CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	3/26/2024
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OSE Sentinel Team Leader:	Sarah Dutcher, PhD Regulatory Science Staff
Subject:	ARIA Sufficiency Memo for Safety Concerns: Thrombotic vascular events, hospitalization for heart failure, and serious gastrointestinal bleeds
Drug Name:	Vadadustat (VAFSEO®)
Application Type/Number:	NDA 215192
Applicant/sponsor:	Akebia Therapeutics
TTT #:	2023-6571

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type			
-Final		X	
Source of safety concern			
-Peri-approval		X	
-Post-approval			
Is ARIA sufficient to help characterize the safety concern?			
-Yes			
-No		X	
If "No", please identify the area(s) of concern.	Thrombotic vascular events	Hospitalization for heart failure	Serious gastrointestinal bleeding
-Surveillance or Study Population			
-Exposure			
-Outcome(s) of Interest			
-Covariate(s) of Interest	X	X	X
-Surveillance Design/Analytic Tools			

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Vadadustat is an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis. In pivotal phase-3 trials, vadadustat demonstrated non-inferiority to darbepoetin alfa in raising and maintaining hemoglobin (Hb) up to a treatment period of at least 52 weeks. Vadadustat provides convenience of an oral treatment option over erythropoiesis stimulating agent (ESA) injections which are considered the current standard therapy for the treatment of anemia in patients with CKD.

Daprodustat (Jesduvrop®) is currently the only FDA-approved HIF-PH-based oral therapy. Daprodustat was approved in 2023 for the treatment of anemia due to CKD in adults who have been receiving dialysis for at least four months.

1.2. Describe the Safety Concern

Specific safety concerns of vadadustat identified during the NDA review that need to be addressed in this PMR are thrombotic vascular events including vascular access thrombosis (VAT), hospitalization for heart failure, and serious gastrointestinal bleeds. Of note, all these safety signals are also included in the risk management programs for daprodustat.

1) Thrombotic vascular events including vascular access thrombosis

A concerning signal of thromboembolic (TE) events was identified in the safety analysis of vadadustat pivotal study data with the risk driven by vascular access thrombosis (VAT) that constituted 80% of adjudicated TE events (Hazard Ratio [HR] =1.28, 95% confidence interval [CI]: 1.00-1.63 comparing vadadustat with ESA). It was also noted that the HR for VAT in U.S. patients was higher (HR=1.58, 95% CI: 1.19-2.10) than the HR in the overall study population.[a] Akebia (the Applicant) conducted additional analyses demonstrating that serious consequences of VAT such as dialysis access abandonment and need for revascularization procedures were observed in similar rates in the vadadustat versus darbepoetin alfa arms. Overall, the review team concludes there are increased risks of overall TE events and specifically VAT with vadadustat, however, these risks can be adequately managed with labeling. At this point, the label of vadadustat will include a boxed warning for increased risk of death, arterial and venous thrombotic events.

- "*VAFSEO increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE). Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial and venous thrombotic events, as occurs with erythropoietin stimulating agents (ESAs), which also increase erythropoietin levels.*"

2) Hospitalization for heart failure

Based on FDA's statistical review, the incidence rate of heart failure resulting in hospitalization was 2.68 and 2.81 per 100 person-years (PYs) in the vadadustat and darbepoetin alfa arms, respectively. Thus, the estimated incidence rate difference (IRD) and hazard ratio (HR) was -

[a] Peter Stein. Formal Dispute Resolution Appeal. May 26, 2023. NDA 215192 DARRTS Reference # 5180576.

0.13 (95% CI: -0.95-0.69) and 0.97 (95% CI: 0.72-1.31), respectively.[b] 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. Although heart failure occurred at lower rates in the vadadustat group compared to the darbepoetin alfa group, however, the safety signal has been identified in other approved HIF-PHIs. In addition, the review team believes that there are limited long-term safety data for the development program, therefore the long-term risk of heart failure needs to be assessed in a PMR, as the drug may be administered life-long for this chronic disease.

3) Serious gastrointestinal bleeds

The statistical reviewer (Dr. Joo-Yeon Lee) stated in her review dated February 23, 2024 "In the INNO2VATE trials narrowly defined gastrointestinal erosion events occurred more frequently in the vadadustat arm than the darbepoetin arm (3.8 per 100 PY versus 3.2 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 reviewer also stated "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)." The clinical reviewer recommended that the long-term risk of gastric erosions needs to be assessed in a PMR.

1.3 FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4 Statement of Purpose

The purpose of the memorandum is to discuss the sufficiency of FDA's ARIA system to characterize the long-term (up to 5 years follow-up) safety of vadadustat to treat anemia due to CKD in adult patients on dialysis in the U.S. Specific safety concerns of interest are thrombotic vascular events including VAT; hospitalization for heart failure; and serious gastrointestinal bleeds. The effect of baseline and maximum achieved Hb on the specified safety outcomes should be evaluated. Finally, the regulatory goal for this PMR is signal refinement.[c]

1.5 Effect Size of Interest or Estimated Sample Size Desired

We note that the preapproval safety analysis set includes 3,049 CKD patients on dialysis (n=1,525 in the vadadustat arm; n=1,524 in the darbepoetin alfa arm). The U.S. subgroup consists of 1,873 CKD patients on dialysis (n=942 in the vadadustat arm; n=931 in the darbepoetin alfa arm). It seems reasonable to aim for exceeding the sample size in the safety database, though setting a precise requirement for the number of exposed subjects needed would be speculative.

[b] Joo-Yeon Lee. Statistical review for NDA 215192/S-046. February 23, 2024. Reference ID: 5334607.
[c] McClure DL, et al. Mini-Sentinel methods: framework for assessment of positive results from signal refinement. Pharmacoepidemiol Drug Saf. 2014 Jan;23(1):3-8.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population should include adult patients with anemia due to CKD who are on dialysis, with or without previous treatment with an ESA or daprodustat.

2.2 Is ARIA sufficient to assess the intended population?

Yes. The ICD-10-CM code D63.1 and CPT codes 90935-90999 can be used in combination to identify dialysis-dependent CKD patients in EHRs or insurance claims. Previous validation studies have shown that coding algorithms for identifying CKD patients on chronic dialysis have a good sensitivity and positive predictive value (PPV).[d,e]

Currently in the U.S., most CKD patients receive their dialysis service from one of the outpatient facilities such as DaVita or Fresenius. For these large dialysis clinics, the Sentinel data partners will receive the billing claims for the dialysis service provided by DaVita or similar dialysis centers.

3. EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is vadadustat. National Drug Codes (NDC) available in ARIA can be used to ascertain vadadustat prescriptions.

3.2 Comparator Exposure(s)

For the proposed PMR, an active treatment with similar indication (e.g., daprodustat, ESAs) should be selected as the comparator.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. The Healthcare Common Procedure Coding System (J codes) and the NDC codes that are available in ARIA's administrative claims and electronic health records (EHR) data are sufficient for defining exposure to vadadustat or daprodustat or ESAs.

4 OUTCOME(S)

4.1 Outcomes of Interest

The safety outcomes of interest are thrombotic vascular events including VAT; hospitalization for heart failure; and serious gastrointestinal bleeds.

4.2 Is ARIA sufficient to assess the outcome of interest?

Yes. Thrombotic vascular events including VAT may lead to missed dialysis sessions. Ideally, these conditions should be treated immediately to ensure continued dialysis. For example, initiation of anticoagulants or catheter placement within a narrow period of time of VAT are generally indicative of the presence of complications related to the vascular access. Although we cannot find existing studies that could inform the performance of claims-based coding algorithms to help identify DD-CKD patients with VAT, we anticipate the positive predictive

[d] Gibertoni D, et al. Developing and validating an algorithm to identify incident chronic dialysis patients using administrative data. BMC Medical Informatics and Decision Making. 2020 Dec;20(1):1-7.
[e] Clement FM, et al. Validation of a case definition to define chronic dialysis using outpatient administrative data. BMC medical research methodology. 2011 Dec;11(1):1-6.

value (PPV) for identifying VAT in administrative claims or EHR data such as Sentinel should be acceptable.

ARIA currently permits adequate identification of heart failure, if occurrence results in hospitalization.[f] Likewise, ARIA is also deemed sufficient to identify patients with serious gastrointestinal bleeds.[g]

5 COVARIATES

5.1 Covariates of Interest

Chronic kidney disease and cardiovascular disease share many common etiologic factors such as advanced age, hypertension, coronary artery disease, inflammation, diabetes, history of transient ischemic attack or stroke, and previous thromboembolic events. Certain medicines or have prior treatment history with daprodustat or ESAs including epoetin alpha, epoetin alfa-epbx may also lead to cardiovascular disorders. Specific covariate of interest includes baseline and monthly Hb values, as the goal of the PMR is to assess the effect of Hb values on the specified safety outcomes.

5.2 Is ARIA sufficient to assess the covariates of interest?

No. The ESA and HIF-PH inhibitor labels currently contain a boxed warning for increased risk of cardiovascular mortality and morbidity associated with targeting higher versus lower Hb levels. Thus, the PMR study requires an assessment of the effect of baseline and maximum achieved Hb on the specified safety outcomes, which require access to baseline and monthly Hb levels. Although the Sentinel Common Data Model (SCDM) does capture Hb lab results, it's unlikely that Sentinel Data Partners that have laboratory results have data on monthly Hb levels obtained by dialysis service providers during dialysis treatment. Capturing those lab values require access to EHR data of (b) (4) or other dialysis service providers. The inadequate capture of data on monthly Hb levels or other lab values in EHRs or administrative claims data will render ARIA insufficient.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

ARIA might address the objectives for post-market assessment by conducting analyses in patient cohorts defined by age, index treatment for anemia due to chronic kidney disease, and pre-index medical history. Applicable ARIA analytic tools permit descriptive (Level 1) and comparative (Level 2) analysis, as indicated below.

Level 1 (Descriptive) Analysis

- To determine exposure (number of exposed patients and patient-years at risk).
- To calculate (background) incidence rates for the outcomes of interest.

Level 2 (Comparative) Analysis

[f] Toh S, et al. Risk for Hospitalized Heart Failure Among New Users of Saxagliptin, Sitagliptin, and Other Antihyperglycemic Drugs: A Retrospective Cohort Study. Ann Intern Med. 2016 Jun 7;164(11):705-14.
[g] Sipahi I, et al. A comparison of results of the US food and drug administration's mini-sentinel program with randomized clinical trials: the case of gastrointestinal tract bleeding with dabigatran. JAMA Intern Med . 2014 Jan;174(1):150-1.

- Covariate Stratification – to calculate incidence rates for the outcomes of interest in patient cohorts defined by exposure and other covariates (e.g., age, sex, cardiovascular risk, prior ESA use).

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA's design and analytic tools are expected to be sufficient to assess the question of interest.

7 NEXT STEPS

DEPI-I has determined that the Sentinel ARIA system is **insufficient** to assess the risk of VAT, hospitalization for heart failure, and severe gastrointestinal bleeds in adult patients initiating vadadustat for the treatment of anemia due to CKD. To inform the PMR, potential real-world data sources should integrate both EHRs and other laboratory data such as monthly hemoglobin levels in patients receiving vadadustat. Finally, the final PMR language to guide the assessment of the aforementioned safety outcomes of interest should read as follows:

PMR 4613-2: "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."

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/s/

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03/26/2024 03:59:47 PM

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	3/14/2024
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OSE Sentinel Team:	Patricia Bright, PhD, MSPH Regulatory Science Staff, Office of Surveillance and Epidemiology
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Vadadustat (VAFSEO®)
Application Type/Number:	NDA 215192
Applicant/sponsor:	Akebia Therapeutics
Nexus TTT #:	2024-8670

A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Vadadustat (VAFSEO) is an oral hypoxia inducible factor prolyl-hydroxylase inhibitor (HIF-PHI). The Applicant originally submitted a New Drug Application (NDA 215192) for vadadustat for the treatment of anemia associated with chronic kidney disease in adult patients not on dialysis and on dialysis. The proposed starting dose is 300mg once daily administered orally.

Vadadustat received a Complete Response (CR) on March 29, 2021, and a formal dispute resolution request was denied on May 26, 2023. Consequently, the Applicant submitted a response to the CR on September 27, 2023 seeking an indication only for the dialysis population. Currently, FDA is reviewing this Resubmission of NDA 215192.

The proposed indication for vadadustat is "for the treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis." The currently proposed labeling for vadadustat as of January 29, 2024, includes a boxed warning stating "increased risk of death, myocardial infarction, stroke, and thromboembolism, including vascular access thrombosis."

