11.4.2.3-18 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{last}, area under the curve to the last quantifiable time point; AUC_{tau}, area under the curve during a dosing interval; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Average total (AUC) exposures of simvastatin were about 2-fold higher when simvastatin (40 mg) was administered following multiple doses of vadadustat (600 mg QD) than when simvastatin (40 mg) was given alone. The exposure (AUC and C_{max}) to simvastatin hydroxy acid (active metabolite) was increased approximately 2.5- to 3-fold when simvastatin was administered with vadadustat compared to when simvastatin was administered alone. Statistical analysis of simvastatin and simvastatin hydroxy acid PK exposure parameters after administration of simvastatin alone and with vadadustat are shown in Table 212 and Table 213, respectively.

Table 212. Statistical Analysis for Simvastatin PK Parameters for the Comparison of 40 mg Single Dose Simvastatin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (S+V)/S[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment S+V	Treatment S	(%)	Lower (%)	Upper (%)
AUC_{last}, h·ng/mL	59.0	29.9	197	174	223
AUC_{inf}, h·ng/mL	63.2	32.5	195	170	223
C_{max}, ng/mL	11.3	9.16	123	105	145

Source: Table 11.4.2.3-20 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Table 213. Statistical Analysis for Hydroxy Simvastatin PK Parameters for the Comparison of 40 mg Single Dose Simvastatin Alone and in Combination With 600 mg QD Vadadustat in Healthy Subjects

	Geometric LS Mean		Ratio (S+V)/S[a]	90% Geometric CI[b]	
Parameter (unit)	Treatment S+V	Treatment S	(%)	Lower (%)	Upper (%)
AUC_{last}, h·ng/mL	45.6	17.3	263	236	293
AUC_{inf}, h·ng/mL	49.6	20.2	246	219	277
C_{max}, ng/mL	5.39	1.85	292	260	327

Source: Table 11.4.2.3-14 of CSR AKB-6548-CI-0030
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics

Conclusions

When sulfasalazine, a BCRP substrate, was administered in combination with vadadustat, total (AUC) and peak (C_{max}) systemic exposure to sulfasalazine increased by 4.5-fold and 2.8-fold, respectively. The total (AUC) and peak (C_{max}) exposure to sulfapyridine was relatively unchanged when sulfasalazine was given with vadadustat. The total (AUC) and peak (Cmax) systemic exposure to the active metabolite of sulfasalazine, 5-ASA, were increased about 40% and 20%, respectively. These data suggest that vadadustat has the potential to mediate drug-interaction through inhibition of BCRP. Whereas, regarding the active metabolites of sulfasalazine, there were minimal changes in the exposure of mesalamine (5-ASA) and no increase in the exposure of sulfapyridine. Thus, dose adjustments for sulfasalazine are not recommended in subjects with chronic kidney disease (CKD) on vadadustat.

When pravastatin, an OATP1B1 substrate, was administered in combination with vadadustat, total (AUC) and peak (C_{max}) systemic exposure to pravastatin remained relatively unchanged. These data suggest that it is unlikely that vadadustat will mediate drug interactions via inhibition of OATP1B1.

When atorvastatin was administered in combination with vadadustat, total (AUC) systemic exposures to atorvastatin increased about 40%, whereas peak (C_{max}) systemic exposures did not change. The systemic exposures to o-hydroxy atorvastatin were unchanged when atorvastatin was co-administered with vadadustat, whereas the total (AUC) and peak (C_{max}) exposure to p-hydroxy atorvastatin were increased about 1.8-fold and 2.3-fold, respectively. However, the metabolite to parent ratio for p-hydroxy atorvastatin is 1/10th of atorvastatin. Therefore, dose adjustments for atorvastatin are not recommended in subjects with CKD on vadadustat.

The simvastatin C_{max} and AUC increased 1.2-fold and 2-fold in the presence of vadadustat, respectively. The C_{max} and AUC of simvastatin hydroxy acid, active metabolite, increased 2.9-

fold and about 2.5-fold in the presence of vadadustat, respectively. Considering these results and simvastatin's product label for renal impairment, dosing recommendations were provided for simvastatin when administered concomitantly with vadadustat.

When rosuvastatin (a BCRP and OATP1B1 substrate) was administered with vadadustat, C_{max} and AUC of rosuvastatin increased 2 to 3-fold compared to when rosuvastatin was administered alone. When taken together with the results of both DDI studies with sulfasalazine and pravastatin, the increased exposure of rosuvastatin is mainly caused by the inhibition of BCRP by vadadustat. Considering these results and rosuvastatin's product label for renal impairment, dosing recommendations were provided for rosuvastatin when administered concomitantly with vadadustat.

14.3. Pharmacometrics Review

Review Summary

The Applicant performed population pharmacokinetic (popPK) analysis for vadadustat in both healthy subjects and subjects with anemia associated with chronic kidney disease (CKD), including subjects with dialysis-dependent or non-dialysis dependent CKD (DD and NDD, respectively). The Applicant sought to characterize vadadustat PK across the target populations and quantify covariate impacts from the popPK model development. Subsequent hemoglobin (Hb) PK/PD and exposure-response (E-R) analyses (Hb response and safety events) were conducted based on vadadustat exposure. The popPK model was supportive in estimating population and posterior predictions in DD-CKD and NDD-CKD populations and aided in E-R analyses.

While numeric differences were observed in incidence rates of safety events across vadadustat exposure (as measured by time-averaged daily AUC based on individual actual daily dosage up to safety events of interest), no significant E-R safety relationship was identified. Several key points should also be considered for interpretation of the E-R relationship: 1) Hb targets were different across study regions (United States versus rest of the world), 2) "slow responders" may require higher dose after initiation and dose titration, and 3) the narrow therapeutic target (i.e., Hb target) presented challenges in delineating meaningful vadadustat exposure-safety relationships as the target Hb window dictates the dosage and titration schedule.

14.3.1. Population PK analysis

Introduction

The primary objectives of Applicant's analysis were to:

- Develop a popPK model to characterize vadadustat PK in target populations
- Evaluate the impact from covariates on vadadustat PK
- Assess performance of the final covariate model in describing the PK data
- Perform model-based simulations for comparisons of subgroups
- Derive exposure metrics for E-R analysis (safety)

Model Development

Data

The popPK analysis was based on PK data from 15 studies: 5 Phase 1 and Phase 2 studies with intensive sampling and 10 Phase 2 and Phase 3 studies with sparse sampling. The pooled dataset included 96 healthy volunteers, 2003 subjects with non-dialysis-dependent (NDD) CKD, and 2098 subjects with dialysis-dependent (DD) CKD. Overall, the pooled subjects contributed 18311 PK samples, and 14021 PK samples were retained for popPK analysis. Table 214 lists the summary of studies that contributed to the pooled PK dataset. Table 215 provides an overview of the number of PK observations retained for the final dataset. Table 216 and Table 217 provide continuous and categorical summaries of the baseline characteristics of PK subjects by populations, respectively.

Table 214. Clinical Studies Included in the PopPK Dataset for Model Development

Phase 1

Protocol Number	Population	Regimen and Dose (mg)	Actual Sample Size [1]	PK Sampling	Food Status (If Defined)
CI-0001	Healthy, male subjects	Single dose 80, 160, 300, 600, 900, 1200mg	N=36	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose	Fasted/ Fed
CI-0002	Healthy, male subjects	10 days repeated dosing, 500, 700, 900 mg QD	N=24	Day 1 and Day 7: pre-dose, 1, 2, 4, 6, 8, and 24 hours post dosing	Fasted
CI-0020	Healthy Caucasian and Japanese, male and female subjects	10 days repeated dosing, 150, 300, 600 mg QD	Caucasian N=18; Japanese N=18	Day 1 and Day 10: pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 16 and 24hours post dosing	Fasted

Phase 2

Protocol Number	Population	Regimen and Dose (mg)	Actual Sample Size [1]	PK Sampling	Food Status (If Defined)
CI-0003	Male and female subjects with NDD- CKD Stage 3 and Stage 4	Single dose 500 mg	N=22	Pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dosing	Fed (standard diabetic breakfast)
CI-0007	Male and female subjects with NDD-CKD Stage 3, 4, and 5	20 weeks, starting dose 450 mg QD, dose titration allowed	N=120	Week 12 pre-dose and post-dose (3-5hr) and a post-dose sample at EOT	Not controlled
CI-0021	Japanese, male and female subjects with NDD-CKD	16 weeks, starting dose 150, 300, or 450 mg QD, dose titration allowed	N=37	Week 4 pre-dose	Not controlled

Phase 1 and 2, DD-CKD

Protocol Number	Population	Regimen and Dose (mg)	Actual Sample Size [1]	PK Sampling	Food Status (If Defined)
CI-0009	Subjects with DD-CKD Stage 3 and Stage 4	Two-period, single dose 450 mg. Dosing 4 hr prior initiation or 2 hr after completion of dialysis	N=12	Pre-dose and at 0, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 24, 30, 36, and 48 hours post dosing	Fasted
CI-0011	Subjects with DD-CKD	16 weeks, starting dose 300, 450 mg QD or 450 mg TIW, dose titration allowed	N=87	Before and after dialysis at Week 2 and EOT	Not controlled
CI-0022	Japanese subjects with DD-CKD	16 weeks, Starting dose 150, 300 or 450 mg QD, dose titration allowed	N=38	Week 4 pre-dose	Not controlled

Phase 3, NDD-, and DD-CKD

Protocol Number	Population	Regimen and Dose (mg)	Actual Sample Size[1]	PK Sampling	Food Status (If Defined)
J-01	Japanese subjects with NDD-CKD	52 weeks, starting dose 300 mg QD, dose titration allowed	N=148	Weeks 4, 12, and 24	Not controlled[2]
J-03	Japanese subjects with DD-CKD	52 weeks, starting dose 300 mg QD, dose titration allowed	N=154	Weeks 4, 12, and 24	Not controlled[2]
CI-0014	Subjects with NDD-CKD	52 weeks, starting dose 300 mg QD, dose titration allowed	N=836	Day 1 (0.25 – 1 hr post dose), Weeks 4, 12, 28, and 52	Not controlled[2]
CI-0015	Subjects with NDD-CKD	52 weeks, starting dose 300 mg QD, dose titration allowed	N=840	Day 1 (0.25 – 1 hr post dose), Week 4, 12, 28, and 52	Not controlled[2]
CI-0016	Subjects with DD-CKD	52 weeks, starting dose 300 mg QD, dose titration allowed	N=168	Day 1 (0.25 – 1 hr post dose), Week 4, 12, 28, and 52	Not controlled[2]
CI-0017	Subjects with DD-CKD	52 weeks, starting dose 300 mg QD, dose titration allowed 3	N=1630	Day 1 (0.25 – 1 hr post dose), Week 4, 12, 28, and 52	Not controlled[2]

Source: Applicant's PopPK Analysis Report, Tables 3-1, 3-2, 3-3, 3-4, pages 27-30
[1] Only vadadustat treated subjects for which evaluable PK samples were available.
Dose titration allowed doses of 0, 150, 300, 450, 600 mg
Abbreviations: CKD, chronic kidney disease; DD, dialysis dependent; EOT, end of treatment; hr, hour; NDD, non-dialysis dependent; popPK, population pharmacokinetics; QD, once daily; TIW, three times weekly

Table 215. PK Samples for Pooled Dataset

Reason	Total	HV	Ph2 NDD	Ph2 DD	J-01	J-03	CI-0014	CI-0015	CI-0016	CI-0017
Available in source dataset	18311	1488	610	758	423	436	3403	3449	716	7028
Flag = 20, Flag = 4	75	0	1	0	0	0	20	13	2	39
Flag = 5	533	96	22	12	0	0	117	159	2	125
Flag = 6	2	0	0	0	0	0	0	0	1	1
Flag = 7	679	0	0	0	0	0	49	107	50	473
Flag = 9	16	0	0	16	0	0	0	0	0	0
Flag = 11	9	0	0	0	1	0	0	0	0	8
BLQ samples (after first dose)	2976	5	12	31	11	12	652	504	162	1587
Available for analysis	14021	1387	575	699	411	424	2565	2666	499	4795

BLQ: below the limit of quantification; CWRES: conditional weighted residual: DD; dialysis-dependent; HV: healthy subjects; NDD: non-dialysis-dependent; Ph2: Phase 2 studies; PK: pharmacokinetic.

HV: healthy subjects from Studies CI-0001, CI-0002, and CI-0020; Ph2 subjects with NDD: NDD-CKD from Studies CI-0003, CI-0007, and CI-0021; Ph2 DD: subjects with DD-CKD from Studies CI-0009, CI-0011, and CI-0022

Flag definitions: 20, 4=Time after first dose missing; 5: PK samples with Time after first dose ≤0 and concentration above BLQ; 6=due to missing EXSTDT unknown if dosed on these days for CI-0016 (AKB-6548-CI-0016-(b) (6) and CI-0017 (AKB-6548-CI-0017(b) (6); 7 = Inconsistent dosing information in SUPPPC and/or EX; 9= Subject AKB6548_CI_0009-AKB09_01-112 period 2 samples excluded because of extremely low concentration values (Appendix 10.1, Figure 10-2, panel CI-0009). Flag = 11 (J-01, CI-0017, unreasonable high concentration (CWRES>5) at large time after dose (Appendix 10.1).

Source: Applicant's PopPK Analysis Report, Table 5-2, page 47

Table 216. Summary of Baseline Continuous Covariates by Target Population

Covariate	Mean (CV%) Median [Min, Max]			
	Healthy Subjects (N=96)	NDD-CKD (N=2003)	DD-CKD (N=2089)	All (N=4188)
Age	34.3 (25.9)	66.8 (20)	58.5 (23.3)	61.9 (23.6)
(years)	33 [18, 52]	68 [19, 104]	59 [20, 93]	63 [18, 104]
Weight	78.6 (17.9)	78.5 (27.8)	78.4 (28)	78.5 (27.7)
(kg)	77.6 [50.1, 111]	75 [30.1, 179]	75.3 [32, 204]	75.3 [30.1, 204]
BMI	25.3 (13.1)	29 (24.4)	28 (25.4)	28.4 (24.8)
(kg/m^2)	25.8 [18.6, 30.6]	27.9 [14.8, 69.3]	26.7 [13.4, 84.9]	27.2 [13.4, 84.9]
CrCl	121 (20)	28.7 (70)	10.9 (58.1)	22 (105)
(mL/min)	116 [81.1, 192]	25.2 [4.44, 609]	9.28 [2.56, 66.1]	15.2 [2.56, 609]
eGFR	93.1 (19.2)	22.7 (53.4)	7.06 (64.6)	16.5 (102)
(mL/min/1.73 m^2)	91.3 [62.5, 148]	20.1 [2.82, 98.2]	5.85 [2.18, 75.4]	10.5 [2.18, 148]
sCr	84.9 (15.1)	279 (54.8)	774 (35.8)	522 (64.7)
(µmol/L)	88.4 [53, 115]	241 [19.4, 1760]	766 [83.1, 1940]	440 [19.4, 1940]
Albumin	4.54 (6.36)	3.98 (11.9)	3.98 (10.5)	3.99 (11.3)
(g/dL)	4.5 [3.8, 5.1]	4 [1.6, 5.4]	4 [2, 5.6]	4 [1.6, 5.6]
ALT	20.6 (46.5)	16.1 (69.2)	15.6 (154)	16 (117)
(U/L)	18 [6, 68]	14 [4, 192]	12 [3, 966]	13 [3, 966]
AST	20 (34.2)	18.4 (51.3)	15.4 (93.1)	16.9 (72)
(U/L)	19 [11, 56]	17 [4, 172]	14 [2, 518]	15 [2, 518]
Total bilirubin	0.77 (38)	0.316 (64.5)	0.323 (49.7)	0.33 (60)
(µmol/L)	0.7 [0.3, 1.8]	0.3 [0.1, 3]	0.3 [0.1, 1.9]	0.3 [0.1, 3]
wn-ESA	0 (-)	44.8 (231)	107 (99.7)	74.7 (146)
(IU/week/kg)	0 [0, 0]	0 [0, 1310]	77 [0, 965]	43 [0, 1310]

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; CKD: chronic kidney disease; CrCl: creatinine clearance; CV: coefficient of variation; DD: dialysis-dependent; eGFR: estimated glomerular filtration rate; Max: maximum; Min: minimum; N: sample size; NDD: non-dialysis-dependent; sCr: serum creatinine; wn-ESA: weight-normalized weekly erythropoiesis-stimulating agent.

Note: AKB-6548-CI-0015-[redacted] (b) (6) has a baseline eGFR of 337 mL/min/1.73 m^2, which was imputed with time average mean of all eGFR values at baseline and during treatment (89.0 mL/min/1.73 m^2). Associated CrCL and sCr values were not imputed because these were not considered in the analysis. Summary statistics are based on the imputed value.

Source: Applicant's PopPK Analysis Report, Tables 5-6, page 52

Table 217. Summary of Baseline Categorical Covariates by Target Population

Covariate Category	Number of Subjects (%)			
	Healthy Subjects (N=96)	NDD-CKD (N=2003)	DD-CKD (N=2089)	All (N=4188)
Sex				
Male	91 (94.8)	915 (45.7)	1197 (57.3)	2203 (52.6)
Female	5 (5.2)	1088 (54.3)	892 (42.7)	1985 (47.4)
Race				
White	48 (50)	1227 (61.3)	1234 (59.1)	2509 (59.9)
Black or African American	28 (29.2)	319 (15.9)	466 (22.3)	813 (19.4)
Asian	19 (19.8)	293 (14.6)	279 (13.4)	591 (14.1)
American Indian/Alaskan Native	0 (0)	53 (2.6)	18 (0.9)	71 (1.7)
Native Hawaiian or Other Pacific Islander	0 (0)	7 (0.3)	14 (0.7)	21 (0.5)
Other	1 (1)	86 (4.3)	43 (2.1)	130 (3.1)
Missing	0 (0)	18 (0.9)	35 (1.7)	53 (1.3)
Japanese descent				
Non-Japanese descent	78 (81.2)	1818 (90.8)	1897 (90.8)	3793 (90.6)
Japanese descent	18 (18.8)	185 (9.2)	192 (9.2)	395 (9.4)
Ethnicity				
Not Hispanic or Latino	88 (91.7)	1400 (69.9)	1326 (63.5)	2814 (67.2)
Hispanic or Latino	8 (8.3)	574 (28.7)	712 (34.1)	1294 (30.9)
Missing	0 (0)	29 (1.4)	51 (2.4)	80 (1.9)

CKD: chronic kidney disease; DD: dialysis-dependent; N: sample size; NDD: non-dialysis-dependent.
Source: Applicant's PopPK Analysis Report, Table 5-11, page 57

Base Model

The Applicant employed a stepwise approach for the base structural model development. The general approach included fitting a one- and two-compartment model to intensively sampled PK data and subsequent addition of sparse PK data to develop a stable, base structural model.

The base model was a one-compartment model with a sequential lag time and first-order absorption (oral route). Food effect was modeled on lag time and Ka. CL and V were allometrically scaled by body weight. A power model with estimated glomerular filtration rate (eGFR) was included in CL for healthy and NDD-CKD subjects but not for DD-CKD population.

Inter-individual variability (IIV) was modeled assuming a log-normal distribution for CL and Ka. Residual variability was modeled assuming log-additive distribution and separately for

intensive and sparse sampled PK data. The PK parameters for the base model are listed in Table 218.

Table 218. Base Model PK Parameters

Parameter	Estimate	RSE (%)	Shrinkage (%)
CL/F (L/hr)	1.28	3.2%	-
V2/F (L)	11.8	2.2%	-
KA fasted (1/hr)	2.05	28.3%	-
KA fed (1/hr)	0.485	18.3%	-
KA food not controlled (1/hr)	0.211	4.6%	-
LAGT fasted (hr)	0.344	6.6%	-
LAGT fed (hr)	0.475	0.7%	-
Bodyweight effect on CL/F	0.895	0%	-
Bodyweight effect on V2/F	0.828	7.9%	-
CL/F – eGFR power	0.436	7.8%	-
CL/F – DD effect	-0.267	2.8%	-
Interindividual variability			
CL/F IIV as CV%	48.7%	2.7%	31.6%
KA IIV as CV%[a]	92.8%	10.2%	12.5%
Residual variability			
Log-additive CV% intensive samples	47.2	0.7%	7.5%
Log-additive CV% sparse 1	66.1	2.2%	7.5%
Log-additive CV% sparse 2	117	1.1%	7.5%

Source: Applicant's PopPK Analysis Report, Table 5-15, page 73
[a] IIV for KA was estimated only on intensive sampled subjects dosed under either fasted or fed conditions, not for sparselysampled patients where food conditions were not controlled.
Abbreviations: CL/F, apparent clearance; CV, coefficient of variation (calculated as 100 × square root of variance / mean); eGFR, estimated glomerular filtration rate; IIV, inter-individual variability; KA, absorption rate constant; LAGT, lag time; V2/F: apparent central volume of distribution; Log-additive CV% sparse 1, residual error for sparse data except CI-0016 and CI-0017; Log-additive CV% sparse 2, residual error for sparse data from CI-0016 andCI-0017; RSE, relative standard error (100 × standard error/estimate); SD, standard deviation

Covariate Analysis

Covariate effects were evaluated (Table 219) in a univariate fashion instead of stepwise approach (because of long model run time per Applicant's popPK report). Effects of non-iron containing phosphate binders (NICP) on Frel, bilirubin on CL, oral iron on Frel, and Japanese descent on CL were included in candidate covariate models. Two additional studies (CI-0014 and CI-0015) were added for popPK analysis and covariates were re-evaluated based on the candidate model(s).

Table 219. Covariates Included for Covariate Modeling

Covariate	p-value Random Effects CL/F
Baseline weight (kg)	0.873
Baseline BMI (kg/m^2)	0.445
Age (years)	0.015
Baseline ALT (U/L)	0.004
Baseline AST (U/L)	0.675
Baseline ALB (g/dL)	0.800
Baseline bilirubin (µmol/L)	<0.001
Baseline eGFR (mL/min/1.73 m^2)	0.506
wn-ESA (U/kg/week)	0.084
Sex	0.241
Race	0.005
Japanese descent	<0.001
Ethnicity	0.009

ALB: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BILI: bilirubin; BMI: body mass index; CL/F: apparent clearance; eGFR: estimated glomerular filtration ratio; ETA: random between-subject effect; p-value: p-value from linear regression on ETA vs. log-transformed continuous covariate for continuous, or analysis of variance for categorical covariate; wn-ESA: weight-normalized weekly ESA dose.

Concomitant Medication	p-value Random Effects
F - Non-iron containing phosphate binders	No individual estimates for F available; exploration by correlation and linear regression not feasible
F - Iron containing phosphate binders	
F - Oral iron (including phosphate binders)	
CL/F - OAT1/3 inhibitor agents	0.317

CL/F: apparent clearance; F: absolute bioavailability; OAT: organic anion transporter; p-value: p-value from analysis of variance.

Source: Applicant's PopPK Analysis Report, Tables 5-15 and 5-17, page 75-76

Final Model

Vadadustat PK was adequately described by a one-compartment model with a sequential lag time and first-order absorption and first-order elimination. Food impact was modeled on lag time and Ka parameters. CL and V related terms were allometrically scaled by body weight for both DD- and NDD-CKD populations. Japanese descent (categorical) was included on CL for all subjects. For healthy subjects, bilirubin was modeled as a power function on CL. For the NDD-CKD cohort, a power model with eGFR (at baseline) accounting for the effect of renal function was included on CL. NICP and oral iron were modeled to reflect the relative bioavailability of vadadustat. IIV was modeled on CL and Ka (of note, Ka was modeled from subjects with intensive PK sampling). Log-additive distribution was assumed in the residual error model for both intensive and sparsely sampled PK data. Additionally, separate log-additive error terms were modeled for the sparse data. Table 220 lists the PK parameter estimates for the final model for vadadustat. Goodness-of-fit (GoF) plots and prediction-corrected visual predictive check (pcVPC) are shown in Figure 39 and Figure 40.

Table 220. PK Parameter Estimates for the Final PopPK Model

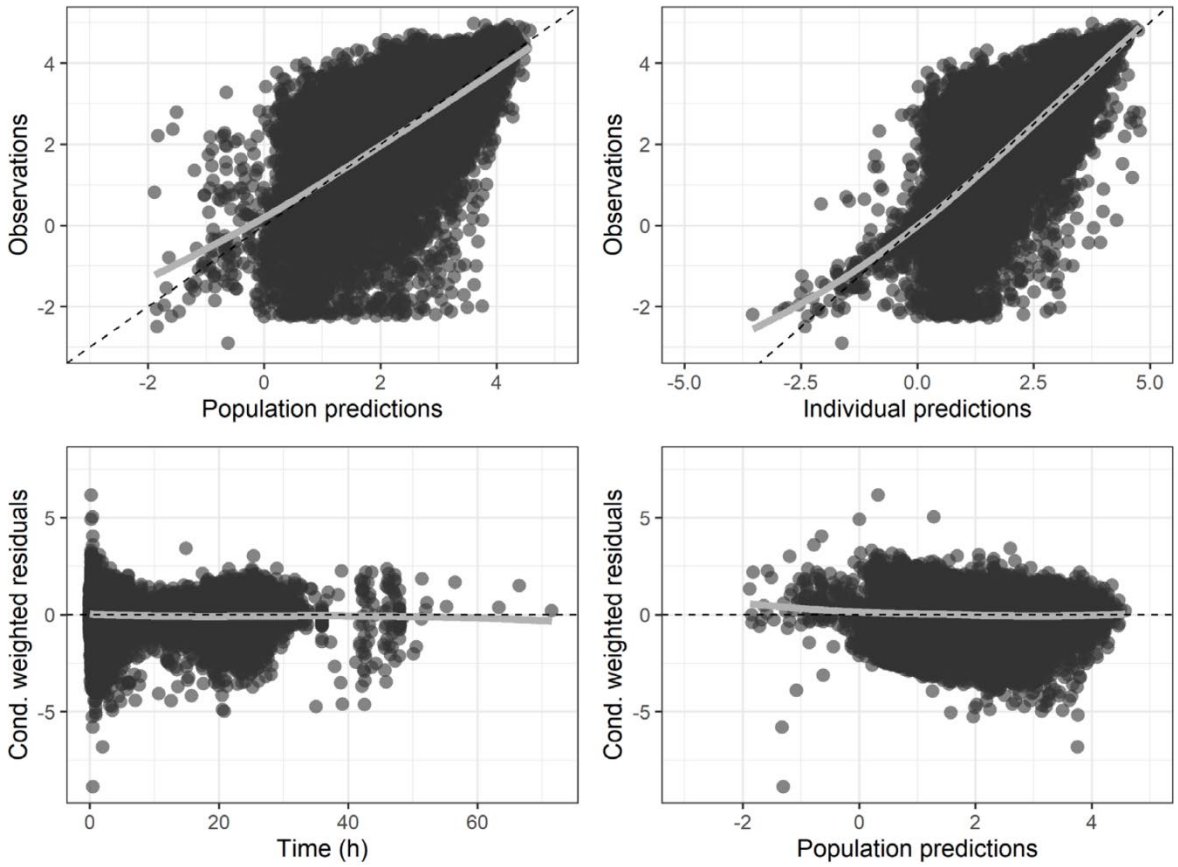
Parameter	Estimate	RSE (%)	2.5th-97.5th Percentile (Bootstrap)	Shrinkage (%)
CL/F healthy (L/hr)	2.01	5.4	1.86; 2.18	-
CL/F CKD (L/hr)	0.722	1.7	0.691; 0.746	-
V2/F (L)	11.6	2.0	10.7; 12.8	-
KA fasted (1/hr)	2.11	11.5	1.66; 2.5	-
KA fed (1/hr)	0.504	14.9	0.262; 1.14	-
KA food not controlled (1/hr)	0.320	3.6	0.274; 0.367	-
LAGT fasted (hr)	0.348	4.1	0.309; 0.386	-
LAGT fed (hr)	0.475	0.6	0.452; 0.49	-
Bodyweight effect on CL/F	0.624	7.4	0.526; 0.706	-
Bodyweight effect on V2/F	0.811	6.9	0.644; 0.962	-
CL/F-NDD eGFR power	0.255	11.3	0.197; 0.314	-
CL/F-bilirubin power	-0.223	10.1	-0.27; -0.185	-
CL/F-Japanese descent	-0.187	16.0	-0.234; -0.143	-
Frel – Non-iron containing phosphate binders	-0.327	4.2	-0.372; -0.282	-
Frel – Oral iron and iron containing phosphate binders	-0.200	9.6	-0.238; -0.161	-
Interindividual Variability				
CL/F IIV as CV%	47.0	1.9	43.3; 50.3	31.6
KA IIV as CV% [a]	88.6	8.3	72.4; 107	13.2
Residual Variability				
Log-additive CV% intensive samples	47.1	1.8	42.1; 52.9	7.6
Log-additive CV% sparse samples 1	63.2	2.2	56.5; 68.1	7.6
Log-additive CV% sparse samples 2	107	0.8	105; 109	7.6

CKD: chronic kidney disease; CL/F: apparent clearance; CV: coefficient of variation (calculated as 100 × square root of variance / mean); eGFR: estimated glomerular filtration rate; F: absolute bioavailability; Frel: relative bioavailability; IIV: inter-individual variability; KA: first-order absorption rate constant; Log-additive CV% sparse 1: residual error for sparse data except CI-0016 and CI-0017; Log-additive CV% sparse 2: residual error for sparse data from CI-0016 and CI-0017; RSE: relative standard error (100 × standard error/estimate; RSE on standard deviation terms is RSE of variance / 2); NDD: non-dialysis-dependent; SD: standard deviation; LAGT: lag time; V2/F: apparent central volume of distribution.

[a] IIV for KA was estimated only on intensive sampled subjects dosed under either fasted or fed conditions, not for sparsely sampled patients where food conditions were not controlled..

Source: Applicant's PopPK Analysis Report, Table 5-21, page 82

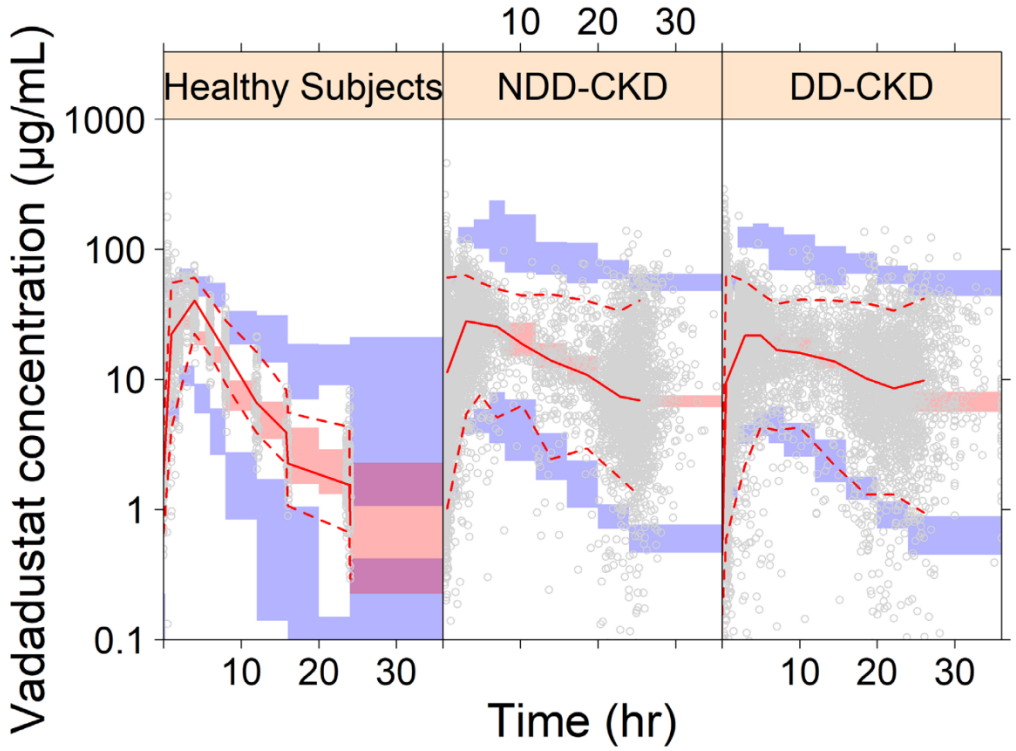
Figure 39. Goodness-of-Fit Plots for the Final PopPK Model



Cond.: conditional; PK: pharmacokinetic.

Source: Applicant's PopPK Analysis Report, Figure 5-13, page 84
Abbreviations: popPK, population pharmacokinetic

Figure 40. PC-VPC for Final Model by Population



CKD: chronic kidney disease; DD: dialysis-dependent; NDD: non-dialysis-dependent; VPC: visual predictive check.
Note: The blue and pink shaded areas represent the 95% confidence interval for the 5th, 50th, and 95th percentiles for 100 simulations, and the red dashed and solid lines represent corresponding statistics for the prediction-corrected observed data. Panels show all data up to 36 hours post last dose included in the analysis and are plotted against time after last dose.

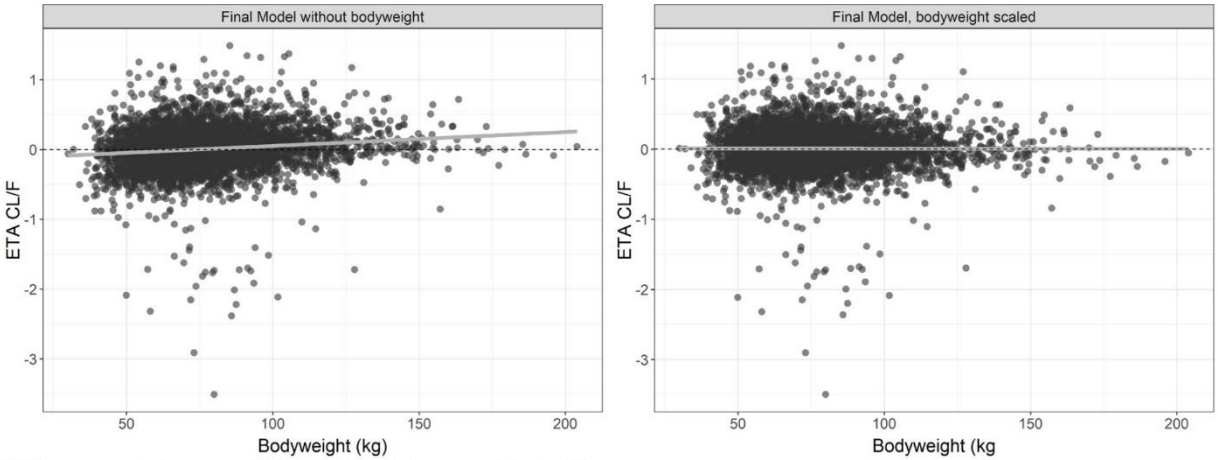
Source: Applicant's PopPK Analysis Report, Figure 5-14, page 85
Abbreviations: popPK, population pharmacokinetic

Reviewer's Comments:

The reviewer was able to reproduce the final popPK model results as listed. The final model reasonably described the PK data. Estimations of the PK parameters were precise with RSE <16.0%, and this was also supported by the 95% CI of bootstrapping results. Shrinkage was low, ranging from 7.6% to 13.2%, except for IIV of CL with a moderate shrinkage of 31.6%. GoF and pcVPC plots demonstrated adequate model fit without obvious bias or misspecification of the final popPK model. Residuals are randomly scattered around y =0 without obvious trends. The reviewer noted that the upper bound of predictions were above 95th percentile observed data for NDD- and DD-CKD populations (and slightly towards end of plotted time frame for healthy subjects). However, the lower bound (25th percentile) and 50th percentile of predictions reasonably captured central tendency of the data across target populations over time.

Figure 41, Figure 42, Figure 43, and Figure 44 showed the ETA of CL versus continuous and categorical covariates before and after including the corresponding covariates in the final popPK model. Collectively, they demonstrated that effects of body weight (continuous), eGFR (continuous), bilirubin (continuous) and Japanese descent (categorical) on CL were adequately captured to characterize vadadustat PK for target populations.

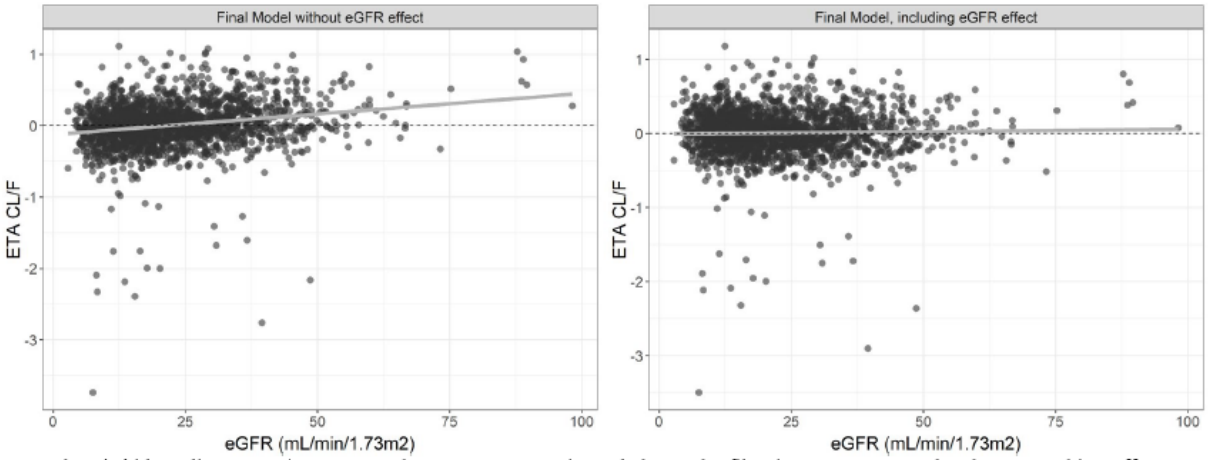
Figure 41. ETA CL Versus Body Weight



CL/F: apparent clearance; ETA: random between subject effect.
Note: Dots represent individual ETA values; solid line represents linear regression line.

Source: Applicant's PopPK Analysis Report, Figure 5-15, page 86

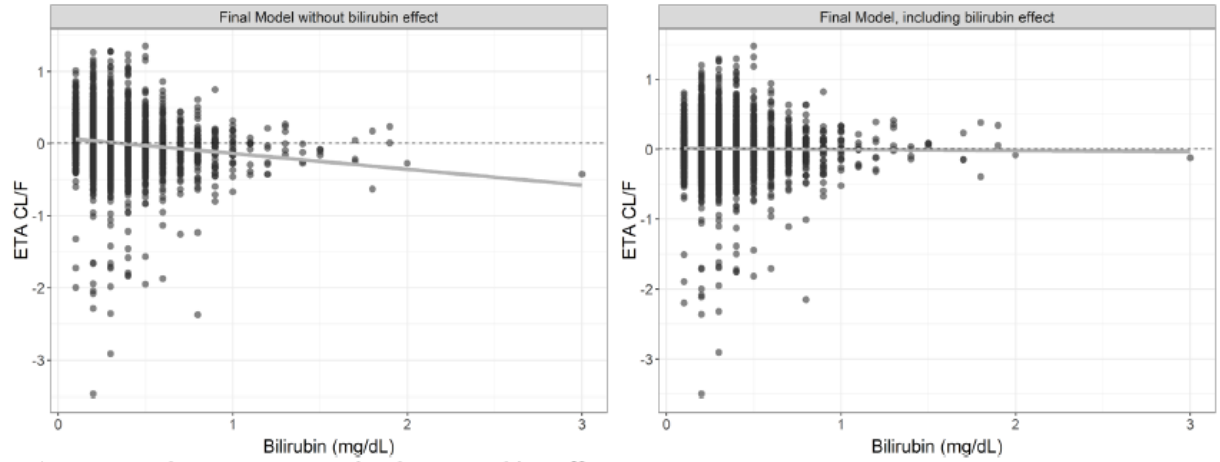
Figure 42. ETA CL Versus eGFR



CKD: chronic kidney disease; CL/F: apparent clearance; eGFR: estimated glomerular filtration rate; ETA: random between subject effect; NDD: non-dialysis dependent.
Note: Dots represent individual ETA values; solid line represents linear regression line.

Source: Applicant's PopPK Analysis Report, Figure 5-17, page 88

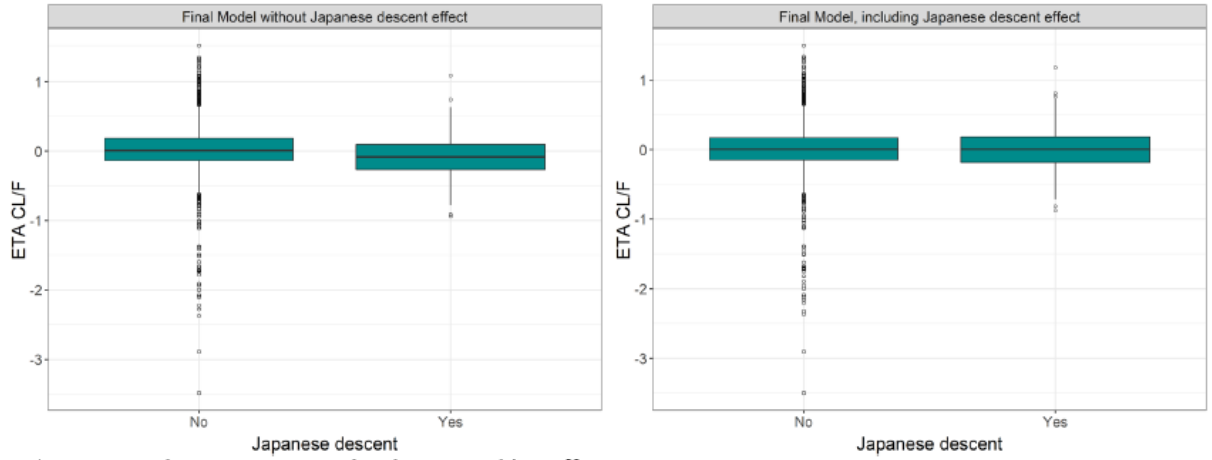
Figure 43. ETAL CL Versus Bilirubin



CL/F: apparent clearance; ETA: random between subject effect.

Source: Applicant's PopPK Analysis Report, Figure 5-17, page 88

Figure 44. ETA CL Versus Japanese Descent



CL/F: apparent clearance; ETA: random between subject effect.
Note: The box denotes the median, 25th and 75th percentiles of the subjects.

Source: Applicant's PopPK Analysis Report, Figure 5-20, page 90

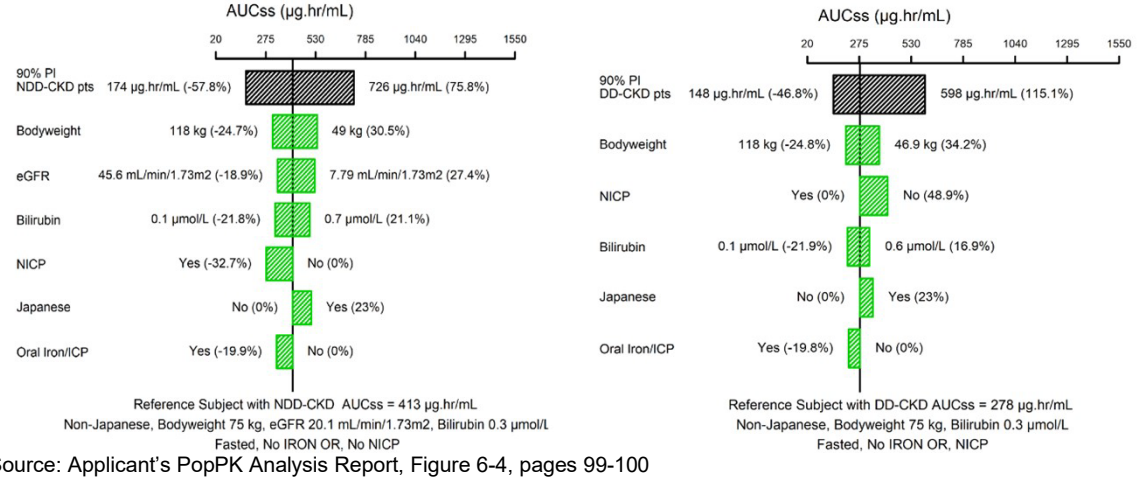
Impact of Covariates and Exposure

Select, significant covariates were evaluated in a univariate fashion to assess their impacts on vadadustat exposure (i.e., steady-state AUC, AUC_{SS}). The referent subjects were defined as:

- NDD-CKD: a non-Japanese subject having a body weight of 75 kg, eGFR of 20.1 mL/min/1.73m^2, bilirubin of 0.3 µmol/L and not treated with NICP or oral iron
- DD-CKD: a non-Japanese subject having a body weight of 75 kg, bilirubin of 0.3 µmol/L, treated with NICP and not treated with oral iron

Figure 45 demonstrated the covariate impact on vadadustat AUC_{SS} at 300 mg QD dosage. Additional plots and tables for covariate impact can be found in Section 6.2 of the Applicant's popPK Analysis Report.

Figure 45. Univariate Impact of Significant Covariates on Vadadustat Exposure (300 mg QD)



Source: Applicant's PopPK Analysis Report, Figure 6-4, pages 99-100
Abbreviations: AUC, area under the curve; DD-CKD, dialysis dependent chronic kidney disease; ICP, iterative closest point; NICP, normal iterative closest point

Reviewer's Comments

(1) *A query for additional covariate analyses was sent to the Applicant regarding: 1) clarification of number of subjects and associated PK samples grouped by hepatic function based on Child-Pugh scorings, 2) evaluation of impact of hepatic function as a categorical covariate (normal, mild, moderate, and severe hepatic impairment) on PK parameters, and 3) comparison of vadadustat clearance and PK exposures (i.e., Cmax, AUC at steady state).*

(2) *The Applicant responded that "The information (ascites and hepatic encephalopathy status) to calculate the Child-Pugh score were not collected for subjects enrolled in the vadadustat clinical studies and hence are not part of the population PK dataset. A dedicated hepatic impairment study (CI-0024) was conducted. This study was not included in the population PK dataset. The results from this study showed that vadadustat apparent clearance and exposures (Cmax and AUC) were similar between subjects with moderate hepatic impairment (Child-Pugh B; n=8) and subjects with normal hepatic function (n=8). Based on these results, it is unlikely that vadadustat PK would be different in subjects with mild hepatic impairment. Overall, the PK and safety data support the position that dose adjustment is unnecessary for subjects with mild to moderate hepatic impairment."*

(3) *A query was sent to further evaluate regional impact on CL and PK exposures at steady state. The Applicant utilized subsets of clinical studies that included regional information (popPK dataset did not) to address this information request. Table 221 summarizes the results of the analyses. The reviewer agreed that observed differences in overall drug exposure (i.e., AUC_{SS}) could likely be due to the lower body weight and CL in subgroups (i.e., Japanese subjects) and not likely be clinically significant. Furthermore, vadadustat dosage would be titrated in a clinical setting based on Hb target rather than a fixed 300 mg QD dosing in the presented simulation.*

Table 221. Summary of Model-Predicted PK Parameters for Vadadustat 300 mg QD at Steady State by Study Region and Patient Populations

Parameter	Study Region	N	GeoMean	GeoCV (%)	GMR (Other Region/US)	GMR (DD/NDD)
NDD						
$AUC_{0\text{-}24hr}$, µg·hr/mL	US	952	313	45.1	1	0.879
	Europe	286	355	42.8	1.13	0.839
	Japan	185	622	39.4	1.99	0.704
	ROW	558	354	39.9	1.13	0.921
C_{max}, µg/mL	US	952	18.4	37.8	1	0.875
	Europe	286	20.7	35.3	1.12	0.855
	Japan	185	33.9	31.7	1.84	0.705
	ROW	558	20.9	33.1	1.14	0.909
CL/F (L/hr)	US	952	0.808	41.9	1	0.963
	Europe	286	0.726	41.2	0.899	1.050
	Japan	185	0.448	39.3	0.554	1.025
	ROW	558	0.725	39.2	0.897	0.979
Frel[a]	US	952	0.847	17.8	1	0.847
	Europe	286	0.865	18.1	1.02	0.880
	Japan	185	0.932	12.6	1.10	0.722
	ROW	558	0.860	18.6	1.02	0.900
DD						
$AUC_{0\text{-}24hr}$, µg·hr/mL	US	1153	275	45.0	1	--
	Europe	268	298	38.0	1.08	--
	Japan	192	438	43.9	1.59	--
	ROW	464	326	41.6	1.19	--
C_{max}, µg/mL	US	1153	16.1	37.0	1	--
	Europe	268	17.7	32.1	1.10	--
	Japan	192	23.9	38.0	1.48	--
	ROW	464	19.0	35.6	1.18	--
CL/F (L/hr)[a]	US	1153	0.778	41.1	1	--
	Europe	268	0.762	32.6	0.979	--
	Japan	192	0.459	35.6	0.590	--
	ROW	464	0.710	37.0	0.913	--
Frel[a]	US	1153	0.717	17.6	1	--
	Europe	268	0.761	20.0	1.06	--
	Japan	192	0.673	19.6	0.939	--
	ROW	464	0.774	22.4	1.08	--

Source: Clinical Information Amendment 1.11.3 (submitted in SN 0021 on September 14, 2021 by the Applicant)
Abbreviations: AUC, area under the curve; CL/F, apparent clearance; Cmax, maximum plasma concentration; DD, dialysis dependent; Frel, relative bioavailability; GeoCV, geometric coefficient of variation; GeoMean, geometric mean; GMR, geometric mean ratio; N, sample size; NDD, non-dialysis dependent; PK, pharmacokinetics

Overall, the final model captured the central tendency of data adequately and informed key PK parameters and covariates impacting vadadustat exposure across healthy, DD, and NDD populations. The final model supported posterior predictions, exposure estimates, and establish exposure-safety analyses.

14.3.2. Population PK/PD and E-R Analyses

The following PK/PD and E-R analyses were conducted:

- Vadadustat exposure (final popPK model) and hemoglobin (Hb) response
- Safety E-R analysis

The objectives of the PK/PD analyses were to evaluate the E-R relationship for Hb response and safety endpoints after initiation of vadadustat. Specifically, the Applicant sought to: 1) develop a PK/PD model for Hb response using two phase 2 and six phase 3 studies and quantify vadadustat exposure on Hb response, 2) explore the relationship between vadadustat exposure and safety

endpoints for diarrhea, nausea, vomiting, gastrointestinal-related events, hepatotoxicity, and hyperkalemia.