The currently proposed labeling for vadadustat as of January 29, 2024, also includes a Limitation of Use stating the drug is "Not indicated for use:

- In patients with anemia associated with CKD not on dialysis.
- As a substitute for red blood cell transfusions in patients who require immediate correction of anemia."

The currently proposed labeling for vadadustat as of January 29, 2024, states in HIGHLIGHTS OF PRESCRIBING INFORMATION, USE IN SPECIFIC POPULATIONS:

(b) (4)

Currently, only one other HIF-PHI (daprodustat) has been approved by the FDA and is marketed in the United States with the same indication as vadadustat.

1.2. Describe the Safety Concern

The mechanism of action of vadadustat and findings from animal studies suggest the potential for maternal and fetal toxicity from exposure to the drug. The risk of adverse maternal and fetal outcomes is of particular concern because CKD (the condition for which vadadustat is being proposed) in pregnancy increases the risk for maternal hypertension, preeclampsia, miscarriage, stillbirth, preterm delivery, low birth weight infants, and polyhydramnios.

The current version of the USPI as of January 29, 2024 indicates that "vadadustat administration orally to pregnant rats and rabbits during the period of organogenesis was associated with reduced fetal weight at doses that caused maternal toxicity". According to the Sponsor's submission

package, a cumulative search of the safety database with search criteria of congenital, familial, and genetic disorders (SMQ, narrow) revealed 5 reports of exposure to vadadustat during pregnancy; 3 of which were associated with treatment-emergent SAEs in the mother receiving vadadustat. These 3 SAEs included: 1) pregnancy resulting in a spontaneous abortion, 2) pregnancy with pre-eclampsia that resulted in elective termination, and, 3) pregnancy with cervical insufficiency and breech presentation that resulted in a premature live birth at 32 weeks via Caesarean section. All treatment-emergent SAEs were assessed as unrelated by investigators and the Sponsor.

Pregnancy among women with end stage kidney disease (ESKD) on dialysis in the United States was reported to be uncommon in a recent retrospective cohort study using data from the United States Renal Data System with Medicare as primary payer (Shah 2019).[1] The pregnancy rate was 17.8 per thousand person years (PTPY) with the highest rate in women aged 20–24 (40.9 PTPY). Overall, 2352 pregnancies were identified in 2008 women. The percentages of fetal outcomes were as follows: live birth (27.1%, n=637), stillbirth (2.6%, n=60), spontaneous abortion (29.4%, n=691), therapeutic abortion (7.6%, n=178), ectopic/trophoblastic pregnancies (2.7%, n=63), and unknown outcome (31.0%, n=730).

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

[1] Shah S, Christianson AL, Meganathan K, Leonard AC, Schauer DP, Thakar CV. Racial Differences and Factors Associated with Pregnancy in ESKD Patients on Dialysis in the United States. J Am Soc Nephrol. 2019 Dec;30(12):2437-2448. doi: 10.1681/ASN.2019030234. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6900804/

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☐ Electronic database study without chart review

☒ Other, please specify: Descriptive pregnancy safety study, which enrolls exposed pregnancies from worldwide sources into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including infant outcomes through at least the first year of life. The study is not expected to have sufficient sample size to support inferential analyses. A descriptive pregnancy safety study is appropriate because use of this drug among pregnant women is expected to be uncommon.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population

☐ Exposures

☒ Outcomes

☒ Covariates

☐ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: There are expected to be very few pregnancies in the dialysis population. Thus, worldwide data collection is needed to increase enrollment. The PMR specifies worldwide safety data collection, however the ARIA study population is limited to United States only.

Outcomes: 1) ARIA lacks access to detailed narratives. The study being considered for broad-based surveillance is descriptive without comparison group(s). Thus, detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and assess causality.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy study being considered would collect detailed narratives with information on potential covariates, such as lifestyle factors, prenatal supplement use.

2.5. Please include the proposed PMR language in the approval letter.

"Conduct a worldwide descriptive study to collect prospective and retrospective data on women exposed to vadadustat 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. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol."

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/s/

STEVEN BIRD
03/19/2024 02:09:08 PM
Orestis Panagiotou was originally the reviewer for this consult, but transferred to CDRH before completion.

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates

Date:	02/09/2024
Reviewer / Team Leader:	CDR Steven Bird, PhD, PharmD, MS Division of Epidemiology 1
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OSE Sentinel Team Leader:	Patricia Bright, PhD, MSPH Regulatory Science Staff
Subject:	ARIA Sufficiency Memo: vadadustat and risk of malignancy
Drug Name:	Vadadustat (VAFSEO®)
Application Type/Number:	NDA 215192
Applicant/sponsor:	Akebia Therapeutics
Nexus TTT #:	2024-8659

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Vadadustat (VAFSEO®) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI). The Applicant originally submitted a New Drug Application (NDA 215192) for vadadustat for the treatment of anemia associated with chronic kidney disease in adult patients not on dialysis and on dialysis. The proposed starting dose is 300mg once daily administered orally.

Vadadustat received a Complete Response (CR) on March 29, 2021, and a formal dispute resolution request was denied on May 26, 2023. Consequently, the Applicant submitted a response to the CR on September 27, 2023 seeking an indication for the treatment of anemia associated with chronic kidney disease in adult patients on dialysis. Currently, FDA is reviewing this Resubmission of NDA 215192 for this indication.

1.2. Safety Concern

Vadadustat's mechanism of action supports concerns about its post-market safety.

Vadadustat is a reversible inhibitor of HIF-prolyl-4-hydroxylases (PH)1, PH2, and PH3 (IC50 in the nM range). This activity results in the stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, and increased production of erythropoietin (EPO). Erythropoietin increases the expression of vascular and endothelial growth factors, promotes cell proliferation, and prevents apoptosis leading to increased levels of hemoglobin and hematocrit. In addition, increased levels of HIF-1 may be associated with unfavorable effects on cancer growth because they activate vascular endothelial growth factor (VEGF) which is a key mediator in tumor angiogenesis. Of note, no evidence of increased carcinogenicity was observed in animal studies.

Vadadustat has not been studied and is not recommended in patients with active malignancies. Malignancies were observed in 2% of patients treated with vadadustat and 2.9% of patients treated with darbepoetin alfa. However, clinical studies of vadadustat have relatively short length compared to the prolonged time to cancer onset or detection after exposure. In addition, these studies are characterized by small samples sizes and the low event rates for cancer. Because of these attributes, they are not sufficient to fully characterize the potential for vadadustat to accelerate tumor growth and therefore, this remains an important potential risk. Consequently, they do not allow for definite conclusions on the long-term risk of vadadustat on tumor progression or development of new malignancies. Although no increased risk of malignancy was demonstrated in clinical studies comparing vadodustat to an ESA control, the mechanistic evidence was considered strong enough to include the risk of malignancy as a Warning and Precaution in the product label.

There is currently one other FDA-approved HIF-PHI, I.e., daprodustat, which is marketed in the United States. Upon approval, daprodustat was issued a post-marketing requirement (PMR) to characterize cancer risk in the post-marketing setting. Similarly to vadadustat, clinical studies of daprodustat did not show an increased risk compared to other ESAs. Yet, the mechanistic evidence was considered strong enough for issuing the PMR.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of the desired post market study is to characterize the risk of malignancies, both solid and hematological ones, in dialysis-dependent (DD) patients receiving vadadustat, and to evaluate the causal effects of vadadustat on the risk of incident cancer as well as cancer progression. The regulatory goal is signal evaluation in the post-marketing setting.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The effect size of interest is a relative risk of 1.5. The study should be sufficiently designed to achieve a targeted sample size to detect this RR of 1.5.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population should include adult patients (18 years of age or older) with anemia due to chronic kidney disease who require chronic dialysis (including hemodialysis or peritoneal dialysis).

2.2 Is ARIA sufficient to assess the intended population?

Yes. ARIA can be used to identify the population of interest. There exist billing codes for anemia due to chronic kidney disease. The ICD-10-CM code is (b) (4). In addition, CPT codes in the range (b) (4) are used to reimburse for dialysis services and procedures. Validated algorithms for identifying CKD and dialysis in claims data are available and can be implemented in ARIA.[1,2,3]

3 EXPOSURES

[1] Zou G, Liu H, Lin K, Zhu K, Hsieh TC. Trends and Outcomes of Hospitalized Influenza Patients With End-Stage Kidney Disease: Insights From the National Inpatient Sample 2010–2019. Cureus. 2022 Apr 25;14(4).
[2] Gibertoni D, Voci C, Iommi M, D'Ercole B, Mandreoli M, Santoro A, Mancini E. Developing and validating an algorithm to identify incident chronic dialysis patients using administrative data. BMC Medical Informatics and Decision Making. 2020 Dec;20(1):1-7.
[3] Clement FM, James MT, Chin R, Klarenbach SW, Manns BJ, Quinn RR, Ravani P, Tonelli M, Hemmelgarn BR. Validation of a case definition to define chronic dialysis using outpatient administrative data. BMC medical research methodology. 2011 Dec;11(1):1-6.

3.1 Treatment Exposure

The treatment exposure of interest is vadadustat, which is administered orally. National Drug Codes available in ARIA can be used to ascertain prescriptions.

3.2 Comparator Exposures

The comparator group of interest includes ESAs used for the treatment of anemia due to chronic kidney disease in DD patients. Eligible comparators will be epoetin alfa, epoetin alfa-epbx, darbepoetin, and methoxy polyethylene glycol-epoetin beta. These drugs are administered intravenously or subcutaneously and can be ascertained using Healthcare Common Procedure Coding System (J codes) or National Drug Codes.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. ARIA is deemed sufficient to capture both the treatment exposure (vadadustat) of interest and the comparator treatments (epoetin alfa, epoetin alfa-epbx, methoxy polyethylene glycol-epoetin beta, darbepoetin), based on Healthcare Common Procedure Coding System (J codes) or National Drug Codes that are available in ARIA's administrative claims and electronic health records. ARIA tools generate longitudinal records of outpatient pharmacy dispensings, which permit construction of patient-specific episodes of treatment with vadadustat.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest are incident cancer and cancer progression. In particular, the interest is primary malignancies (hematological and non-hematological ones) among patients with no cancer history; assessment of these malignancies by type and location is also needed. Additional outcomes of interest include progression-free survival and overall survival in patients with prior cancers.

The National Cancer Institute (NCI) defines malignancy as a disease "in which abnormal cells divide without control and can invade nearby tissues."[4] It also defines progression-free survival as "the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse"[5] and overall survival as "the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive."[6]

4.2 Is ARIA sufficient to assess the outcome of interest?

[4] National Cancer Institute, Dictionary of Cancer Terms. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/malignancy, Accessed January 13, 2023.
[5] National Cancer Institute, Dictionary of Cancer Terms. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/progression-free-survival. Accessed January 13, 2023.
[6] National Cancer Institute, Dictionary of Cancer Terms. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/overall-survival. Accessed January 13, 2023.

No. ARIA is not sufficient to identify incident cancer. To completely and accurately capture this outcome, a method for ascertaining tumor characteristics at the time of diagnosis is required, including site (e.g., cancer of the lung, lymphoma etc.), histology (e.g., non-small cell lung cancer), American Joint Committee on Cancer (AJCC) stage (i.e., stage I, II, III, or IV), and others. This ascertainment would be feasible by linking electronic health records (EHR) or claims data to a population-based cancer registry such as the U.S. Surveillance, Epidemiology, and End Results (SEER) Program or state and territorial cancer registries funded through the CDC's National Program of Cancer Registries (NPCR). However, ARIA capabilities currently exclude linkages to such registries. Even though some Data Partners in ARIA may capture cancer-related information such as stage and histology in their EHR data, this information is not uniformly available in a standardized format across partners. Similarly, diagnostics ICD-10 codes for various cancers lack high sensitivity and specificity for clinically relevant elements such as stage and histology.

ARIA is also not sufficient to identify cancer progression. To completely and accurately capture this outcome, it is necessary to establish when a patient is diagnosed with cancer and to describe their disease trajectory (e.g., when cancer progresses; to which organs it metastasizes). Establishing when a cancer diagnosis occurs in ARIA is challenging because of the lack of linkage to a cancer registry. As outlined in the previous paragraph, diagnostic ICD-10 codes for various cancers lack high sensitivity and specificity for clinically relevant attributes such as stage and histology. Importantly, even though some Data Partners in ARIA may capture cancer-related information such as stage and histology in their EHR data, using such data for the specific regulatory question under consideration will require a validated ascertainment for tumor progression for the progression-free-survival outcome.

Last, ARIA is not sufficient to identify any cancer-related outcome (either incidence, progression, or mortality) that is clinically manifested after more than 5 years, i.e., a period which is considered clinically and biologically relevant. The reason for the ARIA insufficiency is that in Sentinel Distributed Databases less than 25% of patients have continuous follow-up beyond 5 years;[7] the absolute sample size is expected to be even lower for patients on dialysis receiving vadadustat for the treatment of anemia due to chronic kidney disease. This consideration is especially applicable to cancer incidence because from a pathophysiological aspect, cancer has a long latency period and is clinically manifested many years after exposure, thereby requiring long follow-up. It also applies to progression and mortality outcomes, especially for situations where treatments have led to considerable improvements in disease-specific and overall survival among cancer survivors. Hence, the poor patient retention in ARIA limits the usefulness of ARIA for long latency outcomes needed to assess the risk of malignancy due to vadadustat.

5 COVARIATES

5.1 Covariates of Interest

The following covariates are necessary to account for in the design and/or analyses stages:

a. Demographics: age, sex, race/ethnicity

[7] See https://www.sentinelinitiative.org/about/key-database-statistics#length-of-member-enrollment-spans-in-the-sentinel-distributed-database

b. Clinical: body mass index, dialysis type (i.e., hemodialysis or peritoneal dialysis), time since initiation of dialysis, ESA hyporesponsiveness, smoking status, smoking intensity, family history of cancer
c. Comorbid conditions: coronary artery disease, heart failure, angina, atrial fibrillation, myocardial infraction, stroke, transient ischemic attack, cardiac arrest, hypertension, prior cancer, diabetes, thromboembolic event
d. Laboratory values: hemoglobin levels, ferritin, hematocrit, hepcidin, iron, hs-CRP, electrolytes (e.g., potassium), albumin, creatinine, tumor-specific biomarkers

5.2 Is ARIA sufficient to assess the covariates of interest?

No. ARIA is not sufficient to assess key covariates. One such covariate is prior cancer, which is necessary for determining the impact of vadadustat on cancer progression. While available diagnostic codes could be used to determine if a patient had been diagnosed with cancer prior to vadadustat initiation, these codes lack high sensitivity and specificity for clinically relevant elements such as stage and histology. Finally, ARIA does not sufficiently and accurately capture important risk factors for cancer incidence which need to be accounted for as confounders, including smoking status, smoking intensity, alcohol consumption, family history of cancer and others.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

ARIA might address the objectives for post-market assessment by conducting analyses in patient cohorts defined by age, index treatment for anemia due to chronic kidney disease, and pre-index medical history. The study should use a “new user with active comparator” design. Applicable ARIA analytic tools permit descriptive (Level 1) and comparative (Level 2) analysis, as indicated below.

Level 1 (Descriptive) Analysis

- To determine exposure (number of exposed patients and patient-years at risk).
- To calculate (background) incidence rates for the outcomes of interest.

Level 2 (Comparative) Analysis

- Covariate Stratification – to calculate incidence rates for the outcomes of interest in patient cohorts defined by exposure and other covariates (e.g., age, sex, cancer risk).
- Propensity Score Analysis – to estimate the causal effect of vadadustat compared to the comparison treatments. Methods available in ARIA for propensity score analysis include matching, stratification, inverse probability of treatment weighting (IPTW), and stratum weighting.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, we anticipate that ARIA design and analytic tools are sufficient to assess the questions of interest.

7 NEXT STEPS

DEPI-I has determined that the Sentinel ARIA system is insufficient to assess the risk of malignancy in dialysis-dependent patients receiving vadadustat for the treatment of anemia due to chronic kidney disease. DEPI recommends that DNH issues a PMR for conducting an observational study to further characterize and assess the risk of malignancies in dialysis-dependent patients receiving vadadustat for the treatment of anemia due to chronic kidney disease. As of February 02, 2024, the following PMR language is suggested:

> *"Conduct an observational study (at least 5 years follow up) to assess the risk for malignancy (hematological and non-hematological) in dialysis dependent chronic kidney disease adults with anemia treated with VAFSEO versus an erythropoiesis-stimulating agent (ESA) 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."*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEVEN BIRD
03/14/2024 01:53:34 PM
Orestis Panagiotou was originally the reviewer for this consult, but transferred to CDRH before completion.

KIRA N LEISHEAR WHITE
03/14/2024 01:55:20 PM

DAVID G MOENY
03/15/2024 10:53:02 AM

PATRICIA L BRIGHT
03/18/2024 07:55:34 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 15, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 215192
Product Name, Dosage Form, and Strength:	Vafseo (vadadustat) tablets, 150 mg, 300 mg and 450 mg
Applicant Name:	Akebia Therapeutics, Inc. (Akebia)
FDA Received Date:	March 13, 2024
TTT ID #:	2023-6572-1
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Akebia Therapeutics, Inc. (Akebia) submitted revised container labels and carton labeling received on March 13, 2024 for Vafseo. We reviewed the revised container labels and carton labeling for Vafseo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Akebia implemented most of our recommendations. We note the format of the expiration date is YYYY-MM. Akebia does not intend to move forward with the (b) (4) at this time, therefore, (b) (4) were not submitted. However, should they decide to progress with the (b) (4) Akebia confirmed the Agency's recommendations will be implemented. We note the Medication Guide statement was revised; however, the information was not added on the 150 mg container label due to spacing.

We note that Akebia further revised the following:

- Carton Labeling: Revised manufacturing information, trademark symbol, linear barcodes and removed Otsuka's logo
- Container Label: Revised manufacturing information and trademak symbol, added 2D barcode

We find the revised container labels and carton labeling acceptable from a medication error perspective, and we have no additional recommendations at this time.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Black, S. Label and Labeling Review for Vafseo (NDA 215192). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JAN 22. TTT ID: 2023-6572.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUE L BLACK
03/15/2024 08:16:07 AM

NICOLE F IVERSON
03/15/2024 09:06:00 AM

Division of Hepatology and Nutrition

Drug Induced Liver Injury Team

Consultation

NDA	215192
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Vadadustat (VDA)
Indication	Anemia in Chronic Kidney Disease (CKD)
Applicant	Akebia Therapeutics, Inc.
Requesting Division	Division of Non-malignant Hematology (DNH) May Zuwannin, RPM
Primary Reviewer	Eileen Navarro Almario, MD Lead Physician, DILI Team, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Mar 4, 2024

Context: Vadadustat (VDA) stimulates erythropoiesis to treat anemia of chronic kidney disease (CKD) by inhibiting transcriptional factors that regulate adaptation to hypoxia. The Division of Hepatology and Nutrition (DHN) Drug Induced Liver Injury (DILI) Team completed a consult on Feb 7, 2022, for the original NDA.[1] The Division of Non-malignant Hematology (DNH) issued a Complete Response (CR) letter on Mar 29, 2022,[2] upon the finding of hepatotoxicity and thrombotic risks in the original NDA. The Sponsor sought approval for dialysis dependent (DD) patients only, which did not change the CR decision. The Office of New Drugs (OND) denied a dispute resolution request on May 26, 2023, citing an unfavorable risk benefit.[3] Thereafter, there Sponsor resubmitted data from two randomized clinical trials (Studies 036 and 039) that enrolled approximately 500 DD-CKD subjects in the US and European Union (EU), and post-marketing surveillance data for (b) (4) patients treated with VDA following product launch in Japan. The Sponsor concludes that no DILI associated death, hepatic failure or liver transplant emerged from this aggregated data and again proposes a limitation of use, restricting the indication to DD CKD where liver safety of this orally delivered drug can be monitored. In this collaborative review, the DHN DILI Team re-addressed the hepatotoxicity risk based upon the resubmission data. The Office of Surveillance and Epidemiology (OSE) assessed the

[1] Click on link twice, first to open DARRTS session; second to pull document: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806442a5
[2] Click on link twice, first to open DARRTS session; second to pull document: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80653286
[3] Click on link twice, first to open DARRTS session; second to pull document: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806cfc44

Japanese post-market data for whether the proposed label and narrowed indication provide adequate risk mitigation.

Executive Summary:

We can support approval for dialysis dependent (DD) patients if efficacy and need are otherwise favorable and labeling includes hepatotoxicity risk. In this follow-up consult, we focus on the two randomized controlled trials (RCT), and the post-market data from Japan. For our prior assessment of DILI risk, please see our consult note in DARRTS, Feb 7, 2022.[4] No additional cases of Hy's Law or serious DILI were observed among the 500 vadadustat (VDA) 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 (ESAs), 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 assessment is obfuscated by lack of adequate case level data as well as differences in clinical practice and cultural norms between Japan and the US. Differences in potential genetic susceptibility to liver injury are also unknown. Thus, applicability of data from Japan to the US population is unclear. Nevertheless, the lack severe DILI related outcomes suggest an acceptable DILI risk, particularly in the DD CKD population that probably has more frequent contact with medical personnel and higher adherence to laboratory test monitoring.

Follow up Consultation Sections:

Abbreviations:

AE: adverse event
AESI: adverse event of special interest
ADR: adverse drug reaction
AP or ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AE: adverse event
AESI: adverse event of special interest
BMI: body mass index
CKD: chronic kidney disease
CR:; complete response
CRF: case report form
DB: direct bilirubin

[4] Click on link twice, first to open DARRTS session; second to pull document: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806442a5

DD: dialysis dependent
DILI: drug-induced liver injury
EPO: erythropoietin
ESA: erythropoiesis-stimulating agent (e.g., darbepoetin)
EU: European Union
GFR: glomerular filtration rate
GGT: gamma-glutamyl transferase
Hb: hemoglobin
HDS: herbal/dietary supplement
HIP: hypoxia inducible factor
HIF-PH: hypoxia inducible factor prolyl-hydroxylase
IP: investigational product
LDH: lactate dehydrogenase
MACE: major adverse cardiovascular event
NDA: new drug application
NDD: non-dialysis dependent
OSE: Office of Surveillance and Epidemiology
pegEPO: pegylated erythropoietin
QD: once daily
R-value: (ALT/ULN) ÷ (AP/ULN); (R≥5, hepatocellular; R≤2, cholestatic; R 2-5, mixed)
RCT: randomized control trial
SEP: secondary efficacy period
SOC: system organ class
TB: total bilirubin
TEAE: treatment emergent adverse event
TIW: thrice in week
ULN: upper limit of normal
VDA: Vadadustat

1.0 SAFETY FROM RANDOMIZED CLINICAL TRIALS CI-0036 AND CI-0039:

The applicant provided safety summaries from two phase 3b studies[5] treating in DD-CKD. The DILI Team reviewed interim data from Study CI-0036 (Protocol 404-201-00012 or MO2DIFY) and Study CI-0039 (FO2CUS) and updated our assessment with the 120-day safety update.

1.1 Design: Both 036 and 039 have a similar design and are reviewed in tandem. **Figures 1 and 2** show study schematics and schedule of liver analyte checks.

1.1.1 Study 036 compared vadadustat (VDA) to darbepoetin. After eight weeks of screening, subjects were titrated to a hemoglobin (Hb) of 10 and maintained for 52 weeks (**Figure 1)**

[5] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report (#8)

Week 20-26
Primary Efficacy Period

Week 46-52
Secondary Efficacy Period

Table 1.3-1 Schedule of Assessments

Trial Period	Screening		Treatment (Conversion and Maintenance)																			Safety Follow-up	
Visit Type	SV1	SV2	BL									Primary Efficacy Evaluation							Secondary Efficacy Evaluation				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																						
Liver Function Tests [j,f]	X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X		

Figure 1: Study 036 schematic and schedule of assessments related to liver safety.

1.1.2 Study 039 compared VDA thrice weekly (TIW) compared to long-acting erythropoietin in DD-CKD (**Figure 2**).

Study Week

-8 -6 -4 -2 0 | 0 2 4 6 8 12 16 20 24 26 30 34 38 42 46 50 52 | 53 54 55 56

Primary Efficacy Evaluation | Secondary Efficacy Evaluation

Treatment (Conversion and Maintenance)

Table 1 Schedule of Activities

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

Figure 2: Study 039 schematic and schedule of assessments related to liver safety.

1.2 Liver Related Safety Assessments: In studies 036 and 039, 509 participants were exposed to VDA. The safety profile encompasses approximately 50 weeks of VDA treatment. Underlying comorbidities reflected prevalent chronic diseases in DD-CKD patients (e.g., diabetes, hypertension, cardiovascular disease).

1.2.1 Adverse events (AE), Adverse Drug Reactions (ADR) and preferred terms pertinent to liver injury.

Study completion was higher for the comparator arms in both study 036 and 039, but the lower active arm completion rates were not clearly attributable to liver related AEs. There were no liver failures, liver transplants, or deaths amongst subjects with hepatobiliary AEs.