Additionally, the reviewer requested the following analyses

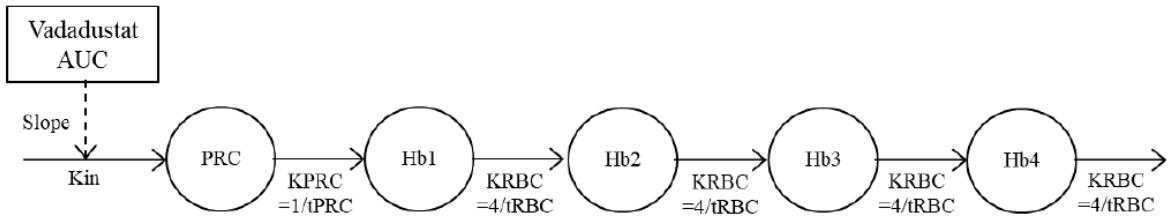
- Assess PK/PD model fit improvement by using a separate residual error term for Japanese subjects
- Evaluate the impact of study region in the PK/PD and E-R safety analyses
- Conduct E-R analyses for additional safety endpoints: major adverse cardiovascular event (MACE) events and non-fatal myocardial infarction (MI)

Hb PK/PD

A total of 47988 Hb observations contributed from 3952 subjects was included in the Hb PK/PD analysis. Figure 46 and Figure 47 provide a schematic of the PK/PD model structure and observed (individual) Hb concentration-time profiles, respectively.

Briefly, the Hb PK/PD model consisted of a precursor cell compartment (PRC) linked to a set of life span compartments (Hb1, Hb2, etc.), indicating the life span of Hb. The subject level vadadustat daily dosage history was utilized to derive cumulative AUC as inputs to the PRC compartment. Vadadustat exposure effect was tested with linear, Emax, or sigmoid Emax models during PK/PD model development. A summary of final PK/PD model parameters is listed in Table 222. Model diagnostic plots are provided in Figure 48, Figure 49, and Figure 50. Figure 51 is the pcVPC from an updated PK/PD model after our Information Request (see reviewer's comments).

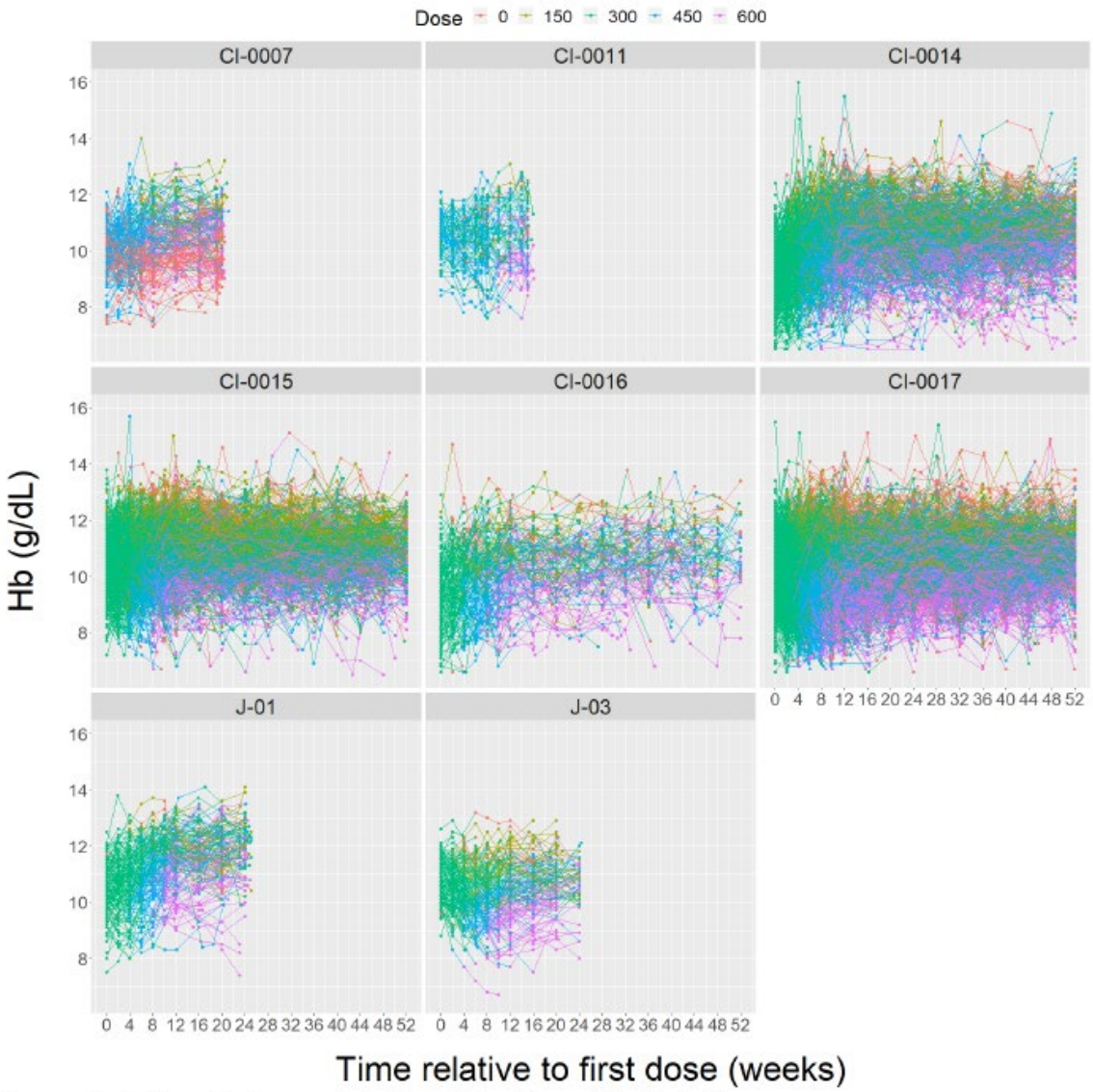
Figure 46. Hb PK/PD Model Schematic



Abbreviations: AUC = area under the concentration-time curve; Hb = hemoglobin; Kin = precursor production rate; Kprc = Transition rate constant from precursor cell to red blood cell; Nrbc = number of red blood cell life span compartments; PK/PD = pharmacokinetic/pharmacodynamic; Trbc = red blood cell life span.

Source: Applicant's PK/PD Analysis Report, Figure 3-1, page 30

Figure 47. Observed Hb Concentration-Time Profiles by Study



Source: Rscript 3. exploratory-analysis-Hb-profiles.; Figure_SP_All_studies.png
Note: Solid lines represent individual Hb time profiles colored following dose level administered. Dots are observation after the first vadadustat administration.
Abbreviation: Hb = hemoglobin.

Source: Applicant's PK/PD Analysis Report, Figure 5-1, page 44

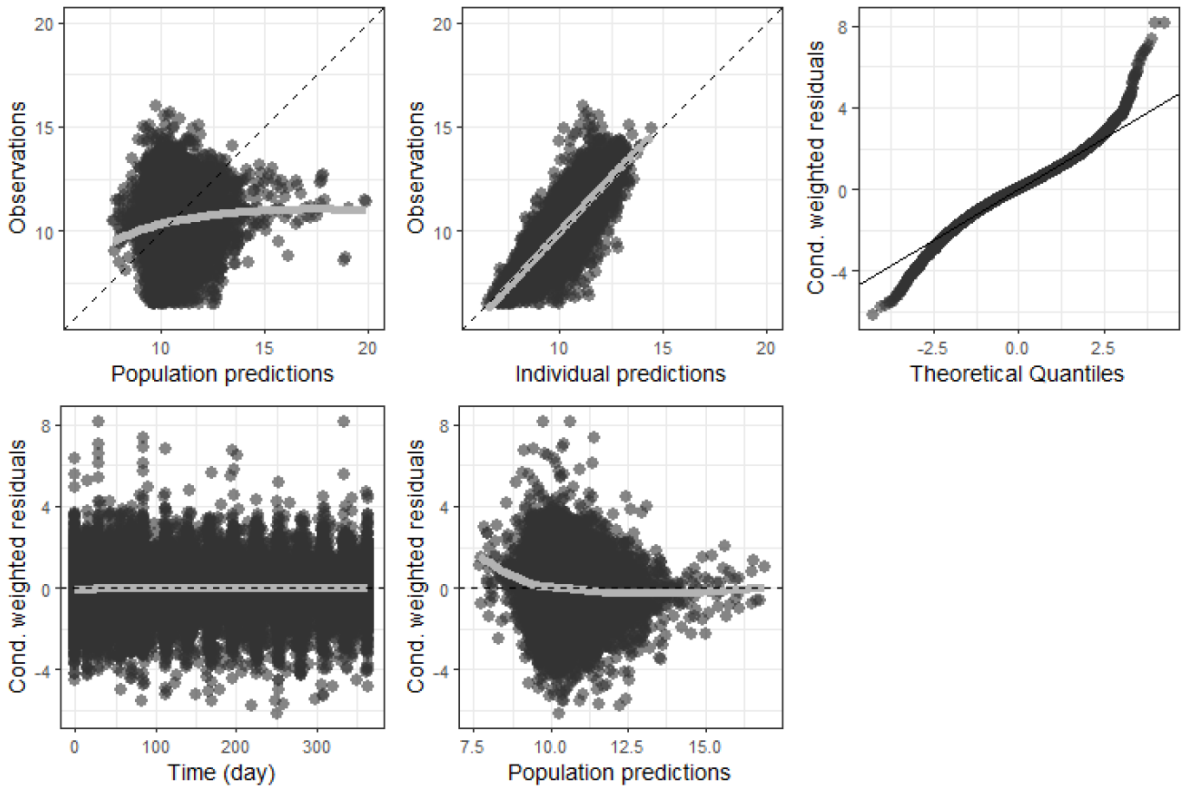
Table 222. Parameter Estimates for the Final Hb PK/PD Model

Parameter	Estimate	RSE (%)[a]	Parameter	Estimate	RSE (%)[a]
	Previous Final Model (Run156bis mod)			Updated Model (Run171 mod)	
Endogenous Hb DD-CKD (Studies CI-0011, CI-0016, and CI-0017; g/dL)	9.40	1.7	Endogenous Hb DD-CKD (Studies CI-0011, CI-0016, and CI-0017; g/dL)	9.38	0.3
Endogenous Hb NDD-CKD (Studies CI-0007, CI-0014, and CI-0015; g/dL)	9.60	0.0	Endogenous Hb NDD-CKD (Studies CI-0007, CI-0014, and CI-0015; g/dL)	9.58	0.2
Endogenous Hb NDD-CKD, Japanese (Study J-01; g/dL)	9.98	0.8	Endogenous Hb NDD-CKD, Japanese (Study J-01; g/dL)	9.98	0.8
Endogenous Hb DD-CKD, Japanese (Study J-03; g/dL)	9.68	0.7	Endogenous Hb DD-CKD, Japanese (Study J-03; g/dL)	9.69	0.6
RSA (-)	0.0976	0.2	RSA (-)	0.1	0.4
tRBC (day)	61.5	0.1	tRBC (day)	60.5	0.2
tPRC (day)	19.2 FIX	--	tPRC (day)	19.2 FIX	--
Slope in non-Japanese (1/(mg·h/mL))	0.346	0.4	Slope in non-Japanese (1/(mg·h/mL))	0.352	3
WNESA ~ endogenous Hb	-0.231	23.3	WNESA ~ endogenous Hb	-0.237	6.6
WNESA on RSA	0.934	2.5	WNESA on RSA	0.947	2
Japanese descent ~ slope	-0.369	11.1	Japanese descent ~ slope	-0.38	12
IIV			**IIV**		
IIV endogenous Hb (SD)	0.799	21.6	IIV endogenous Hb (SD)	0.799	48.5
IIV tRBC (%CV)	127	13.2	IIV tRBC (%CV)	129	4.45
IIV slope (SD)	0.336	2.3	IIV slope in non-Japanese (SD)	0.354	17.8
			IIV slope in Japanese (SD)	0.224	14.9
Residual Variability			**Residual Variability**		
Residual error	0.0604	0.1	Residual error (non-Japanese)	0.0612	0.1
			Residual error (Japanese)	0.041	3.1

Source: pk-prm-table-sensitive analysis.r
[a] The RSEs for omega and sigma are reported on the approximate standard deviation scale (SE/variance estimate/2).
CV: coefficient of variation; Hb: hemoglobin; IIV: inter-individual variability; RSA: residual prior erythropoiesis-stimulating agent effect; RSE: relative standard error; SD: standard deviation; SE: standard error; Slope: slope parameter translating vadadustat exposure to fractional increase in precursor production rate; tPRC: precursor cell residence time; tRBC: red blood cell life span; WNESA: weekly weight-normalized prior erythropoiesis-stimulating agent.
Run171 mod = run156bis.mod + a separate residual error term and a separate IIV term on the slope for the Japanese study population
= run161 + a separate IIV term on the slope for the Japanese study population.

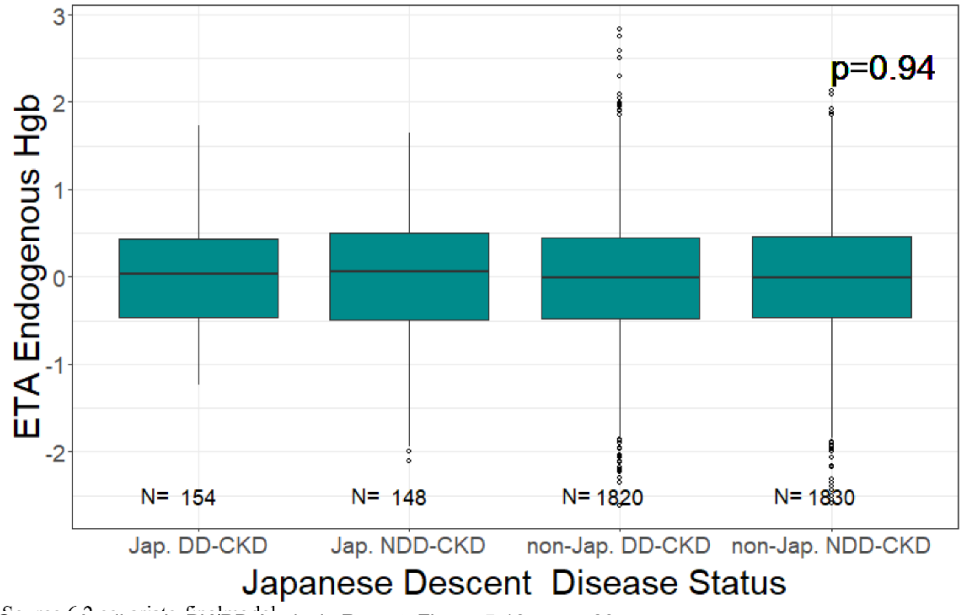
Source: Clinical Information Amendment 1.11.3 (submitted in SN 0021 on 14 September 2021 by the Applicant)

Figure 48. Goodness-of-Fit Plots of the Final PK/PD Model



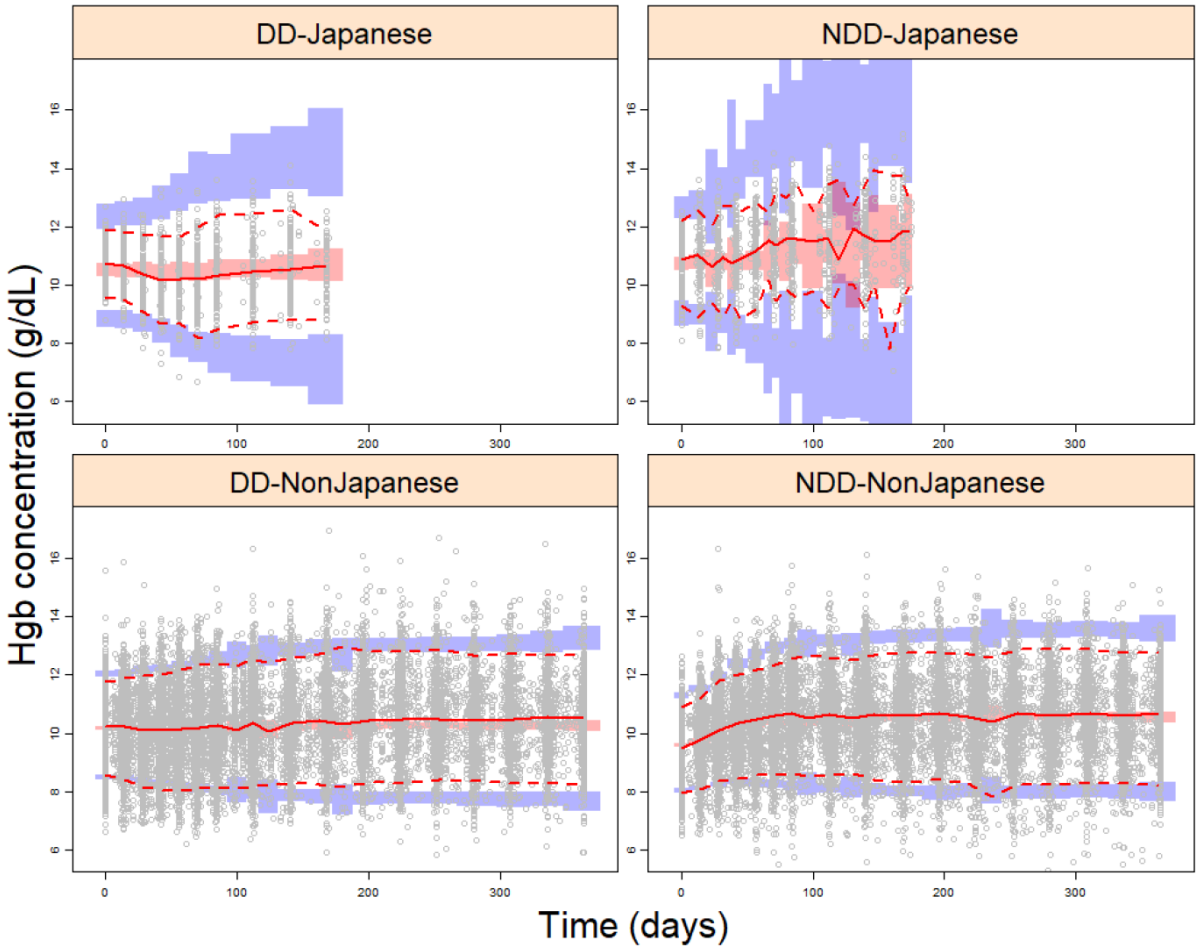
Source: Applicant's PK/PD Analysis Report, Figure 5-9, page 62
Abbreviations: PK/PD, pharmacokinetic/pharmacodynamic

Figure 49. Distribution of ETA Endogenous Hb Versus Japanese Descent and Disease Status



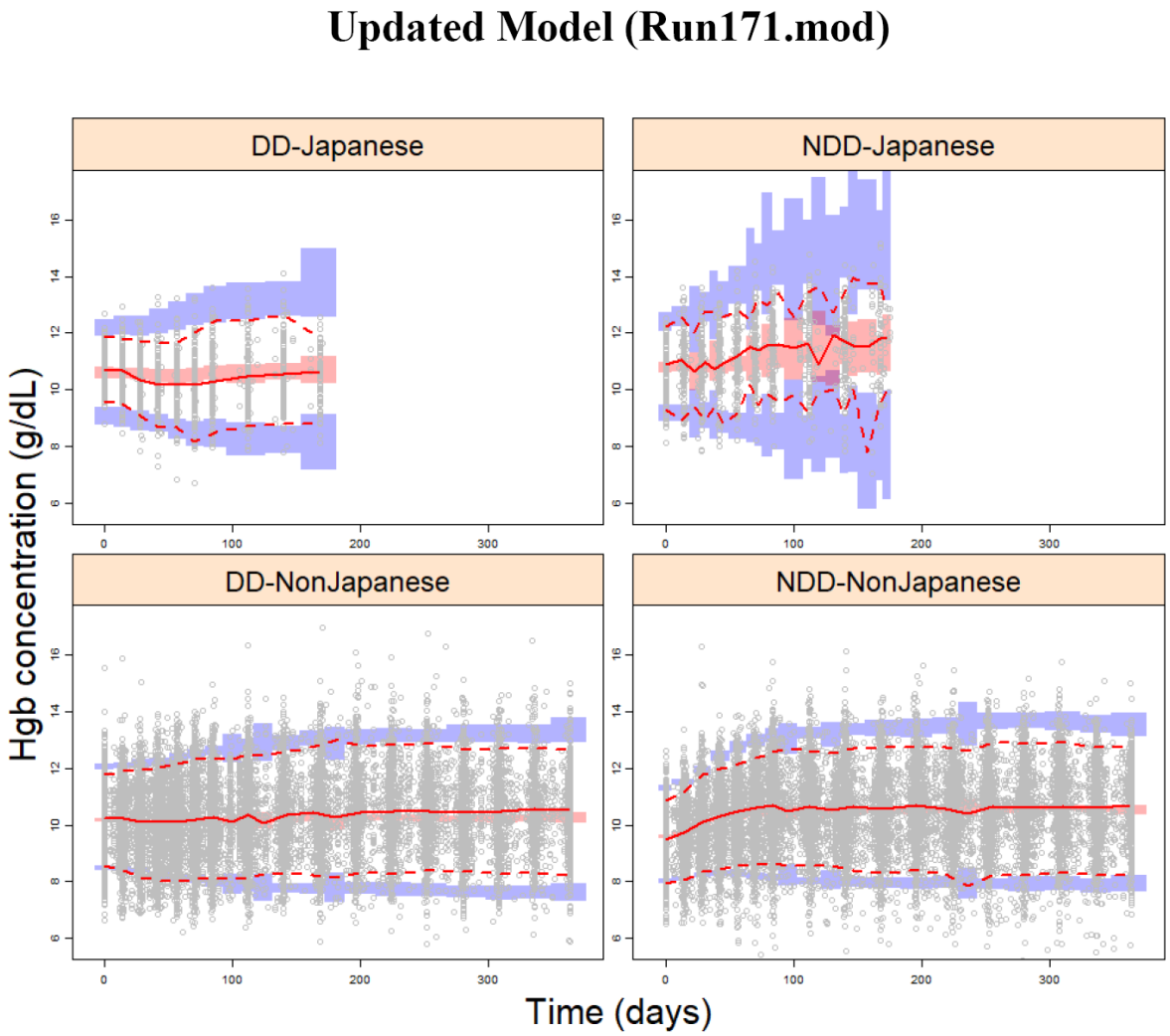
Source: Applicant's PK/PD Analysis Report, Figure 5-10, page 63
Abbreviations: DD-CKD, dialysis dependent chronic kidney disease; ETA, random between subject effect; Hb/Hgb, hemoglobin; N, sample size; NDD-CKD, non-dialysis dependent chronic kidney disease

Figure 50. PC-VPC for the Final Model



Source: Applicant's PK/PD Analysis Report, Figure 5-13, page 65
The gray circles represent the observed data. The red solid and dashed lines represent median and 5th to 95th percentiles of the observed data. The blue and pink areas represent median and 5th to 95th percentiles of the simulated data with their 90% CI.
Abbreviations: CI, confidence interval; DD, dialysis dependent; Hb, hemoglobin; NDD, non-dialysis dependent; pcVPC, prediction-corrected visual predictive check

Figure 51. PC-VPC for the Updated Model (Information Request)



Source: Clinical Information Amendment 1.11.3 (submitted in SN 0021 on 14 September 2021 by the Applicant)
Abbreviations: DD, dialysis-dependent; Hgb, hemoglobin; NDD, non-dialysis dependent; pcVPC, prediction-corrected visual predictive check

Reviewer's Comments:

The final PK/PD model generally captured the central tendency of observed Hb data with precisely estimated PK parameters. GoF plots did not demonstrate obvious trends or bias of the predictions; however, the between-subject variability may have impacted the population predicted values and observed versus population predicted may be a less reliable diagnostic plot. ETA of endogenous Hb centered around 0 across Japanese descent (categorical) and DD- or NDD-CKD populations.

As shown in Table 222, the Applicant fulfilled the Agency's query on modeling a separate residual error term for the Japanese subgroup because of the slight over-predictions seen in the upper right panel (NDD-Japanese) in Figure 50, despite adequately capturing central tendency of observed endogenous Hb data. While the revised PK/PD model had a significant OFV drop (from the original final model) by 526.974, no improvements in pcVPC was observed. An additional step was taken by estimating IIV slope in Japanese versus non-Japanese subjects. As a result, the upper bound of predictions were narrower and closer to the observed data for NDD-Japanese subjects (Figure 51).

Safety E-R Analysis

Briefly, the exposure metrics of vadadustat were derived as following:

Figure 52. Exposure Metrics

- Time-averaged AUC until an event X is derived as follows:

  1. $\frac{\text{Frel} * \text{Cumulative dose before first event X}}{\text{Vadadustat apparent clearance}} / (\text{days to first event X})$

  Frel is the relative bioavailability.

  Days to the first event X = date of the first event X – date of the first dose + 1.

  Cumulative dose before the first event X = total dose before the first event X.

- Time-averaged AUC during 4 weeks preceding the event is derived as follows:

  2. $\frac{\text{Frel} * \text{Cumulative dose 4 weeks before first event X}}{\text{Vadadustat apparent clearance}} / (28\ days)$

  Frel is the relative bioavailability.

  Cumulative dose 28 days before the first event X = total dose administered for 28 days before the first event X.

  In case the event occurs within the first 28 days of start of treatment, the AUC during 4 weeks preceding the event will be equal to the time-averaged AUC until the event.

- In case of no event, the time-averaged AUC over the full treatment period or censoring is defined as follows:

  3. $\frac{\text{Frel} * \text{Cumulative dose}}{\text{Vadadustat apparent clearance}} / (\text{Total days of treatment})$

  Frel is the relative bioavailability.

  Total days of treatment = date of the last dose – date of the first dose + 1.

  Cumulative dose = total dose on treatment.

Source: Applicant's PK/PD Analysis Report, Section 3.4.2, page 36
Abbreviations: AUC, area under the curve

The safety E-R analysis dataset consisted of 1553 evaluable events from 3473 subjects. Table 223 and Table 224 provides a summary of baseline demographics. Table 225 provides safety endpoint incidents by diseases states. Logistic and Cox regressions were utilized for quantifying impact of exposure on safety events, and both analyses showed consistent results and only relevant logistic regression results are shown below.

Table 223. Summary of Baseline Continuous Covariates by Study

Covariate	Mean (CV%) Median [Min, Max]				
	Study CI-0014 (N=836)	Study CI-0015 (N=839)	Study CI-0016 (N=168)	Study CI-0017 (N=1630)	Overall (N=3473)
Age	65.3 (21.9)	67.3 (19.4)	56.9 (26.1)	58 (23.6)	61.9 (23.2)
(years)	67 [19, 97]	68 [22, 104]	57 [24, 90]	59 [20, 93]	63 [19, 104]
eGFR	21.7 (55.7)	23.7 (68.5)	8.89 (56.8)	7.22 (65.1)	14.8 (88.2)
(mL/min/1.73m^2)	18.7 [2.82, 98.2]	21 [4.47, 337]	7.48 [2.68, 30.3]	5.96 [2.18, 75.4]	10.3 [2.18, 337]

Source: Applicant's PK/PD Analysis Report, Table 5-10, page 67
Abbreviations: CV%, coefficient of variation; eGFR, estimated glomerular filtration rate

Table 224. Summary of Baseline Categorical Covariates by Study

Covariate Category	Number of Subjects (%)				
	Study CI-0014 (N=836)	Study CI-0015 (N=839)	Study CI-0016 (N=168)	Study CI-0017 (N=1630)	Overall (N=3473)
Sex					
Male	383 (45.8)	381 (45.4)	96 (57.1)	918 (56.3)	1778 (51.2)
Female	453 (54.2)	458 (54.6)	72 (42.9)	712 (43.7)	1695 (48.8)
Region					
US	509 (60.9)	323 (38.5)	86 (51.2)	980 (60.1)	1898 (54.7)
Europe	66 (7.9)	220 (26.2)	25 (14.9)	243 (14.9)	554 (16)
ROW	261 (31.2)	296 (35.3)	57 (33.9)	407 (25)	1021 (29.4)
Race					
White	523 (62.6)	614 (73.2)	120 (71.4)	1051 (64.5)	2308 (66.5)
Black or African American	183 (21.9)	90 (10.7)	35 (20.8)	401 (24.6)	709 (20.4)
Asian	44 (5.3)	62 (7.4)	12 (7.1)	72 (4.4)	190 (5.5)
American Indian/Alaskan Native	19 (2.3)	31 (3.7)	1 (0.6)	16 (1)	67 (1.9)
Native Hawaiian or Other Pacific Islander	5 (0.6)	2 (0.2)	0 (0)	12 (0.7)	19 (0.5)
Other	59 (7.1)	25 (3)	0 (0)	43 (2.6)	127 (3.7)
Missing	3 (0.4)	15 (1.8)	0 (0)	35 (2.1)	53 (1.5)
ESA status					
Correction	836 (100)	0 (0)	84 (50)	7 (0.4)	927 (26.7)
Conversion	0 (0)	839 (100)	84 (50)	1623 (99.6)	2546 (73.3)
Chronic Kidney Disease stages					
Stage 5	285 (34.1)	231 (27.5)	155 (92.3)	1542 (94.6)	2213 (63.7)
Stage 4	366 (43.8)	392 (46.7)	12 (7.1)	75 (4.6)	845 (24.3)
Stage 3b	147 (17.6)	168 (20)	1 (0.6)	10 (0.6)	326 (9.4)
Stage 3a	31 (3.7)	39 (4.6)	0 (0)	1 (0.1)	71 (2)
Stage 2	6 (0.7)	8 (1)	0 (0)	1 (0.1)	15 (0.4)
Stage 1	1 (0.1)	1 (0.1)	0 (0)	0 (0)	2 (0.1)
Missing	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0)

Source: Applicant's PK/PD Analysis Report, Table 5-12, page 68

Table 225. Summary for Subjects and Incidence of Safety Endpoints

Selected Safety Endpoint	NDD-CKD (N=1675)		DD-CKD (N=1798)		Overall (N=3473)	
	N	Incidence (CI)	N	Incidence (CI)	N	Incidence (CI)
Diarrhea	169	0.101 (0.085 - 0.119)	161	0.0895 (0.075 - 0.106)	330	0.095 (0.0842 - 0.107)
Vomiting	80	0.0478 (0.0368 - 0.0608)	79	0.0439 (0.0338 - 0.056)	159	0.0458 (0.0382 - 0.0544)
Nausea	122	0.0728 (0.0593 - 0.0883)	104	0.0578 (0.0461 - 0.0714)	226	0.0651 (0.056 - 0.0751)
GI disorders	295	0.176 (0.156 - 0.198)	283	0.157 (0.139 - 0.178)	578	0.166 (0.152 - 0.181)
Hepatotoxicity	10	0.00597 (0.00256 - 0.0117)	70	0.0389 (0.0294 - 0.0504)	80	0.023 (0.0177 - 0.0294)
Hyperkalemia	111	0.0663 (0.0533 - 0.0812)	69	0.0384 (0.0289 - 0.0498)	180	0.0518 (0.0437 - 0.0609)

Source: Applicant's PK/PD Analysis Report, Table 5-9, page 66
Abbreviations: CI, confidence interval; GI, gastrointestinal; N, sample size; NDD-CKD, non-dialysis dependent chronic kidney disease

Table 226 and Table 227 provide summaries of E-R relationships for vadadustat exposure and events of interest, and the latter table summarizes the model-predicted incidences of safety events based on logistic regressions (model not shown). Table 228 lists the updated incidences of safety events across vadadustat percentiles by study regions (after our query).

Table 226. Median (5th-95th Percentiles) of Vadadustat Exposures vs. Safety Endpoints

Selected Safety Endpoint	Event	Median (5^{th} – 95^{th} percentile) Average AUC until event
Diarrhea	Yes	348 (140 - 749)
	No	335 (116 - 731)
Vomiting	Yes	326 (125 - 752)
	No	335 (117 - 729)
Nausea	Yes	345 (144 - 881)
	No	335 (117 - 729)
GI disorders	Yes	342 (140 - 789)
	No	336 (116 - 729)
Hepatotoxicity	Yes	337 (116 - 749)
	No	335 (116 - 729)
Hyperkalemia	Yes	365 (165 - 759)
	No	333 (116 - 725)

Source: Applicant's PK/PD Analysis Report, Table 5-15, page 66
Abbreviations: AUC, area under the curve; GI, gastrointestinal

Table 227. Logistic Regression Predicted Safety Event Incidences at 10th, 50th, and 90th Percentiles of Vadadustat Exposures

	Model-Predicted Incidence (95% CI)		
Selected Safety Endpoint	**AUC - P10 (155 µg·h/mL)**	**AUC - P50 (336 µg·h/mL)**	**AUC - P90 (617 µg·h/mL)**
Diarrhea	0.087	0.093	0.104
	(0.076 - 0.1)	(0.084 - 0.104)	(0.091 - 0.118)
Vomiting	0.044	0.045	0.048
	(0.036 - 0.053)	(0.039 - 0.053)	(0.039 - 0.059)
Nausea	0.057	0.063	0.074
	(0.049 - 0.067)	(0.056 - 0.072)	(0.063 - 0.085)
GI disorders	0.153	0.164	0.181
	(0.139 - 0.169)	(0.152 - 0.177)	(0.164 - 0.199)
Hepatotoxicity	0.023	0.023	0.023
	(0.017 - 0.031)	(0.018 - 0.029)	(0.017 - 0.032)
Hyperkalemia	0.047	0.051	0.058
	(0.039 - 0.056)	(0.044 - 0.059)	(0.048 - 0.069)

Source: Applicant's PK/PD Analysis Report, Table 5-18, page 77
Abbreviations: AUC, area under the curve; GI, gastrointestinal

Table 228. Logistic Regression Predicted Safety Events Incidences Stratified by Study Regions

SSE	Region	Model-Predicted Incidence (95% CI)		
		AUC - P10 (155 µg·h/mL)	AUC - P50 (336 µg·h/mL)	AUC - P90 (618 µg·h/mL)
Diarrhea	US	0.1 (0.121; 0.078)	0.125 (0.141; 0.108)	0.149 (0.176; 0.12)
	Europe	0.046 (0.075; 0.017)	0.063 (0.084; 0.041)	0.079 (0.115; 0.042)
	Rest of the World	0.11 (0.147; 0.072)	0.105 (0.125; 0.085)	0.101 (0.13; 0.072)
Vomiting	US	0.059 (0.075; 0.042)	0.057 (0.069; 0.045)	0.056 (0.073; 0.038)
	Europe	0.015 (0.029; 0)	0.031 (0.048; 0.014)	0.056 (0.087; 0.025)
	Rest of the World	0.062 (0.09; 0.032)	0.055 (0.07; 0.04)	0.051 (0.072; 0.03)
Nausea	US	0.077 (0.096; 0.058)	0.09 (0.104; 0.076)	0.102 (0.125; 0.078)
	Europe	0.027 (0.048; 0.005)	0.042 (0.06; 0.024)	0.059 (0.09; 0.027)
	Rest of the World	0.041 (0.064; 0.018)	0.062 (0.079; 0.045)	0.085 (0.113; 0.057)
Gastrointestinal disorders	US	0.188 (0.216; 0.16)	0.215 (0.235; 0.195)	0.239 (0.271; 0.206)
	Europe	0.087 (0.126; 0.047)	0.118 (0.146; 0.089)	0.148 (0.195; 0.099)
	Rest of the World	0.165 (0.208; 0.12)	0.178 (0.203; 0.152)	0.189 (0.226; 0.15)
Hepatotoxicity	US	0.034 (0.048; 0.021)	0.033 (0.042; 0.024)	0.032 (0.045; 0.018)
	Europe	0.014 (0.03; -0.003)	0.012 (0.021; 0.002)	0.01 (0.023; -0.003)
	Rest of the World	0.019 (0.035; 0.003)	0.025 (0.036; 0.014)	0.031 (0.049; 0.014)
Hyperkalemia	US	0.056 (0.073; 0.039)	0.074 (0.087; 0.061)	0.092 (0.115; 0.069)
	Europe	0.007 (0.016; -0.002)	0.017 (0.029; 0.004)	0.034 (0.057; 0.01)
	Rest of the World	0.052 (0.079; 0.025)	0.066 (0.083; 0.048)	0.079 (0.106; 0.051)

AUC: area under the concentration-time curve; CI: confidence interval; P10, P50, and P90: the 10th, 50th, and 90th percentile, respectively; SSE: selected safety endpoint.

Source: Clinical Information Amendment 1.11.3 (submitted in SN 0021 on 28 September 2021 by the Applicant)

Reviewer's Comments

The safety E-R analyses demonstrated that while some numeric changes of safety event incidence were observed across the vadadustat AUC ranges, the reviewer agreed that numerically small incidence rates may not translate to meaningful clinical difference. Nonetheless, the Agency requested additional E-R analysis incorporating study regions (due to Hb target difference during clinical studies and potential practice difference). As shown in Table 228, when study regions were considered in this analysis, similar trends were observed with 95% CIs overlapping across exposure percentiles. The reviewer noted that the 95% CI of model-predicted incidence was likely mistakenly reversed. Overall, the results showed that E-R safety relationships were close to flat and numeric differences may not be clinically meaningful.

MACE and Non-Fatal MI E-R Analysis

Per our query, the Applicant performed E-R analyses for MACE events and non-fatal MI as endpoints. A total of 3455 subjects were included for logistic regression and Cox regression with MACE events up to 52 weeks. The same definition of vadadustat exposure to event of interest was employed (i.e., time-averaged daily AUC up to event of interest). The analyses results are listed in Table 229 and Figure 53.

Table 229. Incidence of MACE and Non-Fatal MI by Exposure Quantiles

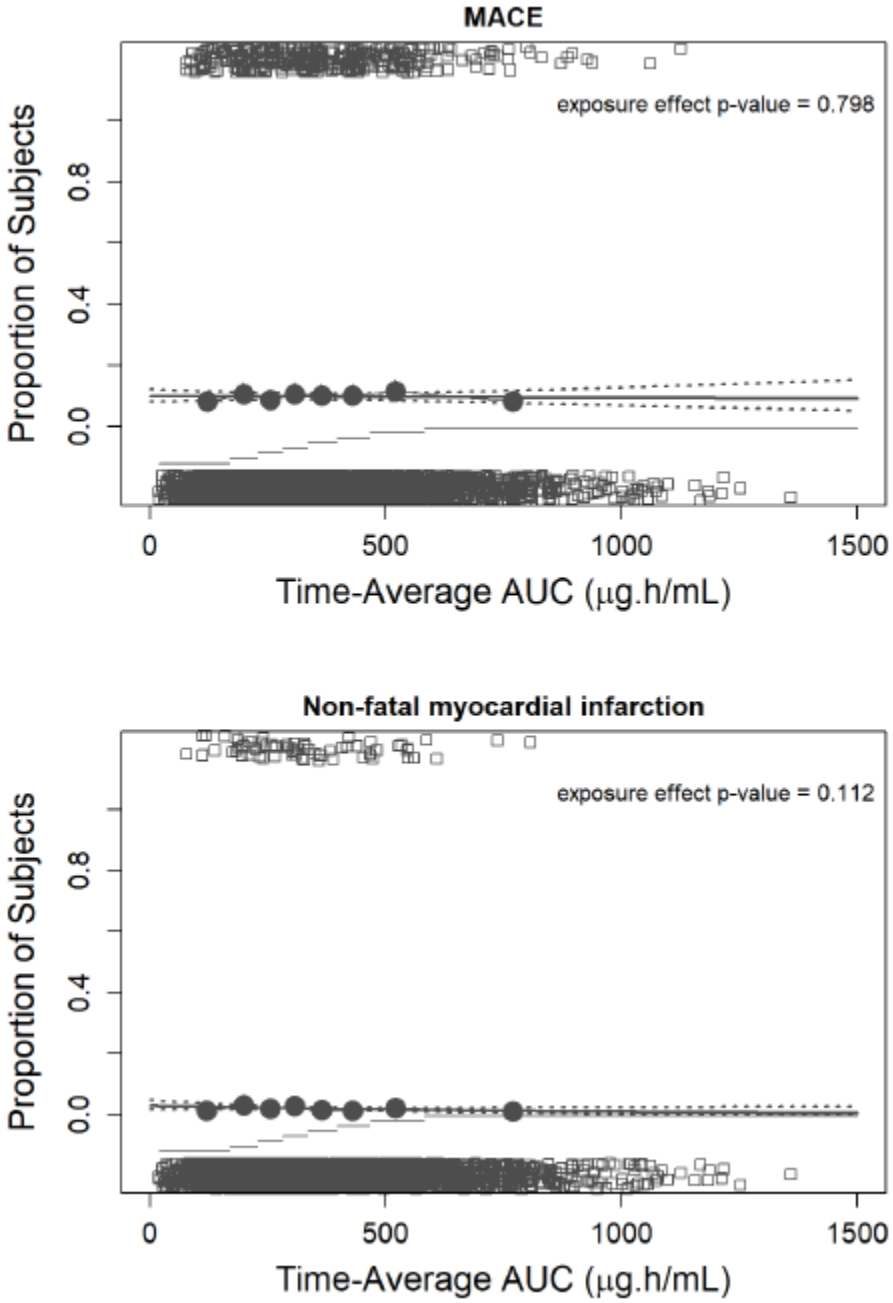
Time-averaged AUC bin	[18;169] (N=432)	[169;228] (N=432)	[228;281] (N=432)	[281;335] (N=432)	[335;397] (N=431)	[397;466] (N=432)	[466;582] (N=432)	[582;5020] (N=432)	Overall (N=3455)
MACE									
No	396 (91.7%)	386 (89.4%)	394 (91.2%)	386 (89.4%)	387 (89.8%)	388 (89.8%)	382 (88.4%)	396 (91.7%)	3115 (90.2%)
Yes	36 (8.3%)	46 (10.6%)	38 (8.8%)	46 (10.6%)	44 (10.2%)	44 (10.2%)	50 (11.6%)	36 (8.3%)	340 (9.8%)

Time-averaged AUC bin	[18;169] (N=432)	[169;228] (N=432)	[228;280] (N=432)	[280;334] (N=432)	[334;396] (N=431)	[396;467] (N=432)	[467;582] (N=432)	[582;5020] (N=432)	Overall (N=3455)
Non-fatal myocardial infarction									
No	426 (98.6%)	418 (96.8%)	423 (97.9%)	419 (97.0%)	425 (98.6%)	426 (98.6%)	422 (97.7%)	428 (99.1%)	3387 (98.0%)
Yes	6 (1.4%)	14 (3.2%)	9 (2.1%)	13 (3.0%)	6 (1.4%)	6 (1.4%)	10 (2.3%)	4 (0.9%)	68 (2.0%)

AUC: area under the plasma concentration-time curve; MACE: major adverse cardiac event.
AUC unit: µg·h/mL.

Source: Clinical Information Amendment 1.11.3 (submitted in SN 0021 on 28 September 2021 by the Applicant)

Figure 53. Incidence of MACE and Non-Fatal MI Versus Exposure (Logistic Regression)



Source: Clinical Information Amendment 1.11.3 (submitted in SN 0021 on 28 September 2021 by the Applicant)
Abbreviations: AUC, area under the curve; MACE, major adverse cardiovascular events; MI, non-fatal myocardial infarction
Open squares represent subjects with event (top of each panel) and with no event (bottom of each panel); solid dots represent incidence within each exposure quantile (eight quantiles total); solid line represents fitted logistic regression {logit[P(event)] * exposure * slope + intercept}; dashed lines represent 95% confidence interval; horizontal lines represent the width of each exposure quantile

Reviewer's Comments

Based on analyses by exposure quantiles, logistic regression, and Cox regression models (for Cox model, refer to Applicant's Information Request response in SN 0021, dated 28 September 2021), vadadustat did not significant impact MACE and non-fatal MI events. Graphical representation showed that model-predicted event incidence rates were similar across time-averaged vadadustat exposures (flat E-R relationship).