For Study 36, hepatotoxicity TEAEs were observed in 3.8%, 2.9%, and 4.6% of subjects in the VDA QD, VDA TIW, and comparator groups, respectively (Table 1)[6]. For study 039, a higher hepatic AE rate was observed with the VDA 900 mg dose (4.7%) compared to VDA 600 mg (2.6%) but the comparator arm was higher than the 600 mg arm (4%). In Study 036[7], AEs related to liver test investigations were 3 (2.9%), 1 (1.0%) and 2 (1.9%) in the VDA QD, VDA TIW and darbepoetin arms, respectively. For Study 039,[8] rates were 0.7%, 2.7%, and 2.7% in the VDA 600 mg, VDA 900 mg and erythropoietin groups, respectively. Thus, there was no obvious imbalances suggesting VDA liver injury by AESI or preferred terms (**Table 1**). Among the preferred terms (PT) and hepatobiliary disorders, elevated bilirubin, elevated INR, and cirrhosis are the most concerning. There was one bilirubin increase and one INR increase in the Peg EPO arm. There was one INR increase in the VDA 600 mg arm. There were no other subjects with INR or bilirubin increases. A few subjects with cirrhosis under hepatobiliary terms appeared across the treatment arms, but an imbalance implicating VDA was not obvious.

Table 1 Summary of Safety from Studies 39 and 36.

	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)

AESI = adverse event of special interest; QD = daily; TIW = thrice weekly; EPO = erythropoietin; Peg = polyethylene glycol.

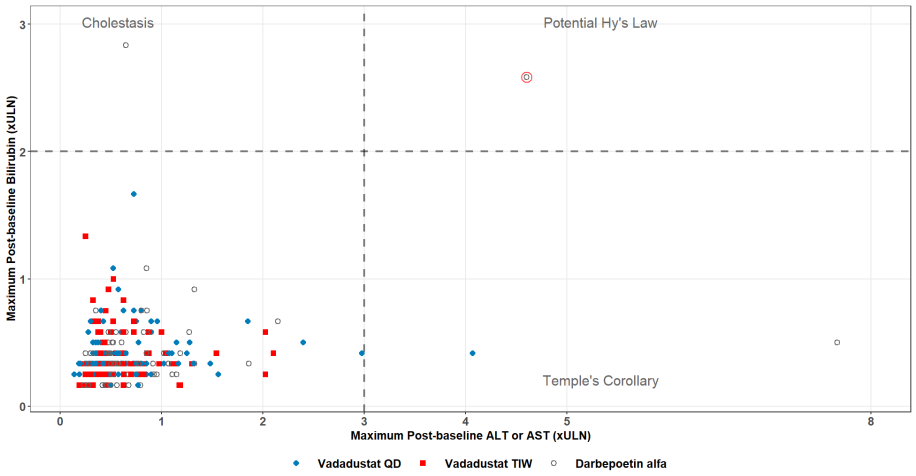
[6] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Study 404-201-00012 (AKB-6548-CI-0036) Synopsis (#7)
[7] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report (#90)
[8] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report (#99)

*Preferred terms: Increases in ALT, AST, liver function test, hepatic enzyme, transaminase, bilirubin, or INR.
Hepatobiliary disorders: hypertransaminasemia, hepatomegaly, cyst, steatosis, cirrhosis.

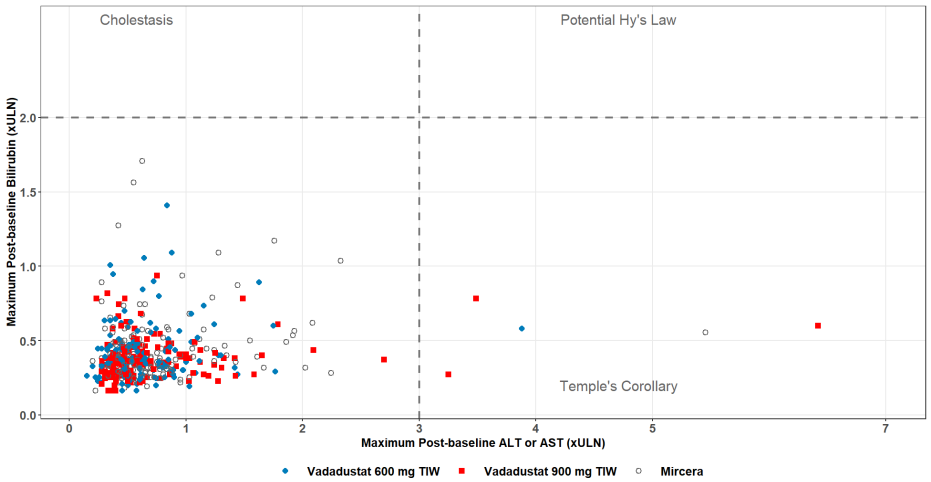
1.2.2 Liver analytes by hepatocellular DILI (eDISH) and cholestatic DILI screening scatterplots

No VDA subjects met Hy's Law criteria by TB >2x ULN and TA elevation >3x ULN criteria. The one subject plotting to the potential Hy's Law quadrant was on placebo. Three VDA and one ESA subjects had ALT >3x ULN in Study 039. There was no excess of ALT or AST elevations >5x ULN for VDA relative to ESA. There was no excess of ALP nor TB at least >2x ULN for VDA relative to comparator ESA (**Figure 3, Table 2**).

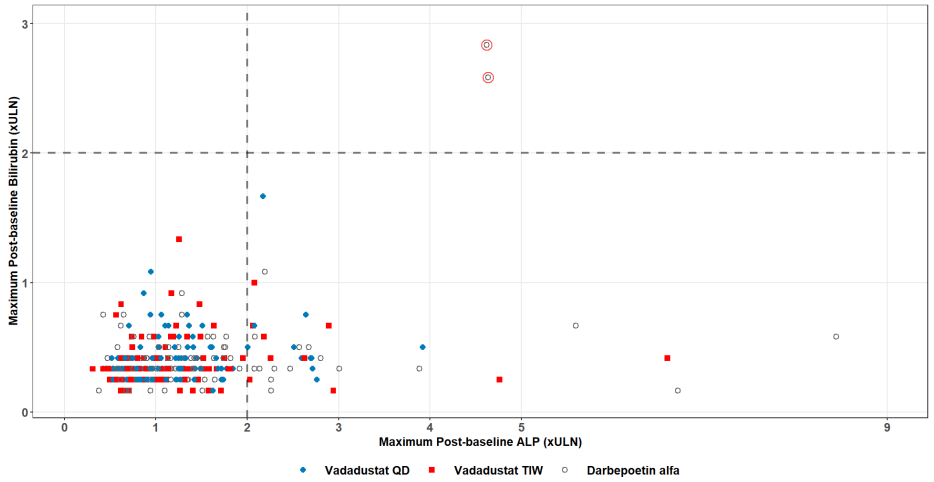
a)



b)



c)



d)

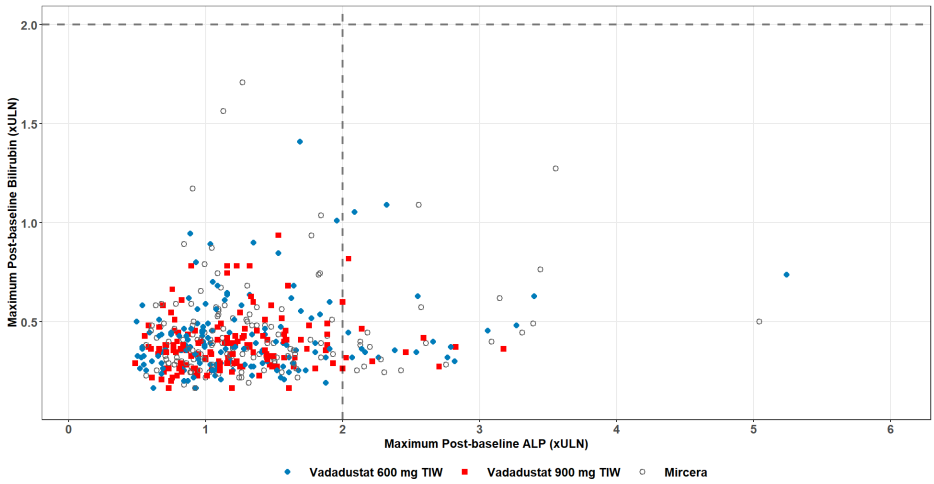


Figure 3: Hepatocellular (eDISH) and cholestatic DILI scatterplots. (a) Study 0036 eDISH plot. (b) Study 0039 eDISH plot. (c) Study 0036 cholestatic plot. (d) study 0039 cholestatic plot.

Table 2. Patients in Each Quadrant in DILI Screening Plots, Safety Population, Trial 0036 and 039

eDISH	VDA QD N=105	VDA TIW N=104	Darbepoetin alfa N=108	VDA 600 mg TIW N=151	VDA 900 mg TIW N=150	Methoxy peg-epoetin beta N=150
Hy's Law	0/102 (0)	0/102 (0)	1/106 (0.9)	0/149 (0)	0/145 (0)	0/149 (0)
Cholestasis	0/102 (0)	0/102 (0)	1/106 (0.9)	0/149 (0)	0/145 (0)	0/149 (0)
Temple's	1/102 (1)	0/102 (0)	1/106 (0.9)	1/149 (0.7)	3/145 (2.1)	1/149 (0.7)
Total	1/102 (1)	0/102 (0)	3/106 (2.8)	1/149 (0.7)	3/145 (2.1)	1/149 (0.7)

Cholestatic Plot	VDA QD N=105	VDA TIW N=104	Darbepoetin alfa N=108	VDA 600 mg TIW N=151	VDA 900 mg TIW N=150	Methoxy peg-epoetin beta N=150
right upper	0/102 (0)	0/102 (0)	2/106 (1.9)	0/149 (0)	0/145 (0)	0/149 (0)
left upper	0/102 (0)	0/102 (0)	0/106 (0)	0/149 (0)	0/145 (0)	0/149 (0)
right lower	11/102 (10.8)	10/102 (9.8)	17/106 (16)	18/149 (12.1)	11/145 (7.6)	20/149 (13.4)
Total	11/102 (10.8)	10/102 (9.8)	19/106 (17.9)	18/149 (12.1)	11/145 (7.6)	20/149 (13.4)

right upper ≥2x ULN Bili ≥ 2x ULN ALP, left upper ≥2x ULN Bili <2x ULN ALP, right lower <2x ULN Bili ≥2x ULN ALP

1.3 Case Level Assessments for Studies 0036 and 0039

We assessed subjects in RLQ with AT >10 ULN or AT>5XULN or in the RUQ of the cholestatic plot for attribution to VDA based on narratives and subject level data. Details are provided in the **Appendix**. Three subjects were considered probable or possible DILI due to VDA, but TA elevations were less than 8x ULN without jaundice in these cases. Therefore, there were no serious DILI cases among 509 subjects in the two randomized controlled studies, compared to one Hy's law case and seven probable liver injury events in the 4,500 subjects reviewed in the original NDA. We found no ADRs of liver failure, transplantation, or death. These data are somewhat reassuring but underpowered to conclude the liver injury signal in the original NDA was spurious or dismissible.

2.0 Safety data from Japanese post-market programs: [9] The Office of Surveillance and Epidemiology (OSE) did the primary analysis of these data. Our analyses were done in close communication with OSE, but we recommend reading their report for a more comprehensive view.

2.1 Design and description of data sources:

Figure 4 shows the five data sources regarding VDA safety from approximately (b) (4) Japanese treated subjects since Jun 19, 2020.[10] Each source is numbered one through five with more details outlined in **Table 3**. Of the five, only number three, post-marketing surveillance (aka VIOLET), has active data collection under a cohort study

[9] NDA215192 (215192 - 0049 - (49) - 2023-11-13 - ORIG-1 /Clinical/Response To Information Request) - Response to FDA CRL Attachment 2 - Japan Data Overview (#9)
[10] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report

protocol. The other four sources rely on passive data reporting. Source number four, Periodic Safety Reports, encompasses sources 1 though 3, and 5.