Table 230. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
(b) (4)		

Source: Reviewer's Analyses
Abbreviations: AUC, area under the curve; Hb, hemoglobin; MACE, major adverse cardiovascular events; NICP, normal iterative closest point; PK/PD, pharmacokinetic/pharmacodynamic; popPK, population pharmacokinetics

14.4. Summary of Bioanalytical Method Validation and Performance

Table 231. Analytical Methods for the Determination of Vadadustat in Human Plasma

Report No.	(b) (4) **09-283**	(b) (4) **11-254**
Clinical studies supported	AKB-6548-CI-0001, AKB-6548-CI-0002, AKB-6548-CI-0003, AKB-6548-CI-0004	AKB-6548-CI-0005, AKB-6548-CI-0006
Analyte	Vadadustat	Vadadustat
Matrix	Human plasma	Human plasma
Assay method	LC-MS/MS	LC-MS/MS
Sample preparation	Supported-liquid extraction (SLE)	SLE
Internal standard	d3-vada	d3-vada
LLOQ (ng/mL)	1	200

Report No.	(b) (4) 09-283	(b) (4) 11-254
Calibration curve range (ng/mL)	1.00 to 500	200 to 20000
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 9 Cumulative accuracy (% bias) from LLOQ to ULOQ: 99% to 103% Cumulative precision (% CV) from LLOQ to ULOQ: ≤9.96%	Number of standard calibrators from LLOQ to ULOQ: 8 Cumulative accuracy (% bias) from LLOQ to ULOQ: 91% to 115% Cumulative precision (% CV) from LLOQ to ULOQ: ≤5.5% to ≤15.1%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs: 91.9% to 118% Inter-batch %CV: ≤12.8%	Cumulative accuracy (%bias) in 4 QCs: 98.3% to 113% Inter-batch %CV: ≤9.97%
Selectivity (6 total lots tested)	Accuracy: 87.7% to 103%	Accuracy: 90.4% to 95.2%
Matrix effect	6 lots tested at 2.50, 40.0, and 400 ng/mL average matrix effect: -28.7%	6 lots tested at 250, 5000, and 35000 ng/mL average matrix effect: 2.20%
Interference and specificity	Interference of vada in blank samples with and without IS: 3.98% and 7.4% Mean interference of d3-vada: 0.391%	6 lots tested; 0.41% IS interference; 1.38% cross-analyte interference
Dilution linearity and hook effect	The highest concentration tested was 50000 ng/mL at a dilution factor of 200 with accuracy of 94.4%, n=6	Not evaluated
Bench-top/process stability	95.1% accuracy at 2.50 ng/mL and 105% accuracy at 400 ng/mL after 23.75 hours at room temperature	107% and 103% accuracy and 4.54% and 1.18% CV after 168 hours at room temperature
Freeze-thaw stability (after 4 freeze-thaw cycles)	95.0% accuracy at 2.50 ng/mL and 94.0% accuracy at 400 ng/mL	101% Accuracy and 2.69% CV
Long-term storage at -70°±10°C for 260 days	Accuracy: 91.6% to 101% CV: 9.2% to 9.8%	Not evaluated
Carryover	1.23% of LLOQ	4.85% of LLOQ

Source: (b) (4) 09-283 and (b) (4) 11-254 Validation Reports
Abbreviations: CV, coefficient of variation; IS, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; SLE, supported-liquid extraction; ULOQ, upper limit of quantification

Table 232. Analytical Methods for the Determination of Vadadustat and Its Metabolites in Human Plasma

Report No.	(b) (4) -797022	(b) (4) -797050/797067
Clinical studies supported	AKB-6548-CI-0007, AKB-6548-CI-0008, AKB-6548-CI-0009, AKB-6548-CI-0010, AKB-6548-CI-0011, AKB-6548-CI-0012	AKB-6548-CI-0013
Analyte	Vadadustat (vada), Vadadustat-O-Glucuronide (vada-OG), and Vadadustat-Acyl-Glucuronide (vada-AG)	Vada, vada-OG, vada-AG
Matrix	Human Plasma	Human Plasma
Assay method	UHPLC-MS/MS	UHPLC-MS/MS
Sample preparation	Solid phase extraction (SPE)	SPE

Report No.	[redacted]-797022	[redacted]-797050/797067
Internal standard	d3-vada, [redacted]	d3-vada, [redacted]
LLOQ (ng/mL)	Vada: 100 Vada-OG: 5 Vada-AG: 5	Vada: 100 Vada-OG: 100 Vada-AG: 10
Calibration curve range (ng/mL)	Vada: 100 to 10000 Vada-OG: 5 to 500 Vada-AG: 5 to 500	Vada: 100 to 20000 Vada-OG: 100 to 20000 Vada-AG: 10 to 2000
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 8 Cumulative accuracy (% RE) from LLOQ to ULOQ: Vada: -3.5% to 2.0% Vada-OG: -1.5% to 0.8% Vada-AG: -1.8% to 1.6% Cumulative precision (% RSD) from LLOQ to ULOQ: Vada: ≤9.2% Vada-OG: ≤7.9% Vada-AG: ≤8.5%	Number of standard calibrators from LLOQ to ULOQ: 9 Cumulative accuracy (% RE) from LLOQ to ULOQ: Vada: -2.0% to 1.5% Vada-OG: -3.5% to 2.5% Vada-AG: -2.5% to 2.0% Cumulative precision (% RSD) from LLOQ to ULOQ: Vada: ≤8.1% Vada-OG: ≤8.7% Vada-AG: ≤10.2%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 5 QCs: Vada: 0.7% to 5.4% Vada-OG: -5.2% to 3.6% Vada-AG: -6.6% to 8.8% Inter-batch %RSD: Vada: ≤10.1% Vada-OG: ≤10.3% Vada-AG: ≤12.2%	Cumulative accuracy (%RE) in 5 QCs: Vada: -3.1% to 1.4% Vada-OG: -3.5% to 1.3% Vada-AG: -2.5% to 3.5% Inter-batch %RSD: Vada: ≤17.6% Vada-OG: ≤14.6% Vada-AG: ≤11.3%
Selectivity (6 total lots tested)	Analyte/IS: 0.00% Cross-analyte: ≤5.11%	Analyte/IS: 0.00% Cross-analyte: ≤6.56%
Matrix effect	6 lots tested average matrix effect (%RE) Vada: -15.9% to -0.963% Vada-OG: -24.3% to -5.01% Vada-AG: -1.82% to 4.15%	6 lots tested average matrix effect (%RE) Vada: -2.8% to 9.0 Vada-OG: -11% to 5.0% Vada-AG: -4.4% to 13%
Dilution linearity and hook effect	Vada: 50-fold dilution of 50000 ng/mL sample; 5.4% RE, 2.6% RSD Vada-OG: 50-fold dilution of 2500 ng/mL sample; 3.6% RE, 1.9% RSD Vada-AG: 50-fold dilution of 2500 ng/mL sample; 8.8% RE, 3.4% RSD	Vada: 80000 ng/mL diluted by factor of 10, 5.1% RSD, 1.4% RE Vada-OG: 80000 ng/mL diluted by factor of 10, 7.9% RSD, -2.5% RE Vada-AG: 8000 ng/mL diluted by factor of 10, 7.9% RSD, 1.3% RE

Report No.	(b) (4)-797022	(b) (4)-797050/797067
Bench-top/process stability	Bench–top stability 6 h over wet-ice Vada: 104% -110% accuracy, 1.6% to 4.7% RSD Vada-OG: 102% -110 accuracy, 2.5% to 5.1% RSD Vada-AG: 97.1% -99.1% accuracy, 3.4% to 6.8% RSD Processed batch stability 5 days at 4°C Vada: 2.0% – 4.0% RSD, 7.1% to 5.0% RE Vada-OG: 1.9% to 7.0% RSD, -7.3% to -6.7% RE Vada-AG: 1.4% to 5.0% RSD, 8.6% to -6.7% RE	Bench-top stability stored on wet ice Vada Stored approximately 23 hours: 4.1% to 8.1% RSD, -5.0% to -1.9% RE Vada-OG Stored approximately 7.5 hours: 9.0% to 13% RSD, -11% to 0.53% RE Vada-AG Stored approximately 23 hours: 4.9% to 8.3% RSD, -8.7% to -1.7% RE
Freeze-thaw stability	After 4 freeze-thaw cycles Vada: 2.3% to 3.2% RSD, 100% to 104% accuracy Vada-OG: 1.5% to 2.9% RSD, 96.2% to 100% accuracy Vada-AG: 1.4 to 2.3% RSD, 91.4% to 95.6% accuracy	After 5 freeze-thaw cycles Vada: 2.2% to 11% RSD, -3.7% to -0.77% RE Vada-OG: 4.0% to 14% RSD, -4.0% to 1.4% RE Vada-AG: 5.7% to 6.2% RSD, -7.2% to 0.92% RE
Long-term storage at -70°C	For 278 days Vada: 7.0% to 9.5% RSD, 96.7% to 103% accuracy Vada-OG: 5.7% to 11.2% RSD, 95.8% to 99.2% accuracy Vada-AG: 1.4 to 2.3% RSD, 92.1% to 103% accuracy	For 358 days Vada: -2.5% to 5.7% RE Vada-OG: -12.5% to -7.3% RE Vada-AG: 1.0% to 5.0% RE
Carryover	≤2.69% of LLOQ for vada, vada-OG, and vada-AG	Met acceptance criteria

Source: (b) (4)-797022, (b) (4)-797050 (b) (4)797067 Validation Reports
Abbreviations: CV, coefficient of variation; UHPLC-MS/MS, ultra-high performance liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; RE, relative error; RSD, relative standard deviation; SPE, solid phase extraction; ULOQ, upper limit of quantification; vada, vadadustat; Vada-AG, vadadustat-Acyl-Glucuronide; vada-OG, vadadustat-O-Glucuronide

Table 233. Analytical Methods for the Determination of Vadadustat and Its Metabolites in Human Plasma

Report No.	151292VRM_AKCM_R1/R2	187190AULR
Clinical studies supported	AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0016, AKB-6548-CI-0017, AKB-6548-CI-0020, AKB-6548-CI-0021, AKB-6548-CI-0022, AKB-6548-CI-0024, AKB-6548-CI-0025, AKB-6548-CI-0027, AKB-6548-CI-0028, AKB-6548-CI-0029, AKB-6548-CI-0033, MT-6548-J01, MT-6548-J03, MT-6548-J05,	AKB-6548-CI-0034, AKB-6548-CI-0037

Report No.	151292VRM_AKCM_R1/R2	187190AULR
Analyte	Vadadustat (vada), Vadadustat-O-Glucuronide (vada-OG), and Vadadustat-Acyl-Glucuronide (vada-AG)	Vada, vada-OG
Matrix	Human plasma	Human plasma
Assay method	Turbo ion spray LC-MS/MS	Turbo ion spray LC-MS/MS
Sample preparation	SPE	SPE
Internal standard	d3-vada, (b) (4)	d3-vada, (b) (4)
LLOQ (ng/mL)	Vada: 100 Vada-OG: 5 Vada-AG: 5	Vada: 100 Vada-OG: 100 Vada-AG: 10
Calibration curve range (ng/mL)	Vada: 100 to 20000 Vada-OG: 100 to 20000 Vada-AG: 10 to 2000	Vada: 100 to 20000 Vada-OG: 100 to 20000
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 9 Cumulative accuracy (% RE) from LLOQ to ULOQ: Vada: -1.5% to 1.0% Vada-OG: -0.8% to 1.0% Vada-AG: -1.3% to 1.0% Cumulative precision (% RSD) from LLOQ to ULOQ: Vada: ≤3.4% Vada-OG: ≤6.4% Vada-AG: ≤6.7%	Number of standard calibrators from LLOQ to ULOQ: 8 Cumulative accuracy (% bias) from LLOQ to ULOQ: Vada: -2.20% to 2.48% Vada-OG: -1.94% to 2.72% Cumulative precision (% CV) from LLOQ to ULOQ: Vada: ≤3.92% Vada-OG: ≤6.51%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 5 QCs: Vada: 1.0% to 5.3% Vada-OG: 0.0% to 4.8% Vada-AG: 0.0% to 9.0% Inter-batch %CV: Vada: ≤6.1% Vada-OG: ≤7.5% Vada-AG: ≤7.8%	Cumulative accuracy (%bias) in 4 QCs: Vada: 1.28% to 3.50% Vada-OG: -3.36% to -1.17% Inter-batch %CV: Vada: ≤5.22% Vada-OG: ≤7.31%
Selectivity (6 total lots tested)	Analyte/IS: ≤5%	-0.23% and -4.44% mean bias for vada and vada-OG
Matrix effect	6 lots tested Normalized Matrix Factor as Mean (%CV) Vada: 1.00 (0.7) Vada-OG: 0.96 (1.8)	8 lots tested Vada: Mean IS-Normalized matrix factor: 0.962 and 0.981, CV: 2.23% and 2.46% Vada-OG:

Report No.	151292VRM_AKCM_R1/R2	187190AULR
	Vada-AG: 1.02 (8.3)	Mean IS-Normalized matrix factor: 1.03 and 1.03; CV: 2.45% and 1.75%
Dilution linearity and hook effect	Vada: 80000 ng/mL, 10-fold dilution CV: 3.7%, RE: -2.5% Vada-OG: 80000 ng/mL, 10-fold dilution CV: 4.2%, RE: -2.8% Vada-AG: 80000 ng/mL, 10-fold dilution CV: 4.3%, RE: -5.8%	98076.92 ng/mL analyzed at a dilution factor of 20, Vada: 4.60% mean bias and 2.45% CV Vada-OG: 0.69% mean bias and 7.72% CV
Bench-top/process stability	Bench–top stability after 24 hours in ice bath Vada: RE: -4.1% to 1.3%, CV: ≤3.5% Vada-OG: RE: -1.1% to 8.0%, CV: ≤2.7% Vada-AG: RE: -2.9% to 3.3%, CV: ≤4.2%	Room temperature (RT) stability for 23 h 26 min and at 4°C for 23 h 23 min at 4°C were as follows: Vada: % bias of 1.12% to 1.22% and ≤4.61% CV at RT, and 1.52% to 3.15% bias, ≤3.85% CV at 4°C Vada-OG: -4.30% to -2.86% and ≤7.06% CV at RT, and -3.03% to -1.72% bias and ≤4.83% CV at 4°C
Freeze-thaw stability	At -70°C after 5 freeze-thaw cycles Vada: RE: 0% to 2.8%, CV: ≤2.5% Vada-OG: RE: -9.3% to -1.8%, CV: ≤1.6% Vada-AG: RE: -13.7% to -8.9%, CV: ≤4.2%	6 cycles at -20°C and -80°C, thaw at 4°C Vada: At -20°C: %bias -6.22% to -5.37% and ≤5.88% CV At - 80°C: % bias -3.43% to -3.36% and ≤4.01% CV Vada-OG: at -20°C: %bias -6.21% to -2.54% and ≤6.37% CV at - 80°C: % bias -8.84% to -2.43% and ≤8.68% CV
Long-term storage at -70°C	For 1159 days Vada: RE: -1.3% to 4.3%, CV: ≤4.3% Vada-OG: RE: -1% to 8%, CV: ≤4.6% Vada-AG: RE: -8.7% to -3.6%, CV: ≤3%	For 569 days Vada: At -20°C: %bias -7.48% to -2.98% and ≤4.68% CV At - 80°C: % bias -6.22% to -3.81% and ≤3.56% CV Vada-OG: At -20°C: %bias -8.46% to -4.30% and ≤3.59% CV At - 80°C: % bias -8.40% to -0.96% and ≤4.52% CV

Report No.	151292VRM_AKCM_R1/R2	187190AULR
Carryover	1st blank <20% of LLOQ response	≤7.67% and ≤1.33% mean interference

Source: 151292VRM_AKCM Method Validation Report and 187190AULR Validation Report
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; RE, relative error; RSD, relative standard deviation; RT, real time; SPE, solid phase extraction; ULOQ, upper limit of quantification; vada, vadadustat; Vada-AG, vadadustat-Acyl-Glucuronide; vada-OG, vadadustat-O-Glucuronide

Table 234. Analytical Methods for the Determination of Vadadustat and Its Metabolites in Human Urine

Report No.	(b) (4) -797023
Clinical studies supported	AKB-6548-CI-0008
Analyte	Vada, vada-OG, and vada-AG
Matrix	Human urine
Assay method	UHPLC-MS/MS
Sample preparation	SPE
Internal standard	d3-vada, (b) (4)
LLOQ (ng/mL)	Vada: 10 Vada-OG: 200 Vada-AG: 20
Calibration curve range (ng/mL)	Vada: 10.0 to 1000 Vada-OG: 200 to 20000 Vada-AG: 20.0 to 2000
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 8 Cumulative accuracy (% RE) from LLOQ to ULOQ: Vada: -1.6% to 1.0% Vada-OG: -1.7% to 3.3% Vada-AG: -1.9% to 2.8% Cumulative precision (% RSD) from LLOQ to ULOQ: Vada: ≤6.4% Vada-OG: ≤10.8% Vada-AG: ≤7.3%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 5 QCs: Vada: -2.3% to 9.2% Vada-OG: -8.5% to 6.0% Vada-AG: -8.3% to 7.0% Inter-batch %CV: Vada: ≤7.4% Vada-OG: ≤11.8% Vada-AG: ≤15.0%
Selectivity (6 total lots tested)	Analyte/IS: ≤5%
Matrix effect	6 lots tested Mean Matrix Factor Vada: 7.81% to 9.91%

Report No.	(b) (4)-797023
	Vada-OG: 9.26% to 14.9%
	Vada-AG: 3.65% to 7.0%
Dilution linearity and hook effect	Vada: 50-fold dilutions of 5000 ng/mL
	≤3.5% CV, 7.6% to 10.6% RE
	Vada-OG: 50-fold dilutions of 100000 ng/mL
	≤3.7% CV, 2.0% to 11% RE
	Vada-AG: 50-fold dilutions of 10000 ng/mL
	≤3.4% CV, 6.0% to 8.0% RE
Bench-top/process stability	Bench–top stability over wet ice established for vada, vada-OG for 6 h; and for vada-AG for 4 h
	Vada: 91.5% to 103% theoretical conc., CV: ≤3.7%
	Vada-OG: 95.9% to 104% theoretical conc., CV: ≤6.4%
	Vada-AG: 91.5% to 101% theoretical conc., CV: ≤6.5%
Freeze-thaw stability	At -70°C after 6 freeze-thaw cycles
	Vada: Accuracy: 101% to 111%, %RSD: ≤4.7%
	Vada-OG: Accuracy: 96.2% to 104%, %RSD: ≤6.3%
	Vada-AG: Accuracy: 93.8% to 96.6%, %RSD: ≤8.0%
Long-term storage at -70°C	For 204 days
	Vada: Accuracy: 109% to 111%, %RSD: ≤7.0%
	For 201 days
	Vada-OG: Accuracy: 96.4% to 105%, %RSD: ≤14.1%
	Vada-AG: Accuracy: 109% to 111%, %RSD: ≤7.1%
Carryover	Met acceptance criteria

Source: (b) (4)-79023 Validation Report
Abbreviations: CV, coefficient of variation; UHPLC-MS/MS, ultra-high performance liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; RE, relative error; RSD, relative standard deviation; SPE, solid phase extraction; ULOQ, upper limit of quantification; vada, vadadustat; Vada-AG, vadadustat-Acyl-Glucuronide; vada-OG, vadadustat-O-Glucuronide

Table 235. Analytical Methods for the Determination of Vadadustat and Vadadustat-O-Glucuronide in Human Urine

Report No.	171641VRM_AKCM	181017VRM_AKCM
Clinical studies supported	AKB-6548-CI-0024, AKB-6548-CI-0029	AKB-6548-CI-0024, AKB-6548-CI-0029
Analyte	Vadadustat	Vadadustat-O-Glucuronide
Matrix	Human Urine	Human Urine
Assay method	Turbo ion spray LC-MS/MS	Turbo ion spray LC-MS/MS
Sample preparation	SPE	SPE
Internal standard	d3-vada	(b) (4)
LLOQ (ng/mL)	10.0	200
Calibration curve range (ng/mL)	10.0 to 1000	200 to 20000

Report No.	171641VRM_AKCM	181017VRM_AKCM
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ: 7 Cumulative accuracy (% RE) from LLOQ to ULOQ: -1.0% to 1.1% Cumulative precision (% CV) from LLOQ to ULOQ: ≤2.7%	Number of standard calibrators from LLOQ to ULOQ: 7 Cumulative accuracy (% bias) from LLOQ to ULOQ: -1.3% to 2.0% Cumulative precision (% CV) from LLOQ to ULOQ: ≤4.8%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 4 QCs: -3.0% to 1.0% Inter-batch %CV: ≤4.9%	Cumulative accuracy (%bias) in 4 QCs: 0.0% to 5.5% Inter-batch %CV: ≤4.8%
Selectivity (6 total lots tested)	Analyte/IS: ≤5%	Analyte/IS: ≤5%
Matrix effect	6 lots tested Normalized matrix factor ranged from 0.96 to 1.03	6 lots tested Normalized matrix factor ranged from 0.93 to 1.05
Dilution linearity and hook effect	The highest concentration tested was 50000 ng/mL at a 100-fold dilution %RE: 0.2% %CV: 4.4%	500000 ng/mL, 50-fold dilution %RE: 6.4% %CV: 3.2%
Bench-top/process stability	At RT established at 24 hours %RE: -3.3% to -1.2% %CV: ≤2.1%	At RT established at 24 hours %RE: 4.3% to 8.0% %CV: ≤3.9%
Freeze-thaw stability	5 cycles at -70°C %RE: -2.4% to 3.4% %CV: ≤2.7%	5 cycles at -70°C %RE: -2.7% to 2.4% %CV: ≤3.9%
Long-term storage	For 183 days %RE: 10.0% to 2.6% %CV: ≤6.5%	For 181 days %RE: 0.7% to 4.8% %CV: ≤4.1%
Carryover	Met acceptance criteria of ≤20% of LLOQ response	Met acceptance criteria of ≤20% of LLOQ response

Source: 171641VRM_AKCM and 181017VRM_AKCM Method Validation Reports
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; RE, relative error; SPE, solid phase extraction; ULOQ, upper limit of quantification

15. Trial Design: Additional Information and Assessment

Important Aspects of Trial Design for Trials 0014, 0015, 0016 and 0017:

The following are <u>not</u> criteria for study completion or for subject withdrawal:

- Need for rescue therapy prior to permanent study drug discontinuation
- Occurrence of a safety endpoint
- Progression to DD-CKD

The following are criteria for permanent discontinuation of study drug, but these subjects will continue to be followed on-study (if alive) and will resume standard of care treatment as deemed appropriate by investigator:

- Unacceptable toxicity, drug intolerability, adverse events, or death (see liver-specific laboratory criteria)
- Investigator discretion
- Subject withdrawal of consent
- Subject becomes pregnant
- Receipt of a kidney transplant (or other types of transplants)
- Lack of efficacy (defined as inadequate response to study drug in the investigator's opinion)
- Specific rules placed in the protocol due to liver enzyme abnormalities:
  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x upper limit of normal (ULN) and total bilirubin >2x ULN
  - ALT or AST >3x ULN and INR >1.5
  - ALT or AST >8x ULN
  - ALT or AST remains >5x ULN over 2 weeks
  - ALT or AST >3x ULN with symptoms such as fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, or eosinophilia
- Other reasons

The following are criteria for temporary interruption of study drug, which will resume, when possible, unless a contraindication is present:

- Receiving ESA rescue, with restarting vadadustat depending on number of days from last dose of ESA: 2 days after Epoetin, 7 days after darbepoetin and 14 days after epoetin beta
- Adverse events

Study drug may be continued during the RBC transfusion period. RBC transfusion as a rescue is up to the discretion of the investigator.

Phlebotomy is indicated if Hb >14 g/dL or rate of rise of Hb is concerning for investigator.

The following are protocol-based guidelines to ESA rescue:

- Starting at week 6, ESA rescue will be allowed
- If possible, ensure patient is on maximum dose of vadadustat for 2 weeks prior to ESA rescue
- If on darbepoetin alfa, patient can be rescued using a different ESA
- Criteria for ESA rescue shown below. An investigator is allowed to use rescue if these criteria are not met but the reason must be provided (stop rescue once Hb ≥9.5 g/dL):
  - The subject has experienced worsening of the symptoms of anemia (e.g., fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared with baseline
  - The subject's Hb is <9.0 g/dL

Prior medication use during the screening period or 30 days prior to first dose was recorded, with special interest in relation to ESA use, blood transfusion, and intravenous (IV) iron infusions.

Summary of Vadadustat Dose Adjustment Algorithm Used for Trials 0014, 0015, 0016 and 0017:

Overall, dose adjustment was based on the investigator's clinical discretion, with the protocol-provided dose adjustment algorithm as a guide, in addition to other subject-specific characteristics (e.g., clinical condition, Hb rate of rise, Hb rate of decline and Hb variability).

The aim of the dosing strategy was to increase and maintain Hb levels of 10.0 g/dL to 11.0 g/dL in the United States and 10.0 g/dL to 12.0 g/dL outside of the United States throughout the trial.

- A rapid rate of rise in Hb is defined as:
  - >1.0 g/dL increase in a 2-week period, or
  - >2.0 g/dL increase in a 4-week period
- Overall, dose reduction was recommended for the following reasons:
  - A rapid rate of rise in Hb
  - Hb above the upper limit of the target Hb (i.e., >11.0 g/dL in the United States or >12.0 g/dL outside of the United States)
- If a dose adjustment was indicated for vadadustat, dose was adjusted by 1 tablet (i.e., 150 mg).
- Dose could not be increased more frequently than once every 4 weeks but there were no limits to the frequency of dose decreases.
- If Hb <10.0 g/dL, without evidence of a rapid rate of rise of Hb and without a dose increase within 4 weeks, dose increase was recommended.
- Recommendation for dose interruption was different, depending on the geographic location of the patient:
  - For subjects in the United States, dose interruption was indicated if Hb >11.0 g/dL. For subjects not on dialysis, resumption of dosing at a reduced dose can occur when Hb falls below 10.5 g/dL on follow-up measurement. For subjects on dialysis, resumption of dosing at a reduced dose can occur when Hb falls below 11 g/dL on follow-up measurement.
  - For subjects outside of the United States, dose interruption was indicated if Hb >13.0 g/dL. Resumption of dosing at a reduced dose can occur when Hb falls below 12 g/dL on follow-up measurement.
- Subjects receiving one tablet of vadadustat prior to interruption will resume treatment with one tablet after interruption.

Summary of Darbepoetin Alfa Dose Adjustment Algorithm Used for Trials 0014, 0015, 0016 and 0017:

Overall, dose adjustment was based on the investigator's clinical discretion, with the protocol-provided dose adjustment algorithm as a guide, in addition to other patient-specific characteristics (e.g., clinical condition, Hb rate of rise, Hb rate of decline and Hb variability).

The aim of the dosing strategy was to increase and maintain Hb levels of 10.0 g/dL to 11.0 g/dL in the United States and 10.0 g/dL to 12.0 g/dL outside of the United States throughout the trial. The dose adjustment approach in the United States was consistent with the recommendations provided in the approved USPI for darbepoetin alfa.

A rapid rate of rise in Hb is defined as:

- >1.0 g/dL increase in a 2-week period, or
- >2.0 g/dL increase in a 4-week period

Overall, dose reduction was to be considered for the following reasons:

- A rapid rate of rise in Hb
- Hb >10.0 g/dL in the United States for subjects who were not on dialysis
- Hb >11.0 g/dL in the United States for subjects who were on dialysis
- Hb >12.0 g/dL in any patient outside of the United States

If a dose adjustment was indicated for darbepoetin alfa, dose was adjusted ~25%.

Dose could not be increased more frequently than once every 4 weeks but there were no limits to the frequency of dose decreases.

If Hb <10.0 g/dL, without evidence of a rapid rate of rise of Hb and without a dose increase within 4 weeks, dose increase was recommended.

Recommendation for dose interruption was different depending on the geographic location and the dialysis-dependent status of the patient. Overall, recommendations were less clear for subjects on darbepoetin alfa, compared to those on vadadustat:

- For subjects in the United States that were not dialysis dependent, dose interruption may be considered if Hb >10.0 g/dL. No recommendations were given to guide investigator on when to resume dosing at a reduced dose level.
- For subjects in the United States that were dialysis dependent, dose interruption may be considered if Hb >11.0 g/dL. No recommendations were given to guide investigator on when to resume dosing at a reduced dose level.
- For subjects outside of the United States, dose interruption was indicated if Hb >12.0 g/dL and Hb continues to increase after a dose reduction. Resumption of dosing at a reduced dose can occur when Hb begins to decrease but no specific Hb level was provided.

Protocol Amendments for Trial 0014 and Trial 0015:

There were seven global amendments to the original protocol of trial 0014 and trial 0015, which were dated October 15th, 2015 and November 10th, 2015, respectively. For trial 0014, the first patient was consented on December 17th, 2015. For trial 0015, the first patient was consented on February 9th, 2016. The majority of amendments contained a large number of changes, with differing importance. In general, we will only include the amendments of most importance in our review:

Amendment 1 (March 17th, 2016):

- Added Exclusion Criterion No. 19: "Hypersensitivity to darbepoetin or vadadustat, or to any of their excipients."
- Defined that the study completion date (end of trial) will take place when 631 major adverse cardiovascular events (MACE) events have accrued over the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015).

- Clarified that the double-barrier contraceptive method should be practiced starting at Screening Visit 1, throughout the study, and for 30 days after the last dose of study medication.

Amendment 2 (April 18th, 2016):

- To update the following exclusion criteria:
  - Exclusion Criterion No. 9: Additional clarification of exclusionary cardiovascular events within 12 weeks prior to screening
  - Exclusion Criterion No. 10: To not exclude subjects with basal cell carcinoma who have been successfully treated with cryotherapy instead of surgical resection
  - Exclusion Criterion No. 13: To specifically exclude subjects with a history of hematopoietic stem cell transplant
  - Exclusion Criterion No. 15: Considering the short half-life of vadadustat and clinical experience in previous Phase 1 and Phase 2 studies in NDD-CKD and DD-CKD subjects, it could be beneficial for subjects who participated in previous vadadustat studies to be considered for this global Phase 3 study, provided the subject meets all eligibility criteria
- To add hospitalization for heart failure (HF) as an adjudicated safety endpoint in addition to MACE and thromboembolic events
- To clarify that the darbepoetin alfa dosing adjustment guidelines are based on the approved local product label for adult subjects with CKD not on dialysis
- To allow subjects who transition to hemodialysis or peritoneal dialysis during the study to continue to receive study medication (vadadustat or darbepoetin alfa). This is supported by acceptable safety data from a recently completed Phase 2 trial of vadadustat in subjects with dialysis-dependent chronic kidney disease (DD-CKD).

Amendment 3 (June 8th, 2017):

- To update the study design from the current screening period of up to 4 weeks to up to 8 weeks and allow iron, vitamin B12, and folate supplementation as needed during the screening period.
- To update the following exclusion criterion:
  - Exclusion criterion no. 3: adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks
  - Deletion of exclusion criterion No. 4: intravenous (IV) iron within 4 weeks prior to or during screening
  - Exclusion criterion no. 5 (now 4): adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks
  - Exclusion criterion no. 10 (now 9): to clarify that benign colonic polyps are not a malignancy, therefore removed to correct the error
  - Exclusion criterion no. 11 (now 10): adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks, and to clarify that chronic treatment with anticoagulants for a history of deep vein thrombosis or pulmonary embolism over 12 weeks prior to randomization is not exclusionary
- Vadadustat dosing and dose adjustment guidelines were updated to clarify that subjects receiving one tablet of dosing prior to interruption will resume treatment with 1 tablet after interruption.

- Executive Steering Committee has been added.
- To clarify darbepoetin alfa administration, darbepoetin alfa should be administered per the label.
- A clarification of the study analysis populations has been provided.

Amendment 4 (January 18th, 2018):

- Secondary efficacy endpoints were updated to reflect addition of several key secondary, other secondary efficacy endpoints and safety endpoints in alignment with the statistical analysis plan (SAP).
- Individual subject discontinuation was updated to add lack of efficacy as a reason for permanent discontinuation of study medication or study participation for accurate data capture.
- Iron supplementation was updated to align with published guidelines to prescribe iron supplementation during the study when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%.
- ESA Rescue (optional) was updated to align with published guidelines and to permit Investigator initiation of rescue when medically necessary even if protocol defined criteria are not met.
- Year 2-4 monthly Hb monitoring was added with the requirement for monthly monitoring of Hb drawn as part of local standard of care labs or via an unscheduled visit.
- Sample size for primary efficacy endpoint was updated to a change in the non-inferiority margin from -0.5 to -1.0 g/dL.
- Sample size for the primary safety endpoint was updated with enrollment projections and median study drug exposure times.
- Subgroups were updated to pre-specify key subgroups for subsequent analysis.
- Analysis of adverse events was updated to provide adverse event (AE) summaries for specific subgroups.

Amendment 5 (September 13th, 2018):

- Study completion was updated to clarify that all enrolled subjects will be allowed to complete the primary evaluation period (Weeks 24-36) prior to global study completion.
- Procedures to support continued study participation were updated to include all options available to the Investigator to follow subjects that permanently discontinue study medication.
- Procedures to prevent “lost to follow-up” details steps to support sites in efforts to identify subjects lost to follow-up.
- Blinding was updated to reflect information for which the Applicant and clinician-reported outcome study teams will remain blinded.
- Rescue therapy was clarified to reflect restarting of study medication after ESA rescue and RBC transfusion.
- Erythropoiesis-stimulating agents were updated to provide clarity on study medication dosing following ESA administration.
- Serious adverse events were updated to indicate that the Applicant has defined events that will be classified as serious regardless of their assessment.
- Data analysis was updated to reflect how baseline will be calculated for Hb.
- Sample size for the primary efficacy endpoint was updated to reflect a change in the non-inferiority margin from -1.0 g/dL to -0.75g/dL.

- Sample size for the primary safety endpoint was modified to include an updated definition for the primary safety endpoint and how noninferiority is established between treatment groups.
- Study analysis populations are updated with definition of full analysis population.
- Primary analysis of primary efficacy endpoint is updated with use of analysis of covariance with multiple imputation, stratified by the randomization strata and using baseline Hb as the covariate.

Amendment 6 (December 18th, 2018):

- HMG-CoA reductase inhibitors (statins) was updated to provide further guidance regarding concomitant use of simvastatin drug interactions with vadadustat.
- Sulfasalazine and other BCRP substrates were added to provide guidance regarding concomitant use of BCRP substrates with vadadustat.
- Liver tests were increased in Year 2, 3, and 4 to include Week 64, 88, 116, 140, 168, and 192 for gathering data to better understand the hepatic profile of vadadustat. This change is reflected in laboratory evaluations, Year 2 treatment period visits (Weeks 53 through 104), Year 3/4 Treatment Period Visits (Weeks 116 through 208), and Appendix A: Schedule of Activities.

Amendment 7 (February 26th, 2019):

- Individual subject discontinuation was updated to include a reference to study medication stopping rules for management of subjects with ALT and AST abnormalities.
- Study medication stopping rules were added to include a table of liver test results that would require permanent discontinuation of vadadustat.
- Adverse events were updated to exclude elevations in ALT or AST >3 times ULN with an elevation of total serum bilirubin >2 times ULN from conditions of temporary discontinuation, as this is now a condition for permanent discontinuation.
- Serious adverse events were updated to include information defining designated medical events.

Protocol Amendments for Trial 0016 and Trial 0017:

There were seven global amendments to the original protocol of trial 0016 and trial 0017, which were dated March 22nd, 2016, and May 22nd, 2016, respectively. For trial 0016, the first patient was consented on July 18th, 2016. For trial 0017, the first patient was consented on August 17th, 2016. The majority of amendments contained a large number of changes, with differing importance. In general, we will only include the amendments of most importance in our review:

Amendment 1 (June 7th, 2017):

- To update the study design from the current screening period of up to 4 weeks to up to 8 weeks and allow iron, vitamin B12, and folate supplementation as needed during the screening period.
- To update the following exclusion criteria:
  - Exclusion criterion 3: adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks.

  - Exclusion criterion 10: to clarify that benign colonic polyps are not a malignancy, therefore removed to correct the error.
  - Exclusion criterion 11: adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks, and to clarify that chronic treatment with anticoagulants for a history of deep vein thrombosis or pulmonary embolism over 12 weeks prior to randomization is not exclusionary.

- Vadadustat dosing and dose adjustment guidelines were updated to clarify that subjects receiving one tablet of dosing prior to interruption will resume treatment with one tablet after interruption.
- Executive Steering Committee has been added.
- To clarify darbepoetin alfa administration, darbepoetin alfa should be administered per the label.
- A clarification of the study analysis populations has been provided.

Amendment 2 (August 28th, 2017) – only applicable to trial 0016:

- To align with standard of care for incident subjects with DD-CKD, restriction on ESA use in the 4 weeks prior to and during the initial screening period has been removed.
- ESA is allowed during screening per standard of care. However, for all subjects, it is recommended that no additional ESA doses be administered after screening visit 2 (SV2) and prior to the randomization visit.

Amendment 3 for trial 0016 and Amendment 2 for trial 0017 (January 18th, 2018):

- Protocol title, primary objective, study design, and sample size determination were updated to reflect that subjects may enter trial on prior ESA therapy – only applicable to trial 0016.
- Secondary efficacy endpoints were updated to reflect addition of several key secondary endpoints, other secondary efficacy endpoints and safety endpoints to align with the statistical analysis plan (SAP).
- Inclusion criterion # 3 was modified to allow subjects who have a mean screening Hb between 8.0 and 11.0 g/dL (inclusive) as determined by the average of 2 Hb values measured by the central laboratory during Screening.
- Exclusion criterion # 19 was added to define and exclude subjects who are hyporesponsive to ESAs within 8 weeks prior to or during screening.
- Individual subject discontinuation was updated to add lack of efficacy as a reason for discontinuation for accurate data capture.
- Iron supplementation was updated to align with published guidelines to prescribe iron supplementation during the study when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%.
- ESA rescue (optional) was updated to align with published guidelines raising the threshold of Hb to 9.5 for initiation of ESA rescue and permitting Investigator to initiate rescue when medically necessary even if protocol defined criteria are not met.
- Year 2-4 monthly Hb monitoring was updated to require monthly monitoring of Hb drawn as part of local standard of care laboratory tests or via an unscheduled visit.
- Sample size for primary efficacy endpoint was updated to reflect a change in the non-inferiority margin from -0.5 g/dL to -1.0 g/dL.

- Sample size for the primary efficacy endpoint was updated with enrollment projections as well as median study medication exposure times.
- Subgroups were updated to pre-specify key subgroups for subsequent analysis
- Analysis of adverse events was updated, and AE summaries will be provided for specific subgroups.

Amendment 4 for trial 0016 and Amendment 3 for trial 0017 (September 13th, 2018):

- Exclusion criteria 3 was updated to clarify RBC transfusions are not allowed within 8 weeks prior to randomization.
- Study completion was updated to clarify that all enrolled subjects will be allowed to complete the primary evaluation period (Weeks 24-36) prior to global study completion.
- Procedures to support continued study participation were updated to include all options available to the Investigator to follow subjects that permanently discontinue study medication.
- Procedures to prevent "lost to follow-up" details steps to support sites in efforts to identify subjects lost to follow-up.
- Blinding was updated to reflect information for which the Applicant and clinician-reported outcome study teams will remain blinded.
- Rescue Therapy was clarified to reflect restarting of study medication after ESA rescue and RBC transfusion.
- Erythropoiesis-stimulating Agents were updated to provide clarity on study medication dosing following ESA administration.
- Transfusions were updated to align with change in exclusion criteria 3 to clarify RBC transfusions.
- Data analysis was updated to reflect how baseline will be calculated for Hb.
- Sample size for primary efficacy endpoint was updated to reflect a change in the non-inferiority margin from -1.0 g/dL to -0.75 g/dL and to indicate approximately 150 subjects per treatment group.
- Sample size for the primary safety endpoint was modified to include updated definition for the primary safety endpoint and how noninferiority is established between treatment groups.
- Study analysis populations was updated with definition of full analysis population.
- Primary analysis of primary efficacy endpoint was updated with use of analysis of covariance with multiple imputation, stratified by the randomization strata and using baseline Hb as the covariate.
- Serious adverse events were updated to indicate that Sponsor has defined events that will be classified as serious regardless of their assessment.

Amendment 5 for trial 0016 and Amendment 4 for trial 0017 (December 18th, 2018):

- HMG-CoA reductase inhibitors (statins) were updated to provide further guidance regarding concomitant use of simvastatin drug interactions with vadadustat.

- Sulfasalazine and other BCRP substrates were added to provide guidance regarding concomitant use of BCRP substrates with vadadustat.
- Liver tests were increased in Year 2, 3, and 4 to include Week 64, 88, 116, 140, 168, and 192 for gathering data to better understand the hepatic profile of vadadustat. This change was reflected in laboratory evaluations, year 2 treatment period visits (Weeks 53 through 104), Year 3/4 Treatment Period Visits (Weeks 116 through 208), and Appendix A: Schedule of Activities.

Amendment 6 for trial 0016 and Amendment 5 for trial 0017 (February 26th, 2019):

- Individual subject discontinuation was updated to include a reference to study medication stopping rules for management of subjects with ALT and AST abnormalities.
- Study medication stopping rules were added to include a table of liver test results that would require permanent discontinuation of vadadustat.
- Adverse events were updated to exclude elevations in ALT or AST >3 times ULN with an elevation of total serum bilirubin >2 times ULN from conditions of temporary discontinuation, as this was now a condition for permanent discontinuation.
- Serious adverse events were updated to include information defining designated medical events.

16. Efficacy: Additional Information and Assessment

16.1. Summary of Protocol Deviations

Important protocol deviations (IPD) were identified by the investigators, determined as IPDs by the Applicant prior to database lock by a blinded assessment and reported in the clinical study report. IPDs were defined as follows:

- Subject randomized but did not meet one or more eligibility criteria (i.e., IPD #1)
- Subject developed a withdrawal criterion but was not withdrawn from the trial (i.e., IPD #2)
- Subject given incorrect dose, despite appropriate dose adjustment, or subject was given wrong dose, not following recommendations based on dose adjustment algorithm (i.e., IPD #3).
- Subject concurrently on study treatment and ESA, due to inadvertent ESA use (i.e., IPD #4)

In the clinical study report, the Applicant had specific criteria for exclusion of subjects from the randomized population to form the per protocol population, based on timing of IPD#3 and IPD#4 within 8 weeks prior to or during the primary efficacy period. However, the review team did not use the per protocol population or their analysis because it did not comply with the standard intent-to-treat approach.

16.1.1. Trial 0014

IPDs were reported for 372/879 (42.3%) and 51/872 (5.8%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively. The following lists the number and percentages of subjects with specific IPDs:

- IPD#1: 39/879 (4.4%) and 17/872 (1.9%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#2: 0/879 (0%) and 0/872 (0%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#3: 340/879 (36.7%) and 15/872 (1.7%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#4: 24/879 (2.7%) and 21/872 (2.4%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively

Overall, protocol deviations that involved eligibility criteria, withdrawal criteria and inadvertent ESA use were comparable between arms. However, subjects on vadadustat had significantly higher rates of incorrect dosing, mainly due to: 1) dosing not permitted by the dosing algorithm, or 2) use of expired medication or medication that had temperature excursions. The higher incidence in IPD#3 occurrence in the vadadustat arm, compared to the darbepoetin alfa arm, is due to two main reasons: 1) As an oral treatment, patients self-administered vadadustat, thus being more prone to error, as compared to darbepoetin alpha, which was generally administered by site staff, and 2) The protocol allowed investigator discretion for darbepoetin alfa dosing, as per the local prescription information, while this same discretion was not allowed for patients on vadadustat. Sensitivity analyses were performed, with no significant differences to report and no impact on the interpretation of the safety or efficacy results of the trials.

16.1.2. Trial 0015

IPDs were reported for 335/862 (38.9%) and 60/863 (7.0%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively. The following lists the number and percentages of subjects with specific IPDs:

- IPD#1: 54/862 (6.3%) and 32/863 (3.7%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#2: 0/862 (0%) and 0/863 (0%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#3: 310/862 (36.0%) and 17/863 (2.0%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#4: 22/862 (2.6%) and 13/863 (1.5%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively

Overall, protocol deviations that involved eligibility criteria, withdrawal criteria and inadvertent ESA use were comparable between arms. However, subjects on vadadustat had significantly higher rates of incorrect dosing, mainly due to: 1) dosing not permitted by the dosing algorithm, or 2) use of expired medication or medication that had temperature excursions. The higher incidence in IPD#3 occurrence in the vadadustat arm, compared to the darbepoetin alfa arm, is due to two main reasons: 1) As an oral treatment, patients self-administered vadadustat, thus being more prone to error, as compared to darbepoetin alpha, which was generally administered

by site staff, and 2) The protocol allowed investigator discretion for darbepoetin alfa dosing, as per the local prescription information, while this same discretion was not allowed for patients on vadadustat. Sensitivity analyses were performed, with no significant differences to report and no impact on the interpretation of the safety or efficacy results of the trials.

16.1.3. Trial 0016

IPDs were reported for 83/181 (45.9%) and 38/188 (20.2%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively. The following lists the number and percentages of subjects with specific IPDs:

- IPD#1: 15/181 (8.3%) and 21/188 (11.2%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#2: 0/181 (0%) and 0/188 (0%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#3: 74/181 (40.9%) and 9/188 (4.8%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#4: 10/181 (5.5%) and 12/188 (6.4%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively

Overall, protocol deviations that involved eligibility criteria, withdrawal criteria and inadvertent ESA use were comparable between arms. However, subjects on vadadustat had significantly higher rates of incorrect dosing, mainly due to: 1) dosing not permitted by the dosing algorithm, or 2) use of expired medication or medication that had temperature excursions. The higher incidence in IPD#3 occurrence in the vadadustat arm, compared to the darbepoetin alfa arm, is due to two main reasons: 1) As an oral treatment, patients self-administered vadadustat, thus being more prone to error, as compared to darbepoetin alpha, which was generally administered by site staff, and 2) The protocol allowed investigator discretion for darbepoetin alfa dosing, as per the local prescription information, while this same discretion was not allowed for patients on vadadustat. Sensitivity analyses were performed, with no significant differences to report and no impact on the interpretation of the safety or efficacy results of the trials.

16.1.4. Trial 0017

IPDs were reported for 885/1777 (49.8%) and 241/1777 (13.6%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively. The following lists the number and percentages of subjects with specific IPDs:

- IPD#1: 100/1777 (5.6%) and 80/1777 (4.5%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#2: 0/1777 (0%) and 0/1777 (0%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#3: 785/1777 (44.2%) and 55/1777 (3.1%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively
- IPD#4: 175/1777 (9.8%) and 115/1777 (6.5%) subjects in the vadadustat and darbepoetin alfa treatment groups, respectively

Overall, protocol deviations that involved eligibility criteria, withdrawal criteria and inadvertent ESA use were comparable between arms. However, subjects on vadadustat had significantly

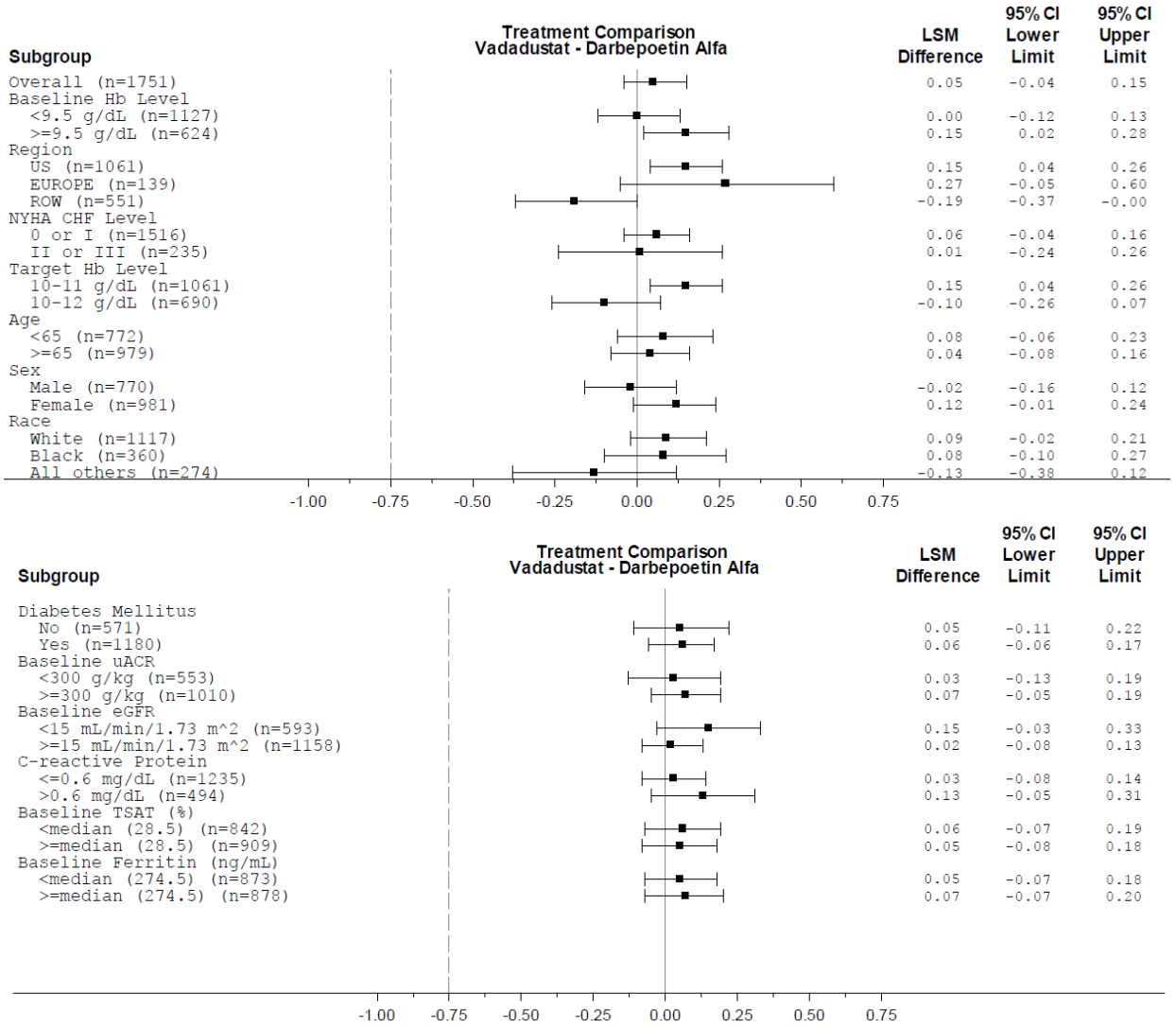
higher rates of incorrect dosing, mainly due to: 1) dosing not permitted by the dosing algorithm, or 2) use of expired medication or medication that had temperature excursions. The higher incidence in IPD#3 occurrence in the vadadustat arm, compared to the darbepoetin alfa arm, is due to two main reasons: 1) As an oral treatment, patients self-administered vadadustat, thus being more prone to error, as compared to darbepoetin alpha, which was generally administered by site staff, and 2) The protocol allowed investigator discretion for darbepoetin alfa dosing, as per the local prescription information, while this same discretion was not allowed for patients on vadadustat. Sensitivity analyses were performed, with no significant differences to report and no impact on the interpretation of the safety or efficacy results of the trials.

16.2. Subgroup Analyses for the Primary Endpoint

The section supplements the analyses and interpretation presented in section II.6.2. Several. Subgroup analyses were conducted to assess the potential for differences in the treatment effect for various baseline demographic and clinical characteristics groups for trials 0014, 0015, 0016 and 0017, the results are presented in Figure 54, Figure 55, Figure 56, and Figure 57, respectively. Overall, the treatment effect of Vadadustat compared to Darbepoetin Alfa appeared consistent across the prespecified subgroups. Of note, the sample sizes for some subgroups were small, which limits the ability to identify trends with certainty. In addition, conducting multiple subgroup analyses without any multiplicity adjustment could result in spurious findings due to chance, even if the observed result for one subgroup is seemingly very different from the other subgroups.

16.2.1. Trial 0014

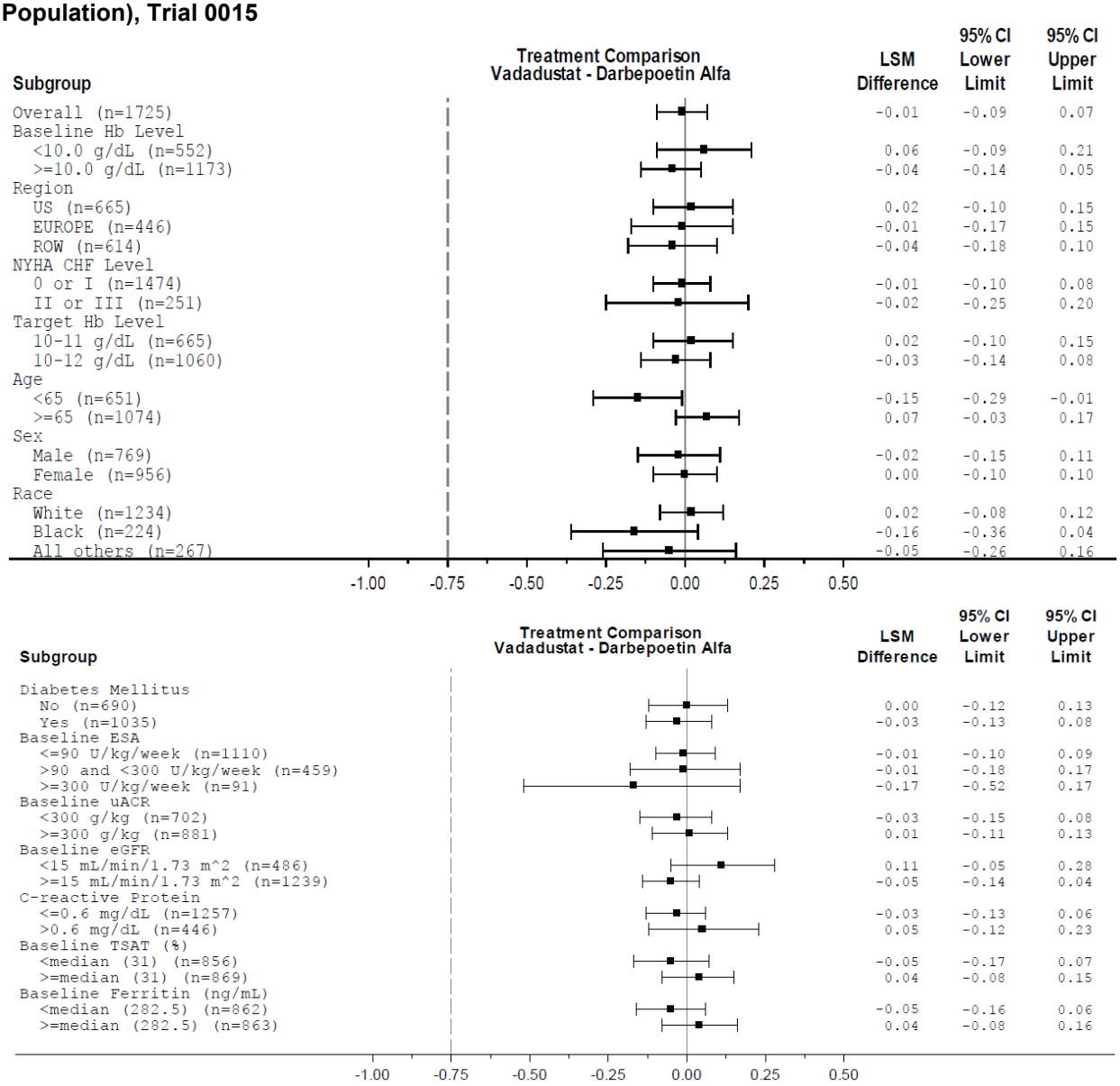
Figure 54. Forest Plot of Subgroup Analysis of Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population), Trial 0014



Source: Study 0014 Clinical Study Report Figure 7 (p. 115), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis stimulating agent; Hb, hemoglobin; LSM, least squares mean; NYHA, New York Heart Association; ROW, rest of world; TSAT, transferrin saturation; uACR, urine albumin-to-creatinine ratio; U.S., United States.