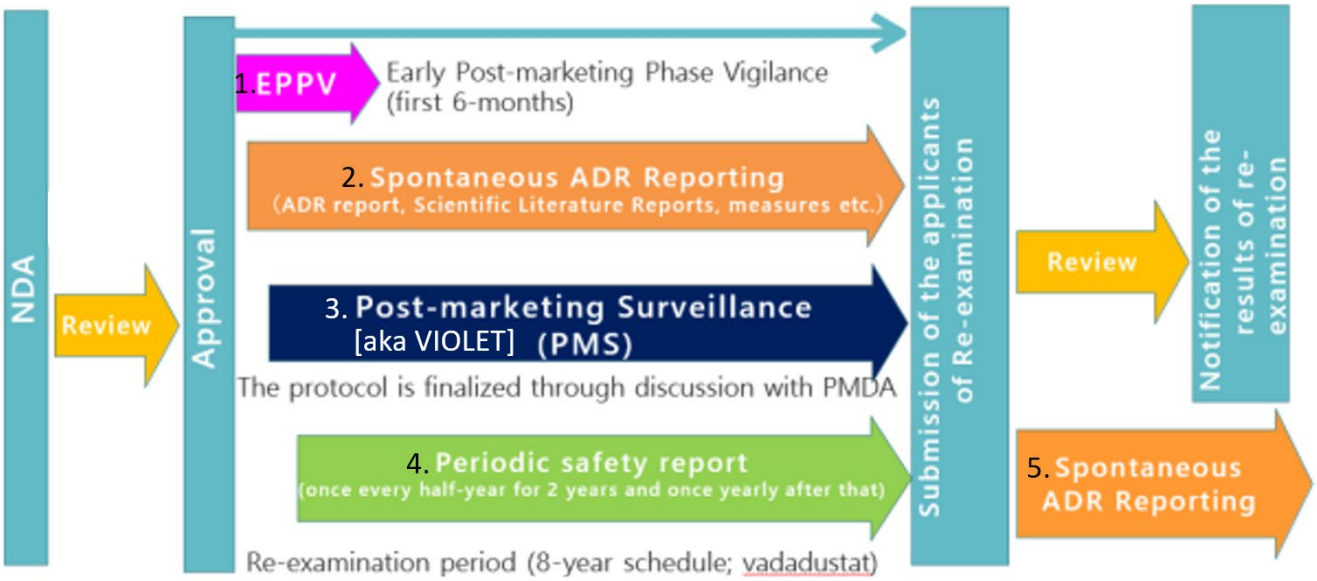


Figure 4: Schematic of data sources from the Japanese pharmacovigilance program.

Table 3: Postmarketing data sources from Japan pharmacovigilance program. Data Source number corresponds to numbers in Figure 4 above.

Data Source	Dates	Source	N	Submissions to FDA
1. EPPV: Passive collection – All AEs[11]	8/26/2020 to 2/25/2021	800 hospitals, 3000 clinics invited to report	one hepatitis AE /4000 CKD[12] (Reviewed in initial NDA)	Initial NDA up to 10/15/2020
				120-day safety report 10/16/2020 to 2/25/2021
				English translated PMDA report 9/27/2023
2. Spontaneous Adverse Drug Reactions – all AEs[13]	6/29/2020 to 6/28/2023	Spontaneous reports	4159 AEs from 2793 cases; 45 hepatobiliary AEs (see **Table 4**)	Appendix 2 of the safety update report submitted 9/27/2023, with hepatobiliary AEs
3. Post-Market Surveillance (PMS): Prospective long term, (VIOLET)[14]	Recruitment: 11/24/2020 – 6/28/2023; Follow-up	431 registered facilities	Target: 2000 VDA-naïve CKD & 1000 w/ 24-mo follow-up;	Appendix 3 of the safety update report 9/27/2023

[11] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 1 - Vafseo EPPV Report
[12] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 2 - Vafseo Post-marketing TLFs (#10)
[13] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 2 - Vafseo Post-marketing TLFs
[14] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 3 - Vafseo PMS TLFs

	thru 11/ 2024		Resubmission has data for 1847 subjects.	
4. Periodic Benefit Risk Evaluation Reports (reports 1-5 [PBRER])	6/29/2020 to 6/28/2023	Inclusive of data sources 1 – 3, & 5		Response to IR Appendix 4;
5. Spontaneous ADR Reporting: Hepatic Events	6/29/2020 to 6/28/2023		52 subjects had 53 hepatic events (see appendix)	Appendix 5 Table 31.1p and Table 31.2p submitted 9/27/2023,

2.2 Study Level Findings from Japanese Post-Market Sources: Overall, five data sources provided safety information on a large number of Japanese patients exposed to VDA. There were no deaths, transplants, or liver failures attributable to VDA by AE terms. However, the subject level data was routinely inadequate to adjudicate for DILI, and there were no comparator arms in these data sources.

2.2.1 *Data source #1, Early postmarketing phase vigilance (EPPV, Appendix 1)*: There was one case of hepatitis listed as a serious adverse reaction among 4000 exposures. Adjudication for attribution to VDA was indeterminate due to lack of adequate data.

2.2.2 *Data source #2, Spontaneous ADR*: Hepatobiliary ADRs represented 1.3% of all AEs reports. Of the 46 AEs under the hepatobiliary system organ class (SOC) including consequent investigations, 14 were serious, but none resulted in liver transplant, liver failure or death (**Table 4**). Eleven of the 14 had preferred terms (PT) suggesting a non-DILI diagnosis. The remaining three had non-specific PTs that could represent DILI (gray highlighted in **Table 4**). Many of these events were listed as "related" but the method of such determinations is unclear to us (**Appendix, Table B**). We considered the case level data typically inadequate for DILI adjudication.

Table 4: Summary of AESIs and serious AEs in the hepatobiliary SOC

	Preferred Term	N events	AE	N SAE	SAE
Hepatobiliary SOC		45	46	13	14
	Alcoholic liver disease	1	1	1	1
	Bile duct stone	1	1	1	1
	Budd Chiari	1	1	1	1
	Cholangitis	1	1	1	1
	Cholangitis acute	1	1	2	2
	Cholecystitis	2	2	1	1
	Cholecystitis, acute	1	1	1	1
	Congestive hepatopathy	2	2	2	2
	Haemobilia	1	1	0	0
	Hepatic function abnormal	27	27	1	1
	Hepatitis	1	1	1	1
	Hyperbilirubinemia	1	1	0	0
	Liver disorder	5	5	1	1
	Portal vein Thrombosis	1	1	1	1
Investigations	ALT increased	4	4	0	0
	AST increased	5	5	0	0
	Blood alkaline phosphatase increased	2	2	0	0
	Blood bilirubin increased	1	1	0	0

	GGT abnormal	1	1	0	0
	GGT increased	2	2	0	0
	Hepatic enzyme abnormal	1	1	0	0
	Hepatic enzyme increased	1	1	0	0
	Liver function test abnormal	1	1	0	0
	Liver function test increased	5	5	0	0
Table reconstructed from Table 30.2.1p Adverse events[15] and 30.2.2p for Serious for Postmarketing in Japan[16]					

2.2.3 *Data source #3, Japan Postmarketing Safety Study Surveillance (PMS) (VIOLET):*

2.2.3.1 Design: VIOLET was designed to collect AEs, onset date, seriousness and criteria for seriousness, outcome, date of outcomes, causality, confounding factors, laboratory values related to AE, date of deaths, causes of death, autopsy findings, clinical course, and treatments as well as free-text fields for additional comments. The schedule of procedures[17] specified pre-dialysis serum liver tests at months -3, -2, 0, 2, 3, 6, 12, 24 and treatment discontinuation, where month 0 is treatment start. Target enrollment was 2000 CKD patients naïve to VDA (> 500 NDD, >500 HDD and 100 PDD) with a target of 1000 to be observed for 24 months. The Sponsor suggests the sample size should have a >95% chance of detecting the serious hepatic event rate of 0.3% rate observed in the original NDA.[18]

2.2.3.2: Study Level Analyses: As of June 28, 2023, 2262 subjects registered in VIOLET of which 1847 (82%) are in the safety population. Of the 1847, 590 and 231 subjects had fixed 3-month and 6-month case report forms (CRF), respectively.[19] The NDD population (1233) was twice larger than the DD population (142 peritoneal; 472 hemodialysis). Summary counts and percentages for this safety population are in **Table 5**. Of these 1847 patients, 528 (29%) discontinued VDA. Thirty percent of the discontinuations were due to an AE.

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 (obstruction of hepatic venous outflow, usually by blood clot). Neither of these are pertinent to hepatocellular DILI risk. Therefore, 1.6% (3 of 1847) of subjects may have discontinued VDA for a DILI in the worst-case scenario (i.e., all three remaining hepatobiliary AEs were due to DILI and led to discontinuation). For comparison, the DILI team found a DILI rate of 0.18% and a serious hepatic event rate of 0.3% in the original NDA.[20]

[15] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 2 - Vafseo Post-marketing TLFs (#10)
[16] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report - Table 31.1p (#5)
[17] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Vafseo Japan Post-Marketing Safety Study Protocol - English Translation (#6)
[18] https://clincalc.com/stats/samplesize.asp
[19] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 4d - JPSUR 4 (#4)

Table 5: Summary of Post Marketing Surveillance Study (VIOLET) [21]

	Category	Incidence rate
Drug Administration	Mean + SD	201.8 ± (138.5) d
Discontinued from Safety population	Observation D/C	220 (12%)
	Hospital transfer	115 (52%)
	No follow up	36 (16%)
	Other reasons	71 (32%)
Initial dose	150 mg/day	146 (7.9%)
	300 mg/day	1673 (90.6%)
	450 mg/day	15 (0.8%)
	600mg/day	11 (1%)
Outcome	Drug discontinued	528 (29%)
Reason for Drug discontinuation	AE	162 (30.68%)
	Ineffective	99 (18.75%)
	Hospitalization	94 (17.8%)
Complications	Hepatic "disorder"	75 (4.06%)
Adverse reactions	Subjects/events	202/1847 (10.94%)
Adverse reaction in subjects with reported hepatic function disorder	No AE	193/1772 (10.89%) (9.5,12)*
	Yes	9/75 (12%) (5.6, 21.6) RR 1.1 (0.6, 2.0)
	Not serious	60/1772 (3.4%) (2.59, 2.34)
	Yes**	3/75 (4) (0.8, 11.25) RR 1.18 (0.38, 3.7)
Adverse reactions And Investigations	Subjects with AEs	N=202/1847 (10.94%)
	Hepatobiliary	5 (0.41%) (2 serious)
	Test	ALT (1) AST 2 GGT (1)
* (95%CI, Fisher Exact yes vs no)=0.707 ** see Table 9 #1 each of Budd Chiari, liver disorder, congestive hepatopathy		

Two liver vein obstructions (hepatic and portal veins) are notable given their rarity, particularly the hepatic vein obstruction because such obstructions are potentially life-threatening. There was also a concern for graft thrombosis with VDA in the initial NDA, and ESAs in general. [22] The rate of one Budd Chiari per (b) (4) subjects is several-fold

[21] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 3 - Vafseo PMS TLFs

[22] Manns BJ, Tonelli M. The new FDA labeling for ESA--implications for patients and providers. Clin J Am Soc Nephrol. 2012 Feb;7(2):348-53. doi: 10.2215/CJN.09960911. Epub 2012 Jan 19. PMID: 22266575; PMCID: PMC3280029.

higher than the reported prevalence of two per million in the Japanese population,[23] but CKD patients are prone to hypercoagulability and may carry a higher rate.[24] The DILI Team could not find incidence or prevalence data on Budd Chiari in NDD and DD-CKD patients. Nevertheless, we reviewed the placebo-controlled studies in the original NDA and found no occurrence of Budd Chiari or portal vein thrombosis.

2.2.3.3 Case Level Analyses (VIOLET): The Sponsor provided case details for four cases from VIOLET, three that met the biochemical criteria for Hy's law and one had an AST >10x ULN without jaundice. We did not attribute any of these cases to DILI (**Table 6**). Moreover, only one had hepatocelluar injury based on R-value using peak AST. The detailed case level summaries with our assessments are in the **Appendix B**. Lack of detailed data hindered assessment in two cases.

Table 6: Four cases from VIOLET that met AT and TB Hy's law criteria or had an AT >10 X ULN (data from response to information request Jan 2024).

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
	5 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

2.2.4 *Data Source #4, Japan Aggregate Reports (J-PSUR):* There have been five PSURS. The fifth covers June 29, 2022, to 28 June 2023, but it includes cumulatively data and reports from Data Sources 1, 2, 3 and 5. Therefore, Source #5 cases are included for this section and will not be discussed separately. Crude cumulative incidence rates for liver related AEs by ND and DD status are in **Table 7**. As discussed above, accurate adjudication for attribution to VDA hepatotoxicity was not possible due to lack of adequate case level data.

[23] Ohfuji S, et al. Japanese periodical nationwide epidemiologic survey of aberrant portal hemodynamics. *Hepatol Res*. 2019 Aug;49(8):890-901. doi: 10.1111/hepr.13343. Epub 2019 Apr 25. PMID: 30945395; PMCID: PMC6850208.
[24] Nunns GR, et al. The hypercoagulability paradox of chronic kidney disease: The role of fibrinogen. *Am J Surg.* 2017; 214:1215-18.