16.2.2. Trial 0015

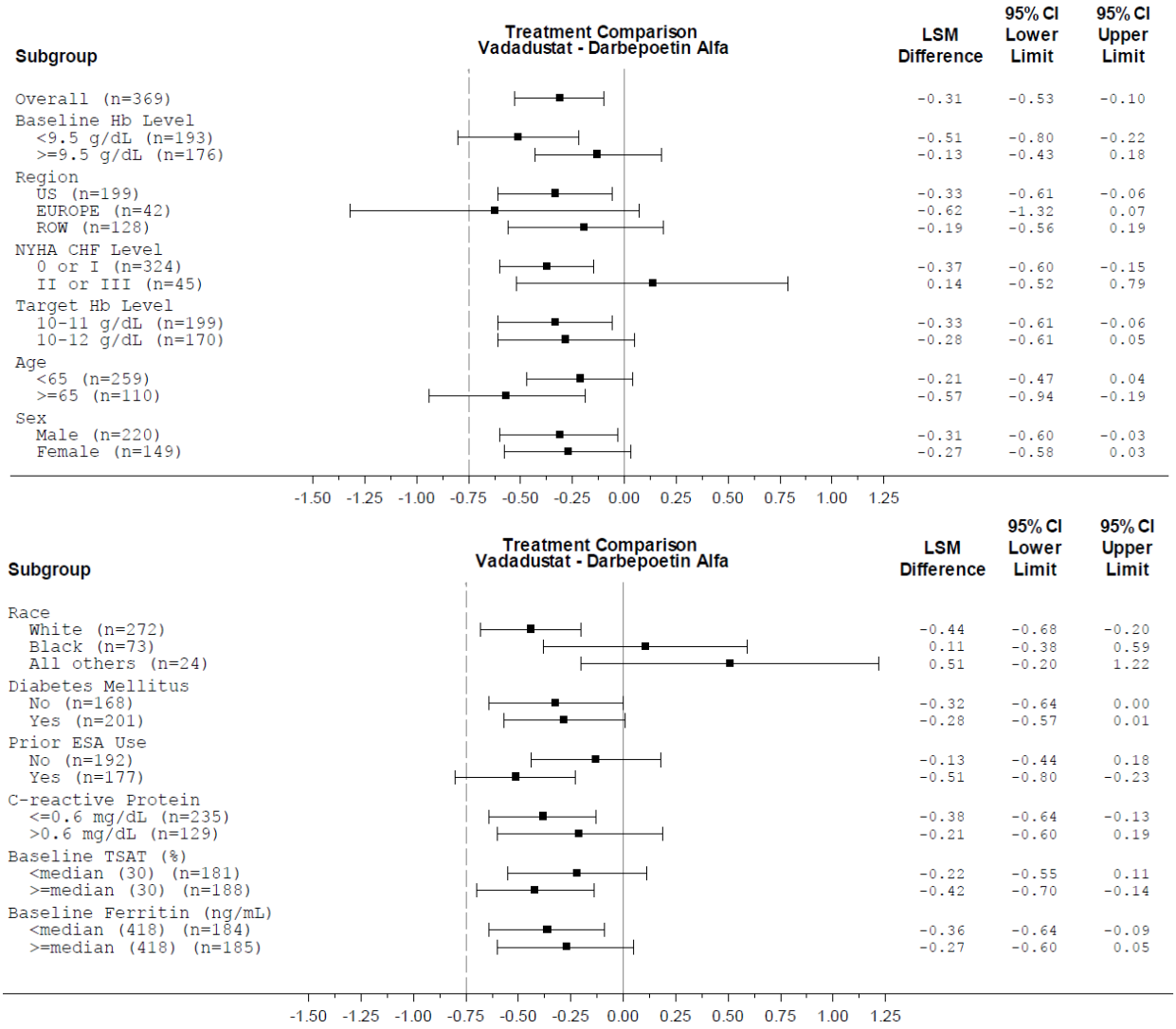
Figure 55. Forest Plot of Subgroup Analysis of Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population), Trial 0015



Source: Study 0015 Clinical Study Report Figure 6 (p. 127), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis stimulating agent; Hb, hemoglobin; LSM, least squares mean; NYHA, New York Heart Association; ROW, rest of world; TSAT, transferrin saturation; uACR, urine albumin-to-creatinine ratio; U.S., United States.

16.2.3. Trial 0016

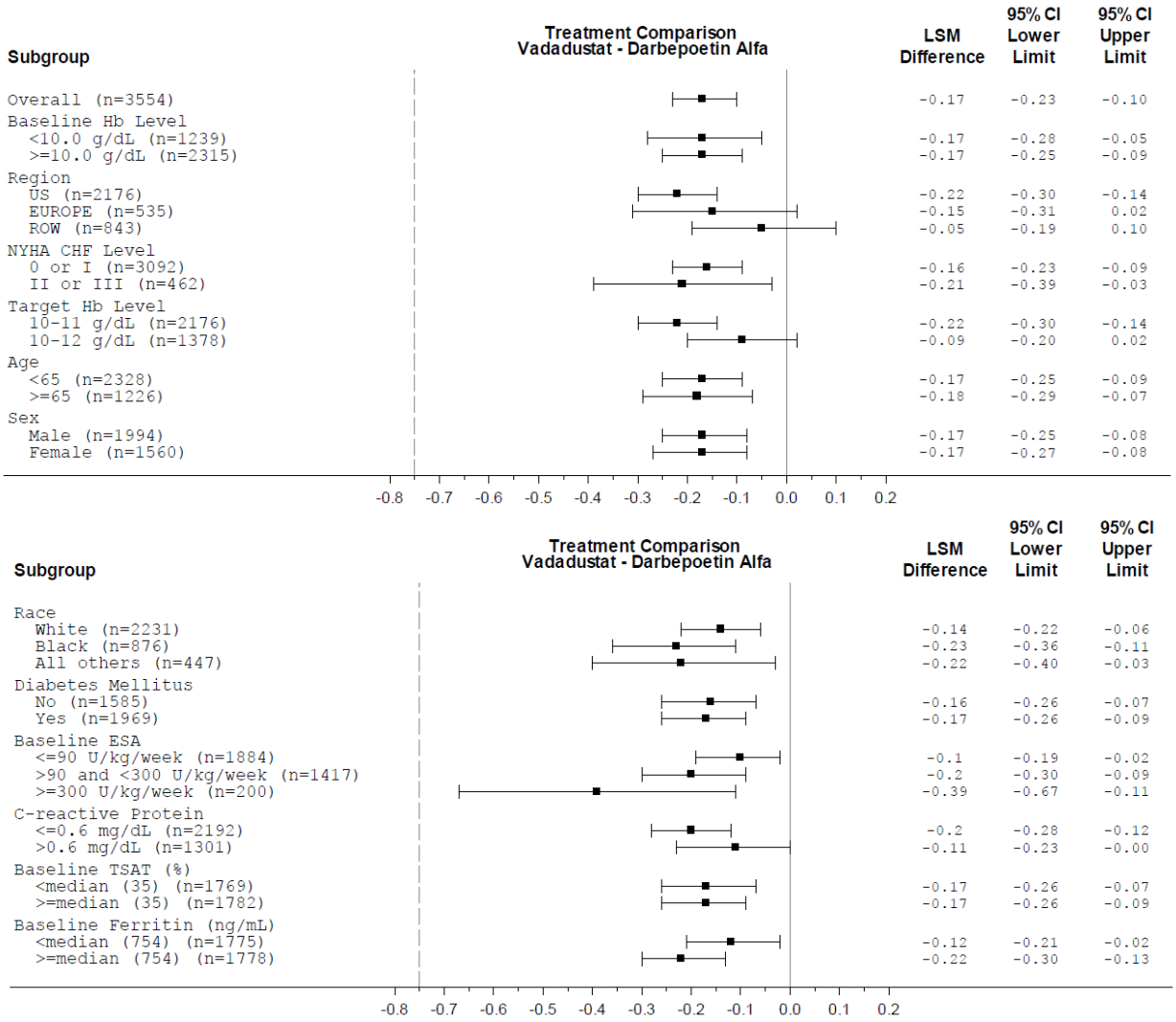
Figure 56. Forest Plot of Subgroup Analysis of Change in Hemoglobin (G/Dl) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population), Trial 0016



Source: Study 0016 Clinical Study Report Figure 5 (p. 109), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CHF, congestive heart failure; ESA, erythropoiesis stimulating agent; Hb, hemoglobin; LSM, least squares mean; NYHA, New York Heart Association; ROW, rest of world; TSAT, transferrin saturation; U.S., United States.

16.2.4. Trial 0017

Figure 57. Forest Plot of Subgroup Analysis of Change in Hemoglobin (G/Dl) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Randomized Population), Trial 0017



Source: Study 0017 Clinical Study Report Figure 5 (p. 108), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CHF, congestive heart failure; ESA, erythropoiesis stimulating agent; Hb, hemoglobin; LSM, least squares mean; NYHA, New York Heart Association; ROW, rest of world; TSAT, transferrin saturation; U.S., United States.

16.2.5. Regional Subgroup Analyses for Darbepoetin Alfa on Hemoglobin Response

Table 236. Subgroup Analysis of Change From Baseline in Hemoglobin (Hb, g/dL) to the Average Over Weeks 24-36 (ANCOVA With Multiple Imputations)[1]

Darbepoetin mean 95% CI	US	ROW	EU	Non-US
Trial 0014	1.0 (0.9, 1.1)	1.6 (1.4, 1.7)	1.4 (1.1, 1.7)	1.6 (1.5, 1.8)
Trial 0015	0.3 (0.2, 0.4)	0.4 (0.2, 0.5)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)
Trial 0016	1.0 (0.7, 1.2)	1.8 (1.5, 2.1)	2.3 (1.5, 3.0)	1.8 (1.5, 2.1)
Trial 0017	0.3 (0.3, 0.4)	0.1 (-0.1, 0.2)	0.3 (0.1, 0.4)	0.2 (0.1, 0.3)

Source: FDA Analysis
1 Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
Abbreviations: US, United States; ROW, rest of world (excludes US and Europe); EU, Europe.

Table 237. Subgroup Analysis of Change From Baseline in Hemoglobin (Hb, g/dL) to the Average Over Weeks 40-52 (ANCOVA With Multiple Imputations)[1]

Darbepoetin mean 95% CI	US	ROW	EU	Non-US
Trial 0014	1.2 (1.1, 1.3)	1.6 (1.5, 1.8)	1.5 (1.2, 1.8)	1.7 (1.5, 1.8)
Trial 0015	0.4 (0.2, 0.5)	0.4 (0.2, 0.5)	0.5 (0.3, 0.5)	0.4 (0.3, 0.5)
Trial 0016	1.0 (0.7, 1.4)	1.9 (1.5, 2.2)	1.8 (1.0, 2.6)	1.9 (1.6, 2.3)
Trial 0017	0.4 (0.3, 0.4)	0.3 (0.1, 0.4)	0.3 (0.1, 0.4)	0.3 (0.2, 0.4)

Source: FDA Analysis
1 Regions are defined by geographical location. Listing of countries can be found in section III.17.4.2.
Abbreviations: US, United States; ROW, rest of world (excludes US and Europe); EU, Europe.

16.3. Analyses of Selected Other Efficacy Endpoints

Analyses for the following additional efficacy endpoints were provided by the Applicant based on FDA review team's request on Dec. 21, 2021.

- Proportion of subjects transitioned to chronic dialysis (for studies AKB-6548-CI-0014 and AKB-6548-CI-0015 only)
- Proportion of subjects that had progression of CKD (for studies AKB-6548-CI 0014 and AKB-6548-CI-0015 only), defined as subjects who experienced any of the following:
  - Transition to chronic dialysis, or
  - Receipt of a kidney transplant, or
  - eGFR <15 mL/min/1.73 m² and confirmed by another measurement with a GFR<15 mL/min/1.73 m², which should be at least 28 days apart from the first reduction, or
  - Reduction in eGFR of 40% or more from Baseline (confirmed by second measurement at least 28 days later).
- Proportion of subjects that received iron supplement (regardless of administration route)

16.3.1. Trial 0014

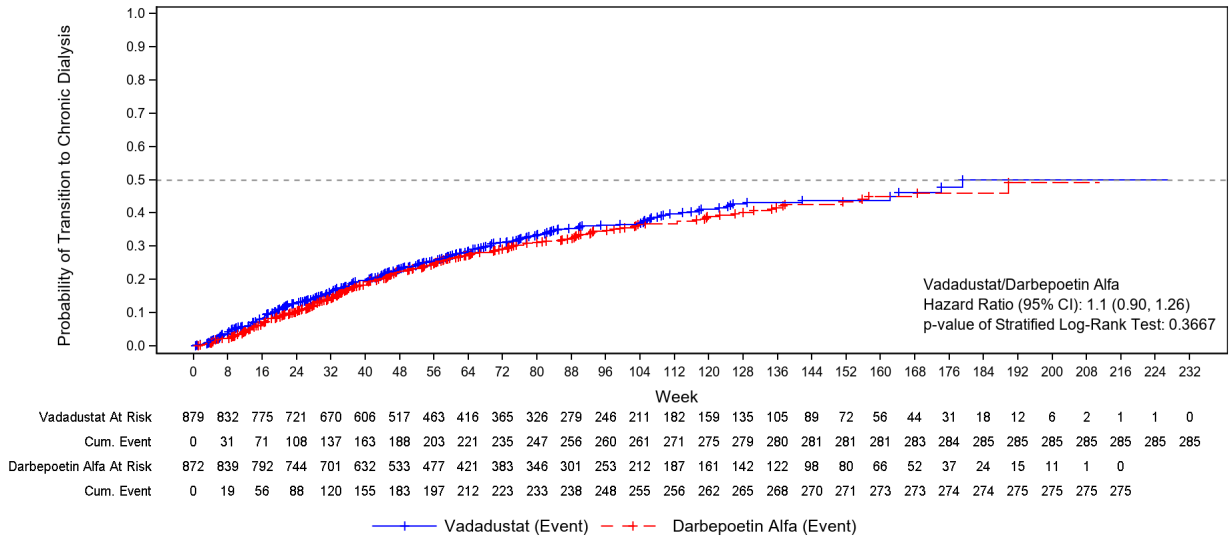
Proportion of Subjects Transitioned to Chronic Dialysis

Table 238. Time to Transition to Chronic Dialysis (Randomized Population), Trial 0014

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
Subjects with transition to chronic dialysis, n (%)	285 (32.4)	275 (31.5)
Subjects censored, n (%)	594 (67.6)	597 (68.5)
Cumulative incidence (95% CI)		
24 Weeks	0.13 (0.11, 0.15)	0.10 (0.09, 0.13)
36 Weeks	0.18 (0.15, 0.21)	0.17 (0.15, 0.20)
40 Weeks	0.20 (0.17, 0.22)	0.19 (0.16, 0.21)
52 Weeks	0.24 (0.22, 0.28)	0.23 (0.20, 0.26)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.37	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	1.1 (0.90, 1.26)	

Source: Applicant's analysis in response to submitted information request

Figure 58. Kaplan-Meier Curve of Time to Transition to Chronic Dialysis (Randomized Population), Trial 0014



Source: Applicant's analysis in response to submitted information request

Proportion of Subjects with Progression of CKD

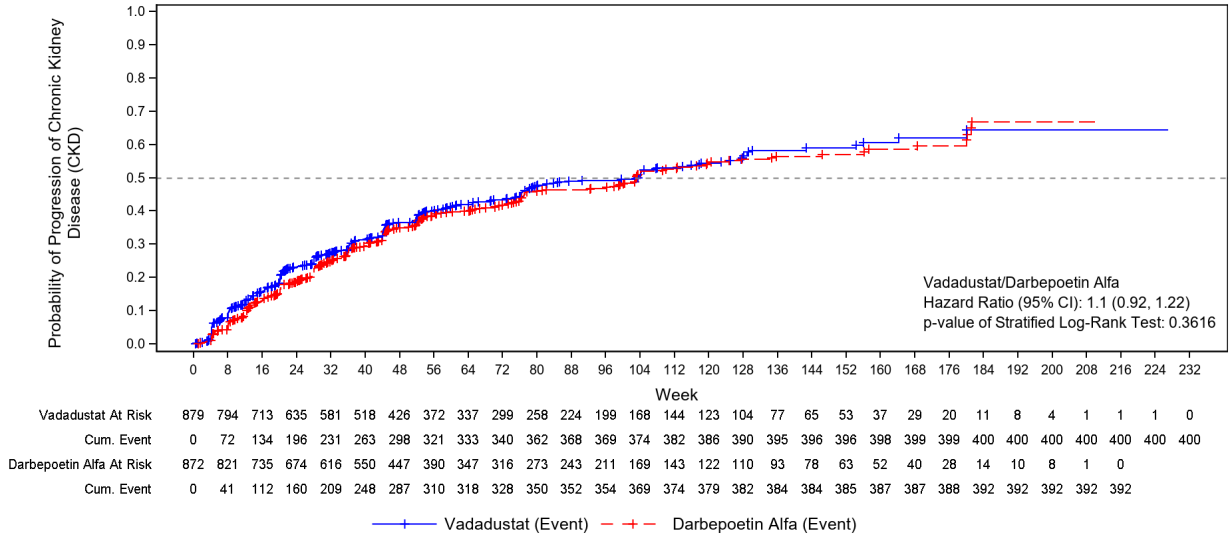
Table 239. Time to Progression of CKD (Randomized Population), Trial 0014

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
Subjects with progression of CKD, n (%)	400 (45.5)	392 (45.0)
Subjects censored, n (%)	479 (54.5)	480 (55.0)
Cumulative incidence (95% CI)		
24 Weeks	0.23 (0.20, 0.26)	0.19 (0.16, 0.22)
36 Weeks	0.28 (0.25, 0.31)	0.28 (0.25, 0.31)
40 Weeks	0.31 (0.28, 0.35)	0.30 (0.27, 0.33)

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
52 Weeks	0.37 (0.34, 0.41)	0.36 (0.33, 0.39)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.36	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.1 (0.92, 1.22)	

Source: Applicant's analysis in response to submitted information request

Figure 59. Kaplan-Meier Curve of Time to Progression of CKD (Randomized Population), Trial 0014



Source: Applicant's analysis in response to submitted information request

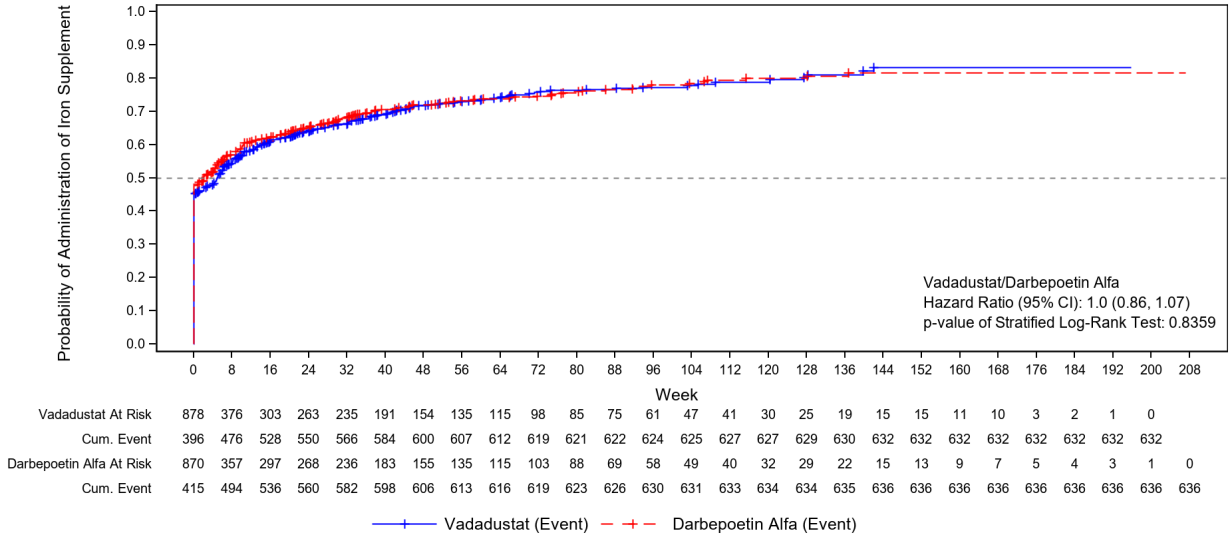
Proportion of Subjects That Received Iron Supplement (Regardless of Administration Route)

Table 240. Time to Administration of Iron Supplement (Randomized Population), Trial 0014

Statistics	Vadadustat N=879	Darbepoetin Alfa N=872
Subjects with administration of iron supplement, n (%)	632 (72.0)	636 (73.1)
Subjects censored, n (%)	246 (28.0)	234 (26.9)
Cumulative incidence (95% CI)		
24 Weeks	0.64 (0.61, 0.67)	0.65 (0.62, 0.68)
36 Weeks	0.68 (0.65, 0.71)	0.69 (0.66, 0.73)
40 Weeks	0.69 (0.66, 0.72)	0.71 (0.67, 0.74)
52 Weeks	0.72 (0.69, 0.76)	0.72 (0.69, 0.76)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.84	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.0 (0.86, 1.07)	

Source: Applicant's analysis in response to submitted information request

Figure 60. Kaplan-Meier Curve of Time to Administration of Iron Supplement (Randomized Population), Trial 0014



Source: Applicant's analysis in response to submitted information request

Sensitivity Analyses Considering Narrow Rescue Therapy

Table 241. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations) Considering Narrow Rescue Therapy, Randomized Population, Trial 0014

Visit Statistics	Vadadustat N=879	Darbepoetin Alfa N=872	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	879	872	
Mean (SD)	9.1 (0.8)	9.1 (0.8)	
Weeks 24 to 36 (observed)			
n	727	750	
Mean (SD)	10.5 (0.9)	10.4 (1.0)	
Weeks 24 to 36 (observed + imputed)			
n	879	872	
Mean (SD)	10.4 (1.0)	10.3 (1.0)	
Change from baseline			
n	879	872	
Mean (SD)	1.3 (1.0)	1.2 (1.0)	
Least squares mean (SEM)	1.4 (0.05)	1.4 (0.05)	0.0 (0.05)
95% CI	(1.3, 1.5)	(1.3, 1.5)	(-0.1, 0.1)

Source: Study 0014 Clinical Study Report Table 19 (p. 81), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.

Table 242. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations) Considering Narrow Rescue Therapy, Randomized Population, Trial 0014

Visit Statistics	Vadadustat N=879	Darbepoetin Alfa N=872	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	879	872	
Mean (SD)	9.1 (0.8)	9.1 (0.8)	
Weeks 40 to 52 (observed)			
N	605	627	
Mean (SD)	10.6 (1.0)	10.5 (1.0)	
Weeks 40 to 52 (observed + imputed)			
n	879	872	
Mean (SD)	10.5 (1.1)	10.4 (1.0)	
Change from baseline			
n	879	872	
Mean (SD)	1.4 (1.0)	1.3 (1.1)	
Least squares mean (SEM)	1.5 (0.1)	1.5 (0.5)	0.1 (0.1)
95% CI	(1.4, 1.6)	(1.4, 1.6)	(-0.04, 0.2)

Source: Study 0014 Clinical Study Report Table 22 (p. 85), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean.
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.

Table 243. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0014

Therapy	Base Mean (SD)	Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n= 879)	9.1 (0.8)	10.3 (1.1)	1.2 (1.1, 1.3)
Darbepoetin Alpha (n= 872)	9.1 (0.8)	10.3 (1.1)	1.2 (1.1, 1.3)
Vada minus Darbe			0.0 (-0.1, 0.1)

Source: FDA analyses. Note that the final number of patients are 832 and 841 for Vada and Darbe's arms, respectively.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation. Patients' last Hb data were carried forward before the use of rescue therapy.

Table 244. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0014

Therapy	Base Mean (SD)	Final Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n= 879)	9.1 (0.8)	10.4 (1.1)	1.3 (1.2, 1.4)
Darbepoetin Alpha (n= 872)	9.1 (0.8)	10.4 (1.1)	1.3 (1.2, 1.3)
Vada minus Darbe			0.0 (-0.1, 0.1)

Source: FDA analyses. Note that the final number of patients are 815 and 829 for Vada and Darbe's arms separately.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation. Patients' last Hb data were carried forward before the use of rescue therapy.

16.3.2. Trial 0015

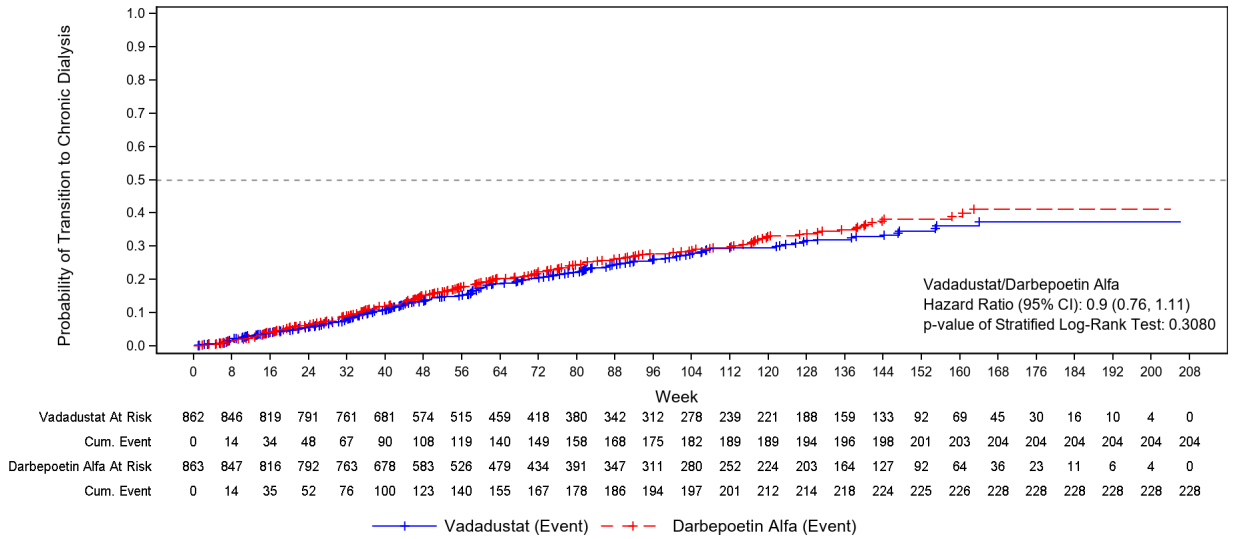
Proportion of Subjects Transitioned to Chronic Dialysis

Table 245. Time to Transition to Chronic Dialysis (Randomized Population), Trial 0015

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
Subjects with transition to chronic dialysis, n (%)	204 (23.7)	228 (26.4)
Subjects censored, n (%)	658 (76.3)	635 (73.6)
Cumulative incidence (95% CI)		
24 Weeks	0.06 (0.04, 0.07)	0.06 (0.05, 0.08)
36 Weeks	0.10 (0.08, 0.12)	0.11 (0.09, 0.13)
40 Weeks	0.11 (0.089, 0.13)	0.12 (0.10, 0.14)
52 Weeks	0.15 (0.12, 0.17)	0.16 (0.14, 0.19)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.31	
Hazard ratio (vadadustat/darbepoetin alfa) (95% CI)	0.9 (0.76, 1.11)	

Source: Applicant's analysis in response to submitted information request

Figure 61. Kaplan-Meier Curve of Time to Transition to Chronic Dialysis (Randomized Population), Trial 0015



Source: Applicant's analysis in response to submitted information request

Proportion of Subjects That Had Progression of CKD

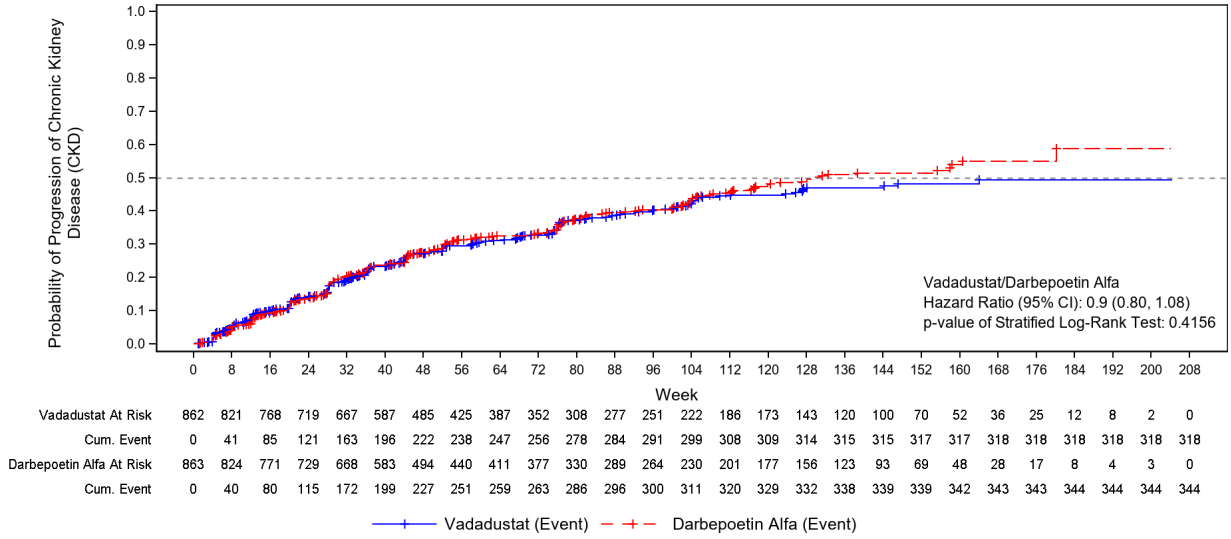
Table 246. Time to Progression of CKD (Randomized Population), Trial 0015

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
Subjects with progression of CKD, n (%)	318 (36.9)	344 (39.9)
Subjects censored, n (%)	544 (63.1)	519 (60.1)
Cumulative incidence (95% CI)		
24 Weeks	0.14 (0.12, 0.17)	0.14 (0.11, 0.16)
36 Weeks	0.21 (0.18, 0.24)	0.22 (0.19, 0.25)
40 Weeks	0.23 (0.21, 0.26)	0.24 (0.21, 0.27)

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
52 Weeks	0.28 (0.25, 0.31)	0.29 (0.26, 0.32)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.42	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	0.9 (0.80, 1.08)	

Source: Applicant's analysis in response to submitted information request

Figure 62. Kaplan-Meier Curve of Time to Progression of CKD (Randomized Population), Trial 0015



Source: Applicant's analysis in response to submitted information request

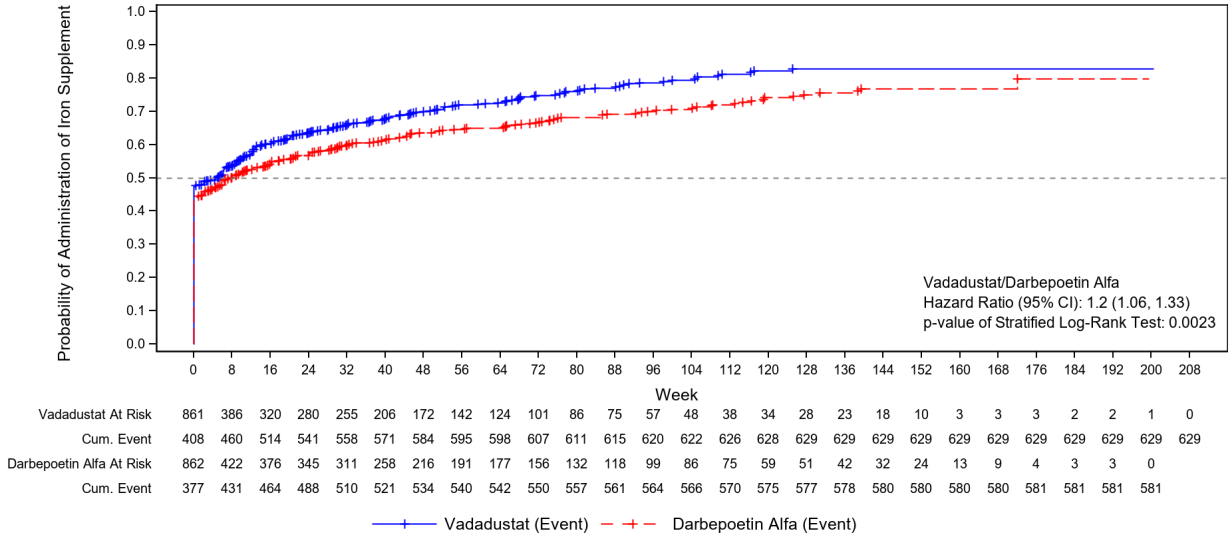
Proportion of Subjects That Received Iron Supplement (Regardless of Administration Route)

Table 247. Time to Administration of Iron Supplement (Randomized Population), Trial 0015

Statistics	Vadadustat N=862	Darbepoetin Alfa N=863
Subjects with administration of iron supplement, n (%)	629 (73.1)	581 (67.4)
Subjects censored, n (%)	232 (26.9)	281 (32.6)
Cumulative incidence (95% CI)		
24 Weeks	0.64 (0.60, 0.67)	0.57 (0.54, 0.60)
36 Weeks	0.67 (0.63, 0.70)	0.61 (0.57, 0.64)
40 Weeks	0.68 (0.65, 0.71)	0.61 (0.58, 0.65)
52 Weeks	0.71 (0.67, 0.74)	0.64 (0.61, 0.68)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.002	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.2 (1.06, 1.33)	

Source: Applicant's analysis in response to submitted information request

Figure 63. Kaplan-Meier Curve of Time to Administration of Iron Supplement (Randomized Population), Trial 0015



Source: Applicant's analysis in response to submitted information request

Sensitivity Analyses Considering Narrow Rescue Therapy

Table 230. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputation), Considering Narrow Rescue Therapy Randomized Population, Trial 0015

Visit Statistics	Vadadustat N=862	Darbepoetin Alfa N=863	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	862	863	
Mean (SD)	10.4 (0.9)	10.4 (0.9)	
Weeks 24 to 36 (observed)			
n	742	792	
Mean (SD)	10.8 (0.9)	10.8 (1.0)	
Weeks 24 to 36 (observed + imputed)			
n	862	863	
Mean (SD)	10.8 (1.0)	10.8 (1.0)	
Change from baseline			
n	862	863	
Mean (SD)	0.4 (1.0)	0.4 (1.0)	
Least squares mean (SEM)	0.4 (0)	0.4 (0)	0 (0)
95% CI	(0.3, 0.5)	(0.4, 0.5)	(-0.1, 0.1)

Source: Study 0015 Clinical Study Report Table 21 (p. 91), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.

Table 231. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Considering Narrow Rescue Therapy Randomized Population, Trial 0015

Visit Statistics	Vadadustat N=862	Darbepoetin Alfa N=863	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	862	863	
Mean (SD)	10.4 (0.9)	10.4 (0.9)	
Weeks 40 to 52 (observed)			
N	605	663	
Mean (SD)	10.9 (1.0)	10.8 (1.0)	
Weeks 40 to 52 (observed + imputed)			
n	862	863	
Mean (SD)	10.8 (1.1)	10.8 (1.1)	
Change from baseline			
n	862	863	
Mean (SD)	0.4 (1.0)	0.4 (1.1)	
Least squares mean (SEM)	0.4 (0)	0.4 (0)	0 (0.1)
95% CI	(0.3, 0.5)	(0.4, 0.5)	(-0.1, 0.1)

Source: Study 0015 Clinical Study Report Table 24 (p. 96), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.

Table 248. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0015

Therapy	Base Mean (SD)	Final Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n= 862)	10.4 (0.9)	10.8 (1.0)	0.4 (0.3, 0.4)
Darbepoetin alpha (n= 863)	10.4 (0.9)	10.8 (1.0)	0.4 (0.3, 0.4)
Vada minus Darbe			0.0 (-0.1, 0.1)

Source: FDA analyses. Note that the final number of patients are 817 and 846 for Vada and Darbe's arms, respectively.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation. Patients' last Hb data were carried forward before the use of rescue therapy.

Table 249. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0015

Therapy	Base Mean (SD)	Final Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n= 862)	10.4 (0.9)	10.8 (1.1)	0.4 (0.3,0.4)
Darbepoetin alpha (n= 863)	10.4 (0.9)	10.8 (1.1)	0.4 (0.3, 0.5)
Vada minus Darbe			0.0 (-0.1, 0.1)

Source: FDA analyses. Note that the final number of patients are 791 and 834 for Vada and Darbe's arms, respectively.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation. Patients' last Hb data were carried forward before the use of rescue therapy.

16.3.3. Trial 0016

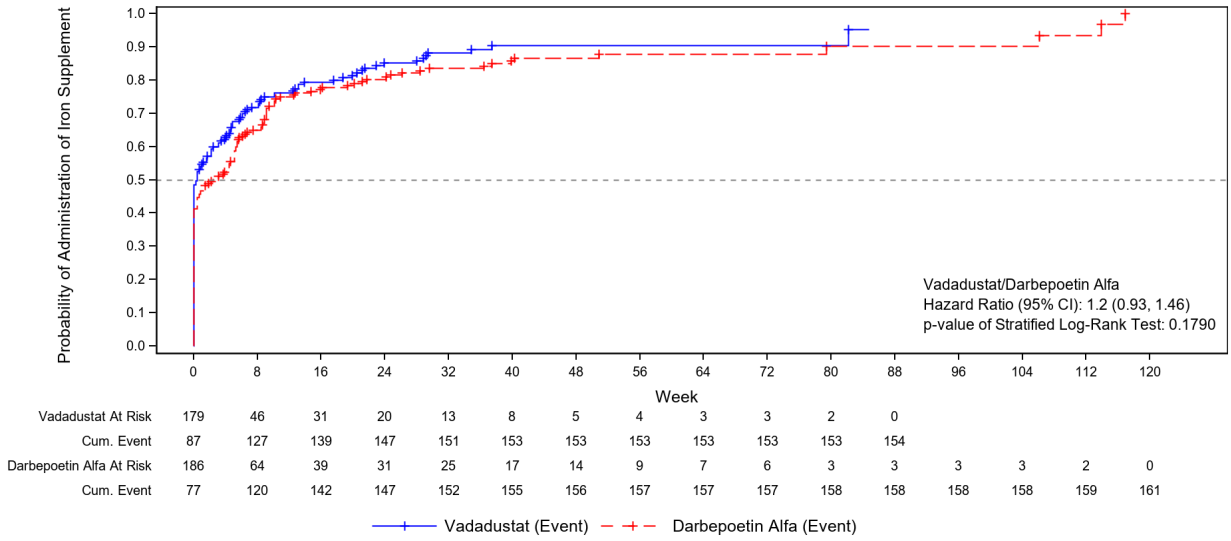
Proportion of Subjects That Received Iron Supplement (Regardless of Administration Route)

Table 250. Time to Administration of Iron Supplement (Randomized Population), Trial 0016

Statistics	Vadadustat N=181	Darbepoetin Alfa N=188
Subjects with administration of iron supplement, n (%)	154 (86.0)	161 (86.6)
Subjects censored, n (%)	25 (14.0)	25 (13.4)
Cumulative incidence (95% CI)		
24 Weeks	0.85 (0.79, 0.90)	0.8 (0.74, 0.86)
36 Weeks	0.89 (0.83, 0.94)	0.84 (0.78, 0.89)
40 Weeks	0.90 (0.85, 0.95)	0.86 (0.80, 0.91)
52 Weeks	0.90 (0.85, 0.95)	0.88 (0.82, 0.92)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.18	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.2 (0.93, 1.46)	

Source: Applicant's analysis in response to submitted information request

Figure 64. Kaplan-Meier Curve of Time to Administration of Iron Supplement (Randomized Population), Trial 0016



Source: Applicant's analysis in response to submitted information request

Sensitivity Analyses Considering Narrow Rescue Therapy

Table 251. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Considering Narrow Rescue Therapy, Randomized Population, Trial 0016

Visit Statistics	Vadadustat N=181	Darbepoetin Alfa N=188	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	181	188	
Mean (SD)	9.4 (1.1)	9.2 (1.1)	
Weeks 24 to 36 (observed)			
n	148	165	
Mean (SD)	10.4 (1.1)	10.7 (0.9)	
Weeks 24 to 36 (observed + imputed)			
n	181	188	
Mean (SD)	10.4 (1.2)	10.6 (0.9)	
Change from baseline			
n	181	188	
Mean (SD)	1.0 (1.3)	1.4 (1.4)	
Least squares mean (SEM)	1.3 (0.1)	1.6 (0.1)	-0.3 (0.1)
95% CI	(1.1, 1.5)	(1.4, 1.8)	(-0.5, -0.1)

Source: Study 0016 Clinical Study Report Table 19 (p. 78), Statistics Reviewer's analysis
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Table 252. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Considering Narrow Rescue Therapy, Randomized Population, Trial 0016

Visit Statistics	Vadadustat N=181	Darbepoetin Alfa N=188	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	181	188	
Mean (SD)	9.4 (1.1)	9.2 (1.1)	
Weeks 40 to 52 (observed)			
n	121	140	
Mean (SD)	10.5 (1.1)	10.6 (1.0)	
Weeks 40 to 52 (observed + imputed)			
N	181	188	
Mean (SD)	10.4 (1.3)	10.5 (1.1)	
Change from baseline			
n	181	188	
Mean (SD)	1.0 (1.4)	1.3 (1.6)	
Least squares mean (SEM)	1.3 (0.1)	1.5 (0.1)	-0.2 (0.1)
95% CI	(1.0, 1.6)	(1.2, 1.8)	(-0.5, 0.1)

Source: Study 0016 Clinical Study Report Table 19 (p. 78), Statistics Reviewer's analysis
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean

Table 253. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0016

Therapy	Base Mean (SD)	Final Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n=181)	9.4 (1.1)	10.4 (1.2)	1.1 (0.9, 1.2)
Darbepoetin alpha (n=188)	9.2 (1.1)	10.6 (1.0)	1.4 (1.2, 1.5)
Vada minus Darbe			-0.3 (-0.5, -0.1)

Source: FDA analyses. Note that the final number of patients are 166 and 179 for Vada and Darbe's arms, respectively.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation. Patients' last Hb data were carried forward before the use of rescue therapy.

Table 254. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0016

Therapy	Base Mean (SD)	Final Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n=181)	9.4 (1.1)	10.4 (1.3)	1.1 (0.9, 1.3)
Darbepoetin alpha (n=188)	9.2 (1.1)	10.6 (1.1)	1.3 (1.1, 1.5)
Vada minus Darbe			-0.2 (-0.5, 0.1)

Source: FDA analyses. Note that the final number of patients are 159 and 179 for Vada and Darbe's arms, respectively.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation. Patients' last Hb data were carried forward before the use of rescue therapy.

16.3.4. Trial 0017

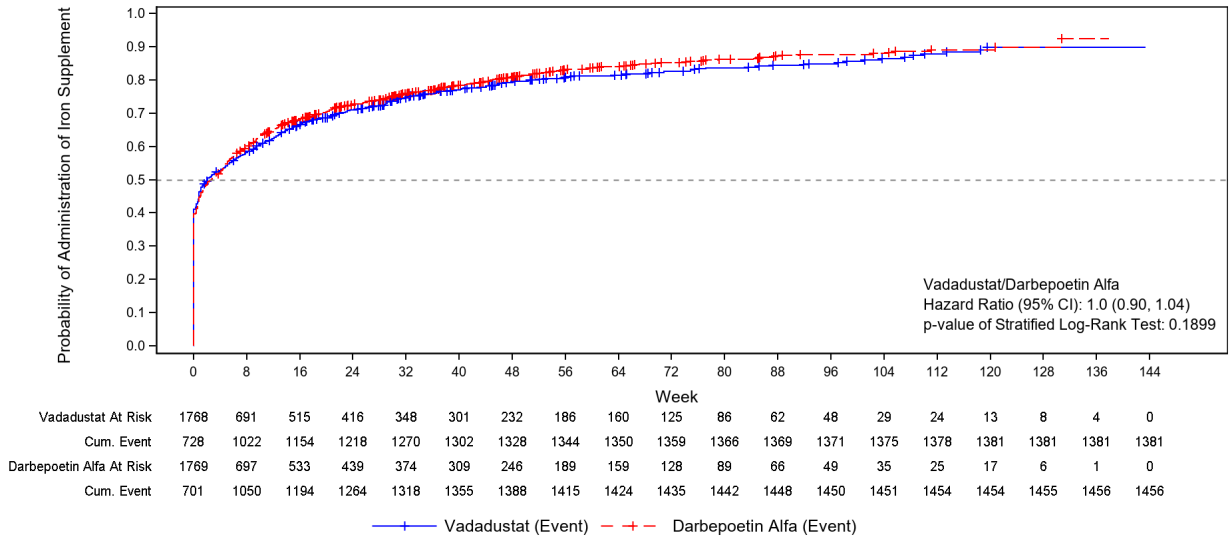
Proportion of Subjects That Received Iron Supplement (Regardless of Administration Route)

Table 255. Time to Administration of Iron Supplement (Randomized Population), Trial 0017

Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777
Subjects with administration of iron supplement, n (%)	1381 (78.1)	1456 (82.3)
Subjects censored, n (%)	387 (21.9)	313 (17.7)
Cumulative incidence (95% CI)		
24 Weeks	0.71 (0.69, 0.73)	0.72 (0.70, 0.74)
36 Weeks	0.76 (0.74, 0.78)	0.77 (0.75, 0.79)
40 Weeks	0.77 (0.75, 0.79)	0.78 (0.76, 0.80)
52 Weeks	0.80 (0.78, 0.82)	0.82 (0.80, 0.84)
Treatment comparison		
p-value of Stratified Log-Rank Test	0.19	
Hazard ratio (vadadustat/ darbepoetin alfa) (95% CI)	1.0 (0.90, 1.04)	

Source: Applicant's analysis in response to submitted information request

Figure 65. Kaplan-Meier Curve of Time to Administration of Iron Supplement (Randomized Population), Trial 0017



Source: Applicant's analysis in response to submitted information request

Table 256. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Multiple Imputations), Considering Narrow Rescue Randomized Population, Trial 0017

Visit Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	1777	1777	
Mean (SD)	10.3 (0.9)	10.2 (0.8)	
Weeks 24 to 36 (observed)			
N	1426	1585	
Mean (SD)	10.4 (1.0)	10.6 (0.9)	
Weeks 24 to 36 (observed + imputed)			
n	1777	1777	
Mean (SD)	10.3 (1.0)	10.5 (1.0)	
Change from baseline			
n	1777	1777	
Mean (SD)	0.1 (1.2)	0.3 (1.1)	
Least squares mean (SEM)	0.2 (0)	0.4 (0)	-0.2 (0)
95% CI	(0.1, 0.2)	(0.3, 0.4)	(-0.3, -0.1)

Source: Study 0017 Clinical Study Report Table 23 (p. 82), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.

Table 257. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Multiple Imputations), Considering Narrow Rescue Randomized Population, Trial 0017

Visit Statistics	Vadadustat N=1777	Darbepoetin Alfa N=1777	Treatment Comparison Vadadustat – Darbepoetin Alfa
Baseline			
n	1777	1777	
Mean (SD)	10.3 (0.9)	10.2 (0.8)	
Weeks 40 to 52 (observed)			
n	1268	1461	
Mean (SD)	10.5 (1.0)	10.6 (0.9)	
Weeks 40 to 52 (observed + imputed)			
n	1777	1777	
Mean (SD)	10.4 (1.0)	10.6 (0.9)	
Change from baseline			
n	1777	1777	
Mean (SD)	0.1 (1.2)	0.4 (1.1)	
Least squares mean (SEM)	0.2 (0)	0.4 (0)	-0.3 (0)
95% CI	(0.1, 0.3)	(0.4, 0.5)	(-0.3, -0.2)

Source: Study 0017 Clinical Study Report Table 23 (p. 82), Statistics Reviewer's analysis
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation; SEM, standard error of mean
Patients who received narrow rescue therapies, either RBC transfusions or ESA rescue therapy had their Hb values within 4-weeks after rescue censored from the primary analysis.

Table 258. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 24 to 36 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0017

Therapy	Base Mean (SD)	Final Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n=1777)	10.3 (0.9)	10.4 (1.0)	0.1 (0.4, 0.1)
Darbepoetin alpha (n=1777)	10.2 (0.8)	10.5 (1.0)	0.3 (0.2, 0.3)
Vada minus Darbe			-0.2 (-0.3, -0.1)

Source: FDA analyses. Note that the final number of patients are 1575 and 1725 for Vada and Darbe's arms, respectively.
Patients' last Hb data were carried forward before the use of rescue therapy.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation.

Table 259. Change in Hemoglobin (g/dL) Between Baseline and Average Values Over Weeks 40 to 52 (ANCOVA With Last Observation Carried Forward) Considering Narrow Rescue Therapy, Randomized Population, Trial 0017

Therapy	Base Mean (SD)	Final Average Mean* (SD)	Difference Mean (95% CI)
Vadadustat (n=1777)	10.3 (0.9)	10.4 (1.0)	0.1 (0.0)
Darbepoetin alpha (n=1777)	10.2 (0.8)	10.6 (1.0)	0.3 (0.0)
Vada minus Darbe			-0.2 (-0.3, -0.1)

Source: FDA analyses. Note that the final number of patients are 1495 and 1695 for Vada and Darbe's arms, respectively.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of subjects; n, number of subjects within specific category; SD, standard deviation. Patients' last Hb data were carried forward before the use of rescue therapy.

17. Clinical Safety: Additional Information and Assessment

17.1. Early Phase Trials in NDD-CKD Population

As noted in section II.7.4, we analyzed the safety data from early phase completed trials in the NDD-CKD population in a descriptive fashion, without any pooling of data, as follows:

AKB-6548-CI-0003 (NCT#04707573):

Title: Phase 2a Single Dose, Open Label Study to Assess the Safety and Pharmacokinetics of AKB-6548 in Subjects with CKD stages 3 and 4

Trial population: Subjects 18-79 years with CKD stage 3 (eGFR 30-59 ml/min) or CKD stage 4 (eGFR <30 ml/min but not on dialysis)

Trial Design: Multi-center, open label, 2-cohort trial (cohort #1 includes subjects with CKD stage 3 and cohort #2 includes subjects with CKD stage 4)

Trial Regimen: Single dose of 500 mg

Trial objectives and endpoints: Assess the PK profile, PD assessment (i.e., change from baseline at 8, 12, and 24 hours in serum EPO and exploratory biomarkers such as vascular endothelial growth factor, hepcidin, transferrin, cystatin-C, adiponectin, and ferritin), safety (i.e., AEs, laboratory tests, vital signs, electrocardiograms [ECGs] and physical exam findings) and tolerability in subjects with Stage 3 and 4 CKD following a single oral dose of vadadustat

Planned subjects / actual subjects / centers / countries: 16-28 / 22 (10 in cohort #1 and 12 in cohort #2) / 2 / 1 (United States)

PD and safety results:

- Mean baseline EPO [SD] in both populations is similar (22.3 [15.1] IU/L). Mean change from baseline to 8- or 12-hours post-dose showed an elevation in CKD stage 4 versus CKD stage 3 (11-12 IU/L versus 5-6 IU/L, respectively) with similar variation. EPO returned to baseline at 24 hours post-dose. There was an observed positive relationship of increased EPO levels with increased vadadustat exposure.
- Mean baseline hepcidin [SD] was appropriately elevated, with higher elevation in CKD stage 4 (194 [246] ng/ml) than CKD stage 3 (91 [58] ng/ml). Mean change from baseline to 24-hours [SD] showed a decrease in levels, which was similar between the two cohorts (30 [30] ng/ml).
- Mean baseline transferrin [SD] was appropriately elevated at similar levels in both cohorts (1835 [343] mg/dL), with similar mean change to 24-hours [SD] between cohorts (115 [173] mg/dL), showing a decrease in levels.
- No trends were observed in the remaining PD markers.
  Eight subjects (36%) experienced 18 TEAEs, with 12 mild TEAEs and 4 moderate TEAEs. One patient experienced the 2 severe TEAEs (tachycardia and hypotension, which were transient), which were considered drug-related by the investigator. One patient in CKD stage 4 cohort had elevated AST to 134 U/L (>3x ULN), which resolved by day 8 visit. Overall, the conclusion was that vadadustat was safe and well-tolerated.

AKB-6548-CI-0004 (NCT#01235936):

Title: Phase 2a Open-Label Pilot Study to Assess the PD Response, PK, Safety, and Tolerability of 28-day Repeat Oral Doses of vadadustat in Subjects with Anemia Secondary to CKD, Stages 3 and/or 4

Trial population: 18-79 years with CKD stage 3 (eGFR 30-59 ml/min) or CKD stage 4 (eGFR <30 ml/min but not on dialysis), Hb <10.5 g/dL with normocytic RBC morphology and transferrin saturation >20%

Trial Design: Multi-center, open label, single arm trial

Trial Regimen:

- Daily dose for 28 days as follows: 400 mg/day in CKD stage 3 (maximum dose of 700 mg) and 300 mg/day in CKD stage 4 (maximum dose of 600 mg).
- Protocol-based dose adjustment by single dose levels of 100 mg, based on hematologic response (assessed with weekly Hb and reticulocyte count). Dose ranged from 300 mg to 700 mg. Final doses were: 300 mg for 1 subject, 400 mg for 1 subject, 500 mg for 2 subjects, 600 mg for 4 subjects, and 700 mg for 2 subjects.
- All subjects were on therapeutic iron supplementation during the treatment period.

Trial objectives and endpoints: Assess hematologic PD response (change from baseline in Hb at end of treatment period, in addition to changes in reticulocyte and iron indices), PK, safety (i.e., AEs, laboratory tests, VS, ECGs and physical exam findings) and tolerability in subjects with Stage 3 and 4 CKD on daily repeat dosing for 28 days.

Number of planned subjects / actual subjects / centers / countries: 15 / 10 (6 subjects with CKD stage 3 and 4 subjects with CKD stage 4) / 2 / 1 (Untied States)

PD and safety results:

- Mean baseline Hb was 9.9 g/dL and mean change in Hb at end of treatment period was 10.5 g/dL, with the majority of subjects having a ≥0.4 g/dL Hb change from baseline. Subjects with mean dose ≤500 mg had 0.6 g/dL change in Hb and subjects with mean dose >500 mg had 0.8 g/dL change in Hb.
- Mean changes in Hb were higher in subjects with CKD stage 3 versus CKD stage 4 (0.8 g/dL versus 0.4 g/dL).
- Five subjects (50%) had ≥1 treatment-emergent adverse event (TEAE). No subjects had AE leading to discontinuation, SAEs, or death. All TEAEs were mild in severity. Most frequent TEAE was diarrhea. Other TEAEs included nausea, peripheral neuropathy, and muscle spasms. There were no significant changes in liver-based laboratory values. Overall, the conclusion was that vadadustat was safe and well-tolerated.

AKB-6548-CI-0005 (NCT#01381094):

Title: Phase 2a Randomized, Double-blind, Placebo-controlled, Dose Range Study to Assess the PD Response, PK, Safety, and Tolerability of 42-day Repeat Oral Doses of AKB-6548 in Subjects with Anemia Secondary to CKD, Stages 3 and 4

Trial population: 18-79 years with CKD stage 3 (eGFR 30-59 ml/min) or CKD stage 4 (eGFR <30 ml/min but not on dialysis and not expected to start dialysis within 3 months), Hb <10.5 g/dL and transferrin saturation >20%

Trial Design: Multi-center, randomized (1:1:1:1:1), double-blind, placebo-controlled trial with stratification by stage of CKD and presence of diabetes mellitus.

Trial regimen:

- Daily dose for 42 days of 1 of 5 starting dose groups: 240 mg (n=18), 370 mg (n=18), 500 mg (n=17), 630 mg (n=19) or placebo (n=19).
- Protocol-based dose adjustment by single dose levels was allowed, based on hematologic response (assessed with weekly Hb and reticulocyte count). Only a one-time dose reduction was allowed, with 5 of the 9 reductions occurring at the highest dose of 630 mg.
- All subjects were on therapeutic iron supplementation during the treatment period.

Trial objectives and endpoints: Assess hematologic PD response (change from baseline in Hb at end of treatment period, in addition to rate of response – defined as increase from pre-dose mean Hb of ≥1 g/dL), PK, safety (i.e., AEs, laboratory tests, VS, ECGs and physical exam findings) and tolerability in subjects with Stage 3 and 4 CKD on daily repeat dosing for 42 days.

Number of planned subjects / actual subjects / centers / countries: 100 (minimum of 25 from each CKD stage) / 91 (23 with stage 3 CKD and 68 with stage 4 CKD) / 29 / 1 (United States)

PD and safety results:

- All dose levels resulted in a statistically significant increase in mean Hb and higher rate of response, compared to placebo, at the end of the treatment period. The magnitude of mean Hb increase (SD) compared to placebo was as follows: 0.8 (0.7), 0.7 (0.6), 1.3 (0.6), 1.4 (0.7), 1.1 (0.7) g/dL for vadadustat 240, 370, 500, 630 mg, respectively.
- Thirty-four subjects (47%) in the vadadustat groups versus 11 subjects (58%) in the placebo group had ≥1 TEAE. The most frequently reported TEAEs were nausea, hyperkalemia, hypoglycemia, headache, and urinary tract infection. The majority of TEAEs were mild or moderate in severity. There were 3 severe TEAEs: coronary artery disease, azotemia, and hypertensive crisis, all in the 370 mg group.
- Four subjects had AE leading to discontinuation, due to: nausea, azotemia, coronary artery disease, mild palpitations and worsening of hypertension.
- Eight subjects had SAEs, none of which occurred in more than 1 subject. The SAEs experienced in subjects receiving vadadustat included: coronary artery disease, gastroenteritis, hypoglycemia, dizziness, azotemia, and hypertensive crisis.
- One patient died, related to progression of CKD, in the 370 mg group. There was no evidence of overall dose effect.
- There were no significant changes in liver-based laboratory values.
  Overall, TEAEs were evenly distributed among vadadustat groups and there was no evidence of overall dose effect. The conclusion was that vadadustat was safe and well-tolerated.

AKB-6548-CI-0007 (NCT#01906489):

Title: Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Assess the PD Response, Safety, and Tolerability to 20 Weeks of Oral Dosing of AKB-6548 in Subjects with Anemia Secondary to CKD, glomerular filtration rate Categories G3a-G5 (Stages 3, 4, and 5) (Pre-Dialysis)

Trial population: ≥18 years old with CKD status (G3a-G5) but not on dialysis and not expected to start dialysis, baseline Hb based on ESA-exposure defined groups, and specific iron studies-based criteria to ensure iron repletion

Trial Design: multi-center, randomized (2:1 within each of the ESA-exposure defined study cohorts), parallel-group, double-blind, placebo-controlled trial with 3 study cohorts, based on ESA status:

- ESA naïve: Never received ESA and had baseline Hb ≤10.5 g/dL (n=107)
- Previously Treated: Subject had received at least 1 dose of ESA in the past but have been off ESA for ≥11 weeks and had baseline Hb ≤10.5 g/dL (n=63)
- Actively Treated: Treated with ESA for at least of 4 months, with at least 2 doses received within the last 4 months prior to screening, the last dose within 6 weeks from screening and had baseline Hb ≥9.5 g/dL and ≤12.0 g/dL (n=40)
- Stratification by CKD status (G3a-G5) and presence of diabetes mellitus

Trial regimen:

- Daily starting dose for 20 weeks of 450 mg.
- Protocol-based dose adjustment by single dose levels was allowed, based on hematologic response (assessed with weekly Hb and reticulocyte count), with maximum dose of 600 mg. Dosing was stopped if Hb was ≥13.0 g/dL and was not restarted until Hb decreased to ≤12.5 g/dL.
- All subjects are on therapeutic iron supplementation during the treatment period.

Trial objectives and endpoints: Assess hematologic PD response (i.e., achieved or maintained a mean Hb ≥11.0 g/dL or experienced an increase in Hb of ≥1.2 g/dL from baseline Hb value, at the end of treatment period), safety (i.e., neurocognitive functioning, patient-reported outcome - based measures, AEs, laboratory tests, VS, ECGs and physical exam findings) and tolerability in subjects with CKD, glomerular filtration rate Categories G3a-G5 (Pre-Dialysis), on daily repeat dosing for 20 weeks. Subjects who received ESA or transfusion rescue were counted as failures.

Number of planned subjects / actual subjects / centers / countries: 200 / 210 (138 on vadadustat versus 72 on placebo) / 61 / 1 (United States)

PD and safety results:

- PD response achieved in 55% of subjects on vadadustat versus 10% of subjects on placebo, which was confirmed with various sensitivity analyses. Similar response was observed in the ESA naïve and previously treated groups, with the previously treated group having a slower response. Response was achieved in the ESA naïve by week 4.
- PD response was not observed in the actively treated group due to the presence of higher baseline Hb but Hb was maintained throughout the trial. Overall, baseline Hb was not a predictor of Hb response. Hb ≥13.0 g/dL occurred in 4% of subjects.
- ESA rescue was needed in 18% of subjects on placebo versus 4% of subjects on vadadustat and only 1 patient needed transfusion rescue, on the placebo arm.
- No clinically important difference was observed in relation to neurocognitive functioning and patient-reported outcome-based measures.
- The most frequently reported TEAEs (≥5%) were diarrhea, nausea, hyperkalemia, and hypertension, with the majority being mild or moderate in severity.

- SAEs occurred in 24% of subjects on vadadustat versus 15% of subjects on placebo, mainly due to a higher incidence of serious renal-related events (10% versus 3%). However, the number of subjects with AE needing dialysis (8% versus 10%) and those having worsening CKD needing dialysis that resulted in treatment discontinuation (4% versus 6%) were comparable between arms.
- One patient on vadadustat had abnormal liver tests that met the criteria of Hy's law, probably related to vadadustat. This case is discussed in the hepatotoxicity section.
- There were more subjects having AEs leading to discontinuation in the vadadustat arm than the placebo arm (7% versus 4%), due to: abnormal liver function test, malaise, diarrhea, nausea, and angioedema.
- Three subjects (2.2%) died on the vadadustat arm versus no death in the placebo arm, with the following causes of death: myocardial ischemia, sudden cardiac death, and cardiac arrest.

AKB-6548-CI-0021 (NCT#03054337)

Title: Phase 2, Randomized, Double-blind, Placebo-Controlled, Dose-Finding Study to Assess the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Vadadustat in Japanese Subjects with Anemia Secondary to NDD-CKD

Trial population: ≥20 years with Anemia Secondary to NDD-CKD (eGFR ≤60 ml/min) but not on dialysis, not expected to start dialysis within 3 months of screening and not being treated with ESA within 6 weeks, Hb ≤10.5 g/dL and specific iron studies-based criteria to ensure iron repletion

Trial Design: multi-center, randomized (1:1:1 between each dose cohort and 3:1 within each of the dose cohorts), double-blind, placebo-controlled trial with 3 dose cohorts.

Trial regimen:

- Daily dose of 1 of 3 starting dose cohorts: 150 mg (n=12), 300 mg (n=12), and 600 mg (n=13), with 4 subjects on placebo per dose cohort (n=14).
- Protocol-based dose adjustment by single dose levels was allowed, based on hematologic response (assessed with weekly Hb and reticulocyte count), only during a 10-week dose adjustment and maintenance period that followed the initial 6-week primary efficacy period, to achieve a target Hb of 10-12 g/dL.
- Even though no increase in dose was allowed during the primary efficacy period, dose was decreased and/or interrupted if Hb increased rapidly (i.e., >1 g/dL in any 2-week period) or Hb >13 g/dL, where dose was not restarted until Hb decreased to ≤12.5 g/dL
- All subjects were on therapeutic iron supplementation during the treatment period.

Trial objectives and endpoints: Assess hematologic PD response (change from baseline in Hb at end of treatment period and time to reach target Hb level between 10 g/dL and 12 g/dL) including dose-response relationship, PK, safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings), and tolerability in Japanese subjects with anemia secondary to NDD-CKD on daily repeat dose.

Number of planned subjects / actual subjects / centers / countries: 48 / 51 / 25 / 1 (Japan)

PD and safety results

- All dose levels resulted in an increase in mean Hb, compared to placebo, at the end of the treatment period. The magnitude of mean Hb increase compared to placebo was as follows: 0.4, 1.1, and 1.6 g/dL for vadadustat 150, 300 and 600 mg, respectively. Statistically significant Hb increase was reached in the 300-mg and 600-mg cohorts but not the 150-mg cohort.
- Reduction in dose during the primary efficacy period occurred in 25% of the 300-mg cohort and 69% of the 600-mg cohort. Hb was above target range at end of treatment in 9% of subjects. Increasing vadadustat dose was associated with a shorter time to reach target Hb range.
- Eighteen subjects (49%) in the vadadustat groups versus 5 subjects (36%) in the placebo group had ≥1 TEAE, with higher but equal incidence in the 300-mg and 600-mg group. The most frequently reported TEAEs were hypertension, nausea, diarrhea, and constipation. The majority of TEAEs were mild or moderate in severity.
- Four subjects had AE leading to discontinuation, due to: abnormal hepatic function, acute kidney injury, worsening renal impairment and lung infection.
- Eleven subjects had SAEs, which included: acute kidney injury, progression of CKD, abnormal hepatic function, duodenal ulcer hemorrhage, lung infection, spinal compression fracture, asthma, and interstitial lung disease.
- There were no deaths in the trial.
- There was one case of increased ALT/AST >3 ULN (this patient did not have bilirubin elevation.)

17.2. Early Phase Trials in DD-CKD Population

As noted in section II.7.4, we analyzed the safety data from early phase completed trials in the DD-CKD population in a descriptive fashion, without any pooling of data, as follows:

AKB-6548-CI-0009:

Title: Phase 1 Open-Label Study to Assess the PK, Safety, and Tolerability of Oral Dosing of Akb-6548 in Subjects with Anemia Secondary To ESRD, Undergoing Chronic Hemodialysis

Trial population: Subjects 18-79 years with CKD stage 5, receiving hemodialysis (HD) for at least 3 months, with baseline Hb ≤12 g/dL and no evidence of iron deficiency

Trial Design: Single-center, 2-period trial (pre-HD and post-HD, with 72-hour washout period in-between), cross-over, randomized (1:1 to receiving pre-HD dose first versus receiving post-HD dose first), open label

Trial Regimen: Two single doses of 450 mg, one dose pre-HD and one dose post-HD

Trial objectives and endpoints: Assess the PK profile, safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) and tolerability in subjects with Stage 5 CKD, before and after an HD session, following a single oral dose of vadadustat

Number of planned subjects / actual subjects / centers / countries: 12 / 12 / 1 / 1 (United States)

Safety Results: Seven subjects (58.3%) experienced 7 TEAEs, with all being mild TEAEs except for one moderate TEAEs of abdominal pain. The majority of TEAEs were GI-related AEs. No

AEs resulted in discontinuation from trial, no SAEs, and no deaths. Overall, the conclusion was that vadadustat was safe and well-tolerated.

AKB-6548-CI-0011 (NCT#02260193):

Title: Phase 2 Open-Label Study to Assess the Efficacy, Safety, and Tolerability of AKB-6548 in Subjects with Anemia Secondary ESRD, Undergoing Chronic Hemodialysis

Trial population: 18-79 years with CKD stage 5, receiving hemodialysis (HD) for at least 3 months, with baseline Hb >9-≤12 g/dL on ESA for past 8 out of 12 weeks, and no evidence of iron deficiency. ESA or RBC transfusion rescue due to worsening of anemia associated with CKD was not allowed, thus occurrence of worsening anemia resulted in withdrawal from trial. ESA was stopped prior to onset of study drug.

Trial Design: Multi-center, open label, uncontrolled trial, with 3 dose cohorts and sequential assignment

Trial regimen:

- Cohort #1 – 300 mg daily, cohort #2 – 450 mg daily, and cohort #3 – 450 three times a week. Duration of therapy was 16 weeks, with fixed dose regimen for first 8 weeks and dose adjustment allowed for the second 8 weeks.
- Protocol-based dose adjustment by single dose levels of 150 mg, based on hematologic response (assessed with weekly Hb and reticulocyte count). Dose ranged from 150 mg to 600 mg.
- All subjects were on therapeutic iron supplementation during the treatment period.

Trial objectives and endpoints: Assess hematologic PD response (change from baseline in Hb at end of treatment period, in addition to changes in reticulocyte and iron indices, and rate of rescue ESA or transfusions), safety（i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) and PK measures in the described trial population.

Number of planned subjects / actual subjects / centers / countries: 90 / 94 (30 subjects in cohort #1, 33 subjects in cohort #2 and 31 subjects in cohort #3) / 22 / 1 (United States)

PD and safety results:

- Hb was maintained throughout trial duration in all 3 cohorts, compared to baseline Hb while on stable ESA dosing. Similar pattern was observed in other PD markers. One patient (1.1%) had dose withheld due to Hb >13 g/dL. Seven subjects (7.4%) had worsening anemia leading to trial withdrawal.
- Seventy-eight subjects (83%) had ≥1 TEAE, with a total of 294 TEAEs, of which 11.7% were severe and 34% were moderate. Most commonly reported TEAEs were nausea (11.7%), diarrhea (10.6%), vomiting (9.6%), headache (8.5%), dizziness (7.4%), abdominal pain (6.4%), muscle spasms (6.4%), arteriovenous fistula thrombosis (5.3%) with 2.1% qualifying as a serious adverse event (SAE), and back pain (5.3%). There was no apparent difference in TEAE or SAEs occurrence among the three cohorts. There were two subjects who had an MI during the trial period. No occurrences of deaths, strokes or TIAs were observed. Eight subjects had AE leading to discontinuation, mainly due to GI AEs. There were no significant changes in liver-based laboratory values, with one patient (1.1%) having elevation in transaminases. Overall, the conclusion was that vadadustat

was safe and well-tolerated, with no apparent different among the 3 dose regimen cohorts. Conclusions are limited due to the lack of a control group.

AKB-6548-CI-0025 (NCT#03799627):

Title: Phase 2, Randomized, Open-Label, Active-Controlled, Efficacy, Safety, PK, and PD Study of Oral Vadadustat for the Treatment of Anemia in Hemodialysis Subjects Converting from Epoetin Alfa (FO_2RWARD-2)

Trial population: ≥18 years with CKD stage 5, receiving hemodialysis (HD) for at least 3 months, with baseline Hb between 8.5-11.0 g/dL on ESA for past 8 weeks prior to enrollment, and no evidence of iron deficiency. There are two trial populations:

ESA responders, who are further stratified into two groups:

- Low ESA dose group (T1 cohort), defined as ESA median dose equivalent of ≤90 U/kg/week of epoetin alfa (randomized in a 3:3:2 ratio)
- High ESA dose group (T2 cohort), defined as ESA median dose equivalent of >90 U/kg/week but of <300 U/kg/week of epoetin alfa (randomized in a 3:3:3:2 ratio)

ESA hypo-responders (T3 cohort), defined as ESA median dose equivalent of ≥300 U/kg/week of epoetin alfa with baseline Hb 8.0-10 g/dL (randomized in a 1:1 ratio)

Trial Design: Multi-center, open label, active-controlled, randomized trial, with 3 trial populations (see above) and multiple arms per population (see below)

Trial regimen:

Within each cohort, there were multiple treatment arms with a treatment duration of 20 weeks, defined by dose of vadadustat versus active control, as follows:

- T1a – vadadustat 300 mg daily versus T1b – vadadustat 450 mg daily versus T1c – epoetin alfa
- T2a – vadadustat 300 mg daily versus T2b – vadadustat 450 mg daily versus T2c – vadadustat 600 mg daily versus T2d – epoetin alfa
- T3a – vadadustat 600 mg daily versus T3b – epoetin alfa

If subjects achieved stable Hb within target Hb range, they were converted from daily dosing to three times a week dosing, after the 12-week treatment period.

Trial objectives and endpoints: Assess hematologic PD response (change from baseline in Hb at primary evaluation period (weeks 10-12) and secondary evaluation period (weeks 18-20), other PD markers such as EPO, rate of rescue ESA or transfusions and exploratory endpoints based on patient-reported outcomes), safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) and PK measures in the described trial population.

Number of planned subjects / actual subjects / centers / countries: 125 / 175 were enrolled but due to the Eurofins ransomware attacks resulting in loss of data, 139 subjects were evaluable (28 subjects in cohort T1a, 26 subjects in cohort T1b, 11 subjects in cohort T2a, 15 subjects in cohort T2b, 15 subjects in cohort T2c and 3 subjects in cohort T3a. Active-control ESA were given to a total of 41 subjects) / 39 / 1 (United States)

Efficacy and safety results:

- Efficacy conclusions based only on ESA responder population, given the small sample size of the ESA hypo-responder population. Vadadustat resulted in lower mean Hb at weeks 10-12, with lower proportions of subjects within the target Hb of 10-11 g/dL and a larger difference in proportion of subjects in the high ESA dose group, compared to epoetin alfa. ESA rescue was higher in the vadadustat arm, but RBC transfusion rescue was similar between arms. Increase in EPO levels was observed in the low ESA group but not the high ESA group.
- The occurrence of any TEAE was similar between arms (65.1% versus 61.1%), with similar severity. Most commonly reported TEAEs were diarrhea (11.6%), headache (6.2%), hypertension (6.2%), and pneumonia (5.4%), all of which were similar in occurrence in the epoetin alfa arm. The occurrence of SAEs was similar between arms in both the low ESA group and the high ESA group. Death occurred in 3 subjects on vadadustat, due to altered mental status, unknown cause, and acute coronary syndrome, and in 1 patient on epoetin alfa, due to cardiac arrest. Overall, there was no dose relation to TEAE occurrence in the vadadustat arm. AEs leading to discontinuation occurred at a higher rate in the vadadustat arm (6.2% versus 0%), with the most common AEs being asthenia, pain, and diarrhea. The following AEs of interest were higher in the vadadustat arm: worsening hypertension (10.9% versus 5.6%), hyperkalemia (4.7% versus 0%), There were no significant changes in liver-based laboratory values, with one patient having elevation in transaminases. Overall, the conclusion was that vadadustat was safe and well-tolerated.

AKB-6548-CI-0034 (NCT#03992066):

Title: A Phase 1b, Randomized, Open-Label Study to Evaluate the PK, PD, and Safety of Vadadustat in Hemodialysis Subjects with Anemia Associated with Chronic Kidney Disease

Trial population: ≥18 years with CKD stage 5, receiving hemodialysis (HD) for at least 3 months, with baseline Hb between 8.5-10.5 g/dL on ESA for past 8 weeks prior to enrollment (with appropriate washout for subjects on vadadustat), and no evidence of iron deficiency

Trial Design: Multi-center, open label, active-controlled, randomized trial (ratio 2:2:2:1) of 3 dose arms

Trial Regimen: Cohort #1: 600 mg daily, cohort #2: 750 mg daily, cohort #3: 900 mg daily, cohort #4: IV ESA (darbepoetin alfa or epoetin alfa). Duration of treatment was 10 days

Trial objectives and endpoints: Assess PK parameters, hematologic PD response (Hb, reticulocytes, EPO, and iron indices), and safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) in the described trial population.

Number of planned subjects / actual subjects / centers / countries: 35 / 46 (39 subjects on vadadustat and 7 subjects on ESA) / 10 / 1 (United States)

PD and Safety Results: There was a dose-dependent increase in EPO. Eleven subjects (28.2%) experienced 20 TEAEs in the vadadustat arm, versus no TEAEs occurred in the ESA arm. All reported TEAEs were mild or moderate in severity and there were no apparent differences between dose levels. The majority of TEAEs were GI-related AEs. No AEs resulted in discontinuation from trial and there were no deaths. There were no significant changes in liver-based laboratory values, but one patient had elevation in transaminases (AST 3.5x ULN and

ALT 7.7x ULN), without elevation in total bilirubin. Overall, the conclusion was that vadadustat was safe and well-tolerated.

17.3. Phase 2/3 Trials in Japan

As noted in section II.7.4, we analyzed the safety data from one phase 2 and four phase 3 completed trials that were conducted in Japan: one trial in the NDD-CKD population and three trials in the DD-CKD population. Our analysis was descriptive, without any pooling of data, as follows:

AKB-6548-CI-0022 (NCT#03054350)

Title: Phase 2, Randomized, Double-blind, Placebo-Controlled, Dose-Finding Study to Assess the Efficacy, Safety, PK, and PD of Vadadustat in Japanese Subjects with Anemia Secondary to Dialysis-Dependent Chronic Kidney Disease (DD-CKD)

Trial population: Japanese subjects ≥20 years with CKD stage 5, receiving hemodialysis (HD) for at least 8 weeks, with baseline Hb <10 g/dL regardless of prior ESA status but needing appropriate washout if ESA was taken, and no evidence of iron deficiency. ESA or RBC transfusion rescue due to worsening of anemia associated with CKD was allowed

Trial Design: multi-center, randomized (ratio of 1:1:1:1), double-blind, placebo-controlled trial, with 3 dose cohorts

Trial regimen:

- Cohort #1 – 150 mg daily, cohort #2 – 450 mg daily, and cohort #3 – 600 mg daily. Duration of therapy is 16 weeks, with fixed dose regimen for first 6 weeks and dose adjustment allowed for the second 10 weeks. Dose was modified during fixed-dose period only for Hb overshoot or rapid rate of rise.
- Subjects who were on placebo during the fixed-dose period randomly received one of the three dose levels of vadadustat
- Protocol-based dose adjustment by single dose levels of 150 mg, based on hematologic response (assessed with weekly Hb and reticulocyte count). Dose ranged from 150 mg to 600 mg

Trial objectives and endpoints:

- Assess hematologic PD response (change from baseline in Hb at end of primary efficacy period of 6 weeks), to define dose-response relationship and inform the starting dose for phase 3 trials. The target Hb level was 10-12 g/dL
- To assess the safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings), tolerability, PK, and PD (i.e., changes in reticulocyte, EPO, and iron indices, and rate of rescue ESA or transfusions) of oral vadadustat QD dosing in Japanese subjects with anemia secondary to DD-CKD during the 6-week primary efficacy period
- To evaluate the effect of dose adjustments and demonstrate the maintenance effect on Hb levels during a 10-week dose-adjustment and maintenance period

Number of planned subjects / actual subjects / centers / countries: 48 / 60 (15 subjects per arm) / 31 / 1 (Japan)

PD and safety results:

- Mean absolute Hb changes in the vadadustat 150 mg, 300 mg, and 600 mg dosing groups at the end of the primary efficacy period were -0.3 g/dL, 0.0 g/dL, and 0.5 g/dL, respectively, whereas placebo was associated with a mean absolute decrease in Hb level of -1.5 g/dL. Similar pattern was observed in other PD markers. One patient (1.1%) had dose withheld due to excessive Hb change in the 600 mg cohort. Hb target was achieved in 71.4% of subjects on vadadustat by the end of the treatment period, with seven subjects (20%) being below target and 8.6% above target.
- There was a higher rate of subjects with ≥1 TEAE in vadadustat, compared to placebo, regardless of dose cohort. Most commonly reported TEAEs were nasopharyngitis (15.6%), diarrhea (8.9%), shunt stenosis (6.7%), and headache (8.3%), of which most were mild or moderate in severity. There was no apparent difference in TEAE or SAEs occurrence among the three dose cohorts. Ten SAEs occurred in 7 subjects, which were: shunt stenosis, AV fistula site complication, cholecystitis acute, pericarditis, toxic encephalopathy, enteritis infectious, gastric ulcer hemorrhage, cerebral hemorrhage, and anxiety. No deaths were observed. Three subjects had AEs leading to discontinuation, due to acute cholecystitis, gastric ulcer hemorrhage and anxiety. There were no significant changes in liver-based laboratory values. Overall, the conclusion was that vadadustat was safe and well-tolerated, with no apparent difference among the 3 dose regimen cohorts.

MT-6548-J01 (NCT#03329196):

Title: Phase 3 Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Subjects With Anemia Associated With Non-Dialysis Dependent Chronic Kidney Disease (Open-Label Comparative Study With Darbepoetin Alfa (Recombinant) as the Control Drug)

Trial population: Japanese subjects ≥20 years with CKD (eGFR <60 ml/min but not on dialysis within 8 weeks and not expected to start dialysis), with baseline Hb 8-<11 g/dL for the correction cohort or 9-<12.5 g/dL for the conversion cohort, and no evidence of iron deficiency

Trial Design: multi-center, randomized (ratio of 1:1), open-label, active-controlled, parallel group trial, with stratification 2:1 of correction cohort (subjects not receiving ESA treatment) to conversion cohort (subjects who were previously treated with ESA)

Trial regimen:

- Starting dose for subjects on vadadustat is 300 mg daily. Protocol-based dose adjustment by single dose levels of 150 mg, based on hematologic response (assessed with weekly Hb and reticulocyte count). Dose ranged from 150 mg to 600 mg
- Starting dose for subjects on darbepoetin in the correction cohort is 30 µg/dose every 2 weeks. Subjects in the conversion cohort will continue their baseline ESA. Protocol-based dose adjustment of ESA treatment was based on hematologic response
- Treatment duration is 52 weeks

Trial objectives and endpoints:

- Assess the non-inferiority of vadadustat, compared to darbepoetin alfa in subjects with anemia and NDD-CKD using hematologic PD response (change from baseline in Hb at end of the primary treatment period of week 20-24, in addition to rate of response –

defined as increase from pre-dose mean Hb of ≥1 g/dL). The target Hb level was 11-13 g/dL

- Assess the effects of vadadustat in improving and maintaining Hb values in correction cohort and assess the effects of vadadustat in switching and maintaining Hb values in conversion cohort
- Assess safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) of long-term administration of vadadustat in the target population

Number of planned subjects / actual subjects / centers / countries: 300 (Target: 100 subjects in the correction set, 200 subjects in the conversion set) / 304 / 86 / 1 (Japan)

Efficacy and safety results:

- The LS Mean (95% CI) for the difference in the mean Hb value after 20 weeks and after 24 weeks using the mixed model repeated measure (MMRM) between the vadadustat arm and the darbepoetin arm were -0.3 g/dL (-0.5, 0). The lower limit for the 95% CI for the difference between the arms was at least -0.75 g/dL, confirming the non-inferiority of the vadadustat arm in relation to the darbepoetin arm
- In the conversion cohort, the mean Hb level in the vadadustat arm increased, reaching the target range after 8 weeks, after which the Hb level remained within the target range up to Week 24 in 66.7% of subjects (compared to 45% at baseline). The mean Hb level in the darbepoetin arm increased, reaching the target range after 6 weeks, and the Hb level remained within the target range up to Week 24 in 82.7% of subjects (compared to 52.4% at baseline)
- In the correction cohort, the mean Hb level in the vadadustat arm increased, reaching the target range after 8 weeks, after which the Hb level remained within the target range up to Week 24 in 69.7% of subjects (compared to 15.5% at baseline). The mean Hb level in the darbepoetin arm increased, reaching the target range after 6 weeks, and the Hb level remained within the target range up to Week 24 in 72.3% of subjects (compared to 9.9% at baseline)
- The rate of TEAEs was 72.2% (109/151 subjects) in the vadadustat arm versus 73.2% (112/153 subjects) in the darbepoetin arm. TEAEs occurring at a rate ≥5% in the vadadustat arm were nasopharyngitis (14.6% versus 12.4%), diarrhea (10.6% versus 3.3%), constipation (5.3% versus 3.9%), and bruising (5.3% versus 1.3%). The rate of SAEs was 13.9% in the vadadustat arm versus 14.4% in the darbepoetin arm. SAEs observed in at least 2 subjects in the vadadustat arm were CKD/ESRD/renal impairment/renal failure (10 versus 2 subjects), pneumonia (2 versus 3 subjects), cataract (2 versus 0 subjects), congestive heart failure (2 versus 0 subjects) and spinal compression fracture (2 versus 0 subjects). One patient died in the darbepoetin arm due to acute myocardial infarction. The rate of AEs that led to discontinuation was 3.3% in the vadadustat arm versus 2.0% in the darbepoetin arm. AEs that led to discontinuation in the vadadustat arm were retinal hemorrhage, abdominal discomfort, malaise, diarrhea, gastrointestinal polyp bleeding, hemoglobin decreased, chronic heart failure, and chronic kidney disease. There was one case of drug-induced liver injury in the vadadustat arm (which is included in the hepatotoxicity section) versus no cases in the darbepoetin arm and the rate of hepatic function abnormality was 2% in the vadadustat arm versus 1.3% in the darbepoetin arm. Overall, the conclusion was that vadadustat was effective and safe in the described patient population.

MT-6548-J02 (NCT#03402386):

Title: Phase 3 Clinical Study of MT-6548 in Peritoneal Dialysis Subjects With Anemia Associated With Chronic Kidney Disease

Trial population: Japanese subjects ≥20 years with CKD on peritoneal dialysis for at least 4 weeks before the screening period, regardless of prior ESA status but needing appropriate washout if ESA was taken, with baseline Hb 8-<11 g/dL for the correction cohort (subjects not receiving ESA treatment) or 9-<12.5 g/dL for the conversion cohort (subjects who were previously treated with ESA), and no evidence of iron deficiency

Trial Design: Multi-center, open-label, uncontrolled trial

Trial regimen: Starting dose for subjects on vadadustat is 300 mg daily. Protocol-based dose adjustment by single dose levels of 150 mg, based on hematologic response (assessed with weekly Hb and reticulocyte count). Dose ranged from 150 mg to 600 mg. Treatment duration is 24 weeks

Trial objectives and endpoints:

- Assess efficacy of vadadustat in subjects with anemia and DD-CKD on peritoneal dialysis using hematologic PD response (change from baseline in Hb at end of the primary treatment period of week 20-24). The target Hb level was 11-13 g/dL
- Assess the effects of vadadustat in improving and maintaining Hb values in correction cohort and assess the effects of vadadustat in switching and maintaining Hb values in conversion cohort
- Assess safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) of long-term administration of vadadustat in the target population

Number of planned subjects / actual subjects / centers / countries: 40 / 42 (2 subjects in the correction cohort versus 40 subjects in the conversion cohort) / 25 / 1 (Japan)

Efficacy and safety results:

- Using the entire efficacy dataset, the LS Mean (95% CI) for the mean Hb value at Week 20-24 was 11.4 g/dL (11.0-11.7 g/dL), with the LS Mean (95% CI) for the conversion group being 11.3 g/dL (10.9-11.6 g/dL). Similar responses were observed in other PD markers.
- The rate of TEAEs was 90.5% (38/42 subjects). TEAEs occurring at a rate ≥5% were catheter site infection (23.8%), diarrhea (19.0%), nasopharyngitis (14.3%), peritonitis (11.9%), vomiting (9.5%), loss of appetite (7.1%), upper abdominal pain (7.1%), and nausea (7.1%). The rate of SAEs was 28.6% (12/42). SAEs observed in at least 2 subjects were peritonitis and peripheral arterial occlusive disease, while the following occurred in 1 patient: sepsis, catheter site infection, cerebral infarction, chronic heart failure, myocardial ischemia, gastric polyp, inguinal hernia, shunt occlusion, peritoneal dialysis complication, and traumatic hemothorax. One patient died due to myocardial ischemia. The rate of AEs that led to discontinuation was 7.1%. AEs that led to discontinuation were cerebral infarction, traumatic hemothorax and myocardial ischemia. There were no significant changes in liver-based laboratory values. Overall, the conclusion was that vadadustat was effective and safe in the described patient population. Conclusions are limited due to the lack of a control arm.

MT-6548-J03 (NCT#03439137):

Title: Phase 3 Double Blind, Confirmatory Study of MT-6548 Compared to Darbepoetin Alfa in Hemodialysis Subjects With Anemia Associated With Chronic Kidney Disease

Trial population: Japanese subjects ≥20 years with CKD on hemodialysis for at least 12 weeks prior to the screening period, who were on stable ESA for at least 8 weeks prior to the screening period, with baseline Hb 9.5-<12 g/dL for the correction cohort or 9-<12.5 g/dL for the conversion cohort, and no evidence of iron deficiency

Trial design: multi-center, randomized (ratio of 1:1), double-blinded, double-dummy, active-controlled, parallel group trial

Trial regimen:

- Starting dose for subjects on vadadustat is 300 mg daily. Protocol-based dose adjustment by single dose levels of 150 mg, based on hematologic response (assessed with weekly Hb and reticulocyte count). Dose ranged from 150 mg to 600 mg
- Starting dose for subjects on darbepoetin will be the same as their baseline ESA. Protocol-based dose adjustment of ESA treatment was based on hematologic response
- Treatment duration is 52 weeks

Trial objectives and endpoints:

- Assess the non-inferiority of vadadustat, compared to darbepoetin alfa in subjects with anemia and DD-CKD on hemodialysis using hematologic PD response (change from baseline in Hb at end of the primary treatment period of week 20-24). The target Hb level was 10-12 g/dL. Other efficacy endpoints include quality of life measures
- Assess the effects of vadadustat in switching and maintaining Hb values in subjects with anemia and DD-CKD on hemodialysis, who were on prior ESA therapy
- Assess safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) of long-term administration of vadadustat in the target population

Number of planned subjects / actual subjects / centers / countries: 300 / 323 / 115 / 1 (Japan)

Efficacy and safety results:

- The LS Mean (95% CI) for the difference in the mean Hb value after 20 weeks and after 24 weeks using the mixed model repeated measure (MMRM) between the vadadustat arm and the darbepoetin arm were -0.1 g/dL (-0.3, 0.2). The lower limit for the 95% CI for the difference between the arms was at least -0.75 g/dL, confirming the non-inferiority of the vadadustat arm in relation to the darbepoetin arm
- The mean Hb level in the vadadustat arm increased, reaching the target range after 8 weeks, after which the Hb level remained within the target range up to Week 24 in 75.4% of subjects (compared to 81.5% at baseline). The mean Hb level in the darbepoetin arm increased, reaching the target range after 8 weeks, and the Hb level remained within the target range up to Week 24 in 75.7% of subjects (compared to 78.9% at baseline)
- The rate of TEAEs was 89.5% (145/162 subjects) in the vadadustat arm versus 88.2% (142/161 subjects) in the darbepoetin arm. TEAEs occurring at a rate ≥5% in the vadadustat arm were nasopharyngitis (19.8% versus 28.6%), diarrhea (10.5% versus 9.9%), shunt stenosis (8.0% versus 12.4%), bruise (6.8% versus 6.2%), retinal hemorrhage (6.2% versus 3.1%), and headache (5.6% versus 1.9%). The rate of SAEs was 13.0% in the vadadustat arm versus 10.6% in the darbepoetin arm. SAEs observed in

at least 2 subjects in the vadadustat arm were pneumonia (3 versus 0 subjects), shunt occlusion (3 versus 0 subjects), shunt stenosis (2 versus 3 subjects), and gastroenteritis (2 versus 0 subjects). One patient died in the vadadustat arm due to pneumonia, while one patient died in the darbepoetin arm due to peripheral artery aneurysm rupture. The rate of AE that led to discontinuation was 6.2% in the vadadustat arm versus 2.5% in the darbepoetin arm. AE that led to discontinuation in the vadadustat arm were drug eruption, pneumonia, breast cancer, gastric cancer, cerebral infarction, cold sweat, chest discomfort, and hemoglobin decreased. There were no significant changes in liver-based laboratory values. Overall, the conclusion was that vadadustat was effective and safe in the described patient population.

MT-6548-J04 (NCT#03461146):

Title: Phase 3 Clinical Study of MT-6548 in Hemodialysis Subjects With Anemia Associated With Chronic Kidney Disease

Trial population: Japanese subjects ≥20 years with CKD on hemodialysis, who were not on prior ESA (if patient was on ESA then an appropriate washout is needed before enrollment), with baseline Hb 8-<10 g/dL, and no evidence of iron deficiency

Trial design: Multi-center, open-label, uncontrolled trial

Trial regimen: Starting dose for subjects on vadadustat was 300 mg daily. Protocol-based dose adjustment by single dose levels of 150 mg, based on hematologic response (assessed with weekly Hb and reticulocyte count). Dose ranged from 150 mg to 600 mg. Treatment duration is 24 weeks

Trial objectives and endpoints:

- Assess efficacy of vadadustat in subjects with anemia and DD-CKD on hemodialysis using hematologic PD response (change from baseline in Hb at end of the primary treatment period of week 20-24 and rate of increase of Hb value). The target Hb level was 10-12 g/dL
- Assess the effects of vadadustat in improving and maintaining Hb values in patients with CKD on hemodialysis and not on prior ESA therapy
- Assess safety (i.e., AEs, laboratory tests, VS, ECGs, and physical exam findings) of long-term administration of vadadustat in the target population

Number of planned subjects / actual subjects / centers / countries: 20 / 24 / 25 / 1 (Japan)

Efficacy and safety results:

- The LS Mean (95% CI) for the Hb value at Week 20-24 was 10.8 g/dL (10.4-11.1 g/dL). The mean Hb level in the vadadustat arm increased, reaching the target range after 8 weeks, after which the Hb level remained within the target range up to Week 24 in 73.7% of subjects (compared to 16.7% at baseline). Similar responses were observed in other PD markers.
- The rate of TEAEs was 95.8% (23/24 subjects). TEAEs occurring at a rate ≥5% were shunt stenosis (25.0%), nasopharyngitis (20.8%), diarrhea (16.7%), skin abrasion (12.5%), and vomiting (8.3%). There were also one case of AV fistula occlusion and vascular access insufficiency. The rate of SAEs was 29.2% (7/24). SAEs observed were due to pneumonia, aneurysm, peripheral arterial occlusive disease, duodenal ulcer

hemorrhagic, clavicle fracture, arteriovenous fistula occlusion, shunt stenosis, pelvic fracture, and vascular access insufficiency. There were no deaths in the trial. The rate of AEs that led to discontinuation was 8.3%. AEs that led to discontinuation were duodenal ulcer hemorrhagic and hemoglobin decreased. There were no significant changes in liver-based laboratory values. Overall, the conclusion was that vadadustat was effective and safe in the described patient population. Conclusions are limited due to the lack of a control arm.

17.4. Definitions of Safety-Related Terms

17.4.1. Grouping Definitions for Causes of Death in Phase 3 Global Trials

Grouping of PT-based patient-specific causes of death was applied by the reviewer according to the groupings listed below in this section. The list of PTs defining each grouping of causes of death was obtained from review of all PT-based causes of death used in the four phase 3 trials. Any specific PT not listed in the grouping definition is not present because it was not listed, at least once, as a cause of death in any of the four phase 3 trials.

Cardiovascular/vascular causes: Acute cardiovascular failure, acute coronary syndrome, acute heart failure, acute myocardial infarction, acute ventricular fibrillation, aortic aneurysm, arrythmia, atherosclerosis, cardiac arrest, cardiovascular insufficiency, cardiogenic shock, congestive heart failure, coronary artery disease, ischemic heart disease, hypertensive heart disease, Morgagni-Adams-Stokes syndrome, myositis, pulmonary embolism, severe aortic valvular stenosis, severe peripheral vascular disease, sudden cardiac death, supravalvular aortic rupture, thrombosis of the superior mesenteric artery, unstable angina, ventricular fibrillation.

Cerebrovascular causes: Acute intracranial event, brain hemorrhage, cerebral atherosclerosis, cerebrovascular accident/disease, chronic cerebral vascular disease, hemorrhagic stroke, ischemic stroke, intracranial bleed, stroke, subdural hematoma.

Infectious causes: Abdominal sepsis, acute cholecystitis, bacteremia, *C. difficile* colitis, complicated appendicitis, cytomegalovirus, diabetic foot infection, diverticulitis, fever, foot gangrene, osteomyelitis, septic shock, peritonitis, pneumonia, pulmonary tuberculosis, pyelonephritis, sepsis, urinary tract infection.

Renal/Electrolyte Disturbances Causes: Acute kidney injury, acute kidney disease, acute renal failure, acute tubular necrosis, calciphylaxis, chronic renal failure, chronic kidney disease, electrolyte imbalance, end stage renal disease/failure, fluid overload, hyperkalemia, nephrotic syndrome, severe metabolic acidosis, uremia, uremic encephalopathy, uremic syndrome.

Acute respiratory causes: Acute respiratory distress/failure/insufficiency, acute respiratory acidosis, chronic obstructive pulmonary disease, dyspnea of unknown origin, hemothorax, interstitial lung disease, pulmonary edema, pulmonary hemorrhage.

Oncological causes: Acute myeloid leukemia, adenocarcinoma of the lung, adenocarcinoma primary location unspecified, astrocytoma, brain tumor, bladder cancer, colon carcinoma, esophageal cancer, liver cancer, metastatic cancer, multiple myeloma, cardiac mass, non-small cell lung carcinoma, ovarian cancer, stomach cancer, pancreatic adenocarcinoma, prostate cancer, squamous carcinoma of the lung.

Non-specific/unknown causes: Acute cardiopulmonary arrest/failure, age related, anoxic brain injury, anoxic encephalopathy, cardiorenal syndrome, coma of unknown origin, fall, hypoglycemia, hypoglycemic encephalopathy, hypotension, multiorgan failure, natural causes/old age, poly-organ failure, post-hemorrhagic anemia, sudden death, unknown.

Other causes: Alzheimer's dementia, bowel obstruction, diabetic coma, duodenal ulcers, end stage liver failure, failure to thrive, gastritis acuta erosive, gastrointestinal perforation, liver cirrhosis, polycystic liver disease, severe malnutrition, gastrointestinal bleed, vehicle accident.

17.4.2. Categorization of Participating Countries

According to FDA-defined Geographic-based Approach:

- North America: United States and Canada
- Western Europe: United Kingdom, Spain, Hungry, Italy, Austria, Germany, France, and Portugal
- Eastern Europe: Bulgaria, Russia, Ukraine, Czech Republic, Romania, Serbia, Slovakia, Turkey, and Poland
- South and Central America: Brazil, Argentina, Mexico, Chile, and Colombia
- Africa: South Africa
- Asia and Australia: Republic of Korea, Israel, Australia, and Malaysia

According to applicant-defined geographic-based approach:

- United States
- Europe: Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Romania, Serbia, Slovak Republic, Spain, Turkey, Portugal, Poland, and United Kingdom.
- Rest of the World (ROW): Argentina, Australia, Brazil, Canada, Chile, Colombia, Israel, Malaysia, Mexico, Republic of Korea, Russian Federation, South Africa, and Ukraine.

According to practice-of-care measures:

- Developed Countries: United States, Canada, United Kingdom, Spain, Italy, Austria, Germany, France, Portugal, Czech Republic, Republic of Korea, Israel, Australia, and Malaysia
- Developing Countries: Hungry, Bulgaria, Russia, Ukraine, Romania, Serbia, Slovakia, Turkey, Poland, Brazil, Argentina, Mexico, Chile, Colombia, and South Africa

17.4.3. Medical Dictionary for Regulatory Activities Preferred Term Splitting/Grouping for AE Evaluation of Safety Population in Phase 3 Trials

Grouping of PT-based patient-specific adverse events was applied by the reviewer according to the groupings listed below in this section. The list of PTs defining each meaningful and consistent grouping of adverse events was obtained from review of all PT-based adverse events used in the four phase 3 trials. If a specific PT was not listed, at least once, as an adverse event in any of the four phase 3 trials, it was not included in the grouping definition.

Unadjudicated cardiovascular thrombotic event: Acute myocardial infarction, acute coronary syndrome, coronary artery thrombosis, myocardial infarction, myocardial ischemia, cardiovascular event, angina unstable.

Unadjudicated cardiac life-threatening event: Cardiac arrest, cardiac death, cardiogenic shock, cardio-respiratory arrest, cardiopulmonary failure, sudden cardiac death, circulatory collapse.

Unadjudicated cerebrovascular accident: Ischemic stroke, ischemic cerebral infarction, lacunar infarction, lacunar stroke, cerebral small vessel ischemic disease, embolic stroke, cerebellar stroke, cerebral infarction, cerebral ischemia, hemorrhagic stroke, basal ganglia infarction, brain stem stroke.

Transient ischemic attack

Arterial thrombosis: Aortic thrombosis, arterial thrombosis, atheroembolism, mesenteric artery thrombosis, peripheral artery thrombosis, retinal artery occlusion, retinal artery thrombosis, subclavian artery thrombosis, vertebral artery thrombosis, vertebral artery occlusion.

Venous thromboembolic disease (VTE): Administration site thrombosis, arteriovenous fistula site thrombosis, arteriovenous fistula occlusion, arteriovenous fistula thrombosis, arteriovenous graft thrombosis, arteriovenous shunt thrombosis, catheter site thrombosis, device occlusion, device related thrombosis, graft thrombosis, injection site thrombosis, medical device site thrombosis, prosthetic cardiac valve thrombosis, shunt occlusion, shunt thrombosis, thrombosis in device, vascular access site thrombosis, vascular graft occlusion, vascular access site occlusion, vascular access site thrombosis, vascular graft thrombosis, vascular stent occlusion, vascular stent thrombosis, atrial thrombosis, brachiocephalic vein occlusion, deep vein thrombosis, brachiocephalic vein thrombosis, cardiac ventricular thrombosis, mesenteric vein thrombosis, subclavian vein thrombosis, vena cava thrombosis, pelvic venous thrombosis, renal vein thrombosis, thrombosis, transverse sinus thrombosis, jugular vein thrombosis, venous thrombosis limb, venous thrombosis, embolism venous, intracardiac thrombus, pulmonary embolism, pulmonary thrombosis, renal vascular thrombosis, retinal vein occlusion, retinal vein thrombosis, septic pulmonary embolism, thrombophlebitis, thrombophlebitis superficial, vascular insufficiency, vascular pseudoaneurysm thrombosis, vascular occlusion.

Access-related VTE: Administration site thrombosis, arteriovenous fistula site thrombosis, arteriovenous fistula occlusion, arteriovenous fistula thrombosis, arteriovenous graft thrombosis, arteriovenous shunt thrombosis, catheter site thrombosis, device occlusion, device related thrombosis, graft thrombosis, injection site thrombosis, medical device site thrombosis, prosthetic cardiac valve thrombosis, shunt occlusion, shunt thrombosis, thrombosis in device, vascular access site thrombosis, vascular graft occlusion, vascular access site occlusion, vascular access site thrombosis, vascular graft thrombosis, vascular stent occlusion, vascular stent thrombosis.

Access unrelated VTE: Atrial thrombosis, brachiocephalic vein occlusion, deep vein thrombosis, brachiocephalic vein thrombosis, cardiac ventricular thrombosis, mesenteric vein thrombosis, subclavian vein thrombosis, vena cava thrombosis, pelvic venous thrombosis, renal vein thrombosis, thrombosis, transverse sinus thrombosis, jugular vein thrombosis, venous thrombosis limb, venous thrombosis, embolism venous, intracardiac thrombus, pulmonary embolism, pulmonary thrombosis, renal vascular thrombosis, retinal vein occlusion, retinal vein thrombosis, septic pulmonary embolism, thrombophlebitis, thrombophlebitis superficial, vascular insufficiency, vascular pseudoaneurysm thrombosis, vascular occlusion.

Arteriovenous connection stenosis: Anastomotic stenosis, arteriovenous fistula site stenosis, shunt stenosis, arteriovenous graft site stenosis, vascular access site stenosis, vascular access stenosis, vascular graft stenosis, vascular stent stenosis.