Interestingly, PD patients had no liver related AEs which may reflect underpowering (only 142 PD patients), selection bias, reporting bias, or a combination of these issues. PD patients may be more stable than hemodialysis patients and therefore less likely to have liver AEs, but this bias should not affect idiosyncratic DILI risk. Under reporting of AEs could occur because of decreased contact with medical personnel, but this bias would likely be neutral or lead to more reporting when compared to ND subjects.

Table 7: Hepatic Adverse Events of Special Interest & Drug Related AESI by CKD population

Event	**All**	**Non-Dialysis**	**Peritoneal Dialysis**	**Hemodialysis**
Category:	**N=1847**	**1233**	**142**	**472 (%)**
AESI	13 (0.7%)	11(0.9)	0	2 (0.4)
Serious AESI	3	2 (0.16)	0	1 (0.2)
ADRSI	9 (0.48%)	7 (0.6)	0	2 (0.4)
Serious ADRSI	2	1	0	1 (0.2)
Compiled from Tables 7.3.2.[25]				

2.3 Comparability of Japanese and US data

Differences between Japan and US demography are pronounced in terms of genetic polymorphisms that could impact on the DILI risk. The DILI Team did consider risk of DILI with immunoallergic features because there are data for underlying genetic predispositions with drug reaction with eosinophilia and systemic symptoms (DRESS).[26,27] and there was one case of rash requiring systemic corticosteroid therapy accompanying liver injury. The case raised the possibility of immunogenicity to protein adducts created via VDA acyl glucuronidation. Differences in genetic polymorphisms of the metabolizing enzymes (UGT1A1 and 2B7)[28] could theoretically lead to adduct accumulation crossing a threshold of clinically apparent allergic reaction. However, the signal is weak (1 in (b) (4) exposures) and acyl glucuronides constitute <1% of the total drug metabolites, at least in serum. Thus, we did not feel this risk and possible pathophysiology warrants further study or impacts on the approval decision. Should VDA be approved and immunoallergic DILI cases arise post-market, additional investigations may be warranted.

Otherwise, searching for differences in genetic predisposition for VDA hepatoxicity between US and Japanese patients is not warranted nor possible. No such genetic predisposition VDA liver injury was identified in the NDA cases, and the post-market

[25] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report Appendix 3 - Vafseo PMS TLFs

[26] Wu X, et al. Clinical, Viral and Genetic Characteristics of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in Shanghai, China. *Acta Derm Venereol*. 2018; 98:401-405.

[27] Asif BA, et al. Vancomycin-Induced Liver Injury, DRESS, and HLA-A∗32:01. *J Allergy Clin Immunol Pract*. 2024; 12:168-174.

[28] Bhasker C, et al. Genetic polymorphism of UDP-glucuronosyltransferase 2B7 (UGT2B7) at amino acid 268: ethnic diversity of alleles and potential clinical significance. *Pharmacogenetics* 10(8):p 679-685, November 2000.

Japanese cases had too few cases of clear VDA hepatotoxicity to warrant investigation. In other words, differences in DILI risk between the two populations based on genetic differences remains unknown. For similar, reasons, we cannot address how cultural differences (e.g., medial practice, patient compliance), may impact on differences in DILI risk.

3 Conclusions and Recommendations:

3.1 Conclusions: Overall, the two additional randomized control trials (RCT) and Japanese post-market data do not change the DILI Team's opinion on liver injury risk. DILI rate appears low, but injury can be substantial based on the original NDA data. We can support approval for use in dialysis dependent (DD) CKD patients if efficacy and need are substantial. Our support for approval is bolstered, in part, because we believe DD patients have increased contact with medical personnel and higher chance of adhering to liver monitoring, though we acknowledge that 12-13% of dialysis in the US is done at home, and this percent is gradually increasing.[29] We are encouraged that the Japanese patients on peritoneal dialysis (PD) had no liver related AEs. Selection bias and underpowering could explain this lack of AEs. Nevertheless, 97% of home dialysis in the US is by PD and selection biases favoring safety may be similar in the US. We defer to the primary review division to consider the frequency of contacts with medical personnel and likelihood of adherence to monitoring in the US home PD population.

The additional two RCTs did not suggest a higher DILI rate over comparator arms. While treatment discontinuation rates were higher in the VDA arms and hepatobiliary AEs did contribute to these discontinuations, there were no liver failures, liver transplants or liver related deaths. Lack of serious liver injuries could suggest successful risk mitigation in a clinical trial setting. Moreover, the RCT trials were substantially smaller than the original NDA phase 3 trials, and thus not powered to detect a Hy's Law case at the rate detected in the original NDA. Therefore, the two RCT did not add greatly to the NDA data in terms of power or our assessment of DILI risk.

Similarly, the five sources for Japanese post-market data did not show a substantial risk of serious DILI. The VIOLET cohort study was the only source of actively procured data, while the other four sources relied on passive reporting. There were no comparator arms in the Japanese data. Case level analyses of liver injury cases from VIOLET did not yield any DILIs clearly attributable to VDA, but case level data were routinely inadequate for adjudication. However, based on AE data, there were no Hy's Law cases, deaths or transplants due to VDA. The discontinuation rate due to AEs was substantial at 31%. Details for all discontinuations were not available, but just five (0.4%) had hepatobiliary AEs with two being "serious."

Beside lack of detailed case level data, applicability of Japanese data to the US population is problematic. In Japan, 98% of the population is of Japanese ancestry

[29] US Renal Data System Annual Report. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/2-home-dialysis#figure-2-3a-section

while in the US, Japanese account for less than 1%. Idiosyncratic DILI risk may be based on genetic susceptibilities, such as HLA haplotypes that can vary by race. Moreover, such susceptibilities are generally drug specific, and we do not have a genetic risk marker for VDA liver injury. Thus, we have no markers to test in the two populations. Also, clinical practices and cultural norms are different between the two countries. Herbal or dietary supplements (HDS) are more often used in mainstream Japanese medical practice than in the US. Such HDS use obfuscated our ability to assess VDA hepatotoxicity in at least two liver injury cases. The Japanese population also may adhere to social norms and medical advice more readily compared to the US population.[30] Thus, a low rate of serious liver injury in the Japanese population may not be reproducible in the US.

Overall, the additional data provided since the CR and denial of dispute resolution, do not raise our concerns for DILI. However, the RCT data lack power, while the post-market data lack sensitivity and specificity for DILI detection and have unclear applicability to the US. The data do not greatly change our assessment created by the original NDA data. Rather, the most consequential change that occurred since our original consult, was the limitation of use to dialysis dependent (DD) CKD patients in the US. We recognize that many DD patients may be on home dialysis in the US, but nearly 90% are not. We believe the level of care, surveillance for adverse events, and adherence to any liver monitoring will be higher for DD compared to non-DD patients. We can support approval, but labeling and patient education material should include the risk of DILI. Monitoring of liver enzymes is recommended, but only for the first few months as the cases seen in the NDA had relatively short latencies.

3.2 Recommendations

1. Do not hold up approval solely for DILI risk.
2. If VDA is approved, we recommend the following:
    a) Label for hepatotoxicity risk.
    b) Baseline liver analytes should be checked with monthly monitoring during the first few months of use.
    c) Use in patients with cirrhosis or active, acute liver disease should be discouraged.
    d) Enhanced pharmacovigilance
    e) Expedited reporting of serious liver related adverse events received by the Sponsor.

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[30] Rich M, et al. Japan's Secret to Taming the Coronavirus: Peer Pressure. New York Times. https://www.nytimes.com/2022/07/02/world/asia/japan-covid.html

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Appendix A: Summary Tables of Patients with Liver Injury from Studies 036 and 039, and from Post-market Japanese Data.

Table A: Summary of liver injury cases for (i) Study 036 and (ii) Study 039:

(i) Study 036

Subject ID	Causality Score^	Alternate Cause	Age (yr.)/Sex Race	eDISH quadrant	Latency (da)		Peak		
					Drug Start	Drug Stop	AST	ALT	R value
(b) (6)	4	Unknown	54 F AA	Temple's	365	365	175	142	2.8
	Not assessed**	Unknown	73 F W	Left lower quadrant	111	NA	2.9x ULN	<3x ULN	NA

(ii) Study 039

Subject ID	Causality Score^	Alternate Cause	Age (yr.)/Sex Race	eDISH quadrant	Latency (da)		Peak		
					Drug Start	Drug Stop	AST U/L	ALT U/L	R value
(b) (6)	6	Unknown	Missing info	Temple's	NA	NA	NA	NA	NA
	4	acetaminophen	44 F AA	Temple's	171	NA	117	41	NA
	Not assessed**	Unknown	47 F AA	Left lower quadrant	277	NA	60	89	NA
	5	Metastatic liver cancer	57 M AA	Temple's	25	NA	276	47	NA
	3 or 4	Unknown	89 M Asian	Temple's	211	NA	150	93	2.8

AA = African American or Black; F = female; M = male; NA = not available; W = White
R-value: (ALT/ULN) ÷ (AP/ULN); R value $\geq$ 5, hepatocellular; R-value $\leq$2, cholestatic; R-value 2-5, mixed.
^ 1 definite, 2 highly likely, 3 probable, 4 possible, 5 unlikely, 6 indeterminate
*No SAE narrative in the information response; case not considered an AESI
** Transaminases <3X ULN without jaundice (did not warrant assessment for clinically important DILI)

Table B: Cases listed in Table 31.2p (60 cases with hepatic events from Postmarketing in Japan.[31] (AE = adverse event; BLN = baseline; DC = dechallenge; NA = not available; RC = rechallenge.)

#	Age/Sex/Race Dose	Case ID (VIOLET subject ID)	DILI Team Notes	System Organ Class (SOC)	Preferred term (PT) for hepatic AE (co-occurring AES)	SAE	Case Outcome	Reported Relationship	Action Taken	Latency (days)/ AE duration	Peak Test values as XULN	De-/ Re-Challenge (DC/RC)
1	80+ F 300 mg	(b) (6)	Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Recovering Resolving	Related	Drug withdrawn	? (AE start 25/11/20)	?	?
2	100+ F 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Cholecystitis acute	Yes	Unknown	Not Related	?	?	?	?
3	85 F 300 mg		Insufficient information Missing date drug stopped	Hepatobiliary disorders	Hepatitis	Yes	Recovered Resolved	Related	Drug withdrawn	49/7	ALT 7 AST 5 ALP 7 TB?	+/?
4	60+, M 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Related	Drug withdrawn	?	?	?
5	86 F 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Recovered Resolved	Related	Drug withdrawn	8/49	?	?
6	72, M 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Portal vein thrombosis, hematemesis, variceal hemorrhage	Yes	Fatal	Not Related	Drug withdrawn	11/?	?	?
7	63 F 150 then 300mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Not recovered Not resolved	Related	Drug withdrawn	9/?	?	?
8	60+ F 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Related	Drug withdrawn	?	?	?
9	M 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Recovering Resolving	Related	Drug withdrawn	?	?	?

[31] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report - Table 31.2p (#2)

10	76 F 150 mg	(b) (6)	Insufficient information Missing test values urosodeoxycholic	Hepatobiliary disorders	Hepatic function abnormal	No	Recovered Resolved	Related	Drug withdrawn	?	?	?
11	90s M 150 mg		Unlikely, AE occurred pre drug	Hepatobiliary disorders	Liver disorder	No	Recovered Resolved	Related	Drug withdrawn	?	ALT3.6 AST 3	DC positive
12	53 M 300 mg		Insufficient information Missing date drug stopped	Hepatobiliary disorders	Hepatic function abnormal	No	Recovered Resolved	Related	Drug withdrawn	42(conflicting info in report – 316 in table)	ALT 3.4	DC positive
13	85, M 300 mg		Insufficient information Missing test values at time of event ursodeoxycholic	Hepatobiliary disorders	Cholangitis	Yes	Unknown	Not Reported	Drug withdrawn	43/53	No labs at time of AE	?
					Cholecystitis	Yes	Recovered Resolved	Not Related	Drug withdrawn	43/53	No labs at time of AE	?
14	75 F 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal (with drug eruption)	No	Unknown	Related	Drug withdrawn	19	?	?
15	50 F 300 mg		Insufficient information Missing test values	Investigations	Alanine aminotransferase increased	No	Recovered Resolved	Related	Drug withdrawn	22/69	?	?
					Aspartate aminotransferase increased	No	Recovered Resolved	Related	Drug withdrawn	22/69	?	?
16	93 F 300 mg		Unlikely DILI, biliary obstruction pancreatic cancer	Not reported as a Hepatobiliary AE, narrative listing based on laboratory data	Cooccurring AEs Cardiac failure Pancreatic cancer	Yes	Fatal – Pancreatic cancer	Unrelated	Drug withdrawn	318	ALT 2.1 AST 3.8 ALP 4.5 Bili 5.3	?
17	90s M 300 then 450 mg		Missing test values	Hepatobiliary disorders	Liver disorder	No	Unknown	Related	Drug withdrawn	?	?	?
18	90s M 150 mg		Missing date drug stopped	Hepatobiliary disorders	Hepatic function abnormal	No	Recovered Resolved	Related	Drug withdrawn	62/34	ALT 1.6 AST 2.6	DC positive
19	66 M 150 mg		Missing date drug stopped SCORE 4 Cholestatic RLQ	Hepatobiliary disorders	Hepatic function abnormal	No	Ongoing	Related	Drug withdrawn	78/113	ALT ~1 AST~1 ALP 3 GGT also elevated from base-line but BILI remained ~1X	DC positive