Arteriovenous fistula maturation failure

Atherosclerotic disease: Angina pectoris, aortic arteriosclerosis, arteriosclerosis, arteriosclerotic retinopathy, brachiocephalic vein stenosis, basilar artery stenosis, carotid arteriosclerosis, carotid artery stenosis, carotid artery occlusion, cerebrovascular disorder, cerebral arteriosclerosis, cerebrovascular insufficiency, coronary artery disease, coronary artery stenosis, arteriosclerosis coronary artery, diabetic vascular disorder, intestinal infarction, ischemic skin ulcer, peripheral artery disease, peripheral artery occlusion, peripheral ischemia, peripheral arterial occlusive disease, peripheral vascular disorder, intermittent claudication, peripheral artery stenosis, peripheral venous disease, venous stenosis, retinal vascular disorder, subclavian artery stenosis, subclavian vein stenosis, vascular stenosis, coeliac artery occlusion, coeliac artery stenosis, hepatic artery stenosis, iliac vein stenosis, intestinal ischemia, mesenteric artery stenosis, penile vascular disorder, peripheral vein stenosis, renal artery stenosis, renal infarct, vertebral artery stenosis, vertebral foraminal stenosis.

Coronary disease: Angina pectoris, coronary artery disease, coronary artery stenosis, arteriosclerosis coronary artery.

Cerebrovascular disease: Basilar artery stenosis, carotid arteriosclerosis, carotid artery stenosis, carotid artery occlusion, cerebrovascular disorder, cerebral arteriosclerosis, cerebrovascular insufficiency, vertebral artery stenosis, vertebral foraminal stenosis.

Vascular disease: Aortic arteriosclerosis, arteriosclerosis, arteriosclerotic retinopathy, brachiocephalic vein stenosis, diabetic vascular disorder, intestinal infarction, ischemic skin ulcer, peripheral artery disease, peripheral artery occlusion, peripheral ischemia, peripheral arterial occlusive disease, peripheral vascular disorder, intermittent claudication, peripheral artery stenosis, peripheral venous disease, venous stenosis, retinal vascular disorder, subclavian artery stenosis, subclavian vein stenosis, vascular stenosis, coeliac artery occlusion, coeliac artery stenosis, hepatic artery stenosis, iliac vein stenosis, intestinal ischemia, mesenteric artery stenosis, penile vascular disorder, peripheral vein stenosis, renal artery stenosis, renal infarct.

Unadjudicated cardiac function failure: Acute left ventricular failure, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiovascular insufficiency, chronic left ventricular failure, diastolic dysfunction, dilatation ventricular, ejection fraction decreased, left ventricular dilatation, left ventricular dysfunction, left ventricular failure, right ventricular dilatation, right ventricular enlargement, right ventricular dysfunction, right ventricular failure, systolic dysfunction, ventricular dysfunction.

Hypertension: Blood pressure increased, blood pressure inadequately controlled, accelerated hypertension.

Hypertension emergency: Hypertensive crisis, hypertensive urgency, malignant hypertension.

Hypertension caused pathology: Hypertensive angiopathy, hypertensive encephalopathy, hypertensive heart disease, hypertensive nephropathy.

Seizures: Epilepsy, epileptic encephalopathy, seizure, generalized tonic-clonic seizure, idiopathic partial epilepsy, partial seizures, tonic convulsion, focal dyscognitive seizures, frontal lobe epilepsy and status epilepticus.

Hepatotoxicity: Acute hepatic failure, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, blood bilirubin increased, chronic hepatic failure, coma hepatic, drug-induced liver injury, hepatic cirrhosis, hepatic encephalopathy, hepatocellular injury, liver function test abnormal, hepatitis, hepatitis acute, hepatitis chronic active, liver injury, hepatic enzyme abnormal, hepatic failure, hepatic function abnormal, hepatitis toxic, hepatocellular injury, liver function test abnormal, liver function test increased, transaminases abnormal, transaminases increased, hepatic enzyme increased.

Systemic infection: Arthritis bacterial, arthritis infective, *Aspergillus* infection, bacteremia, bronchopulmonary aspergillosis, bone tuberculosis, coccidioidomycosis, cryptosporidiosis infection, cytomegalovirus infection, dengue fever, device related sepsis, encephalitis brain stem, encephalitis viral, endocarditis bacterial, endocarditis, subacute endocarditis, fungal peritonitis, HIV infection, H1N1 influenza, infective periostitis, infectious encephalopathy, influenza, influenza like illness, helminthic infection, medical device site joint infection, measles, meningitis staphylococcal, *Microsporum* infection, necrotizing fasciitis, osteomyelitis, osteomyelitis chronic, peritonitis, pulmonary tuberculosis, tuberculous pleurisy, salmonellosis, sepsis, septic shock, urosepsis, syphilis.

Localized infection: Abscess, acute sinusitis, arteriovenous fistula site infection, arteriovenous graft site infection, anal fistula infection, atypical pneumonia, bacterial vaginosis, balanitis candida, blister infected, breast abscess, bronchitis bacterial, campylobacter gastroenteritis, candidiasis of trachea, catheter site infection, cellulitis, cellulitis gangrenous, chronic sinusitis, chronic tonsillitis, clostridium difficile colitis, cytomegalovirus colitis, device related infection, conjunctivitis bacterial, covid-19 pneumonia, dermatitis infected, diabetic foot infection, diarrhea infectious, ear infection, ear infection fungal, empyema, enteritis, enterocolitis bacterial, epididymitis, erysipelas, eye infection, eyelid infection, fungal skin infection, gastroenteritis clostridial, gastroenteritis salmonella, gastroenteritis *Escherichia coli*, gastroenteritis viral, gastrointestinal infection, gastrointestinal viral infection, giardiasis, hematoma infection, herpangina, herpes ophthalmic, herpes zoster, genital candidiasis, genital herpes, herpes simplex, implant site cellulitis, infected bunion, infected bite, infected cyst, infected fistula, infected skin ulcer, infected varicose vein, localized infection, latent tuberculosis, lower respiratory tract infection, mastitis fungal, mastoiditis, medical device site infection, mumps, necrotizing soft tissue infection, esophageal candidiasis, oral candidiasis, oral fungal infection, oral herpes, oropharyngeal candidiasis, otitis externa, otitis externa fungal, otitis media, otitis media chronic, peritonsillar abscess, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, pneumonia, pneumonia aspiration, pneumonia influenza, pneumonia respiratory syncytial viral, post procedural cellulitis, post procedural infection, postoperative wound infection, pulmonary tuberculosis, pyelonephritis, prostate infection, renal graft infection, respiratory tract infection bacterial, respiratory tract infection fungal, shunt infection, sinusitis, skin candida, soft tissue infection, stoma site cellulitis, tinea capitis, tinea pedis, tinea versicolor, tonsillitis, tooth infection, tracheitis, tonsillitis, tracheobronchitis, upper respiratory tract infection bacterial, urinary tract candidiasis, urinary tract infection, urinary tract infection fungal, urogenital infection bacterial, uterine infection, vaginal infection, vaginitis chlamydial, varicella, vascular access site infection, vascular device infection, viral diarrhea, vulvovaginal candidiasis, vulvovaginal mycotic infection, wound infection, gastroenteritis, cholecystitis infective.

Gastrointestinal acid-related disease: Duodenal ulcer, duodenal ulcer perforation, erosive duodenitis, duodenitis, dyspepsia, gastroesophageal reflux disease, duodenogastric reflux, acid peptic disease, erosive duodenitis, erosive esophagitis, gastric pH decreased, gastric ulcer, gastric

perforation, gastric ulcer perforation, gastritis, gastritis erosive, chronic gastritis, reflux gastritis, gastrointestinal erosion, esophageal ulcer, esophageal ulcer hemorrhage, esophagitis, peptic ulcer

Gastrointestinal symptoms: abdominal pain, abdominal discomfort, abdominal pain lower, abdominal pain upper, epigastric discomfort, abdominal distention, nausea, vomiting, diarrhea, constipation, delayed gastric emptying, flatulence.

Any bleeding adverse event: Abdominal wall hematoma, arteriovenous fistula site hematoma, arteriovenous fistula site hemorrhage, arteriovenous graft site hematoma, arteriovenous graft site hemorrhage, bleeding varicose vein, catheter site bruise, catheter site hematoma, catheter site hemorrhage, cephalohematoma, chest wall hematoma, conjunctival hemorrhage, contusion, ear hemorrhage, ecchymosis, epistaxis, eye contusion, eye hemorrhage, eye hematoma, gingival bleeding, hematoma, hematoma infection, hemorrhage, increased tendency to bruise, injection site bruising, incision site hematoma, medical device site hemorrhage, mouth hemorrhage, periorbital hematoma, petechiae, post procedural contusion, post procedural hematoma, post procedural hemorrhage, procedural hemorrhage, puncture site hematoma, subcutaneous hematoma, tongue hemorrhage, traumatic hematoma, traumatic hemorrhage, vascular access site bruising, vascular access site hematoma, vascular access site hemorrhage, vessel puncture site bruise, wound hemorrhage, hematemesis, hemorrhagic erosive gastritis, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melaena, upper gastrointestinal hemorrhage, gastrointestinal vascular malformation hemorrhagic, hematochezia, rectal hemorrhage, duodenal ulcer hemorrhage, gastrointestinal polyp hemorrhage, intestinal hemorrhage, small intestinal hemorrhage diverticulum intestinal hemorrhagic, gastric hemorrhage, occult blood positive, esophageal varices hemorrhage, large intestinal hemorrhage, chronic gastrointestinal bleeding, gastrointestinal ulcer hemorrhage, esophageal ulcer hemorrhage, peptic ulcer hemorrhage, brain stem microhemorrhage, brain stem hemorrhage, cerebral hemorrhage, hemarthrosis, hematoma muscle, hemoperitoneum, hemorrhage intracranial, hemorrhagic ovarian cyst, hemothorax, hepatic hemorrhage, intra-abdominal hematoma, intracranial hematoma, intraventricular hemorrhage, pericardial hemorrhage, renal cyst hemorrhage, perirenal hematoma, peritoneal hemorrhage, renal cyst hemorrhage, renal hemorrhage, renal hematoma, retinal hemorrhage, retinal hemorrhage, retroperitoneal hemorrhage, subarachnoid hemorrhage, subdural hematoma, subdural hemorrhage, subgaleal hemorrhage, traumatic hemothorax, traumatic intracranial hemorrhage, pulmonary contusion, pulmonary hemorrhage, vitreous hemorrhage, cystitis hemorrhagic, blood urine present, dysfunctional uterine bleeding, hematospermia, hematuria, post procedural hematuria, urethral hemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, menometrorrhagia, menorrhagia, metrorrhagia, penile hemorrhage.

Gastrointestinal bleeding: Hematemesis, hemorrhagic erosive gastritis, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melaena, upper gastrointestinal hemorrhage, gastrointestinal vascular malformation hemorrhagic, hematochezia, rectal hemorrhage, duodenal ulcer hemorrhage, gastrointestinal polyp hemorrhage, intestinal hemorrhage, small intestinal hemorrhage diverticulum intestinal hemorrhagic, gastric hemorrhage, occult blood positive, esophageal varices hemorrhage, large intestinal hemorrhage, chronic gastrointestinal bleeding, gastrointestinal ulcer hemorrhage, esophageal ulcer hemorrhage, peptic ulcer hemorrhage.

Mucocutaneous bleeding: Abdominal wall hematoma, arteriovenous fistula site hematoma, arteriovenous fistula site hemorrhage, arteriovenous graft site hematoma, arteriovenous graft site hemorrhage, bleeding varicose vein, catheter site bruise, catheter site hematoma, catheter site hemorrhage, cephalohematoma, chest wall hematoma, conjunctival hemorrhage, contusion, ear hemorrhage, ecchymosis, epistaxis, eye contusion, eye hematoma, eye hemorrhage, gingival

bleeding, hematoma, hematoma infection, hemorrhage, increased tendency to bruise, injection site bruising, incision site hematoma, incision site hemorrhage, medical device site hematoma, medical device site hemorrhage, mouth hemorrhage, periorbital hematoma, petechiae, post procedural contusion, post procedural hematoma, post procedural hemorrhage, procedural hemorrhage, puncture site hematoma, scrotal hemorrhage, skin hemorrhage, skin ulcer hemorrhage, subcutaneous hematoma, tongue hemorrhage, traumatic hematoma, traumatic hemorrhage, vascular access site bruising, vascular access site hematoma, vascular access site hemorrhage, vessel puncture site hematoma, vessel puncture site bruise, vessel puncture site hemorrhage, wound hemorrhage.

Visceral bleeding: Brain stem hemorrhage, brain stem microhemorrhage, cerebral hematoma, cerebral hemorrhage, hemarthrosis, hematoma muscle, hemoperitoneum, hemorrhage intracranial, hemorrhagic ovarian cyst, hemothorax, hepatic hematoma, hepatic hemorrhage, internal hemorrhage, intra-abdominal hemorrhage, intraventricular hemorrhage, intracranial hematoma, pericardial hemorrhage, perirenal hematoma, peritoneal hemorrhage, renal cyst hemorrhage, renal hematoma, renal hemorrhage, retinal hemorrhage, retroperitoneal hematoma, retroperitoneal hemorrhage, subdural hematoma, subdural hemorrhage, subarachnoid hemorrhage, subdural hematoma, subdural hemorrhage, subgaleal hemorrhage, traumatic hemothorax, traumatic intracranial hematoma, traumatic intracranial hemorrhage, pulmonary contusion, pulmonary hemorrhage, vitreous hemorrhage.

GU bleeding: Blood urine present, hematuria, cystitis hemorrhagic, menometrorrhagia, menorrhagia, metrorrhagia, post procedural hematuria, uterine hemorrhage, vaginal hemorrhage, dysfunctional uterine bleeding, hematospermia, penile hemorrhage, urethral hemorrhage.

Cancer: Acute myeloid leukemia, abdominal mass, adenocarcinoma, adenocarcinoma gastric, adenocarcinoma of colon, adenocarcinoma pancreas, adrenal mass, axillary mass, adrenal neoplasm, astrocytoma, astrocytoma, low grade, basal cell carcinoma, basal cell carcinoma, bladder cancer, bladder cancer recurrent, bladder mass, bladder transitional cell carcinoma, brain neoplasm, breast cancer, breast cancer metastatic, breast mass, bronchial carcinoma, chronic lymphocytic leukemia, cerebellar tumor, cervix carcinoma, chest wall mass, choroid melanoma, cholangiocarcinoma, clear cell renal cell carcinoma, colon cancer, colorectal adenocarcinoma, endometrial adenocarcinoma, follicular thyroid cancer, gallbladder cancer, gastric cancer, gastric cancer stage IV, gastrointestinal mass, genitourinary tract neoplasm, hairy cell leukemia, hepatic cancer, hepatic lesion, hepatic mass, hepatic neoplasm, hepatocellular carcinoma, inguinal mass, colon neoplasm, intestinal mass, intracardiac mass, intraductal papillary mucinous neoplasm, intraductal papilloma of breast, invasive ductal breast carcinoma, invasive lobular breast carcinoma, laryngeal cancer, limb mass, lip squamous cell carcinoma, lung adenocarcinoma, lung cancer metastatic, lung carcinoma cell type unspecified recurrent, lung neoplasm, lung neoplasm malignant, malignant neoplasm of pleura, metastases to central nervous system, lung squamous cell carcinoma metastatic, malignant melanoma, marginal zone lymphoma, metastases to liver, metastases to lymph nodes, meningioma, metastases to spine, metastatic renal cell carcinoma, mixed hepatocellular cholangiocarcinoma, neck mass, neoplasm skin, non-Hodgkin's lymphoma, neoplasm, metastatic bronchial carcinoma, neoplasm malignant, non-small cell lung cancer, non-small cell lung cancer stage I, esophageal carcinoma, esophageal mass, esophageal squamous cell carcinoma, esophageal adenocarcinoma stage II, ovarian mass, ovarian neoplasm, pancreatic carcinoma, pancreatic carcinoma metastatic, pancreatic mass, pancreatic neoplasm, non-small cell lung cancer metastatic, esophageal squamous cell carcinoma stage 0, ovarian cancer metastatic, papillary renal cell carcinoma, papillary thyroid cancer, pelvic mass, plasma

cell myeloma, plasma cell myeloma recurrent, pancreatic carcinoma, prostate cancer, prostate cancer recurrent, prostate cancer stage II, pulmonary mass, rectal cancer, rectal neoplasm, renal cancer stage II, rectosigmoid cancer stage IV, renal cell carcinoma, renal cancer, renal cancer metastatic, renal mass, renal cell carcinoma stage I, renal neoplasm, skin cancer, salivary gland mass, skin mass, squamous cell carcinoma of lung, squamous cell carcinoma of pharynx, squamous cell carcinoma of skin, sarcoma metastatic, small cell lung cancer metastatic, squamous cell carcinoma of the tongue, stomach mass, thyroid mass, transitional cell carcinoma, uterine mass, vulval cancer, vulval cancer metastatic, vulval cancer stage 0.

Acute kidney injury

Hyperkalemia: Blood potassium increased, hyperkalemia

Hyperphosphatemia: Blood phosphorus increased, hyperphosphatemia

Falls

Fractures: Acetabulum fracture, ankle fracture, avulsion fracture, bone density decreased, cervical vertebral fracture, clavicle fracture, compression fracture, costal cartilage fracture, comminuted fracture, facial bones fracture, femoral neck fracture, femur fracture, fibula fracture, foot fracture, fracture, fracture displacement, fracture nonunion, forearm fracture, fractured sacrum, hand fracture, hip fracture, humerus fracture, jaw fracture, limb fracture, Lisfranc fracture, lower limb fracture, lumbar vertebral fracture, multiple fractures, osteopenia, osteoporosis, patella fracture, pelvic fracture, pubis fracture, periprosthetic fracture, radius fracture, rib fracture, skull fracture, spinal compression fracture, spinal fracture, sternal fracture, scapula fracture, stress fracture, traumatic fracture, thoracic vertebral fracture, tibia fracture, ulna fracture, upper limb fracture, wrist fracture.

17.4.4. General Safety-related Terms

Adverse event (AE): is any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a study drug, regardless of having a causal relationship with this treatment.

Treatment-emergent adverse event (TEAE): is an AE that occurred on or after the day of treatment initiation.

Adverse reaction: is an AE that is considered to be related to the study drug within reasonable possibility.

Serious adverse event: is an AE that was fatal, immediately life threatening, resulted in persistent or significant disability or incapacity, constitutes a birth defect or congenital anomaly, requires or prolongs inpatient hospitalization, or is considered otherwise needing medical or surgical intervention to prevent one of the outcomes listed in the definition. A life-threatening event is defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

AE severity grading is defined as follows:

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated; clinical or diagnostic observations only; intervention is not indicated.

- Moderate: Enough discomfort to cause interference with usual age-appropriate instrumental Activity of Daily Living (ADL); minimal, local, or non-invasive intervention indicated.
- Severe: Incapacitating or causing inability to work or to perform usual self-care ADL; hospitalization or prolongation of hospitalization indicated but not immediately life-threatening.

17.4.5. Definitions of Clinically Significant Covariates Used in the FDA Exploratory Analyses

Exploratory analyses were conducted to evaluate the impact of the following covariates on the risk of occurrence of key safety endpoints in the pooled NDD-CKD population and DD-CKD population, between the two study arms. There were 3 main categories of covariates:

Covariates based on baseline characteristics:

- Regional designation based on practice-of-medicine categorization (see section III.17.4.2)
- Regional designation based on geographic location relative to the United States (i.e., United States versus Ex-U.S. designation), which also reflects regional difference in target hemoglobin (i.e., 10 – 11 g/dL in the US versus 10 – 12 g/dL outside the United States) and dose adjustment approaches.
- Baseline ESA exposure categorization, based on weight-based weekly dosing, in trials where patient eligibility allowed for ESA use prior to enrollment (i.e., trials 0015, 0016 and 0017). The definitions of baseline ESA exposures were as follows:
  - Low ESA dose:
    - Erythropoietin / epoetin alfa: ≤90 U/kg/week
    - Darbepoetin alfa: ≤0.45 µg/kg/week
    - Methoxy polyethylene glycol / Epoetin beta: ≤0.45 µg/kg/week
  - High ESA dose:
    - Erythropoietin / epoetin alfa: >90 to ≤300 U/kg/week
    - Darbepoetin alfa: >0.45 to ≤1.5 µg/kg/week
    - Methoxy polyethylene glycol / Epoetin beta: >0.45 to ≤1.5 µg/kg/week
  - Very high ESA dose:
    - Erythropoietin / epoetin alfa: >300 U/kg/week
    - Darbepoetin alfa: >1.5 µg/kg/week
    - Methoxy polyethylene glycol / epoetin beta: >1.5 µg/kg/week
- Mean baseline hemoglobin, defined as above or below a trial-specific hemoglobin threshold, as follows:
  - Trial 0014 and Trial 0016: mean baseline hemoglobin <9.5 g/dL versus ≥9.5 g/dL
  - Trial 0015 and Trial 0017: mean baseline hemoglobin <10 g/dL versus ≥10 g/dL

Covariates based on hemoglobin-based response characteristics:

- Maximum hemoglobin achieved at any time during the on-treatment period, defined as above or below a specific hemoglobin threshold, as follows:
  - Maximum hemoglobin ≤11 g/dL versus >11 g/dL
  - Maximum hemoglobin ≤12 g/dL versus >12 g/dL
- Any occurrence of rapid rate of rise in hemoglobin, defined as >1.0 g/dL increase in a 2-week period, or >2.0 g/dL increase in a 4-week period

Covariates based on other post-baseline characteristics:

- Maximum erythropoietin levels achieved at any time during the on-treatment period, defined as elevated (i.e., ≥18 IU/L) versus non-elevated (i.e., <18 IU/L) (Grote Beverborg et al. 2015).
- Subjects who needed transfusion rescue versus subjects who did not need transfusion rescue, during the on-study period
- Subjects who needed ESA rescue versus subjects who did not need ESA rescue, during the on-study period
- For the NDD-CKD population, subjects who needed acute dialysis versus subjects who did not need acute dialysis, during the on-study period
- For the NDD-CKD population, subjects who progressed to needing chronic dialysis versus subjects who did not progress to needing chronic dialysis, during the on-study period
- For the DD-CKD population, subjects who are on hemodialysis versus subjects who are on peritoneal dialysis, during the on-study period

17.5. Results of Covariate-Based Analyses in Pooled Phase 3 Safety Populations

Exploratory univariate sensitivity analyses were conducted by the clinical reviewer, on the pooled NDD-CKD population and the pooled DD-CKD population, to evaluate the impact of both pre- and post-baseline, clinically significant, covariates on the unadjusted on-study time-to-first-event analysis of the following key safety endpoints: MACE, cardiovascular (CV) MACE, thromboembolic (TE) events (broad) and VTE (see section II.7.4 for definitions of these key safety endpoints). Definitions of the covariates used can be found in section III.17.4.5. Results and conclusions of the covariate analyses are summarized below. These results may guide future drug development in relation to study population selection, dosing schedule modification and proposed dosing approaches.

NDD-CKD Safety Population

Based on the exploratory analyses, baseline ESA dose category was the only baseline covariate that may have contributed to the higher probability of adjudicated MACE observed with the use of vadadustat in the NDD-CKD population, with higher probabilities observed in patients on low dose baseline ESA. In contrast, analyses of the following baseline covariates did not demonstrate a significant contribution to the observed higher probability of adjudicated MACE with the use of vadadustat in the NDD-CKD population: regional designation based on practice-of-medicine categorization, geographic designation based on geographic location relative to the U.S., and

mean baseline hemoglobin category. In addition, none of the exploratory analyses examining the post-baseline covariates demonstrated a significant contribution to the observed higher probability of adjudicated MACE with the use of vadadustat in the NDD-CKD population.

Given the large proportion of non-thrombosis deaths included in the all-cause mortality component of adjudicated MACE, when the impact of covariate analysis on the more specific safety outcome of adjudicated CV MACE was examined, the following covariates may have contributed to the higher probability of adjudicated CV MACE in the NDD-CKD population:

- Living in the U.S.
- Being on low dose baseline ESA prior to start of vadadustat therapy
- Having a lower mean baseline hemoglobin
- Achieving a maximum hemoglobin below the designated threshold definition
- Occurrence of high erythropoietin levels
- Need for transfusion rescue
- Need for ESA rescue
- Need for dialysis, both acute and chronic

Based on exploratory analyses, the presence or absence of excessive rate of rise of hemoglobin did not seem to impact the probability of adjudicated CV MACE occurrence in the NDD-CKD population.

DD-CKD Safety Population

Based on the exploratory analyses, there were three baseline covariates that may have contributed to the higher probability of unadjudicated VTE, observed with the use of vadadustat in the DD-CKD population: 1) Regional designation based on practice-of-medicine categorization, with higher probabilities in patients living in the U.S., 2) Geographic designation based on geographic location relative to the U.S., with higher probabilities in patients living in the U.S., and 3) Baseline ESA dose category, with higher probabilities in patients on high dose baseline ESA. Mean baseline hemoglobin category, as a baseline covariate, did not contribute to the observed higher probability of unadjudicated VTE with the use of vadadustat in the DD-CKD population.

Based on exploratory analyses, occurrence of maximum erythropoietin levels above the upper limit of normal was the only post-baseline covariate that may have contributed to the higher probability of unadjudicated VTE with the use of vadadustat in the DD-CKD population. In contrast, analysis of the following post-baseline covariates did not contribute to the observed higher probability of unadjudicated VTE with the use of vadadustat in the DD-CKD population: occurrence of maximum hemoglobin above the designated threshold, occurrence of excessive rate of rise of hemoglobin, occurrence of maximum erythropoietin level above the upper limit of normal, need for ESA or RBC transfusion rescue or type of dialysis used.

To determine specific sub-group characteristics that may be associated with higher probability of unadjudicated VTE in the DD-CKD population, we conducted univariate unadjusted exploratory analyses that suggested the following covariates may have contributed to the observed higher probability of unadjudicated VTE in the DD-CKD population:

- Living in the United States.
- Being on high dose baseline ESA prior to start of vadadustat therapy
- Achieving a maximum hemoglobin above the designated threshold

- Occurrence of excessive rate of rise of hemoglobin
- Occurrence of high erythropoietin levels
- Need for ESA or RBC transfusion rescue
- Use of hemodialysis, compared to peritoneal dialysis

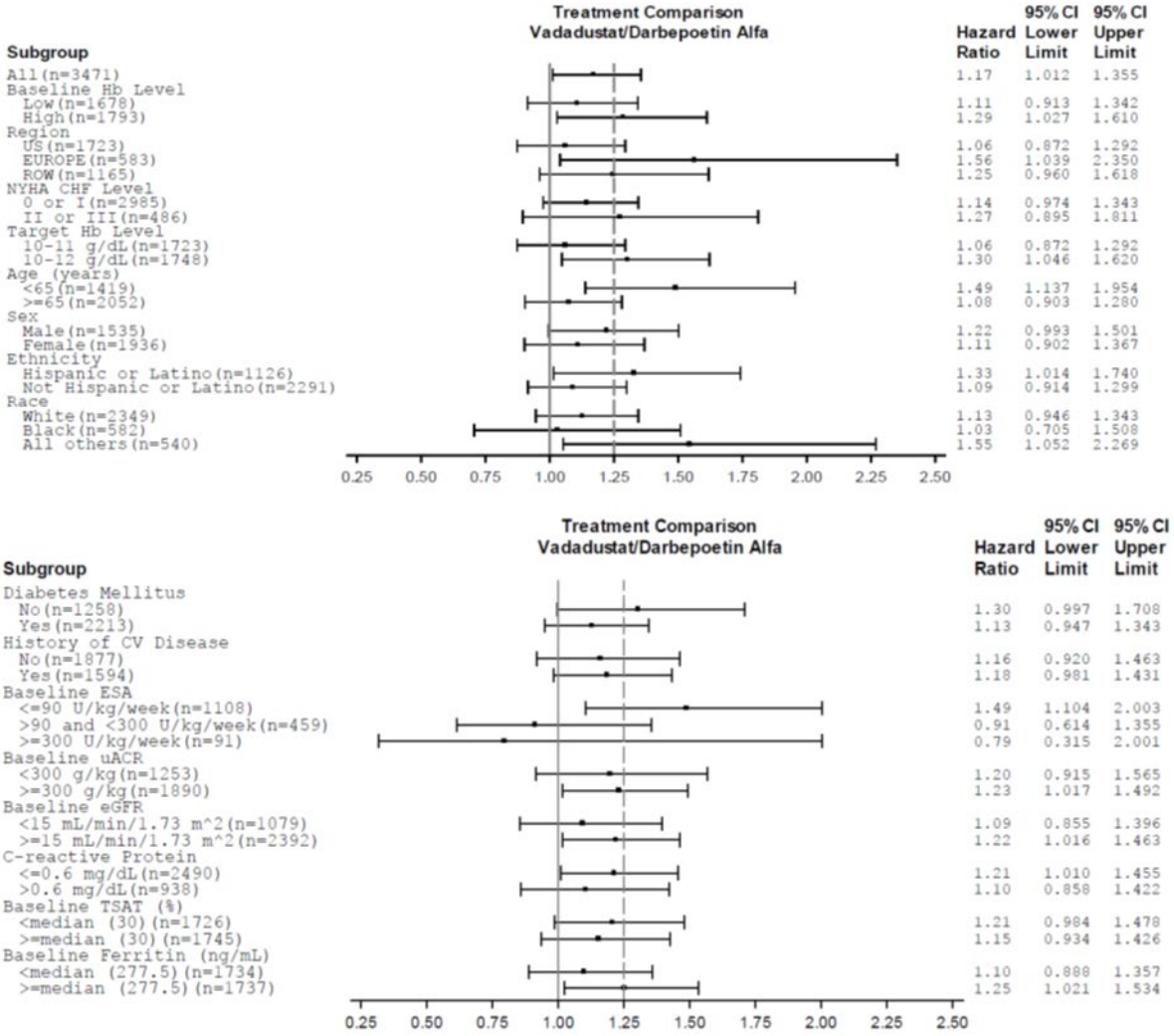
17.6. Results of Subgroup Analysis of Adverse Events of Special Interest

The Applicant conducted subgroup analyses for the following baseline variables:

- Geographic region (U.S. / Europe / ROW)
- NYHA heart failure class
- Baseline Hb level
- Target Hb levels (10.0 to 11.0 g/dL / 10.0 to 12.0 g/dL)
- Age
- Sex
- Ethnicity
- Race (white/Black or African American/Other)
- Diabetes mellitus
- History of Cardiovascular disease
- Baseline ESA dose (<90 U/kg/week /≥90 U/kg/week to <300 U/kg/week / or ≥300 U/kg/week)
- Baseline laboratory measurements such as urine albumin creatinine ratio, eGFR, c-reactive protein, transferrin saturation and Ferritin

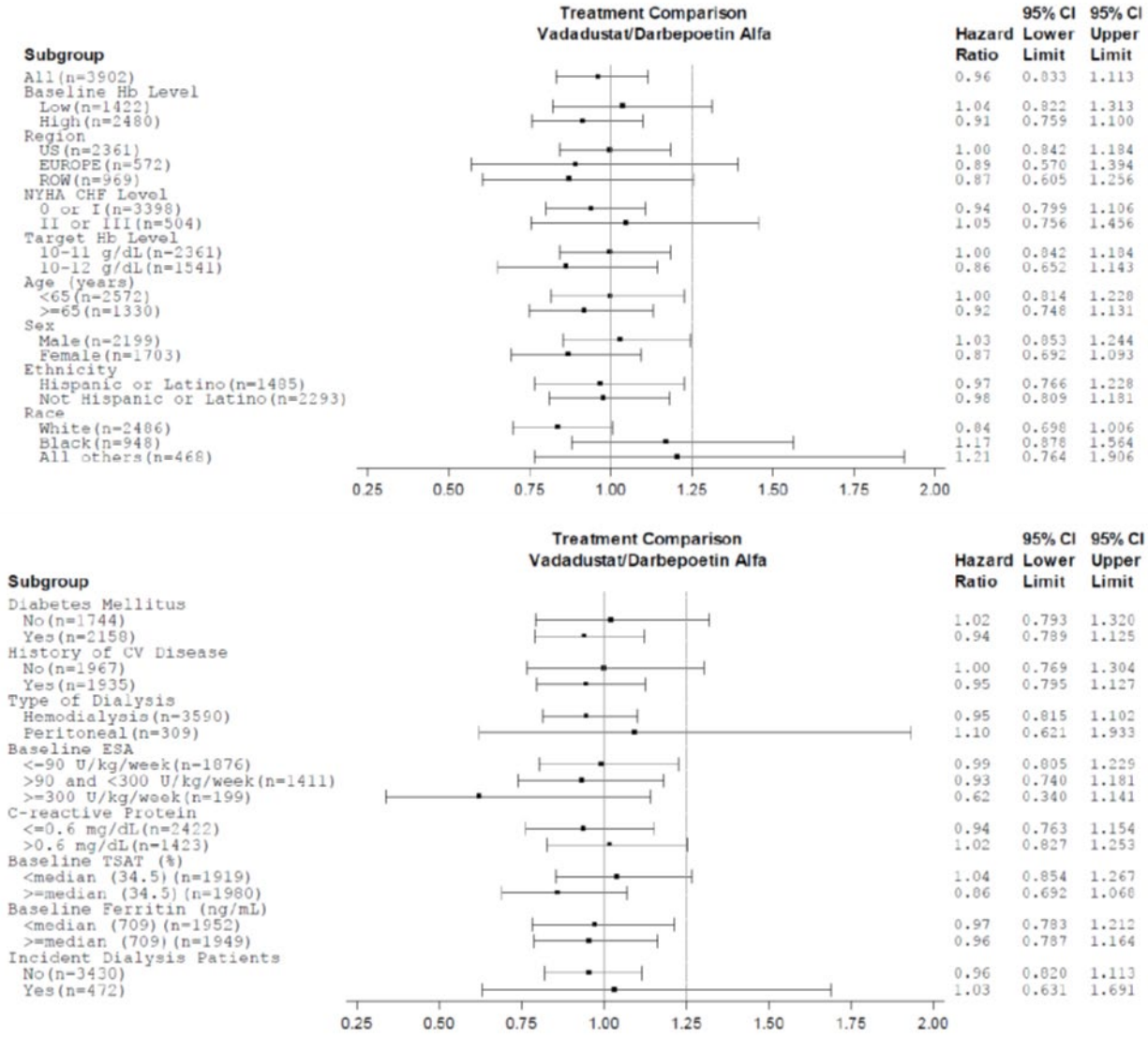
Figure 66 and Figure 67 present the forest plot of subgroup analyses for MACE in the NDD-CKD population and DD-CKD population, respectively. In the NDD-CKD population, all subgroups had a degree of overlap in their 95% CI, which may limit our degree of certainty in our conclusions. However, the following subgroups showed higher estimated HRs and smaller overlap in their 95% CIs: subjects younger than 65 years of age, subjects with a higher target Hb level of 10-12 g/dL and subjects who were on a lower dose of ESA at baseline. In the DD-CKD population, all subgroups had significant overlap in their 95% CI, thus not demonstrating a meaningful degree of difference between subgroups.

Figure 66. Subgroup Analysis of Time to First MACE: NDD-CKD Population.



Source: The Applicant's Study Report (PRO_2TECT, pages 75-76)
Abbreviations: CV, cardiovascular; DD-CKD, dialysis-dependent chronic kidney disease; ESA, erythropoietin stimulating agent; MACE, major adverse cardiovascular event; TSAT, transferrin saturation.

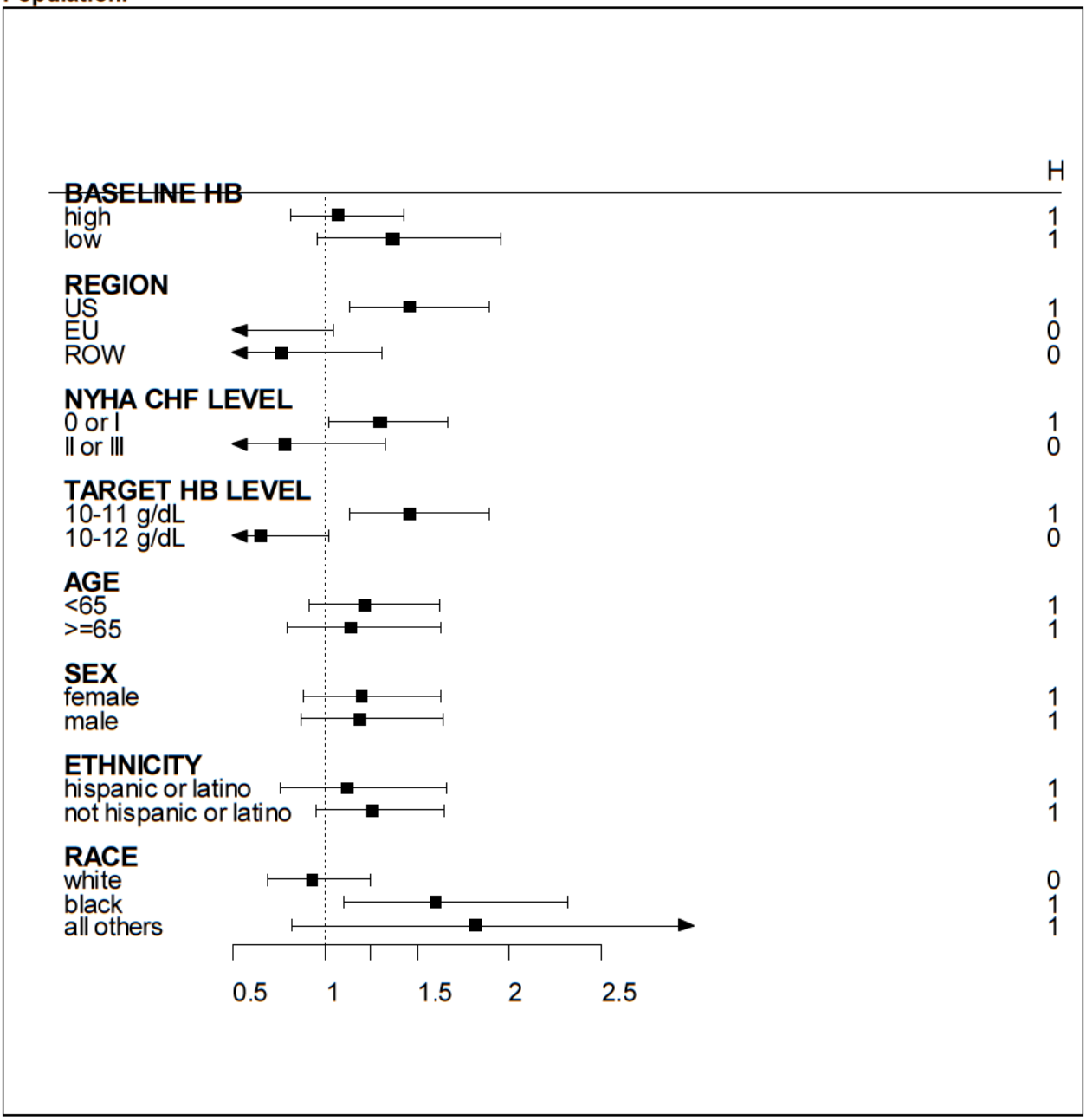
Figure 67. Subgroup Analysis of Time to First MACE: DD-CKD Population.

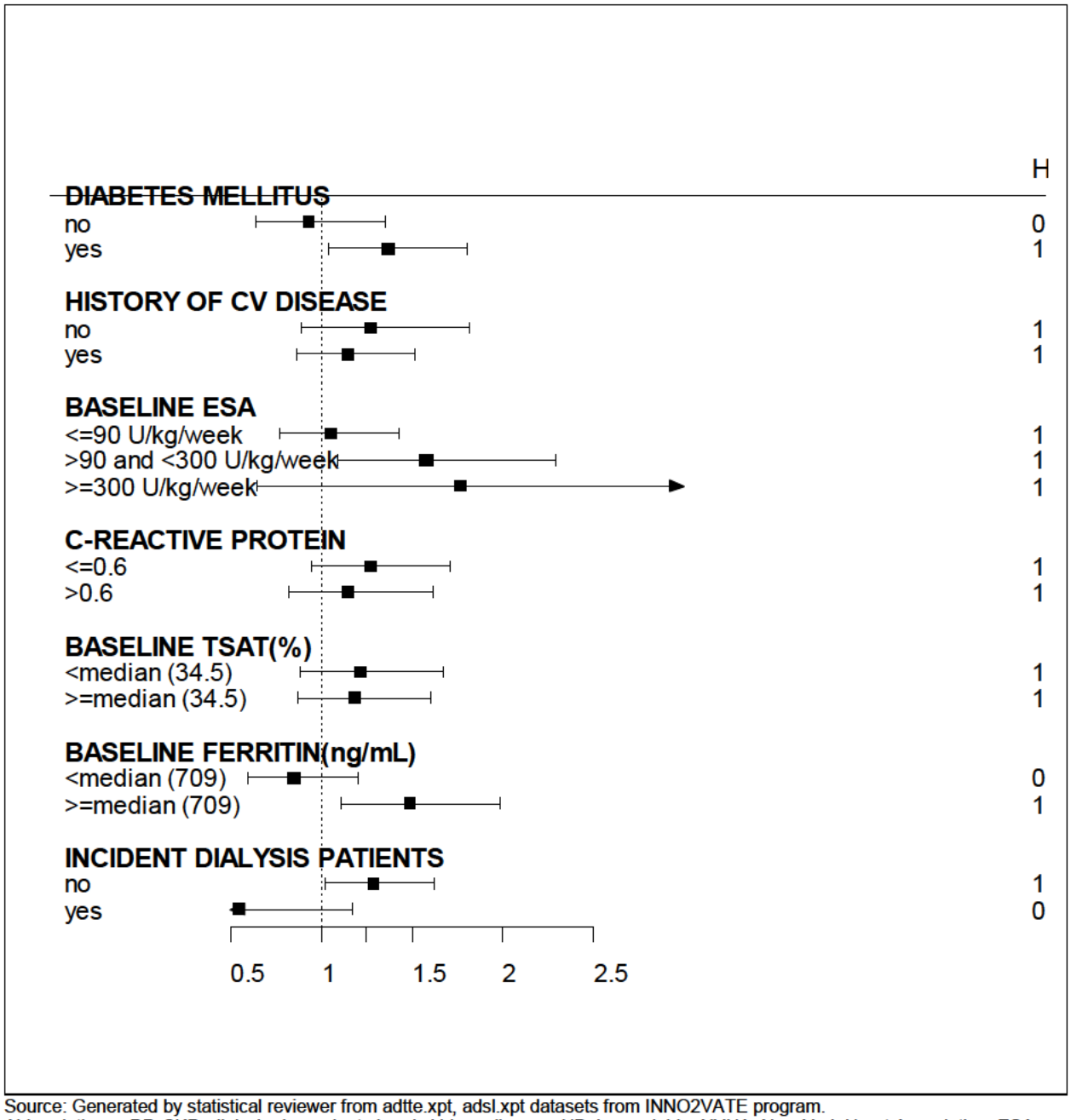


Source:
Abbreviations: CV, cardiovascular; DD-CKD, dialysis-dependent chronic kidney disease; ESA, erythropoietin stimulating agent; MACE, major adverse cardiovascular event; TSAT, transferrin saturation.

The Agency conducted post-hoc additional subgroup analyses for the adjudicated TE event and the Agency-defined VTE event for the DD-CKD population, and the results are presented in Figure 68 and Figure 69. For the adjudicated TE event, the subjects with low target Hb level (10-11 g/dL), which align with subjects in the US, showed higher HR than those with high target Hb level (10-12 g/dL), which align with subjects in the non-US regions. All other subgroups had a degree of overlap in their 95% CI, which may limit our degree of certainty in our conclusions. However, the following subgroups showed higher estimated HRs and smaller overlap in their 95% CIs: subjects of African American race, subjects with diabetes mellitus, subjects with ferritin ≥ 709 ng/ml, and subjects who were on a higher dose of ESA at baseline. With the exception of diabetes mellitus, results from the subgroup analyses of the Agency-defined VTE event were similar to those of the adjudicated TE event, in the DD-CKD population.

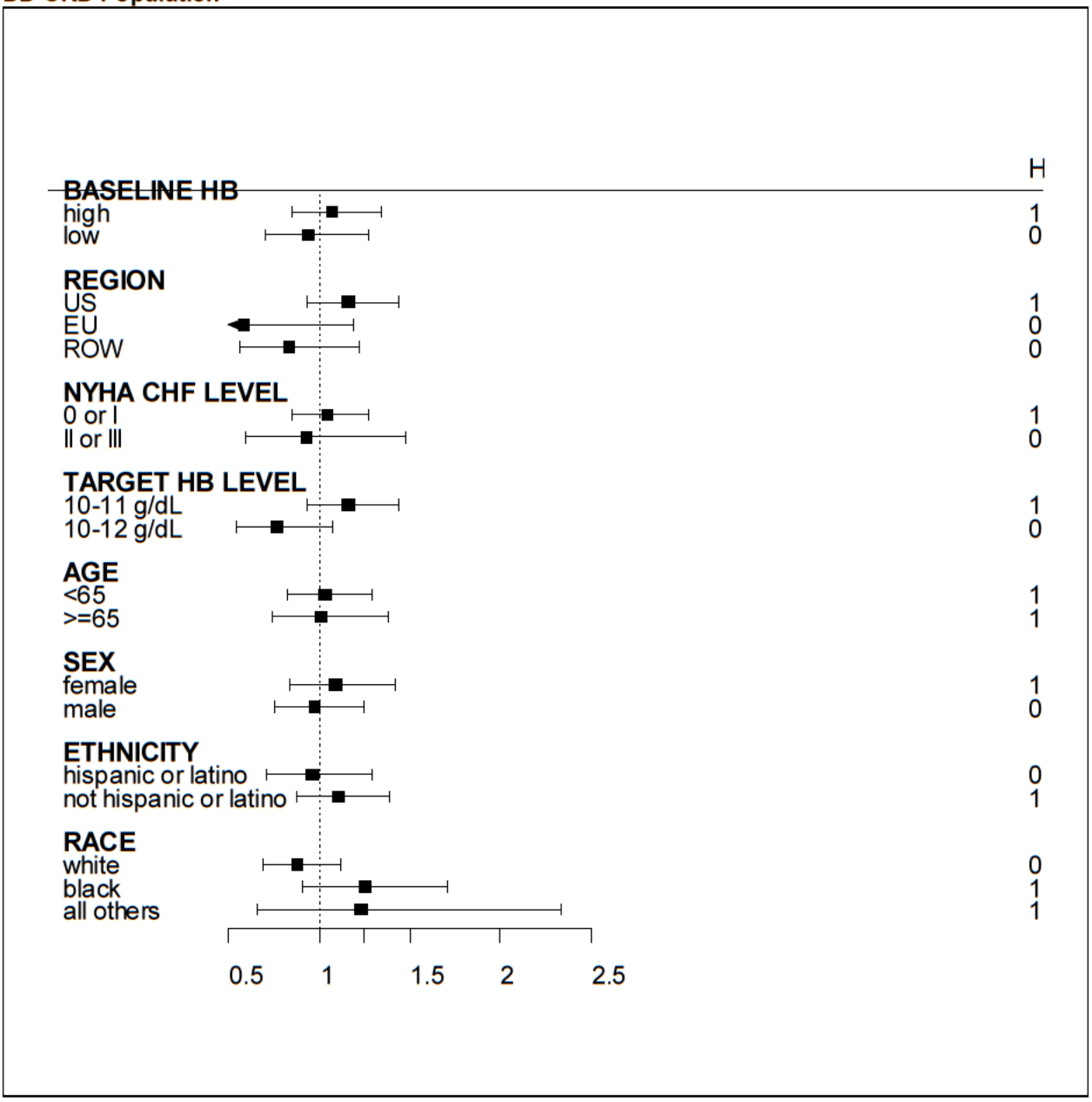
Figure 68. Subgroup Analyses of Time to First Adjudicated Thromboembolic Event: DD-CKD Population.

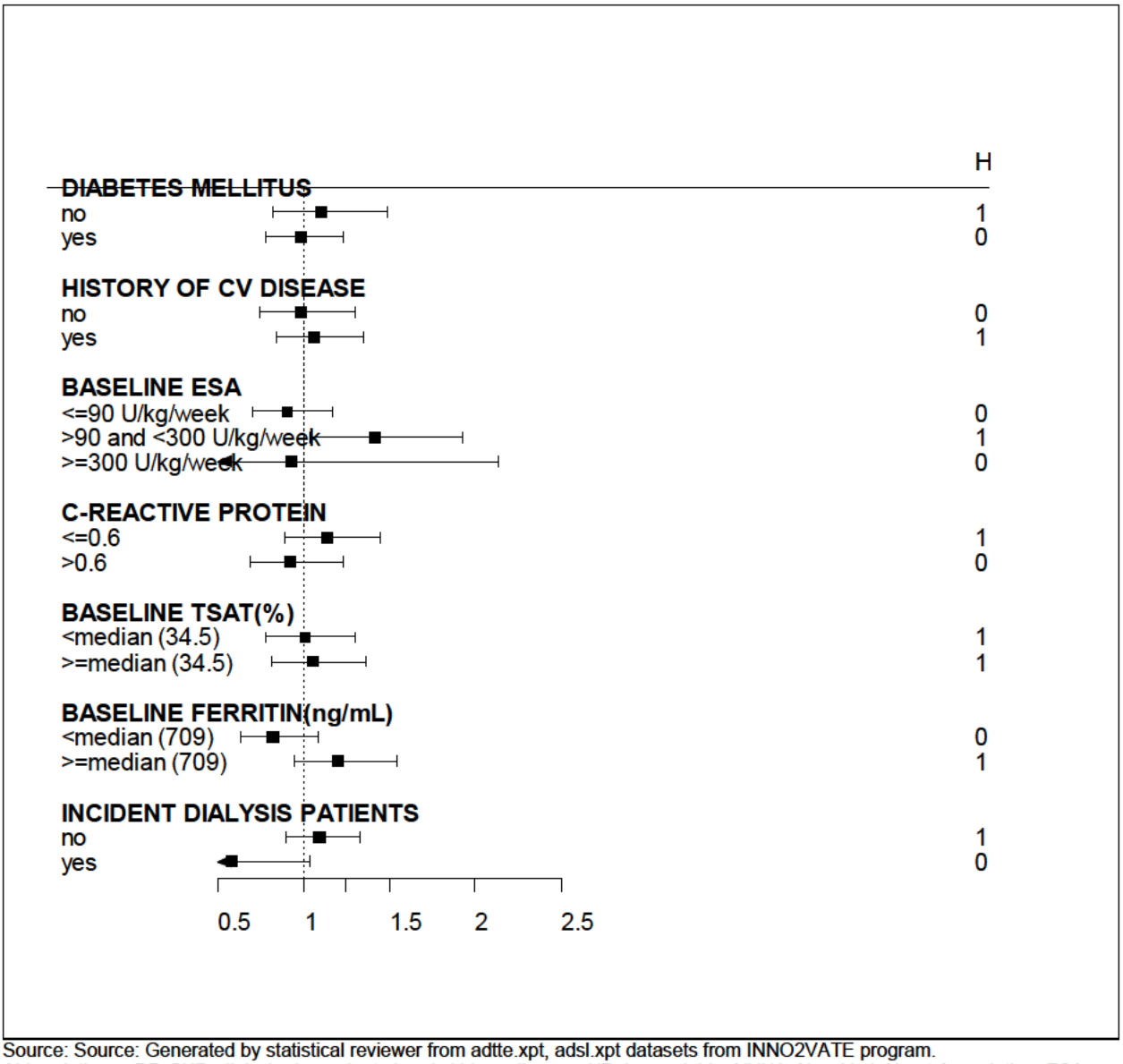




Source: Generated by statistical reviewer from adtte.xpt, adsl.xpt datasets from INNO2VATE program.
Abbreviations: DD-CKD, dialysis-dependent chronic kidney disease; HB, hemoglobin, NYHA, New York Heart Association, ESA, erythropoietin stimulating agent; TSAT, transferrin saturation.

Figure 69. Subgroup Analyses of Time to First Agency-Defined Venous Thromboembolic Event: DD-CKD Population





Source: Source: Generated by statistical reviewer from adtte.xpt, adsl.xpt datasets from INNO2VATE program.
Abbreviations: DD-CKD, dialysis-dependent chronic kidney disease; HB, hemoglobin, NYHA, New York Heart Association, ESA, erythropoietin stimulating agent; TSAT, transferrin saturation.

17.7. Details of Hepatotoxicity Evaluation

The Applicant submitted information to the FDA concerning a signal of abnormal liver tests and potential drug-induced liver injury (DILI) occurrence in October 2018. At the time, an independent review by unblinded external expert hepatologists was conducted, which identified 6 cases that were possibly or probably consistent with DILI, with an estimated frequency of DILI of 0.2%, and one of the cases met the criteria for Hy's Law. As a result, the FDA required the Applicant to implement the following interventions to their ongoing drug development program:

- Submit quarterly hepatic safety reports of ongoing trials, starting on January 14th, 2019
- Amend the protocols of ongoing trials to require permanent discontinuation of vadadustat for subjects with:
  - ALT or AST >3x ULN and total bilirubin >2x ULN

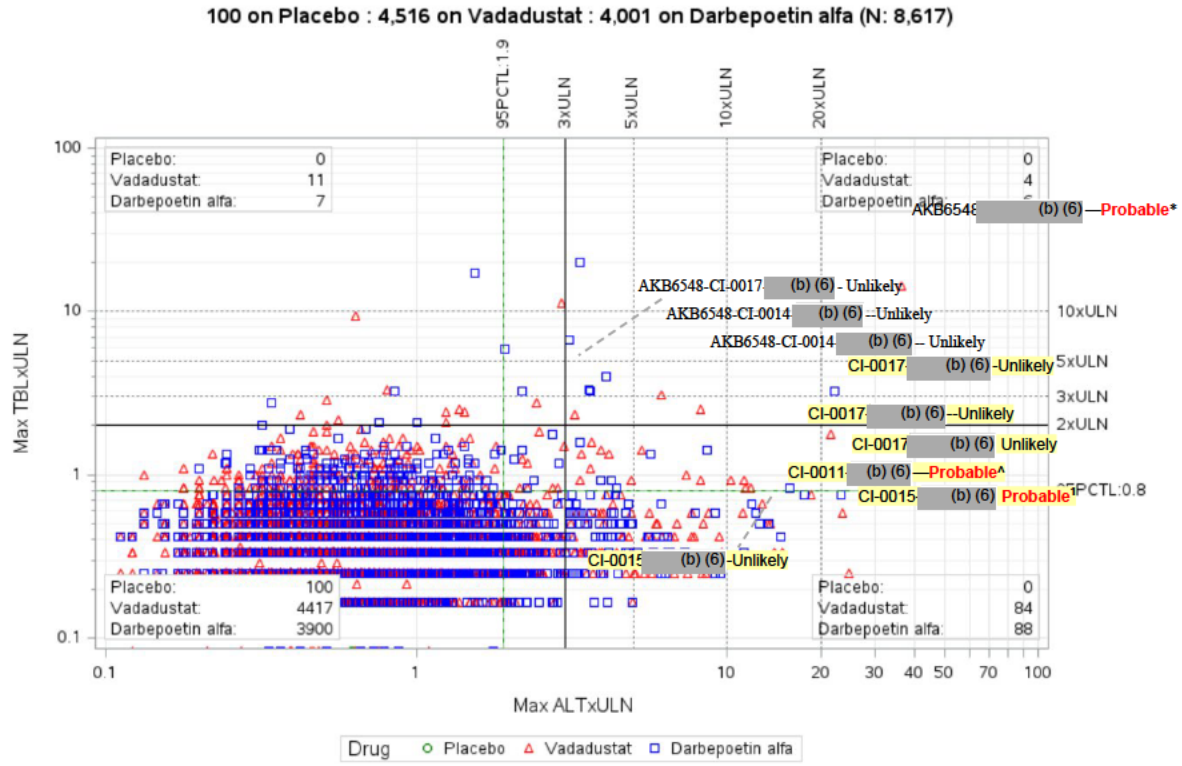
  - ALT or AST >3x ULN and INR >1.5
  - ALT or AST >8x ULN
  - ALT or AST remains >5x ULN over 2 weeks
  - ALT or AST >3x ULN with symptoms including e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, or eosinophilia

- Update informed consent forms and the vadadustat investigator's brochure to reflect information on identified hepatic risks

The Applicant instituted two hepatology assessment committees (HAC), to adjudicate AEs for drug-related hepatic disorders, each with different members. The first committee was unblinded and found increased attribution to vadadustat in the treatment arm compared to control. The second committee was blinded and did not find increase attribution to vadadustat in the treatment arm compared to control. As noted by the FDA DILI team, "knowledge of medications taken is core to DILI causality accuracy, particularly when the control medication has known, low DILI potential. We believe blinding fundamentally eroded the accuracy of causality assessment. While blinding reviewers to study arm removed treatment arm bias, it gained another bias that is troublesome: DILI causality misclassification from lack of necessary data. Such non-differential, misclassification biases toward the null. Therefore, the blinded HAC's increase in possible and probable cases in the control arm leading to a null finding is expected and does not dismiss the findings of the prior unblinded HAC or the DILI Team's case assessments." The content of the DILI team consult is summarized below for reference.

Figure 70 graphs the maximal ALT values on the X-axis versus the maximal total bilirubin results, for each patient, both as a multiple of ULN values. All cases in Temple's Corollary with ALT >5x ULN were assessed individually. Due to crowding of data points on the ALT scatter plot, the remaining case assessments are shown in Table 260, which summarizes the DILI team and HAC case level assessments of cases with ALT >5x ULN and total bilirubin <2x ULN, with the first 7 cases listed having ALT >10x ULN.

Figure 70. Maximal ALT Values Versus Maximal Total Bilirubin Values for Subjects Enrolled on Vadadustat Trials



Source: DILI team consult
* HAC assessment: 6 probable.
^ HAC assessment: No assessment provided.
[1] HAC assessment: 3 probable, 2 possible.
Abbreviations: DILI, drug-induced liver injury; HAC, hepatology assessment committee; ALT, alanine aminotransferase; ULN, upper limit of normal.

Table 260. DILI Team and HAC Case Level Assessment Outcome[1]

Case	(b) (6)	DILI Team Assessment	HAC[2] Assessment
CI-0017		**Possible**	Split decision; no consensus provided (possible or unlikely)
CI-0014		Unlikely	All reviewers: unlikely
CI-0016		Unlikely	All reviewers: unlikely
CI-0014		**Probable**	All reviewers: probable
CI-0014		**Probable**	Split decision; no consensus provided (probable or indeterminant)
CI-0016		**Probable**	Split decision; no consensus provided (probable, possible, indeterminate)
CI-0017		Unlikely	Split decision; no consensus provided (probable, possible, or indeterminate)
CI-0017		**Possible**	Split decision; no consensus provided (probable, possible or unlikely)
CI-0015		Unlikely	All reviewers: unlikely
CI-0017		Unlikely	Split decision; no consensus provided (possible or unlikely)
CI-0017		Unlikely	Split decision; no consensus provided (probable or possible)
CI-0014		**Possible**	Split decision; no consensus provided (probable or possible)
CI-0014		Unlikely	Split decision; no consensus provided (possible or unlikely)
CI-0017		No narrative	No assessments
CI-0014		Unlikely	All reviewers: unlikely
CI-0015		**Probable**	All reviewers: probable

Case	(b) (6)	DILI Team Assessment	HAC[2] Assessment
CI-0014		Indeterminant	Split decision; no consensus provided (probable or possible)
CI-0034		**Probable**	Split decision; no consensus provided (probable or possible)
CI-0017		Unlikely	Split decision; no consensus provided (possible or unlikely)
CI-0015		Unlikely	Split decision; no consensus provided (probable, possible or unlikely)
CI-0014		**Possible**	Split decision; no consensus provided (probable, possible, unlikely, indeterminant)
CI-0014		Unlikely	Split decision; no consensus provided (possible or unlikely)
CI-0014		Unlikely	Split decision; no consensus provided (probable or possible)
CI-0017		**Possible**	Split decision; no consensus provided (possible or unlikely)
CI-0014		Unlikely	Split decision; no consensus provided (probable or possible)
CI-0016		Unlikely	Split decision; no consensus provided (probable or possible)
CI-0015		**Possible**	Split decision; no consensus provided (probable or unlikely)
CI-0017		**Possible**	All reviewers: probable
CI-0015		Unlikely	Split decision; no consensus provided (probable or unlikely)
CI-0014		Unlikely	Split decision; no consensus provided (probable, possible or unlikely)
CI-0016		Unlikely	All reviewers: unlikely
CI-0017		No narrative	Not available
CI-0015		Unlikely	Split decision; no consensus provided (probable, possible or unlikely)
CI-0015		No narrative	Not available.
CI-0017		Indeterminant	Split decision; no consensus provided (probable or possible)
CI-0017		No narrative	Not available
CI-0014		Unlikely	All reviewers: unlikely
CI-0017		No narrative	Not available

Source: DILI team consult
[1] Included cases had ALT >5x ULN and total bilirubin <2x ULN.
[2] HAC member was unblinded to study drug assignment.
* These cases had ALT >10x ULN.
Abbreviations: DILI, drug-induced liver injury; HAC, hepatology assessment committee; ALT, alanine aminotransferase; ULN, upper limit of normal.

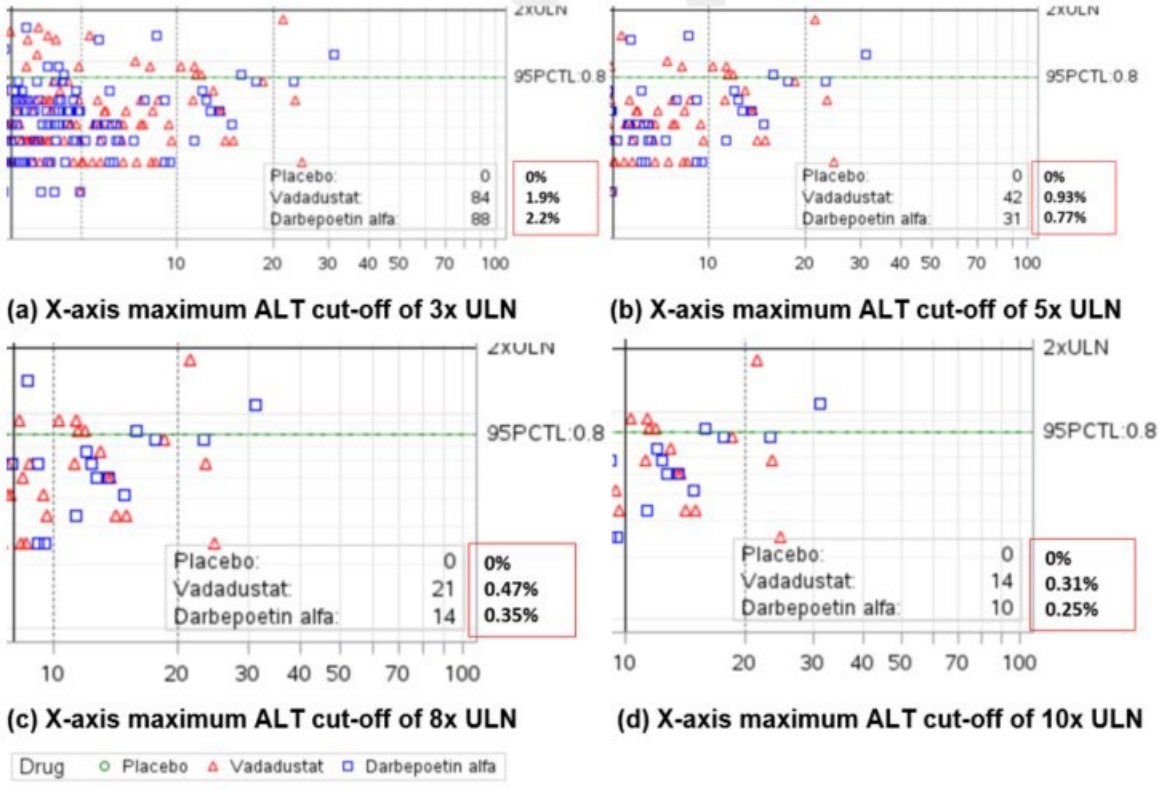
To evaluate the cases in Temple's Corollary quadrant, the Applicant evaluated the abnormal ALT values using applicant-determined ranges, such as >2-≤3x ULN, >3-≤5 ULN and >5-≤10 ULN. This approach revealed similar numbers of subjects with abnormal ALT values in each treatment arm, as shown in Table 261. However, when specific cut-off values, such as 3x ULN, 5x ULN, 8x ULN and 10x ULN, were considered by the DILI team, there was a shift towards higher ALT levels in the vadadustat arm, as shown in Figure 71. The assessment using cut-off values was more sensitive that the bound category approach, thus was better at detecting the hepatotoxicity safety signal.

Table 261. Number of Subjects With Abnormal Liver Enzyme Results, Pooled CKD Population, Safety Population

Parameter Criterion	Vadadustat N=4515 n (%)	Darbepoetin Alfa N=4001 n (%)
Alanine aminotransferase		
N1	4437	3949
>2 × and ≤3 × ULN	80 (1.8)	81 (2.1)
>3 × and ≤5 × ULN	42 (0.9)	61 (1.5)
>5 × and ≤10 × ULN	25 (0.6)	18 (0.5)
>10 × ULN	15 (0.3)	11 (0.3)
Aspartate aminotransferase		
N1	4437	3949
>2 × and ≤3 × ULN	91 (2.1)	102 (2.6)
>3 × and ≤5 × ULN	41 (0.9)	58 (1.5)
>5 × and ≤10 × ULN	26 (0.6)	23 (0.6)
>10 × ULN	12 (0.3)	13 (0.3)
Bilirubin		
N1	4437	3948
>2 × and ≤3 × ULN	10 (0.2)	3 (0.1)
>3 × ULN	5 (0.1)	10 (0.3)

Source: Integrated Summary of Safety Table 14.3.5.8c
If there were assessments falling into different categories of criteria for a subject, then the subject was counted in the worst category only.
Abbreviations: CDK, dialysis-dependent chronic kidney disease; N, number of subjects; n, number of subjects with events; N1, number of subjects with any non-missing post-baseline assessments; ULN, upper limit of normal.

Figure 71. Maximal ALT Values Versus Maximal Total Bilirubin Values for Subjects Enrolled on Vadadustat Trials, in x ULN[1]



Source: DILI team consult
[1] Only right lower quadrant shown using different maximum ALT cut-offs. Tallies and percentages reflect only subjects in the right lower quadrants.
Abbreviations: DILI, drug-induced liver injury; ALT, alanine aminotransferase; ULN, upper limit of normal.

The DILI team conducted a case level analysis, with summary data of 8 probable DILI cases with ALT >5x ULN, as shown in Table 260. There were no cases of significant cholestasis (i.e., AP >3x ULN with bilirubin >2x ULN, in the absence of high transaminases). In these eight probable DILI cases, the injury had a median latency of 56 days (range 9-168). Overall, the injury pattern was mostly compatible with hepatocellular injury (median R-value$_{ALT}$ 7.1, range 4.1 to 19.2). One subject had mild injury and developed tolerance as vadadustat was continued and enzyme elevations resolved. Two cases had a mixed injury picture (R-values 4.1 and 4.9).

In addition, the DILI team provided cases summaries and assessments for three of the eight cases of probable DILI as examples, including the patient that qualified as a Hy's Law case. These summaries and assessments are provided as follows:

Case (b) (6) *(Trial 0017)*: This is a 69-year-old female with high transaminases starting about 4 weeks after start of vadadustat. She became jaundiced. She had multiple medical problems including diabetes, hyperlipidemia, acute kidney injury, CKD, and hypertension, but was not on dialysis. She was status post cholecystectomy. Medications included benazepril/ hydrochlorothiazide, saxagliptin (b) (6) start), simvastatin ((b) (6) start; dose lowered 40 to 20 mg (b) (6) glipizide, hydrochlorothiazide, and linagliptin (start (b) (6)), chlorthalidone ((b) (6) start). She was not on any herbal/dietary supplements. She started vadadustat 450 mg daily on (b) (6). Her liver tests were normal. At week 4, her ALT and AST climbed to 64 and 51 U/L, respectively. By week 8 ((b) (6) (b) (6)), they were 161 and 97 U/L, respectively. Vadadustat dose was decreased to 150 mg daily. Simvastatin had already been decreased on (b) (6). ALT and AST kept climbing to 1166 and 1045 U/L, respectively, between (b) (6) Vadadustat and several other medications, including simvastatin and linagliptin, were all stopped. Total bilirubin rose to 11 mg/dL (direct bilirubin 6.4), followed by a peak of 17.3 mg/dL. She was asymptomatic. INR remained normal, and she was not hospitalized. She denied travel, sick contacts, new medications, or herbal/dietary supplements. Ultrasound was unremarkable. Hepatitis A-E tests were negative. IgG level was normal, and antinuclear antibodies was negative. No liver biopsy was done. Liver enzymes and bilirubin quickly fell by 50% but took several weeks to return to normal.

- *Assessment*: We assessed this case as probable DILI due to vadadustat. This case is important because it is the only one in Hy's Law quadrant that is causally linked to vadadustat. Latency and washout are consistent. Simvastatin competes some but latency is a bit long at 6.5 months. Evaluation testing was negative for other diagnoses. There was no testing for EBV or CMV, but she had no symptoms. Applicant's HAC considered this case "probable" DILI due to vadadustat. Though the alkaline phosphatase was >2x ULN, we consider this a Hy's Law case. There was hepatocellular injury with jaundice based on (a) the absolute values of ALT and AST >1000 U/L, (b) bilirubin of 17.3 mg/dL and (c) R values >5 using (as shown in 244).

Case (b) (6) *(Trial 0015)*: This is a 56-year-old Black female with elevation in transaminases without jaundice occurring 4 weeks after vadadustat start (300 mg daily). She had a history of hepatitis B, diabetes mellitus, hyperlipidemia, hypertension, and anemia associated with CKD. She had normal liver tests at baseline. She started valsartan as the only new medication in the prior 6 months (started on (b) (6) and continued through the event). She started vadadustat on (b) (6) at 300 mg daily. At her 4-week visit she had asymptomatic elevation of ALT and AST (816 U/L and 646 U/L, respectively) without bilirubin or alkaline phosphatase rise. She denied illicit drug use, new medications, or herbal/dietary supplement use.

Evaluation testing included HBsAg (-), anti-HBc (+) and anti-HBs (-), HCV Ab (-) and HIV (-). No imaging or other testing noted. Vadadustat was stopped with rapid decline in liver tests to normal.

- *Assessment*: This is probable DILI due to vadadustat. Latency and washout consistent with DILI. Evaluation testing was limited. Gallstone disease and viral infections compete, though she was asymptomatic and resolution too quick for viral hepatitis. No competing medications or herbal-dietary supplements.

Case (b) (6) *(Trial 0016)*: This is a 50-year-old Caucasian male enrolled in (b) (6) who had elevation in transaminases without jaundice 24 weeks after starting vadadustat 300 mg daily. The patient had diabetes mellitus, hypertension, NYHA II heart failure, "hepatosis" and coronary artery disease at baseline. He was on several medications, but none started within 4 years of injury onset. He had normal liver tests at baseline and experienced a rise in ALT and AST starting on Day 117 (ALT rose from 9 U/L to 37 U/L) and about 85 days after dose increase to 450 mg daily. ALT and AST rose further to 469 and 274 U/L, respectively. Alkaline phosphatase also rose to 349 U/L. Vadadustat was stopped on (b) (6) (day 196). ALT fell by 50% in 28 days and back to normal by 87 days. AST was back to normal within 28 days. Narrative is limited and does not mention any symptoms. AE tabular data includes only ALT and AST increases. No mention of gallstone disease, abdominal pain, viral hepatitis, or fever. No evaluation testing or details given.

- *Assessment*: This is probable DILI due to vadadustat based on latency and dechallenge. Although narrative data are sparse, the lack of any other AEs suggest no symptoms that would suggest viral infection or gallstone disease.

There was also a DILI team evaluation during the application review of roxadustat, the first-in-class HIF-PH inhibitor. That evaluation did not identify a clinically significant hepatotoxicity risk that was attributable to the drug, thus this finding does not seem to be related to the class of drugs. In addition, the following are important aspects of the hepatic non-clinical evaluation of vadadustat:

- In vitro studies suggest vadadustat is hepatically metabolized but not to any significant degree by the cytochrome p450 system. Rather, vadadustat undergoes phase II metabolite formation, resulting in glucoronidated and glycosylated compounds.
- Long-term exposure in animals (9-month Beagle dog; 3-month Wistar rat) did not show significant liver histopathology.
- In humans, the major route of metabolite elimination is urinary (59%). Vadadustat median half lives in healthy volunteers and subjects were 4.7 and 7.0 hours, respectively.
- Vadadustat was evaluated in a hepatic impairment trial (Trial 0024), where subjects with moderate hepatic dysfunction (Child Pugh B) were studied, demonstrating a 33% longer half-life in these subjects.

The following conclusions were supported by the evaluation of the DILI team:

- Currently, the mechanism of liver injury of vadadustat is unclear. However, given the available data, it is presumably that the injury is due to a phase II metabolite.
- The lack of DILI signal in non-clinical studies does not impact the possibility of a DILI signal in humans, since up to 1 in 5 drugs with DILI findings will have no DILI signals in their non-clinical studies.

- Given the assumption that the DILI signal detected is idiosyncratic and since cirrhosis does not increase the risk of idiosyncratic DILI, the small sample of subjects with cirrhosis enrolled in trial 0024 would not allow for proper detection of a DILI signal. As a result, the lack of occurrence of DILI in that trial does not support the absence of DILI risk with vadadustat.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment:

Not Applicable.

19. Other Drug Development Considerations: Additional Information and Assessment:

Not applicable since there are no other drug development considerations for this application.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Data quality was ensured by the Applicant through periodic monitoring with primary source verification of trial data at all trial sites. In addition, quality assurance audits were performed to further ensure data quality. Throughout the application review period, data quality was evaluated by the clinical review team using several approaches:

- Using the FDA CDER Clinical Investigator Site Selection Tool (v.2.9.05) and the Applicant-provided BIMO dataset for the four phase 3 global trials, we suggested the following sites for inspection to the FDA Office of Scientific Investigations: Trial 0014 – site 10013 and site 10006; Trial 0015 – site 10006; and Trial 0017 – site 10008, site 10506, and site 10304. Given the limitation of travel and access to sites outside of the United States due to the COVID-19 Pandemic, these sites were limited in location to the United States. Our selection was based on many factors, with the following factors having stronger contribution to the site ranking: 1) Total number of subjects per site, 2) Treatment efficacy results and site-specific treatment effect, 3) SAE ratio and 4) Principal Investigator and site regulatory history. The inspections of all sites were unremarkable, resulting in No Action Indicated letters.
- The Office of Computational Science provided data quality evaluation reports using the FDA Validator tool, which were reviewed by the clinical reviewer to assess the validity of any data quality findings and no data quality issues were identified.
- The clinical review team independently reviewed the provided datasets and noted no anomalies in enrollment characteristics, patterns of protocol violations reported, patterns of efficacy reporting, or patterns of SAE reporting. Sensitivity analyses were performed when appropriate, with no significant differences to report.

As a result of these assessments, there was no significant issues with data quality or integrity that affected interpretation of this review.

21. Labeling Summary of Considerations and Key Additional Information

This section is not applicable because labeling negotiations were deferred due to the planned complete response action.

22. Postmarketing Requirements and Commitments

Given that the decision on this application is a Complete Response action, no postmarketing requirements (PMRs) or postmarketing commitments (PMCs) will be issued. We will reassess the need for PMRs or PMCs if/when vadadustat can be approved.

23. Financial Disclosure

Table 262. Covered Clinical Trial: AKB-6548-CI-0014

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1514		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (since N/A)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (since N/A)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 8		
Is an attachment provided with the reason:	Yes ☒	No ☐

Table 263. Covered Clinical Trial: AKB-6548-CI-0015

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1623		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (since N/A)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (since N/A)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 12		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 264. Covered Clinical Trial: AKB-6548-CI-0016

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 546		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (since N/A)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (since N/A)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request list from Applicant)

Table 265. Covered Clinical Trial: AKB-6548-CI-0017

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1366		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (since N/A)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (since N/A)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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25. Review Team

Table 266. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	May Zuwannin, Carleveva Thompson
Nonclinical Reviewer	Karen Hao
Nonclinical Team Leader	Pedro DelValle
Office of Clinical Pharmacology Reviewer(s)	Anusha Ande, Jiajun Liu
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan, Liang Li
Associate Director for Labeling	Virginia Kwitkowski
Clinical Reviewer	Fadi Nossair
Clinical Team Leader	Albert Deisseroth
Statistical Reviewer(s)	Xiaoyu Cai, Joo-Yeon Lee
Statistical Team Leader(s)	Yeh-Fong Chen, Clara Kim
Cross-Disciplinary Team Leader	Albert Deisseroth
Division Director (pharm/tox)	Todd Bourcier
Division Deputy Director (OCP)	Doanh Tran
Division Director(s) (OB)	Thomas Gwise, Mark Levenson
Division Director (clinical)	Ann Farrell
Office Director (or designated signatory authority)	Hylton Joffe

Abbreviations: OB; Office of Biostatistics; OCP; Office of Clinical Pharmacology

Table 267. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Dan Berger, Ben Zhang, Liya Tang, Nadia Ahmed
Microbiology	NA
OPDP	Rebecca Falter
OSI	
OSE/DEPI	Steve Bird, Fang Tian
OSE/DMEPA	Hina Mehta, Stephanie DeGraw
OSE/DRISK	Naomi Boston, Carolyn Tieu, Victoria Sammarco
Other	

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Table 252. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Fadi Nossair, MDCM, MS-BATS,	OCHEN/DNH	2, 3, 4, 6.2, 6.3, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 8.3, 10, 15, 16.1, 17.1, 17.2, 17.3, 17.4, 17.5, 17.7, 201, 21, 22, 23, 24 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Fadi F. Nossair -S Digitally signed by Fadi F. Nossair -S Date: 2022.03.24 16:28:19 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved1
Clinical	Albert Deisseroth, MD, PhD	OCHEN/DNH	All Sections ☒ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead/Deputy Director	**Signature:** Albert B. Deisseroth -S Digitally signed by Albert B. Deisseroth -S Date: 2022.03.25 15:38:46 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Huiqing Karen Hao, PhD	OND/DPTCHEN	5.1, 7.1, 8.3, 8.4, 13.1. ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Pedro L. Del Valle -S Digitally signed by Pedro L. Del Valle -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001000884, cn=Pedro L. Del Valle -S Date: 2022.03.24 15:45:05 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 252. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Pedro DelValle, MS, PhD, FATS	OND/DPTCHEN	5.1, 7.1, 8.3, 8.4, 13.1. ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Pedro L. Del Valle -S Digitally signed by Pedro L. Del Valle -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001000884, cn=Pedro L. Del Valle -S Date: 2022.03.24 11:27:53 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Todd Bourcier, PhD	OND/DPTCHEN	5.1, 7.1, 8.3, 8.4, 13.1. ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Todd M. Bourcier -S Digitally signed by Todd M. Bourcier -S Date: 2022.03.24 13:06:26 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Anusha Ande, PhD	OTS/OCP/DCEP	5 (Table 7), 6.1, 8.1, 8.2, 14.1, 14.2, 14.4 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Anusha Ande -S Digitally signed by Anusha Ande -S Date: 2022.03.23 13:50:13 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Sudharshan Hariharan, PhD	OTS/OCP/DCEP	5 (Table 7), 6.1, 8.1, 8.2, 14.1, 14.2, 14.4 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Sudharshan Hariharan -S Digitally signed by Sudharshan Hariharan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000394743, cn=Sudharshan Hariharan -S Date: 2022.03.23 16:16:23 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 252. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Jiajun Liu, PharmD, MSc	OTS/OCP/DPM	5 (Table 7), 6.1, 14.3 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Jiajun Liu -S Digitally signed by Jiajun Liu -S Date: 2022.03.23 16:00:10 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Liang Li, PhD	OTS/OCP/DPM	5 (Table 7), 6.1,14.3 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Liang Li -S Digitally signed by Liang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Li -S, 0.9.2342.19200300.100.1.1=2001459144 Date: 2022.03.23 16:06:47 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Doanh Tran, PhD	OTS/OCP/DCEP	5 (Table 7), 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4 ☐ Authored ☐ Contributed ☒ Approved
Deputy Director	**Signature:** Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2022.03.23 16:44:29 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Xiaoyu Cai, PhD	OTS/OB/DBIX	6.2, 16.1 & 16.2 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Yeh Fong Chen -S Digitally signed by Yeh Fong Chen -S Date: 2022.03.23 17:00:28 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 252. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Yeh-Fong Chen, PhD	OTS/OB/DBIX	6.2, 16.1 & 16.2 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Yeh Fong Chen -S Digitally signed by Yeh Fong Chen -S Date: 2022.03.23 17:01:06 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Thomas Gwise, PhD	OTS/OB/DBIX	6.2, 16.1 & 16.2 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300369224, cn=Thomas E. Gwise -S Date: 2022.03.24 07:27:39 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Joo-Yeon Lee, PhD	OTS/OB/DBVII	7.4, 7.6, 7.7,17.6 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	**Signature:** Clara Y. Kim -S Digitally signed by Clara Y. Kim -S Date: 2022.03.23 10:00:34 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Clara Kim, PhD	OTS/OB/DBVII	7.4, 7.6, 7.7,17.6 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Clara Y. Kim -S Digitally signed by Clara Y. Kim -S Date: 2022.03.23 10:00:07 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
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Continued: Table 252. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Mark Levenson, PhD	OTS/OB/DBVII	7.4, 7.6, 7.7,17.6 ☐ Authored ☒ Contributed ☒ Approved
Division Director	**Signature:** Mark S. Levenson -S Digitally signed by Mark S. Levenson -S Date: 2022.03.23 11:56:33 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Carleveva Thompson, MS	ORO/DROCHEN	Section 12 ☒ Authored ☐ Contributed ☐ Approved
Regulatory Project Manager	**Signature:** Carleveva Thompson Digitally signed by Carleveva Thompson Date: 2022.03.24 13:01:17 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Charlene Wheeler, MSHS	ORO/DROCHEN	Section 12 ☐ Authored ☐ Contributed ☒ Approved
Chief, Project Management	**Signature:** Charlene N. Wheeler -S Digitally signed by Charlene N. Wheeler -S Date: 2022.03.24 15:58:24 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

HYLTON V JOFFE
03/29/2022 09:50:42 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 215192
Drug Name:	AKB-6548
Indication:	Treatment of anemia associated with chronic kidney disease
Studies:	Carcinogenicity Studies in Rats for 104 Weeks and Mice for 26 Weeks
Applicant:	Study Sponsor: Akebia Therapeutics 245 First Street, Suite 1100 Cambridge, MA 02142 United States Rat Study Testing Facility: (b) (6)
Documents Reviewed:	Electronic submission: Submitted on April 27 2021 Electronic data: Submitted on April 27 2021
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Dr. Hepei Chen
Concurring Reviewer:	Dr. Karl Lin
Medical Division:	Division of Pharmacology Toxicology for Cardiology, Hematology, Endocrinology & Nephrology
Reviewing Pharmacologist:	Dr. Karen Hao
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to determine the potential oncogenicity of AKB-6548, when given orally for a minimum of 104 weeks to rats, and 6 months to CByB6F1/Tg rasH2 hemizygous (transgenic) mice.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred and fifty rats of each sex were assigned randomly in size of 70 rats per group. The dose levels for the three treated groups were 2, 7, and 20 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The rats in the water control group and the vehicle control groups were administrated with RODI Water and the vehicle [Reverse Osmosis Deionized (RODI) Water], respectively, and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male (Group #)	Female (Group #)
1	70	70	Water control	0	0
2	70	70	Vehicle control	0	0
3	70	70	AKB-6548 Low	2	2
4	70	70	AKB-6548 Mid	7	7
5	70	70	AKB-6548 High	20	20

Low numbers of surviving animals due to age-related mortality resulted in early discontinuation of dose administration for Group 5 female rats (reaching 20 on Day 592, Week 85), and termination of all male rats (Day 652, Week 94) and female rats (Day 602, Week 86) due to the number of surviving control animals (vehicle control for male rats and water control for female rats) reaching 20 animals on these days. Therefore, surviving male rats were euthanized as soon as practical beginning on Day 652, Weeks 94 through 95 and surviving female rats were euthanized beginning on Day 603, Weeks 87 through 90.

Throughout the study, all animals were observed for general health/mortality and moribundity twice daily, once in the morning and once in the afternoon. Cage side observations were performed once weekly for all animals, including toxicokinetic and hematology animals, beginning during Week 1. Each carcinogenicity animal was removed from the cage, and a detailed clinical observation was performed at least once weekly, beginning during Week -1. Beginning on Week 26, detailed clinical observations for carcinogenicity animals included a palpable mass examination (including the occurrence, size, location, and description of palpable

masses). A necropsy was conducted for carcinogenicity animals that died on study, and specified tissues were saved. Carcinogenicity animals surviving until scheduled euthanasia were euthanized by isoflurane followed by exsanguination. When possible, the animals were euthanized rotating across dose groups such that similar numbers of animals from each group, including controls, were necropsied at similar times throughout the day. Carcinogenicity animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues. Histopathological evaluation was performed by a board-certified veterinary pathologist.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor’s report, Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. A log-rank test for survival was used to make the following comparisons:
1) pairwise comparisons of each treated group with the vehicle control group and water control group and
2) trend tests for treated groups with each control group utilizing ordinal coefficients, and
3) pairwise comparison of the vehicle and water control groups.

All tests were 2- sided and conducted at the 0.05 significance level. Survival times in which the status of the animal's death was classified as an accidental death or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor’s findings:

The sponsor’s analysis showed that the numbers of rats surviving to their terminal necropsy were 24 (34%), 20 (29%), 21 (30%), 16 (23%), and 22 (31%) in the water control, the vehicle control, the low, mid, and high dose groups for male rats, respectively, and 19 (27%), 30 (43%), 24 (34%), 29 (41%), and 18 (26%) for female rats respectively. In the sponsor’s analysis, no statistically significant findings were noted for both male and female rats.

2.1.2. Tumor data analysis

In the sponsor’s analysis, statistical analysis of the tumor incidence data was conducted in accordance with the FDA draft Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals.

The incidence of tumors was analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortalityindependent) in which tumors were observed. The following fixed intervals were used for incidental tumor analyses in male rats: Weeks 1-50, 51-80, 81 to end of study (up to but not including terminal sacrifice), and terminal sacrifice. Due to the sparse number of necropsies and early termination, the following

fixed intervals were used for incidental tumor analyses in female rats: Weeks 1-50, 51 to end of study (up to but not including terminal sacrifice), and terminal sacrifice.

All animals that died or were sacrificed after the first animal of that sex was terminally sacrificed were included in the terminal sacrifice interval for the incidental finding analyses. For example, among males terminal sacrifices began on study day 652. All male natural deaths and sacrifices that occurred after the first male sacrifice on study day 652 were included in the terminal sacrifice interval.

All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis. Tumors classified as mortality-independent were analyzed with Peto's mortalityindependent method incorporating the day of detection. Each diagnosed tumor type was analyzed separately and, at the discretion of the Study Director, analysis of combined tumor types was performed. In addition, all leukemias or other systemic tumors were grouped under "hemolymphoreticular neoplasm". Finally, all metastases and invasive tumors were considered secondary and not included in the analyses unless the primary tumor could not be identified.

All analyses were conducted separately for each sex. For each tumor type, the following analyses were conducted:
1) 1-sided pairwise comparison of each treated group with water control group 1 and vehicle control group 2;
2) 1-sided trend test with the treated groups and water control group 1 and, separately, with vehicle control group 2 utilizing ordinal coefficients; and
3) 1-sided pairwise comparison of vehicle control group 2 with water control group 1.

In the case of sparse tables (<3 total in a stratum), p-values were computed using exact permutation distributions. Otherwise, p-values were computed using standard normal approximations with a continuity correction. Tests resulting in a p-value less than 0.05 were identified.

Adjustment for multiple testing:

In the sponsor's report, statistical significance was determined according to the following guidelines: trend tests were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. Pairwise comparisons with the control group were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively. A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1%.

Sponsor's findings:

As indicated in the sponsor's report (Table 2), no statistically significant tumor findings were noted among male rats. For female rats, there was a statistically significant increase in the incidence of benign granular cell tumor in the cervix when comparing the vehicle control to the water control. There was a statistically significant increasing trend in the incidence of malignant pheochromocytoma in the adrenal gland, and hepatocellular adenoma in the liver, when comparing the active treatment groups to both water control and vehicle control. There were no other statistically significant tumor findings among female rats.

Table 2: Results of Statistical Analyses of Neoplastic Lesions from Sponsor's Report

Organ	Tumor	R/C		Water Control	Vehicle Control	2 mg/kg/day	7 mg/kg/day	20 mg/kg/day	Trend
GLAND, ADRENAL	TOTAL EXAMINED		(N)	70	70	70	70	70	
	PHEOCHROMOCYTOMA, MALIGNANT/BENIGN	C	(a)	8	2	6	6	8	
			(pWC)		0.9467	0.6100	0.5780	0.3941	0.3836
			(pVC)			0.0836	0.0972	0.0321	0.0442
HEMOLYMPHORETICULAR TISSUE	TOTAL EXAMINED		(N)	70	70	70	70	70	
	HISTIOCYTIC SARCOMA (M)	C	(a)	0	1	1	4	1	
			(pWC)		0.4792	0.4681	0.0452	0.4783	0.1565
			(pVC)			0.7328	0.1937	0.7645	0.3857
PANCREAS	TOTAL EXAMINED		(N)	70	70	70	70	70	
	ISLET CELL CARCINOMA/ADENOMA	C	(a)	7	2	3	8	5	
			(pWC)		0.9341	0.8712	0.3378	0.6908	0.5001
			(pVC)			0.5286	0.0459	0.1437	0.0838

Organ	Tumor	R/C		Water Control	Vehicle Control	2 mg/kg/day	7 mg/kg/day	20 mg/kg/day	Trend
CERVIX	TOTAL EXAMINED		(N)	70	70	70	70	70	
	GRANULAR CELL TUMOR, BENIGN (B)	R	(a)	2	7	4	0	0	
			(pWC)		0.0373*	0.2630	1.0000	1.0000	0.9772
			(pVC)			0.7994	0.9971	0.9983	0.9996
GLAND, ADRENAL	TOTAL EXAMINED		(N)	70	70	70	70	70	
	PHEOCHROMOCYTOMA, MALIGNANT (M)	R	(a)	0	0	0	0	3	
			(pWC)		1.0000	1.0000	1.0000	0.1099	0.0077*
			(pVC)			1.0000	1.0000	0.0563	0.0057*
	PHEOCHROMOCYTOMA, MALIGNANT/BENIGN	C	(a)	0	2	1	1	3	
			(pWC)		0.2531	0.4634	0.4133	0.1099	0.0460
			(pVC)			0.8899	0.8770	0.3527	0.3297
GLAND, PITUITARY	TOTAL EXAMINED		(N)	70	70	70	70	70	
	ADENOMA (B)	C	(a)	52	49	54	53	52	
			(pWC)		0.9091	0.7064	0.7894	0.3777	0.4334
			(pVC)			0.1768	0.2878	0.0491	0.0682
LIVER	TOTAL EXAMINED		(N)	70	70	70	70	70	
	HEPATOCELLULAR ADENOMA (B)	R	(a)	0	0	0	0	2	
			(pWC)		1.0000	1.0000	1.0000	0.2297	0.0374*
			(pVC)			1.0000	1.0000	0.1356	0.0297*

(N) Number of animals examined
(a) Number of animals with tumor
(pWC) p-values: Listed under individual treatment group 1-sided pairwise comparison with water control
Listed under 'Trend': 1-sided trend test including water control and active treatment groups
(pVC) p-values: Listed under individual treatment group: 1-sided pairwise comparison with vehicle control
Listed under 'Trend': 1-sided trend test including vehicle control and active treatment groups
(B) - Benign (M) - Malignant
Statistical significance: Rare Tumor - $p \leq 0.05$ (Trend), $p \leq 0.05$ (Pairwise); Common Tumor - $p \leq 0.01$ (Trend), $p \leq 0.01$ (Pairwise)
* Statistically Significant at the defined significance level

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all five groups (Groups 1, 2, 3, 4, and 5) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 2, 3, 4, and 5 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female rats, respectively. The intercurrent mortality data of all five groups and the results of the tests for dose response relationship and homogeneity of survivals for Groups 2, 3, 4, and 5 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 24 (34%), 20 (29%), 21 (30%), 16 (23%), and 22 (31%) in the water control, the vehicle control, the low, mid, and high dose groups for male rats, respectively, and 19 (27%), 30 (43%), 24 (34%), 29 (41%), and 18 (26%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across the vehicle control group, and low, mid, and high dose groups, and pairwise comparisons of each of the three treated groups and the water control group against the vehicle control group, using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^* i is defined as $R^*_i = \sum W_{ij}$ where w_{ij} is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / tsacr)^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the *j*-th animal in the *i*-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij} = 1$ since t_{ij} = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as $w_{ij} = 1$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr, regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis

of this data.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one two-year study in one species and one short-term study with another species, in order to keep the overall false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control group, however, the guidance indicated that the corresponding multiple testing adjustment is still under development and not yet available. To be conservative, the test level of α=0.05 was used for pairwise comparisons of treated group with control group for both rare and common tumors in this study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-k tests.

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report. That is, if the number of animals bearing tumors in the vehicle control group is 0, then this tumor is considered as the rare tumor; otherwise, if the number of animals bearing tumors in the control group is greater than or equal to 1, then this tumor is considered as the common tumor.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 3.

Based on the criteria of adjustment for multiple testing discussed above, a statistically significant increase in the incidence of malignant pheochromocytoma in adrenal gland in male rats was noted in the water control group when comparing to the vehicle control group (p-value = 0.0252). A statistically significant increading trend across the vehicle control group and the three treated groups was noted in the incidence of malignant pheochromocytoma in adrenal gland in female rats (p-value = 0.0120) if this tumor is considered to be rare. No other statistically significant findings were noted in tumor data for both male and female rats.

Table 3: Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle control Group in Rats

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Male						
Gland, Thyroid	C-Cell Adenoma	3/70 (31)	2/70 (33)	3/70 (33)	7/69 (34)	8/70 (39)
		0.0386 @	0.8415	0.6938	0.1921	0.1832
Gland, Adrenal	Pheochromocytoma, Malignant	0/70 (30)	4/70 (33)	4/70 (33)	4/70 (33)	6/70 (38)
		0.1557	0.0687	0.0687	0.0687	0.0252 $
Female						
Gland, Adrenal	Pheochromocytoma, Malignant	0/70 (28)	0/70 (28)	0/70 (28)	3/70 (26)	0/70 (26)
		0.0120 $	NC	NC	0.1048	NC

[&] X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
NC = Not calculable.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 4, in each of these two experiments there were three treated groups, one water control, one vehicle control, and one positive control group. One hundred fourty transgenic hemizygous Tg.rasH2 mice of each sex were assigned randomly in size of 25 mice per group except for the positive control group which was consisted of 15 mice. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for both male and female mice, respectively. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The mice in the water control (Group 1), the vehicle control (Group 2), and the positive control group (Group 6) were administrated with RODI water, the vehicle [0.25% (w/v) Hydroxypropyl Methyl Cellulose (HPMC; 3500-5600 cP)/0.1% (w/v) TWEEN® 80 in RODI Water], and the citrate buffer vehicle, respectively, and handled for the same duration and in the same manner as the treated groups.

Table 4: Experimental Design in Mouse Study

Group No.	No. of Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	25	25	Water Control	0	0
2	25	25	Vehicle Control	0	0
3	25	25	AKB-6548 Low	5	5
4	25	25	AKB-6548 Mid	15	15
5	25	25	AKB-6548 High	50	50
6	15	15	Positive Control (NMU)	0	0

The same in-life procedures, observations, and measurements, laboratory evaluations, and terminal procedures applied to the rats were also applied to the mice.

3.1. Sponsor's analyses

Because the mouse study was conducted by the same testing facility as the rat study, the sponsor used the same methodologies that were used for the analyses of the rat survival and tumor data.

3.1.1. Survival analysis

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 25 (100%), 24 (96%), 25 (100%), and 25 (100%) in the water control, vehicle control, low, mid, and high groups for male mice, respectively, and 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 25 (100%) for female mice, respectively. The sponsor's analysis showed no statistically significant findings in survival rates for both male and female mice.

3.1.2. Tumor data analysis

Multiple testing adjustment:

The same multiple testing adjustment used in the rat study was used in the mouse study.

Sponsor's findings:

Table 5: Results of Statistical Analyses of Neoplastic Lesions from Sponsor's Report

Sex	Organ	Tumor	R/C		Water Control	Vehicle Control	5 mg/kg/day	15 mg/kg/day	50 mg/kg/day	Trend
M	LUNG	TOTAL EXAMINED		(N)	25	25	25	25	25	
		ADENOMA; BRONCHIOLAR; ALVEOLAR (B)	C	(a)	0	1	4	5	5	
				(pWC)		0.5000	0.0502	0.0251*	0.0251*	
				(pVC)			0.1616	0.0947	0.0947	0.0706
M	LUNG	TOTAL EXAMINED		(N)	25	25	25	25	25	
		CARCINOMA/ADENOMA BRONCHIOALVEOLAR	C	(a)	0	1	4	6	5	
				(pWC)		0.5000	0.0502	0.0111*	0.0251*	
				(pVC)			0.1616	0.0491*	0.0947	0.0600
M	SPLEEN	TOTAL EXAMINED		(N)	25	25	25	25	25	
		HEMANGIOSARCOMA (M)	C	(a)	1	1	0	2	4	
				(pWC)		0.7551	1.0000	0.5000	0.1743	
				(pVC)			1.0000	0.5000	0.1743	0.0413
F	HARDERIAN GLANDS	TOTAL EXAMINED		(N)	25	25	24	25	25	
		ADENOMA (B)	C	(a)	0	0	1	0	5	
				(pWC)		1.0000	0.4898	1.0000	0.0251*	
				(pVC)			0.5000	1.0000	0.0279*	0.0062*
F	HARDERIAN GLANDS	TOTAL EXAMINED		(N)	25	25	24	25	25	
		ADENOCARCINOMA/ADENOMA	C	(a)	0	0	1	0	6	
				(pWC)		1.0000	0.4898	1.0000	0.0111*	
				(pVC)			0.5000	1.0000	0.0127*	0.0018*

(N) Number of animals examined
(a) Number of animals with tumor
(pWC) p-values:
Listed under individual treatment group: 1-sided pairwise comparison with water control
Listed under 'Trend': 1-sided trend test including water control and active treatment groups
(pVC) p-values:
Listed under individual treatment group: 1-sided pairwise comparison with vehicle control
Listed under 'Trend': 1-sided trend test including vehicle control and active treatment groups
(B) - Benign (M) - Malignant
Statistical significance: Rare Tumor - $p \leq 0.05$ (trend), $p \leq 0.05$ (pairwise); Common Tumor - $p \leq 0.01$ (trend), $p \leq 0.05$ (pairwise)
* Statistically significant at the defined significance level

As indicated in the sponsor's report (Table 5), for male mice, there was a statistically significant increase in the incidence of adenoma bronchioalveolar, and the incidence of carcinoma/adenoma bronchioalveolar combination in lung when comparing the mid and high dose groups with the water control group. In addition, there was a significant increase in the incidence of carcinoma/adenoma bronchioalveolar combination in lung when comparing the mid dose group with the vehicle control group. For female mice, there were statistically significant increasing

trends in the incidence of adenoma, and adenocarcinoma/adenoma combination in harderian glands when compared to the vehicle control group. Additionally, the incidences of these tumors were significantly greater in the high dose group when compared with the water and vehicle control groups. There were no other statistically significant tumor findings among male and female mice.

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 25 (100%), 24 (96%), 25 (100%), and 25 (100%) in the water control, vehicle control, low, mid, and high groups for male mice, respectively, and 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 25 (100%) for female mice respectively. There were no statistically significant findings in mortality was noted for both male or female mice.

3.2.2. Tumor data analysis

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and 4B in the appendix for male and female mice, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 6.

Based on the criteria of adjustment for multiple testing discussed above, for the male mice, a statistically significant increading trend across the vehicle control group and the three treated groups were noted in the incidence of hemangiosarcoma in the whole body (p-value = 0.0083) regardless the tumor classification (rare or common), without corresponding statistically significant pairwise comparisons. Also, a statistically significant increase in the incidence of combined adenoma, bronchiolar, alveolar and carcinoma, bronchioalveolar in lung was noted in the mid dose group when comparing to the vehicle control group (p-value = 0.0491) regardless the tumor classification (rare or common).

For female mice, statistically significant increasing trends across the vehicle control group and the three treated groups were noted in the incidence of adenoma and combined adenoma and

adenocarcinoma in harderian gland (p-value = 0.0025 and 0.0006, respectively), along with the statistically significant increases in the high dose group when comparing to the vehicle control group (p-value = 0.0251 and 0.0111, respectively), regardless the tumor classification (rare or common).

No other statistically significant finding was noted in the reviewer's analysis for both male and female mice.