20	85 M 300 to 450 to 600mg	(b) (6)	Missing date drug stopped; Hy's RLQ Cholestatic RLQ	Hepatobiliary disorders	Cholangitis acute Cerebral infarction	Yes	Recovering Resolving	Not Related	Drug withdrawn	37	ALT 3 AST11 ALP 3.6 Bili just above ULN (1.4)	DC positive
21	74 F 300 mg		Unlikely Test values within normal (Statins, CPK elevation, herbal with active drug substances – sulfonylureas and SGLT inhibitor)	Investigations	Aspartate aminotransferase increased (CPK increased)	No	Recovered Resolved	Related	Drug withdrawn	50/41	AST 1* (35 with ULN of 34) ALT 1 TB 1 AP-no data	?
22	49 M 300 mg		Unlikely Score = 0 (Statin, CHF)	Hepatobiliary disorders (Congested liver – investigator verbatim)	Congestive hepatopathy Cardiac tamponade	Yes	Recovered Resolved	Related	Drug withdrawn	5	ALT 4.3 AST 2.7 ALP 3.3 Bili <1	?
23	No age, M 150 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Related	Unknown action with drug	?	?	?
24	84 M 300 mg		Unlikely Score=0 (Ceftriaxone, Herbal [Yokukansan][32] with green tea extract (catechin polyphenols[33])[5]	Not reported as a Hepatobiliary AE, narrative listing based on laboratory data	Co-occurring AEs Pneumonia Cardiac failure chronic	yes	Fatal	Unrelated	Unknown action with drug	24	ALT 1X AST 3.9 AP 2.6 TB 2.7 AP elevated at baseline	?
25	80s, M 150 mg		Unlikely Score =1 Ap/TB missing. (Medical history of Abnormal liver tests)	Hepatobiliary disorders	Hepatic function abnormal	No	Not recovered Not resolved (inconsistent with lab data showing resolution)	Related	Drug withdrawn	54/23	ALT 3.8 AST 4.6 AP–no data TB–no data	DC positive
26	65 M 300 mg		Unlikely Score = 1 Rash Hemolysis	Not reported as a Hepatobiliary AE, but in	Co-Occurring AEs Epidural hematoma (d39) Drug eruption (d51)	Yes	Fatal	Unrelated	Unknown action with drug	65/?	ALT 26X AST 32X	?

[32] https://www.drugs.com/npp/yi-gan-san.html -

[33] https://www.uptodate.com/contents/hepatotoxicity-due-to-herbal-medications-and-dietary-supplements#references George JN, Nester SM.Thrombotic microangiopathies (TMAs) with acute kidney injury (AKI) in adults: CM-TMA and ST-HUS. In: UpToDate, Post TW (Ed), Wolters Kluwer. https://www.uptodate.com (Accessed on December 6, 2023.)

			Herbal use is a confounder [JIDABOKUIPPO] [5]	listing from lab data	[onset abnormal liver test d65) Atypical HUS (d72) Bronchopulmonary aspergillosis (d72) [peak abnormal liver test d78)						AP 9.9X TB 2.9X ULN	
27	59 M 300 mg QD then EOD	(b) (6)	Unlikely Score = 0 but Missing ALP test values ? LEAN NASH No testing from day 0-155, unclear if symptoms-initiated testing	Hepatobiliary disorders	Liver disorder	Yes	Recovering/Resolving	Related	Drug withdrawn	155/ unresolved at day 435 (280 days)	ALT 3.9 AST 2.9 AP no tests. TB 0.4	
28	74 M 300 mg		Score = 4 ? Lean NASH – baseline AST elevated	Hepatobiliary disorders	Hepatic function abnormal	Yes	Recovered Resolved	Related	Drug withdrawn	29/7	ALT13 AST 72 AP 1.1 TB 0.3	DC positive
29	80 F 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Related	Drug withdrawn	?	NA	NA
30	78 M 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Related	Drug withdrawn	?	NA	NA
31	49 M 300 mg		Weak possible Score = 3 Clostridium butyricum Iron	Hepatobiliary disorders	Hepatic function abnormal	No	Recovering Resolving	Related	Drug withdrawn	8/15	~3X ULN ALT and AST ~2XULN	DC positive
32	90s F 150 mg, 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Haemobilia	No	Recovering Resolving	Not Related	Drug withdrawn	?	NA	NA
33	84 M 300 mg, 450 mg		Test values within normal (ULN missing)	Hepatobiliary disorders	Hepatic function abnormal UTI, CHF	No	Recovering Resolving	Not Related	No action taken	75	ALT ~1 AST ~1 AP ~1 TB ~1	NA
34	56 F 300 mg		Insufficient information Bilirubin not fractionated, AT and ALP are normal. Gilbert's?	Hepatobiliary disorders	Hyperbilirubinemia	No	Unknown	Related	Drug withdrawn		ALT ~1 AST ~1 AP ~1 TB at peak was 1.5 mg/dL	

		(b) (6)	Kousezai (per reporter) antibiotic hydroxyethypenam									
35	72 F 300 mg		Weak possible Score = 3 Herbal product ? NASH	Investigations	High GGT, LDH – but no values	No	Recovered Resolved	Related	Drug withdrawn	?	?	NA
					Alanine aminotransferase increased					8/7	AST 3.4 ALT 1.9 ALP 1.5 TB ~0.5	DC positive
					Aspartate aminotransferase increased					4/3		
36	61 M 300 mg		Insufficient information Missing information	Hepatobiliary disorders	Liver disorder	No	Recovered Resolved	Related	Drug withdrawn	42/50	ALT 3.5 AST 3.4 AP no data TB .4	DC positive
37	80s M 150 mg, 300 mg QD		Insufficient information Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Related	Drug withdrawn	?	AST “in the 100s”	?
38	100 M 300 mg		Insufficient information Missing test values	Hepatobiliary disorders	Drug eruption Hepatic function abnormal	No	Resolved	Not Related	Drug withdrawn	?		?
39	68 F 300 mg		Weak Possible Score = 4 Al Phos, Bili missing. Iron	Investigations	Hepatic enzyme increased	No	Recovering Resolving	Related	Drug withdrawn	27	~3x ULN ALT AST	?
40	68 M 150mg		Excluded Score=0 Cholestasis antedating cholecystitis by 10 days	Hepatobiliary disorders	Cholecystitis	Yes	Fatal	Not Related	No information	Labs 90 Cholecystic 111	ALT 2.2 AST 7.8 ALP 6.3 TB ~1	?
41	90 F 150 mg, 300 mg		Missing test values	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Not Related	Drug withdrawn	32	?	?
42	86 F 150 mg, 300 mg		Excluded Score -1 Medical history: Undefined liver, gallbladder disease iron, levothyroxine[34], chloramphenicol	Hepatobiliary disorders	Hepatic function abnormal	Yes	Recoverin /Resolving	Not Related	Drug withdrawn	15	ALT 3.4 AST 3.6 ALP 22 TB 1.4	?
43	? M 300 mg		Insufficient information	Hepatobiliary disorders	Hepatic function abnormal	No	Recovered Resolved	Not Reported	Drug withdrawn	146	ALT 1.6 AST 2.0	NA

[34] Possible racial basis for reaction to levothyroxine in Japanese subjects https://www.ncbi.nlm.nih.gov/books/NBK548497/

		(b) (6)	AT elevations ~2X									
44	79 M 300 mg		Unlikely	Hepatobiliary disorders	Congestive heart failure Hepatic function abnormal	No	Recovered Resolved	Not Reported	No AE	280	>1XULN ALT/AST	NA
45	70 F 300 mg, 450 mg		Unlikely No fractionation of bilirubin but with history of hemolytic anemia and SLE, isolated bilirubin elevation could be indirect bilirubin from hemolysis.	Investigations	Anemia Blood bilirubin increased	No	Recovered Resolved	Not Related	Dose increased	6 months, 21 d	Max bili 1.7	NA
46	67 F 300 mg, 450 mg		Unlikely. Isolated ALT of 34 w/ an ULN of 23. Rest of lab values normal CHF	Hepatobiliary disorders	Congestive hepatopathy	No	Recovered Resolved	Not Related	Drug withdrawn	70/26	ALT 1.5 AST <1 AP <1 TB <1	NA
47	80 F 300 m g, 450 mg to 300 mg after AE		Unlikely Insufficient information	Investigations	Alanine aminotransferase increased Aspartate aminotransferase increased	No	Recovered Resolved	Not Related Not Related	Dose reduced	~120 days	?	NA
48	70 F 300 mg, 150 mg, 300 mg, AE 450 mg, 300 mg		Unlikely Score 1 Osteoporosis (baseline ALP high) Thyroxine	Investigations	Hepatic enzyme abnormal	No	Recovered Resolved	Not Related	Dose reduced	32/222	AST 2 ALT1.5 ALP 407 baseline, then max 1.7	NA
49	80s F 300 mg		Insufficient information Missing test values Methotrexate Rheumatoid arthritis	Hepatobiliary disorders	Proteinuria, CRP+ Hepatic function abnormal	No	Unknown	Not Related	Drug withdrawn	~130	?	?
50	73 F 300 mg		Unlikely Score=-2 Avacopan [6, 7] Ursodeoxycholic for microscopic polyangiitis and ANCA vasculitis	Hepatobiliary disorders	Hepatic function abnormal	No	Recovering Resolving	Not Related	No change	61	ALT 2 AST2.2 ALP 2.1 TB<1	NA

		(b) (6)										
50	88 F 300 mg		Not DILI. No liver test abnormalities Unlikely Score -1 Hepatic involvement in a systemic thrombotic disorder.	Hepatobiliary disorders	DVT Osteoarthritis Budd-Chiari syndrome	Yes	Recovering Resolving	Not Reported	Drug withdrawn	206	ALT 1 AST 1 ALP 1 TB<1	?
51	81 M 150 mg		Not DILI Unlikely Score -2 Baseline ALP elevated, Hyperphosphatemia of CKD or bone metastases from lung cancer	Hepatobiliary disorders	Small cell cancer Liver disorder	No	Not recovered Not resolved	Not Related	Drug withdrawn	51	ALT 2 AST 2 ALP3.8 even at baseline	?
52	91 F 300 mg		Insufficient information Missing liver test data. No confounders	Hepatobiliary disorders	Hepatic function abnormal	No	Unknown	Not Reported	Drug withdrawn	339	Single value ALP 2.7	NA
				Investigations	Alanine aminotransferase increased		Unknown				No data	
				Investigations	Aspartate aminotransferase increased		Unknown			339	Single value AST 3.2	
53	49 M 300 mg		Mild liver injury Not DILI Alcohol use Congestive heart failure Baseline values elevated.	Hepatobiliary disorders	Alcoholic liver disease	Yes	Not recovered Not resolved	Not Related	Drug withdrawn	70	ALT 6 AST 21 AP 1.4 TB<1	Elevated at BLN
54	63 M 150 mg		Missing liver test data Cholelithiasis	Hepatobiliary disorders	Bile duct stone	Yes	Recovering Resolving	Not Related	No change	49	?	?

Appendix B: Case Level Assessments from VOILET Study (Japan).

1. Subject [redacted] (b) (6) (VIOLET Identifier [redacted] (b) (6): We assessed this case as unlikely to indeterminant DILI due to VDA.

This 65-year-old Japanese man with chronic anemia from CKD on hemodialysis enrolled in the VIOLET post market trial. He developed hepatocellular injury with jaundice 78 days after starting VDA 300 mg. He had hypertension, diabetes with microvascular and macrovascular complications (CVA, hemorrhagic stroke), obesity[35] and was on clopidogrel and rosuvastatin.