Table 6. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle control Group in Mice

		Water (W)	Vehicle (C)	Low (L)	Mid (M)	High (H)	Positive (P)
			0 mg	5 mg	15 mg	50 mg	
Organ name	Tumor name	P-C vs W	P-Trend	P-C vs L	P-C vs M	P-C vs H	P-C vs P
Male							
Lung	Adenoma, Bronchiolar, Alveolar/ Carcinoma, Bronchioalveolar	0/25 (25)	1/25 (25)	4/25 (24)	6/25 (25)	5/25 (25)	3/15 (8)
		0.5000	0.1508	0.1616	0.0491 $	0.0947	0.0359 $
Spleen	Hemangiosarcoma	1/25 (25)	1/25 (25)	0/25 (24)	2/25 (25)	4/25 (25)	2/15 (6)
		0.7551	0.0250 @	1.0000	0.5000	0.1743	0.0879
Whole Body	Hemangiosarcoma	1/25 (25)	1/25 (25)	0/25 (24)	2/25 (25)	5/25 (25)	2/15 (6)
		NC	0.0083 $	0.4898	0.5	0.0947	0.0879
Female							
Harderian Glands	Adenoma	0/25 (25)	0/25 (25)	1/24 (24)	0/25 (25)	5/25 (25)	3/15 (8)
		NC	0.0025 $	0.4898	NC	0.0251 $	0.0103 $
	Adenocarcinoma/Adenoma	0/25 (25)	0/25 (25)	1/24 (24)	0/25 (25)	6/25 (25)	3/15 (8)
		NC	0.0006 $	0.4898	NC	0.0111 $	0.0103 $

[&] X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
NC = Not calculable.
$ = Statistically significant in common tumor at 0.005 level for test of dose response relationship.
@ = Not statistically significant in common tumor at 0.01 level for test of pairwise comparisons;

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to determine the potential oncogenicity of AKB-6548, when given orally for a minimum of 104 weeks to rats, and 6 months to CByB6F1/Tg rasH2 hemizygous (transgenic) mice.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred and fifty rats of each sex were assigned randomly in size of 70 rats per group. The dose levels for the three treated groups were 2, 7, and 20 mg/kg/day for both male and female rats.

Low numbers of surviving animals due to age-related mortality resulted in early discontinuation of dose administration for Group 5 female rats (reaching 20 on Day 592, Week 85), and termination of all male rats (Day 652, Week 94) and female rats (Day 602, Week 86) due to the

number of surviving control animals (vehicle control for male rats and water control for female rats) reaching 20 animals on these days. Therefore, surviving male rats were euthanized as soon as practical beginning on Day 652, Weeks 94 through 95 and surviving female rats were euthanized beginning on Day 603, Weeks 87 through 90.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 24 (34%), 20 (29%), 21 (30%), 16 (23%), and 22 (31%) in the water control, the vehicle control, the low, mid, and high dose groups for male rats, respectively, and 19 (27%), 30 (43%), 24 (34%), 29 (41%), and 18 (26%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

In the reviewer's analysis, a statistically significant increase in the incidence of malignant pheochromocytoma in adrenal gland in male rats was noted in the water control group when comparing to the vehicle control group (p-value = 0.0252). A statistically significant increasing trend across the vehicle control group and the three treated groups was noted in the incidence of malignant pheochromocytoma in adrenal gland in female rats (p-value = 0.0120). No other statistically significant findings were noted in tumor data for both male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups, one water control, one vehicle control, and one positive control group. One hundred forty transgenic hemizygous Tg.rasH2 mice of each sex were assigned randomly in size of 25 mice per group except for the positive control group which was consisted of 15 mice. The dose levels for the three treated groups were 5, 15, and 50 mg/kg/day for both male and female mice, respectively.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 25 (100%), 25 (100%), 24 (96%), 25 (100%), and 25 (100%) in the water control, vehicle control, low, mid, and high groups for male mice, respectively, and 25 (100%), 24 (96%), 24 (96%), 25 (100%), and 25 (100%) for female mice respectively. There were no statistically significant findings in mortality was noted for both male and female mice.

In the reviewer's analysis, for the male mice, a statistically significant increading trend across the vehicle control group and the three treated groups were noted in the incidence of hemangiosarcoma in the whole body (p-value = 0.0083) regardless the tumor classification (rare or common), without corresponding statistically significant pairwise comparisons. Also, a statistically significant increase in the incidence of combined adenoma, bronchiolar, alveolar and carcinoma, bronchioalveolar in lung was noted in the mid dose group when comparing to the vehicle control group (p-value = 0.0491) regardless the tumor classification (rare or common). For female mice, statistically significant increasing trends across the vehicle control group and the three treated groups were noted in the incidence of adenoma and combined adenoma and adenocarcinoma in harderian gland (p-value = 0.0025 and 0.0006, respectively), along with the statistically significant increases in the high dose group when comparing to the vehicle control group (p-value = 0.0251 and 0.0111, respectively), regardless the tumor classification (rare or

common). No other statistically significant finding was noted in the reviewer's analysis for both male and female mice.

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5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle (VC)		Low (L)		Mid (M)		High (H)		Water (WC)	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	13	18.57	9	12.86	9	12.86	10	14.29	3	4.29
53 - 78	23	51.43	24	47.14	23	45.71	24	48.57	22	35.71
79 - 91	11	67.14	14	67.14	18	71.43	13	67.14	15	57.14
92 - 94	3	71.43	2	70.00	4	77.14	1	68.57	5	64.29
Accidental Death									1	1.43
Terminal sacrifice	20	28.57	21	30.00	16	22.86	22	31.43	24	34.29
Total	70		70		70		70		70	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High	Vehicle Control vs. Water
Dose-Response (Likelihood Ratio)	0.6787	0.6423	0.8967	0.5700	0.1442
Homogeneity (Log-Rank)	0.8844	0.6387	0.8956	0.5663	0.1386

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle (VC)		Low (L)		Mid (M)		High (H)		Water (WC)	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	10	14.29	8	11.43	9	12.86	10	14.29	7	10.00
53 - 78	23	47.14	26	48.57	26	50.00	34	62.86	35	60.00
79 - 86	6	55.71	12	65.71	5	57.14	7	72.86	9	72.86
Accidental Death	1	1.43			1	1.43	1	1.43		
Terminal sacrifice	30	42.86	24	34.29	29	41.43	18	25.71	19	27.14
Total	70		70		70		70		70	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High	Vehicle Control vs. Water
Dose-Response (Likelihood Ratio)	0.0714	0.5635	0.8785	0.0789	0.1187
Homogeneity (Log-Rank)	0.2373	0.5594	0.8773	0.0744	0.1143

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Bone, Femur	Osteosarcoma	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (32)	0/70 (36)
		0.2540	NC	NC	0.5161	NC
Brain	Ependymoma, Malignant	0/70 (30)	0/70 (32)	0/70 (32)	0/70 (32)	1/70 (36)
		NC	NC	NC	NC	0.5455
	Glioma, Malignant	0/70 (30)	1/70 (33)	1/70 (33)	2/70 (33)	1/70 (37)
		0.1288	0.5238	0.5238	0.2704	0.5522
	Granular Cell Tumor, Benign	1/70 (30)	0/70 (32)	0/70 (32)	0/70 (32)	0/70 (36)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Granular Cell Tumor, Malignant	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (32)	0/70 (36)
		0.2540	NC	NC	0.5161	NC
	Granular Cell Tumor, Benign/ Granular Cell Tumor, Malignant	1/70 (30)	0/70 (32)	0/70 (32)	1/70 (32)	0/70 (36)
		0.4450	1.0000	1.0000	0.7700	1.0000
	Meningioma, Malignant	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (33)	0/70 (36)
		0.2598	NC	NC	0.5238	NC
	Oligodendroglioma, Malignant	0/70 (30)	0/70 (32)	0/70 (32)	0/70 (32)	2/70 (37)
		NC	NC	NC	NC	0.3012
Eye	Melanoma, Benign	0/70 (30)	0/70 (32)	0/69 (31)	1/70 (32)	0/70 (36)
		0.2560	NC	NC	0.5161	NC
Gland, Adrenal	Cortical Adenoma	0/70 (30)	2/70 (33)	1/70 (32)	0/70 (32)	4/70 (37)
		0.7441	0.2704	0.5161	NC	0.0862
	Cortical Carcinoma	0/70 (30)	0/70 (32)	1/70 (32)	0/70 (32)	0/70 (36)
		0.5079	NC	0.5161	NC	NC
	Cortical Adenoma/ Cortical Carcinoma	0/70 (30)	2/70 (33)	2/70 (32)	0/70 (32)	4/70 (37)
		0.7510	0.2704	0.2623	NC	0.0862
	Pheochromocytoma, Benign	2/70 (30)	2/70 (33)	2/70 (32)	4/70 (33)	2/70 (36)
		0.1726	0.7291	0.7180	0.3831	0.7592
	Pheochromocytoma, Malignant	0/70 (30)	4/70 (33)	4/70 (33)	4/70 (33)	6/70 (38)
		0.1557	0.0687	0.0687	0.0687	0.0252 $
	Pheochromocytoma, Benign/ Pheochromocytoma, Malignant	2/70 (30)	6/70 (34)	6/70 (34)	8/70 (35)	8/70 (38)
		0.0849	0.1727	0.1727	0.0700	0.0916
Gland, Harderian	Adenoma	1/70 (30)	1/70 (33)	0/70 (32)	1/70 (33)	2/69 (36)
		0.5525	0.7773	1.0000	0.7773	0.5691
Gland, Mammary	Fibroadenoma	1/59 (25)	0/55 (24)	1/55 (25)	0/58 (25)	1/59 (30)
		0.7576	1.0000	NC	1.0000	0.7980

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Gland, Parathyroid	Adenoma	3/55 (26)	1/57 (27)	0/54 (26)	2/56 (27)	0/64 (33)
		0.5343	0.9489	1.0000	0.8364	1.0000
Gland, Pituitary	Adenoma	38/70 (51)	34/70 (51)	41/70 (55)	41/70 (55)	37/70 (54)
		0.3385	0.8614	0.5859	0.5859	0.8145
	Carcinoma	1/70 (30)	2/70 (33)	2/70 (33)	0/70 (32)	2/70 (36)
		0.8624	0.5363	0.5363	1.0000	0.5691
	Adenoma/Carcinoma	39/70 (52)	36/70 (52)	43/70 (56)	41/70 (55)	39/70 (55)
		0.4081	0.8090	0.5027	0.6085	0.7556
Gland, Prostate	Carcinoma	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (33)	1/70 (36)
		0.2598	NC	NC	0.5238	0.5455
	Fibrosarcoma	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (33)	0/70 (36)
		0.2598	NC	NC	0.5238	NC
Gland, Thyroid	C-Cell Adenoma	3/70 (31)	2/70 (33)	3/70 (33)	7/69 (34)	8/70 (39)
		0.0386 @	0.8415	0.6938	0.1921	0.1832
	C-Cell Carcinoma	1/70 (30)	0/70 (32)	2/70 (33)	2/69 (33)	2/70 (36)
		0.1839	1.0000	0.5363	0.5363	0.5691
	C-Cell Adenoma/ C-Cell Carcinoma	4/70 (31)	2/70 (33)	5/70 (34)	9/69 (35)	10/70 (40)
		0.0218	0.9154	0.5605	0.1598	0.1664
	Follicular Cell Adenoma	0/70 (30)	0/70 (32)	0/70 (32)	2/69 (33)	1/70 (36)
		0.0660	NC	NC	0.2704	0.5455
	Follicular Cell Carcinoma	1/70 (30)	1/70 (32)	1/70 (32)	1/69 (32)	0/70 (36)
		0.5299	0.7700	0.7700	0.7700	1.0000
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	1/70 (30)	1/70 (32)	1/70 (32)	3/69 (33)	1/70 (36)
		0.1260	0.7700	0.7700	0.3435	0.7972
Gland, Zymbals	Squamous Cell Carcinoma	0/67 (28)	1/65 (30)	0/58 (26)	0/67 (31)	1/65 (33)
		0.7565	0.5172	NC	NC	0.5410
Hemolymphoretic ular Tissue	Histiocytic Sarcoma	1/70 (30)	1/70 (32)	4/70 (34)	1/70 (33)	0/70 (36)
		0.5417	0.7700	0.2190	0.7773	1.0000
	Leukemia, Granulocytic	1/70 (31)	0/70 (32)	0/70 (32)	0/70 (32)	2/70 (36)
		1.0000	1.0000	1.0000	1.0000	0.5567
	Lymphoma, Malignant	0/70 (30)	4/70 (34)	1/70 (32)	2/70 (33)	4/70 (38)
		0.4287	0.0730	0.5161	0.2704	0.0906
Kidney	Carcinoma	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (33)	0/70 (36)
		0.2598	NC	NC	0.5238	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Large Intestine, Cecum	Granular Cell Tumor, Benign	0/70 (30)	1/70 (32)	1/70 (32)	0/70 (32)	0/70 (36)
		0.6380	0.5161	0.5161	NC	NC
Large Intestine, Rectum	Leiomyosarcoma	0/69 (30)	0/70 (32)	0/69 (32)	1/70 (33)	0/70 (36)
		0.2598	NC	NC	0.5238	NC
Liver	Hepatocellular Adenoma	0/70 (30)	0/70 (32)	1/70 (32)	0/70 (32)	0/70 (36)
		0.5079	NC	0.5161	NC	NC
	Hepatocellular Carcinoma	0/70 (30)	1/70 (32)	2/70 (32)	2/70 (33)	0/70 (36)
		0.1531	0.5161	0.2623	0.2704	NC
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	0/70 (30)	1/70 (32)	3/70 (33)	2/70 (33)	0/70 (36)
		0.1802	0.5161	0.1374	0.2704	NC
Lung	Bronchioloalveolar Adenoma	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (32)	0/70 (36)
		0.2540	NC	NC	0.5161	NC
	Bronchioloalveolar Carcinoma	0/70 (30)	0/70 (32)	1/70 (32)	0/70 (32)	0/70 (36)
		0.5079	NC	0.5161	NC	NC
	Bronchioloalveolar Adenoma/ Bronchioloalveolar Carcinoma	0/70 (30)	0/70 (32)	1/70 (32)	1/70 (32)	0/70 (36)
		0.1930	NC	0.5161	0.5161	NC
	Squamous Cell Carcinoma	1/70 (30)	0/70 (32)	0/70 (32)	0/70 (32)	0/70 (36)
		1.0000	1.0000	1.0000	1.0000	1.0000
Lymph Node, Mesenteric	Hemangioma	1/70 (30)	0/70 (32)	2/70 (33)	0/70 (32)	0/70 (36)
		0.6994	1.0000	0.5363	1.0000	1.0000
	Hemangiosarcoma	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (33)	0/70 (36)
		0.2598	NC	NC	0.5238	NC
	Hemangioma/Hemangiosarcoma	1/70 (30)	0/70 (32)	2/70 (33)	1/70 (33)	0/70 (36)
		0.3916	1.0000	0.5363	0.7773	1.0000
Pancreas	Acinar Adenoma	2/70 (31)	3/70 (33)	3/70 (33)	0/70 (32)	3/70 (37)
		0.9388	0.5302	0.5302	1.0000	0.5848
	Islet Cell Adenoma	2/70 (30)	1/70 (32)	6/70 (34)	3/70 (34)	4/70 (37)
		0.3057	0.8926	0.1727	0.5604	0.4422
	Islet Cell Carcinoma	0/70 (30)	2/70 (33)	2/70 (33)	2/70 (33)	3/70 (37)
		0.2356	0.2704	0.2704	0.2704	0.1622
	Islet Cell Adenoma/ Islet Cell Carcinoma	2/70 (30)	3/70 (33)	8/70 (35)	5/70 (34)	7/70 (38)
		0.1955	0.5461	0.0700	0.2685	0.1445

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Skin	Basal Cell Tumor, Malignant	0/70 (30)	0/70 (32)	1/70 (32)	0/70 (32)	0/70 (36)
		0.5079	NC	0.5161	NC	NC
	Fibroma	5/70 (32)	2/70 (33)	0/70 (32)	0/70 (32)	4/70 (37)
		0.9997	0.9522	1.0000	1.0000	0.8288
	Fibrosarcoma	1/70 (30)	0/70 (32)	1/70 (32)	1/70 (32)	0/70 (36)
		0.4023	1.0000	0.7700	0.7700	1.0000
	Fibroma/Fibrosarcoma	6/70 (32)	2/70 (33)	1/70 (32)	1/70 (32)	4/70 (37)
		0.9693	0.9759	0.9946	0.9946	0.8992
	Keratoacanthoma	3/70 (31)	3/70 (33)	1/70 (32)	0/70 (32)	2/70 (37)
		0.9857	0.6938	0.9472	1.0000	0.8720
	Squamous Cell Carcinoma	1/70 (30)	1/70 (32)	0/70 (32)	0/70 (32)	1/70 (36)
		0.9448	0.7700	1.0000	1.0000	0.7972
	Keratoacanthoma/ Squamous Cell Carcinoma	4/70 (32)	4/70 (33)	1/70 (32)	0/70 (32)	2/70 (37)
		0.9957	0.6634	0.9736	1.0000	0.9303
	Lipoma	0/70 (30)	1/70 (32)	0/70 (32)	0/70 (32)	0/70 (36)
		0.7619	0.5161	NC	NC	NC
	Papilloma	2/70 (30)	0/70 (32)	2/70 (32)	0/70 (32)	1/70 (37)
		0.8234	1.0000	0.7180	1.0000	0.9152
	Schwannoma, Malignant	1/70 (30)	0/70 (32)	0/70 (32)	1/70 (32)	1/70 (36)
		0.4450	1.0000	1.0000	0.7700	0.7972
	Sebaceous Cell Adenoma	0/70 (30)	0/70 (32)	1/70 (32)	0/70 (32)	1/70 (36)
		0.5079	NC	0.5161	NC	0.5455
Stomach	Leiomyosarcoma	0/70 (30)	0/70 (32)	0/70 (32)	0/70 (32)	1/70 (36)
		NC	NC	NC	NC	0.5455
	Papilloma	0/70 (30)	0/70 (32)	0/70 (32)	1/70 (33)	0/70 (36)
		0.2598	NC	NC	0.5238	NC
Testis	Interstitial (Leydig) Cell Adenoma	0/70 (30)	1/70 (33)	1/70 (32)	0/70 (32)	1/70 (36)
		0.6359	0.5238	0.5161	NC	0.5455
	Seminoma, Benign	0/70 (30)	0/70 (32)	0/70 (32)	0/70 (32)	1/70 (36)
		NC	NC	NC	NC	0.5455
Thymus	Squamous Cell Carcinoma	1/64 (28)	0/70 (32)	0/69 (31)	0/66 (31)	0/69 (35)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Thymoma, Malignant	0/64 (27)	0/70 (32)	0/69 (31)	0/66 (31)	1/69 (36)
		NC	NC	NC	NC	0.5714

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Brain	Granular Cell Tumor, Benign	0/70 (28)	1/70 (29)	0/70 (28)	0/70 (25)	0/70 (26)
		0.7455	0.5088	NC	NC	NC
	Meningioma, Benign	0/70 (28)	1/70 (29)	0/70 (28)	0/70 (25)	0/70 (26)
		0.7455	0.5088	NC	NC	NC
Cervix	Granular Cell Tumor, Benign	7/70 (32)	4/70 (30)	0/70 (28)	0/70 (25)	2/70 (27)
		0.9999	0.8879	1.0000	1.0000	0.9752
	Granular Cell Tumor, Malignant	0/70 (28)	0/70 (28)	1/70 (28)	0/70 (25)	0/70 (26)
		0.4862	NC	0.5000	NC	NC
	Granular Cell Tumor, Benign/ Granular Cell Tumor, Malignant	7/70 (32)	4/70 (30)	1/70 (28)	0/70 (25)	2/70 (27)
		0.9994	0.8879	0.9959	1.0000	0.9752
Gland, Adrenal	Cortical Adenoma	4/70 (30)	4/70 (31)	3/70 (29)	4/70 (26)	5/70 (28)
		0.3912	0.6653	0.7740	0.5619	0.4543
	Cortical Carcinoma	1/70 (28)	0/70 (28)	0/70 (28)	1/70 (25)	0/70 (26)
		0.4077	1.0000	1.0000	0.7257	1.0000
	Cortical Adenoma/ Cortical Carcinoma	5/70 (30)	4/70 (31)	3/70 (29)	5/70 (27)	5/70 (28)
		0.3401	0.7802	0.8620	0.5636	0.5885
	Pheochromocytoma, Benign	2/70 (29)	1/70 (29)	1/70 (28)	0/70 (25)	0/70 (26)
		0.9121	0.8816	0.8751	1.0000	1.0000
	Pheochromocytoma, Malignant	0/70 (28)	0/70 (28)	0/70 (28)	3/70 (26)	0/70 (26)
		0.0120 $	NC	NC	0.1048	NC
	Pheochromocytoma, Benign/ Pheochromocytoma, Malignant	2/70 (29)	1/70 (29)	1/70 (28)	3/70 (26)	0/70 (26)
		0.1703	0.8816	0.8751	0.4470	1.0000
Gland, Mammary	Adenocarcinoma	19/70 (38)	12/70 (35)	15/70 (37)	11/70 (31)	13/70 (34)
		0.7866	0.9449	0.8542	0.9275	0.8928
	Adenoma	4/70 (30)	5/70 (31)	7/70 (31)	7/70 (29)	5/70 (29)
		0.1471	0.5217	0.2733	0.2329	0.4776
	Adenocarcinoma/Adenoma	21/70 (39)	16/70 (37)	19/70 (38)	16/70 (34)	16/70 (36)
		0.5989	0.8758	0.7141	0.7919	0.8519
	Carcinosarcoma	2/70 (29)	1/70 (29)	0/70 (28)	0/70 (25)	0/70 (26)
		0.9835	0.8816	1.0000	1.0000	1.0000
	Fibroadenoma	24/70 (40)	29/70 (43)	22/70 (39)	19/70 (35)	28/70 (43)
		0.8195	0.3168	0.7093	0.7682	0.3995
Gland, Parathyroid	Adenoma	1/48 (20)	1/65 (27)	0/62 (25)	0/59 (21)	1/59 (23)
		0.9556	0.8242	1.0000	1.0000	0.7896

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Gland, Pituitary	Adenoma	49/70 (57)	54/70 (61)	53/70 (60)	52/70 (59)	52/70 (59)
		0.4357	0.4434	0.4571	0.4711	0.4711
	Carcinoma	2/70 (29)	1/70 (29)	1/70 (28)	4/70 (28)	2/70 (27)
		0.0845	0.8816	0.8751	0.3180	0.6667
	Adenoma/Carcinoma	51/70 (59)	55/70 (61)	54/70 (61)	56/70 (62)	54/70 (60)
		0.3338	0.3631	0.4721	0.3509	0.3756
Gland, Thyroid	C-Cell Adenoma	6/70 (31)	6/70 (31)	1/70 (28)	2/70 (26)	5/70 (28)
		0.9415	NC	0.9923	0.9539	0.6833
	C-Cell Carcinoma	0/70 (28)	0/70 (28)	0/70 (28)	1/70 (25)	3/70 (28)
		0.2294	NC	NC	0.4717	0.1182
	C-Cell Adenoma/ C-Cell Carcinoma	6/70 (31)	6/70 (31)	1/70 (28)	3/70 (27)	8/70 (30)
		0.8554	NC	0.9923	0.8914	0.3543
	Follicular Cell Adenoma	1/70 (28)	0/70 (28)	1/70 (28)	1/70 (25)	1/70 (26)
		0.3627	1.0000	NC	0.7257	0.7358
	Follicular Cell Carcinoma	1/70 (28)	0/70 (28)	0/70 (28)	0/70 (25)	1/70 (27)
		1.0000	1.0000	1.0000	1.0000	0.7455
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	2/70 (29)	0/70 (28)	1/70 (28)	1/70 (25)	2/70 (27)
		0.5261	1.0000	0.8751	0.8527	0.6667
Hemolymphoreticular Tissue	Histiocytic Sarcoma	1/70 (28)	0/70 (28)	0/70 (28)	0/70 (25)	1/70 (26)
		1.0000	1.0000	1.0000	1.0000	0.7358
	Lymphoma, Malignant	0/70 (28)	1/70 (29)	0/70 (28)	1/70 (25)	3/70 (28)
		0.2877	0.5088	NC	0.4717	0.1182
Kidney	Adenoma	0/70 (28)	0/70 (28)	1/70 (29)	0/70 (25)	1/70 (27)
		0.4909	NC	0.5088	NC	0.4909
	Lipoma	0/70 (28)	0/70 (28)	1/70 (28)	0/70 (25)	0/70 (26)
		0.4862	NC	0.5000	NC	NC
Large Intestine, Rectum	Granular Cell Tumor, Benign	1/70 (28)	0/70 (28)	0/70 (28)	1/70 (25)	0/69 (25)
		0.4077	1.0000	1.0000	0.7257	1.0000
Liver	Hepatocellular Adenoma	0/70 (28)	0/70 (28)	0/70 (28)	2/70 (26)	0/70 (26)
		0.0542	NC	NC	0.2271	NC
Lymph Node, Mesenteric	Hemangiosarcoma	0/69 (27)	1/70 (29)	0/70 (28)	0/70 (25)	0/70 (26)
		0.7523	0.5179	NC	NC	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Ovary	Granulosa Cell Tumor, Malignant	0/70 (28) NC	0/70 (28) NC	0/70 (28) NC	0/70 (25) NC	1/70 (26) 0.4815
	Hemangiosarcoma	0/70 (28) NC	0/70 (28) NC	0/70 (28) NC	0/70 (25) NC	1/70 (27) 0.4909
	Mixed Sex Cord Stromal Tumor, Benign	1/70 (28) 1.0000	0/70 (28) 1.0000	0/70 (28) 1.0000	0/70 (25) 1.0000	0/70 (26) 1.0000
	Thecoma, Malignant	0/70 (28) 0.7455	1/70 (29) 0.5088	0/70 (28) NC	0/70 (25) NC	0/70 (26) NC
Pancreas	Acinar Adenoma	0/70 (28) 0.2294	0/70 (28) NC	0/70 (28) NC	1/70 (25) 0.4717	0/70 (26) NC
	Islet Cell Adenoma	2/70 (29) 0.8644	0/70 (28) 1.0000	1/70 (28) 0.8751	0/70 (25) 1.0000	2/70 (27) 0.6667
	Islet Cell Carcinoma	0/70 (28) 0.2294	0/70 (28) NC	0/70 (28) NC	1/70 (25) 0.4717	0/70 (26) NC
	Islet Cell Adenoma/ Islet Cell Carcinoma	2/70 (29) 0.5261	0/70 (28) 1.0000	1/70 (28) 0.8751	1/70 (25) 0.8527	2/70 (27) 0.6667
Skin	Basal Cell Tumor, Malignant	0/70 (28) 0.7455	1/70 (29) 0.5088	0/70 (28) NC	0/70 (25) NC	0/70 (26) NC
	Fibrosarcoma	1/70 (28) 1.0000	0/70 (28) 1.0000	0/70 (28) 1.0000	0/70 (25) 1.0000	0/70 (26) 1.0000
	Keratoacanthoma	0/70 (28) 0.7455	1/70 (29) 0.5088	0/70 (28) NC	0/70 (25) NC	1/70 (27) 0.4909
	Schwannoma, Malignant	0/70 (28) 0.7455	1/70 (29) 0.5088	0/70 (28) NC	0/70 (25) NC	0/70 (26) NC
Stomach	Papilloma	0/70 (28) NC	0/70 (28) NC	0/69 (28) NC	0/70 (25) NC	1/70 (26) 0.4815
Thymus	Thymoma, Malignant	0/68 (26) NC	0/66 (27) NC	0/69 (28) NC	0/67 (24) NC	1/68 (25) 0.4902

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 7 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Uterus	Endometrial Stromal Polyp	3/70 (29)	3/70 (30)	3/70 (29)	2/70 (26)	3/70 (28)
		0.6352	0.6811	NC	0.7883	0.6479
	Endometrial Stromal Sarcoma	0/70 (28)	0/70 (28)	1/70 (29)	1/70 (26)	0/70 (26)
		0.1767	NC	0.5088	0.4815	NC
	Endometrial Stromal Polyp/ Endometrial Stromal Sarcoma	3/70 (29)	3/70 (30)	4/70 (30)	3/70 (27)	3/70 (28)
		0.4487	0.6811	0.5196	0.6299	0.6479
	Granular Cell Tumor, Benign	1/70 (28)	1/70 (29)	1/70 (28)	0/70 (25)	0/70 (26)
		0.8154	0.7632	NC	1.0000	1.0000
	Granular Cell Tumor, Malignant	1/70 (28)	0/70 (28)	0/70 (28)	0/70 (25)	0/70 (26)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Granular Cell Tumor, Benign/ Granular Cell Tumor, Malignant	2/70 (29)	1/70 (29)	1/70 (28)	0/70 (25)	0/70 (26)
		0.9121	0.8816	0.8751	1.0000	1.0000
Vagina	Granular Cell Tumor, Benign	1/70 (28)	0/70 (28)	1/70 (28)	0/70 (25)	0/70 (26)
		0.7384	1.0000	NC	1.0000	1.0000
Uterus/Vagina	Granular Cell Tumor, Benign/ Granular Cell Tumor, Malignant	3/70 (29)	1/70 (29)	2/70 (29)	0/70 (25)	0/70 (26)
		0.9249	0.9440	0.8238	1.0000	1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

	0 mg/kg/day Vehicle Control		5 mg/kg/day Low		15 mg/kg/day Mid		50 mg/kg/day High		Water Control		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13			1	4.00								
14 - 27											13	86.67
Terminal sacrifice	25	100.00	24	96.00	25	100.00	25	100.00	25	100.00	2	13.33
Total	25		25		25		25		25		15	

Test	All Dose Groups	Vehicle vs. Low	Vehicle vs. Mid	Vehicle vs. High	Vehicle vs. Water Control	Vehicle vs. Positive Control
Dose-Response (Likelihood Ratio)	0.4373	0.2390	NC	NC	NC	<.0001**
Homogeneity (Log-Rank)	0.3916	0.3173	NC	NC	NC	<.0001**

#All Cum. % Cumulative Percentage except for Terminal sacrifice.

* = Significant at 5% level; ** = Significant at 1% level.

Table 3B: Intercurrent Mortality Rate in Female Mice

	0 mg/kg/day Vehicle Control		5 mg/kg/day Low		15 mg/kg/day Mid		50 mg/kg/day High		Water Control		Positive Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13											2	13.33
14 - 27	1	4.00	1	4.00							11	86.67
Terminal sacrifice	24	96.00	24	96.00	25	100.00	25	100.00	25	100.00	2	13.33
Total	25		25		25		25		25		15	

Test	All Dose Groups	Vehicle vs. Low	Vehicle vs. Mid	Vehicle vs. High	Vehicle vs. Water	Vehicle vs. Positive
Dose-Response (Likelihood Ratio)	0.1335	0.9885	0.2390	0.2390	0.2390	<.0001**
Homogeneity (Log-Rank)	0.5681	0.9885	0.3173	0.3173	0.3173	<.0001**

#All Cum. % Cumulative Percentage except for Terminal sacrifice.

* = Significant at 5% level; ** = Significant at 1% level.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Water (W) P-C vs W	Vehicle (C) 0 mg P-Trend	Low (L) 5 mg P-C vs L	Mid (M) 15 mg P-C vs M	High (H) 50 mg P-C vs H	Positive (P) P-C vs P
Harderian Glands	Adenocarcinoma	2/25 (25)	0/25 (25)	1/25 (24)	0/25 (25)	0/25 (25)	0/15 (6)
		0.2449	0.5051	0.4898	NC	NC	NC
	Adenoma	0/25 (25)	1/25 (25)	0/25 (24)	2/25 (25)	0/25 (25)	0/15 (6)
		1.0000	0.6473	1.0000	0.5000	1.0000	1.0000
	Adenocarcinoma/Adenoma	2/25 (25)	1/25 (25)	1/25 (24)	2/25 (25)	0/25 (25)	0/15 (6)
		0.5000	0.7974	0.7449	0.5000	0.5000	0.1935
Intestine-Large, Cecum	Adenocarcinoma	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	2/13 (5)
		NC	NC	NC	NC	NC	0.0230 $
Intestine-Small, Ileum	Adenoma	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	1/11 (5)
		NC	NC	NC	NC	NC	0.1667
Lung	Adenoma, Bronchiolar, Alveolar	0/25 (25)	1/25 (25)	4/25 (24)	5/25 (25)	5/25 (25)	3/15 (8)
		1.0000	0.1362	0.1616	0.0947	0.0947	0.0359 $
	Carcinoma, Bronchioalveolar	0/25 (25)	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (25)	0/15 (6)
		NC	0.2525	NC	0.5000	NC	NC
	Adenoma, Bronchiolar, Alveolar/ Carcinoma, Bronchioalveolar	0/25 (25)	1/25 (25)	4/25 (24)	6/25 (25)	5/25 (25)	3/15 (8)
		0.5000	0.1508	0.1616	0.0491 $	0.0947	0.0359 $
Salivary Gland	Carcinoma, Squamous Cell	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	1/14 (6)
		NC	NC	NC	NC	NC	0.1935
Spleen	Hemangiosarcoma	1/25 (25)	1/25 (25)	0/25 (24)	2/25 (25)	4/25 (25)	2/15 (6)
		0.7551	0.0250 @	1.0000	0.5000	0.1743	0.0879
Stomach	Carcinoma, Squamous Cell	0/25 (25)	0/25 (25)	1/25 (25)	1/25 (25)	0/25 (25)	2/15 (7)
		NC	0.5000	0.5000	0.5000	NC	0.0423 $
	Papilloma Squamous Cell	1/25 (25)	0/25 (25)	0/25 (24)	1/25 (25)	1/25 (25)	10/15 (12)
		0.5000	0.1907	NC	0.5000	0.5000	0.0000 $
Testes	Hemangiosarcoma	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/25 (25)	0/15 (6)
		NC	0.2525	NC	NC	0.5000	NC
Whole Body	Hemangiosarcoma	1/25 (25)	1/25 (25)	0/25 (24)	2/25 (25)	5/25 (25)	2/15 (6)
		NC	0.0083 $	0.4898	0.5	0.0947	0.0879

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Water (W) P-C vs W	Vehicle (C) 0 mg P-Trend	Low (L) 5 mg P-C vs L	Mid (M) 15 mg P-C vs M	High (H) 50 mg P-C vs H	Positive (P) P-C vs P
Harderian Glands	Adenocarcinoma	0/25 (25) NC	0/25 (25) 0.2525	0/24 (24) NC	0/25 (25) NC	1/25 (25) 0.5000	0/15 (7) NC
	Adenoma	0/25 (25) NC	0/25 (25) 0.0025 $	1/24 (24) 0.4898	0/25 (25) NC	5/25 (25) 0.0251 $	3/15 (8) 0.0103 $
	Adenocarcinoma/Adenoma	0/25 (25) NC	0/25 (25) 0.0006 $	1/24 (24) 0.4898	0/25 (25) NC	6/25 (25) 0.0111 $	3/15 (8) 0.0103 $
Lung	Adenoma, Bronchiolar, Alveolar	1/25 (25) 0.7551	1/25 (25) 0.6775	3/25 (25) 0.3046	3/25 (25) 0.3046	1/25 (25) 0.7551	3/15 (8) 0.0359 $
Lymph Node, Mesenteric	Adenocarcinoma, Metastatic	0/23 (23) NC	0/20 (20) NC	0/22 (22) NC	0/24 (24) NC	0/24 (24) NC	2/11 (6) 0.0462 $
Ovaries	Adenocarcinoma, Tubulostromal	0/24 (24) NC	0/24 (24) NC	0/24 (24) NC	0/23 (23) NC	0/25 (25) NC	1/13 (7) 0.2258
Spleen	Hemangiosarcoma	0/25 (25) 1.0000	2/25 (25) 0.3516	0/25 (25) 1.0000	4/25 (25) 0.3336	2/25 (25) 0.6954	0/15 (7) 1.0000
Stomach	Carcinoma, Squamous Cell	0/25 (25) NC	0/24 (24) NC	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	2/15 (8) 0.0565
	Papilloma Squamous Cell	0/25 (25) 1.0000	1/24 (24) 0.7576	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	13/15 (13) 0.0000 $
Uterus	Hemangiosarcoma	0/25 (25) NC	0/25 (25) 0.5000	1/25 (25) 0.5000	0/25 (25) NC	0/25 (25) NC	2/15 (8) 0.0530
Vagina	Hemangiosarcoma	0/24 (24) NC	0/24 (24) NC	0/24 (24) NC	0/25 (25) NC	0/25 (25) NC	1/15 (8) 0.2500
Whole Body	Hemangiosarcoma	0/25 (25) 1.0000	2/25 (25) 0.3516	1/25 (25) 0.5000	4/25 (25) 0.3336	2/25 (25) NC	2/15 (8) 0.2412

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

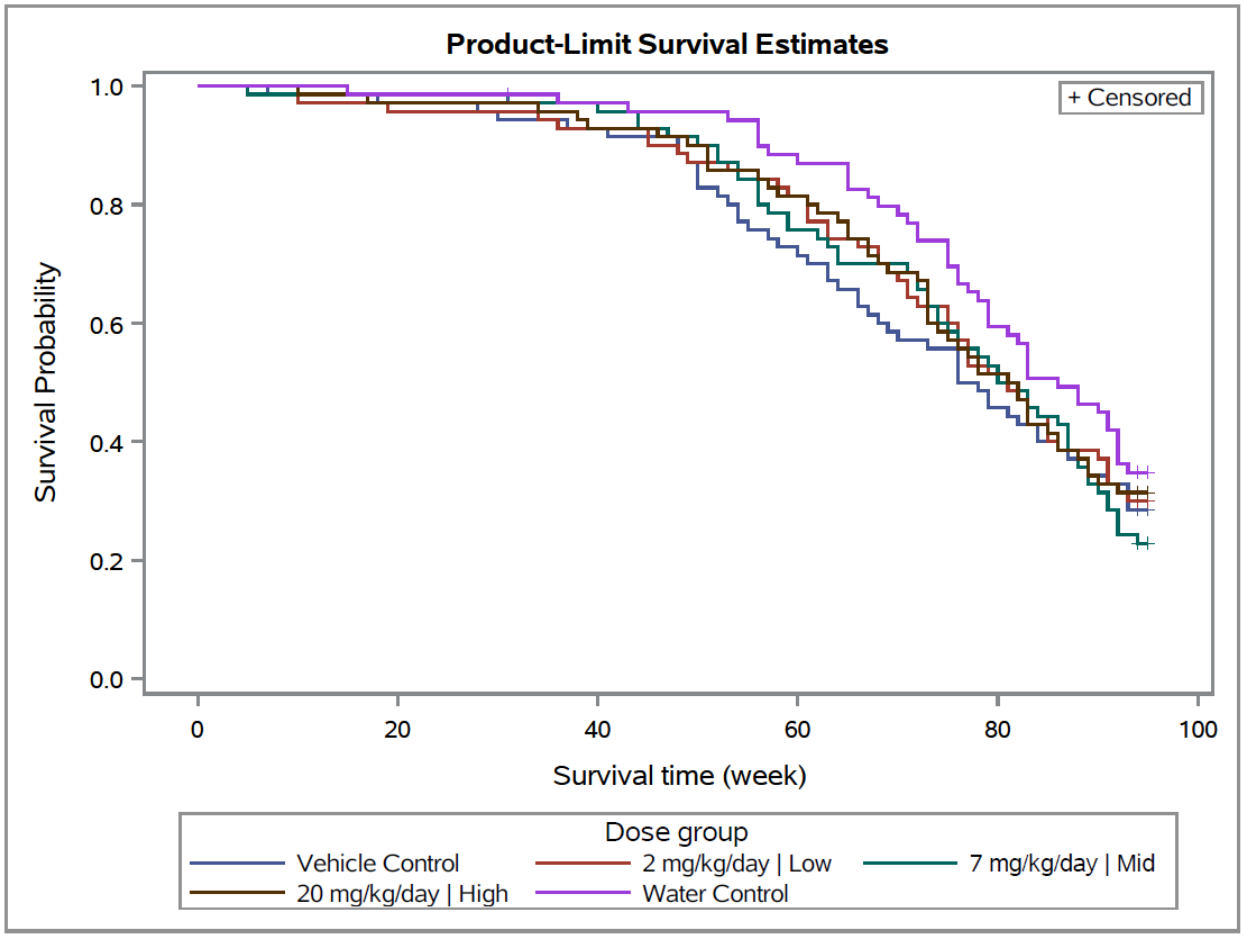


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

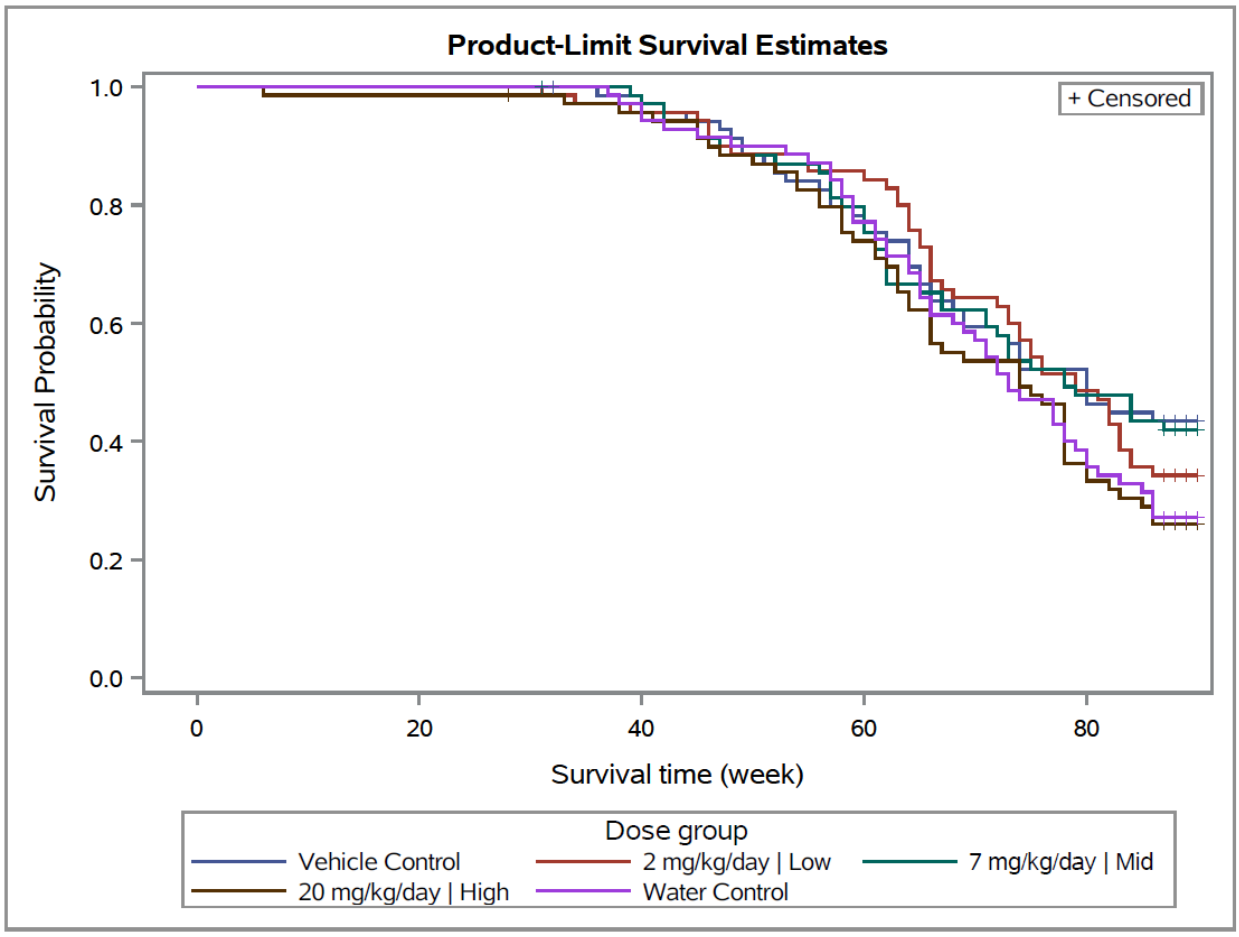


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

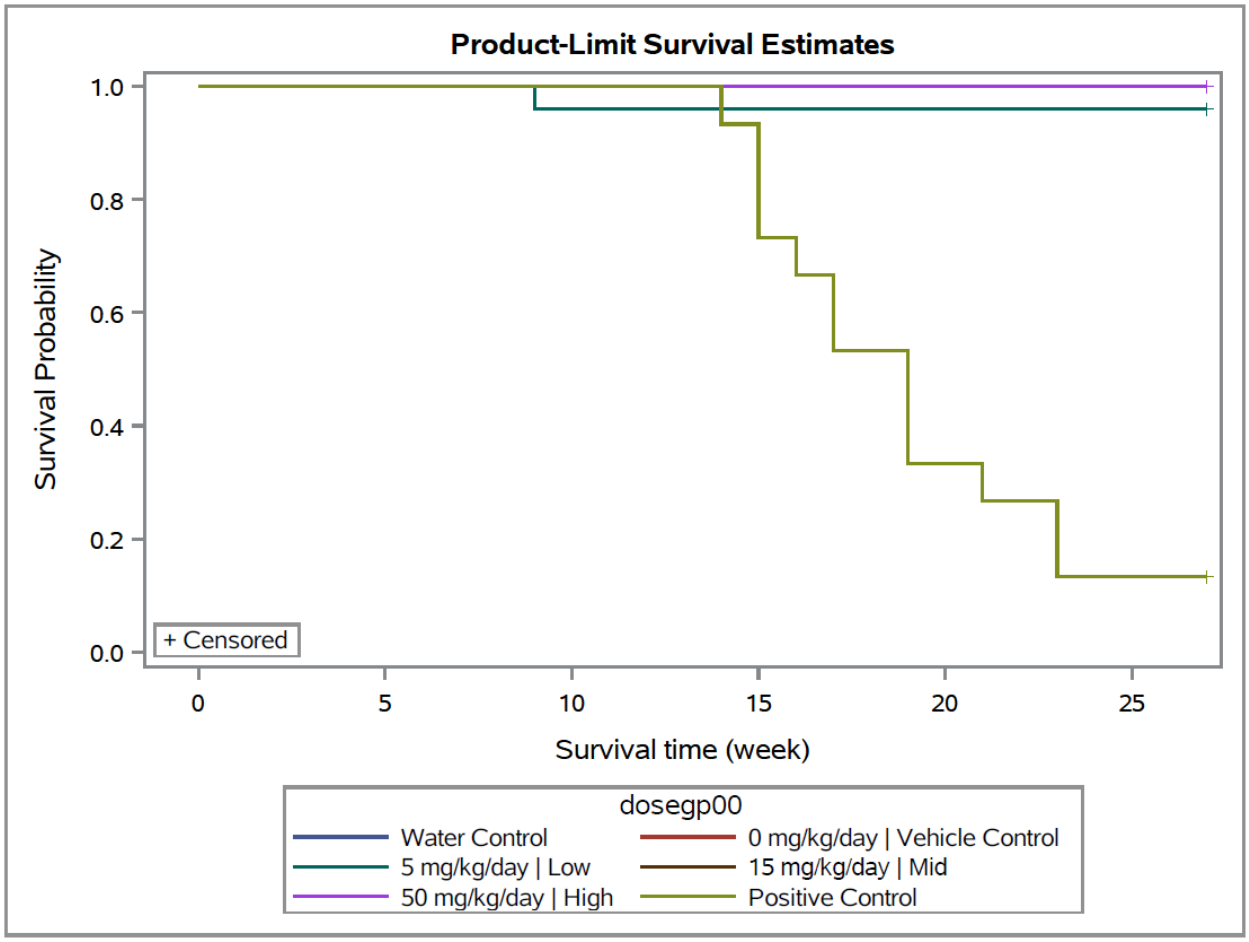
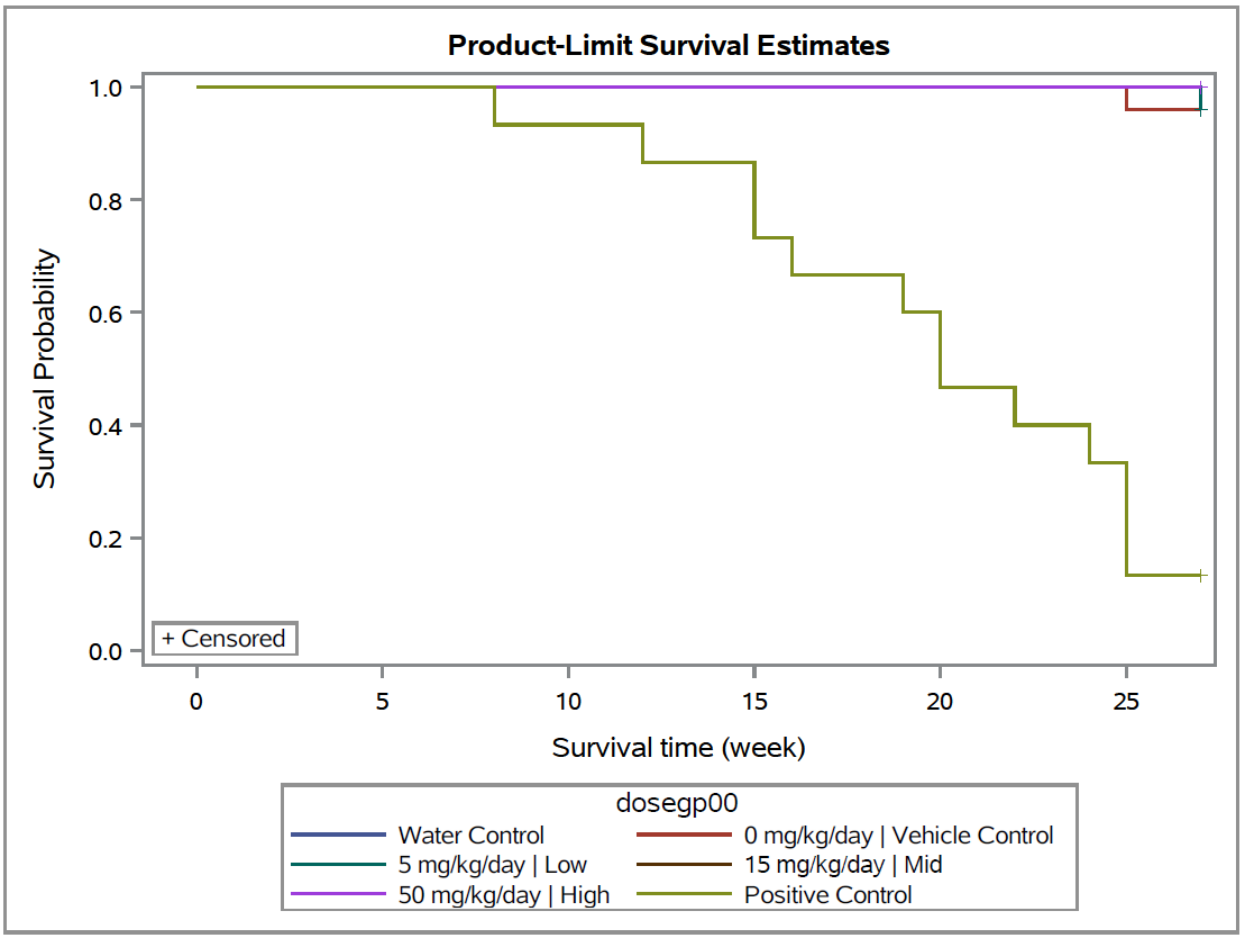


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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