BMI was 29.6 kg/m^2. Alcohol history was not provided. ALT, AST, ALP, and TB values were 38 U/L, 27 U/L, 65 U/L and missing, respectively at baseline, and 62 U/L, 41 U/L, 74 U/L and 0.3 mg/dL on Day 39. On Day 39, he had a subdural hematoma that was treated with a herbal medication to reduce cerebral edema. On Day 51 a drug rash developed that improved with prednisone, 15 mg/day. On Day 65, ALT and AST increased to >3X ULN peaking on day 78 (ALT137 to 881, AST 64 to 995, ALP 78 to 1030 [all in U/L] and TB 0.3 to 3.5 mg/dL) (**Figure A**). The narrative is limited in clinical detail beyond this point. There is no mention of a febrile illness, diarrhea, abdominal pain, pruritus, jaundice, cough, or pleuritic symptoms. On Day 72 (19 days after rash), atypical hemolytic uremic syndrome attributed to clopidogrel and invasive bronchopulmonary aspergillosis were diagnosed. Bilirubin was elevated but unfractionated. The patient died on Day 104, and autopsy confirmed bronchopulmonary aspergillosis; there was no description of the liver on autopsy. No eosinophilia was reported. End of treatment is not specified, but VDA likely was discontinued at the peak of liver injury. No evaluation testing was provided. Imaging information was not available. No symptoms or physical findings are reported.

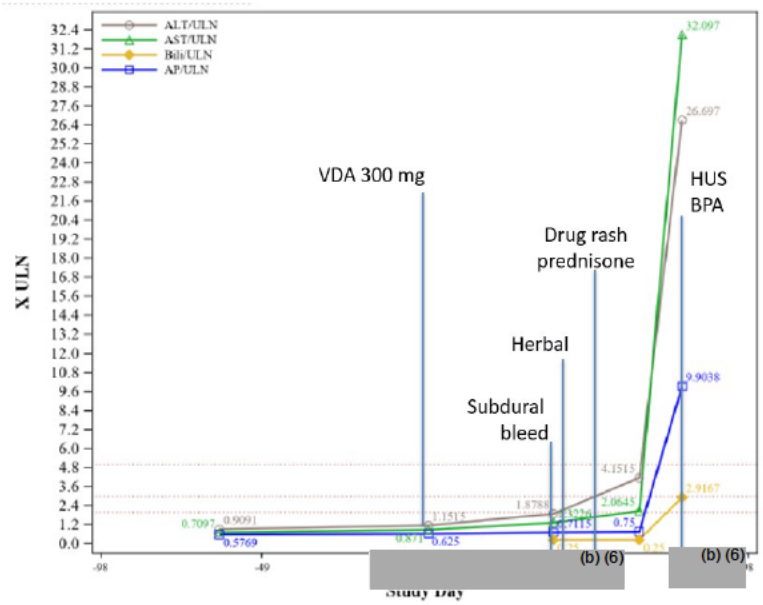

Figure A: Reported adverse events, liver analytes and drug exposures over time for subject [redacted] (b) (6)

Assessment: We assessed this case as indeterminate to unlikely. Latency is appropriate for DILI, but other events including herbal/dietary supplement (HDS) use, a stroke, pneumonia, and hemolytic uremic syndrome (HUS) cloud attribution to VDA. The narrative is limited considering the case

[35] Kanazawa M, et al. Criteria and classification of obesity in Japan and Asia-Oceania. *World Rev Nutr Diet*. 2005;94:1-12. doi: 10.1159/000088200. PMID: 16145245.

complexity. The HDS, jidaboikuippo is used for cerebral decompression following surgical procedures.[36] It started two days after the stroke. Liver enzymes were already elevated before the HDS started, but subsequent course is confounded by its use. The rash raised the possibility of immune-mediated liver injury from VDA or the HDS. HUS is not typically associated with DILI, and hemolysis can increase AST and ALT. High ALP (>1000 U/L) suggest a mixed pattern injury (R-value <5), not hepatocellular. Thus, in ability to attribute the injury to VDA, competing etiologies, and liver enzyme pattern are all inconsistent with DILI and Hy's Law.

2. Subject [redacted] (b) (6) (VIOLET identifier [redacted] (b) (6)): We assessed this case as unlikely DILI due to VDA.

Summary: This 93-year-old Japanese female, with CKD anemia who developed a mixed pattern liver injury (R-value 2 to 5) 318 days after starting VDA 300 mg.

At baseline, he was on several medications for hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, hypothyroidism, and hyperuricemia. He was also on ursodeoxycholic acid and pancreatic enzymes. no herbal/dietary supplements (HDS) were reported. He had a history of hepatitis C. Alcohol history was not provided. His ALT, AST, and AP were 51 U/L, 75 U/L, 153 U/L at baseline. VDA dose started at 300 mg/d but was adjusted to 450 mg on Day 14, and 600 mg around Day 30. On Day 318, ALT, AST, and AP were 32 U/L, 60 U/L, and 231 U/L respectively. No symptoms were reported, and no bilirubin values were available on this date. No diagnostic testing was done until day 392 when pancreatic cancer was reported with mixed-cholestatic injury and jaundice (AP 5.5x ULN, AST 4x ULN, ALT 2x ULN and TB 5.3x ULN). There is conflicting information on date of drug discontinuation, but the subject died on Day 393 (**Figure B**). No evaluation testing is provided. Pancreatic cancer is presumed to have been diagnosed with imaging; no biopsy findings are reported. No symptoms or physical findings are reported.

[36] Nakae H, et al. Application of Traditional Japanese Drug Jidabokuippo in a Modern Society. *Front Pharmacol*. 2022; 13: 1-9.

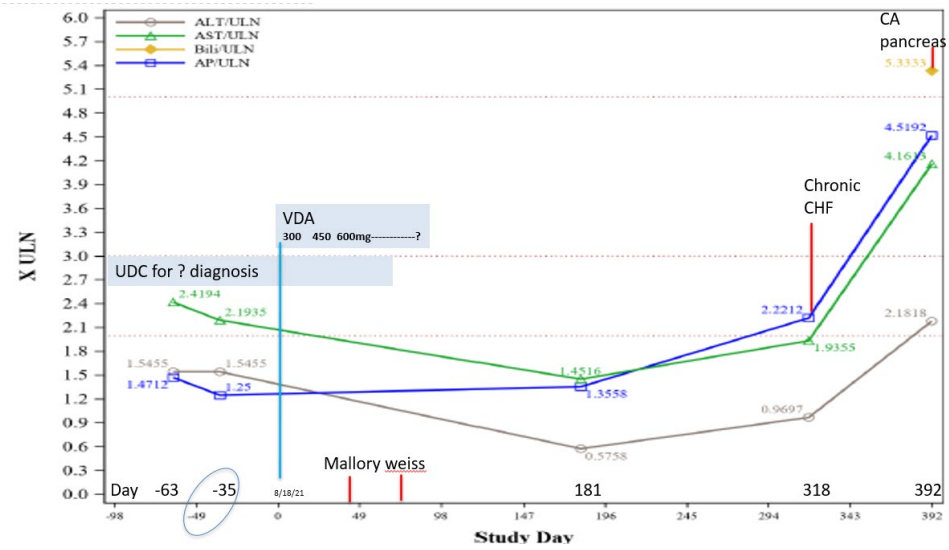

Figure B: Reported adverse events, liver analytes and drug exposures over time for subject [redacted] (b) (6)

Assessment: We assessed this case as unlikely DILI because of the long latency and concurrent pancreatic cancer suggesting probable biliary obstruction.

3. Subject [redacted] (b) (6) (VIOLET Identifier [redacted] (b) (6)): We assessed this case as unlikely DILI due to VDA.

This 84-year-old male with CKD anemia who developed a elevation in AST and TB approximately three weeks after starting VDA.

He had baseline elevations in their AP to 3x ULN (315 IU/L). ALT, AST and TB were all normal. Body mass index was 19.7 kg/m^2. He had diabetes, dyslipidemia, uremic bone disease, coronary artery disease, congestive heart failure (CHF), and dementia. He was on 13 medications. Alcohol history was not provided.

He started VDA at 300 mg daily on Day 1. He developed pneumonia and CHF on Day 24, and received ceftriaxone and Yokokansan, an HDS approved for reimbursement in Japan as a therapeutic option for dementia according to the Japan Neurology Society. With the development of pneumonia, AST and TB rose to 3.9x and 2.6x ULN, respectively, but AP remained stably elevated, and ALT remained normal (**Figure C**).

The patient died a day after onset of pneumonia without further details provided. No evaluation testing is provided. Imaging information is not available. No symptoms or physical findings are reported.

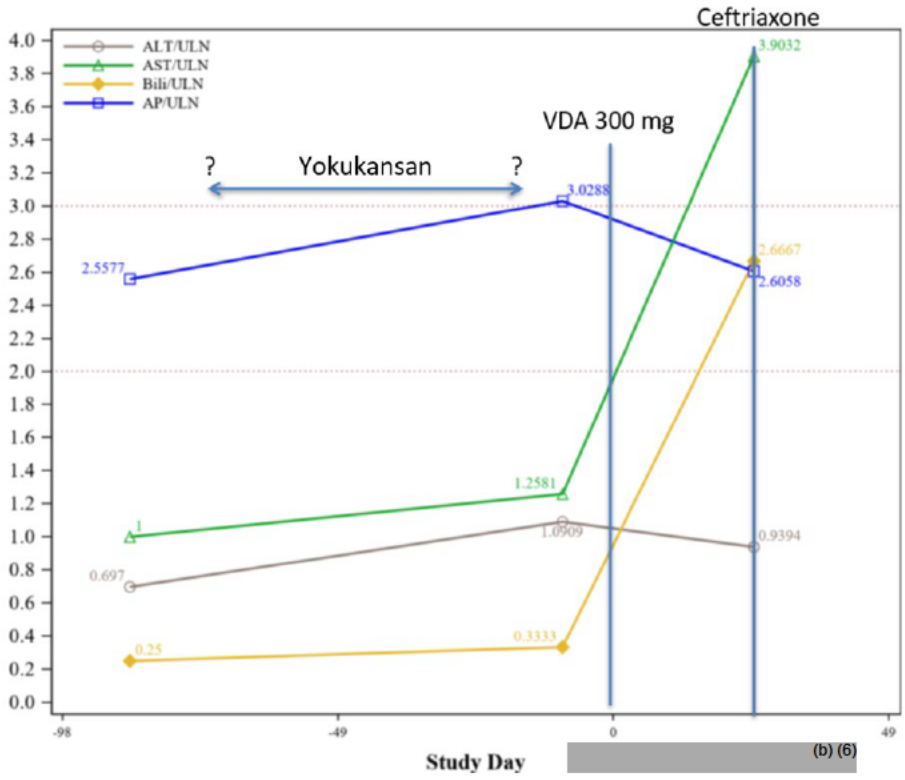

Figure C: Liver analytes and drug exposures over time for subject (b) (6)

Assessment: We assess this liver injury as unlikely DILI due to VDA. While the onset of this hepatotoxic injury is consistent with DILI, the HDS competes as causal. Liver analyte monitoring is recommended for this HDS.[37] Possible liver injury from heart failure and infection (pneumonitis).[38] The isolated AST could be due to a non-liver AST source (e.g., myopathy). Uremic bone disease could explain baseline AP elevations. Single parenteral dose of cephalosporins can cause acute liver injury,[39] but the latency is a too short.

4. Subject (b) (6) (VIOLET identifier (b) (6)): We assessed this case as unlikely DILI or indeterminate.

This 74-year-old male with anemia due to DD-CKD. He had acute hepatocellular liver injury without jaundice 29 days after starting VDA.

At baseline, he had diabetes mellitus, diabetic nephropathy, hypertension, nephrosclerosis, atrial fibrillation, aortic valve stenosis, cerebral infarction, and arteriosclerosis obliterans. He had baseline elevations in ATs and GGT. He started VDA 300 mg once daily on Day 1, and by Day 29, he had acute hepatocellular injury without jaundice leading to VDA discontinuation (**Table A**). LDH has only mildly elevated. There is no description of events preceding the injury or mention of symptoms. There was no information on evaluation testing.

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[37] https://www.drugs.com/npp/yi-gan-san.html -
[38] Okamoto, H., et al., *Yokukan-san: a review of the evidence for use of this Kampo herbal formula in dementia and psychiatric conditions.* Neuropsychiatr Dis Treat, 2014. **10**: p. 1727-42.
[39] LiverTox® https://www.ncbi.nlm.nih.gov/books/NBK547862/

Table A: Liver analytes over time for Subject [redacted] (b) (6)

Laboratory Test Results			
Date/Time (Study Day)		Test Name (Unit)	Result
[redacted] (b) (6)	(-91)	Alanine Aminotransferase (IU/L)	20
	(-91)	Alkaline Phosphatase (IU/L)	65
	(-91)	Aspartate Aminotransferase (IU/L)	50
	(-91)	Bilirubin (mg/dl)	.4
	(1)	Alanine Aminotransferase (IU/L)	32
	(1)	Alkaline Phosphatase (IU/L)	86
	(1)	Aspartate Aminotransferase (IU/L)	62
	(1)	Bilirubin (mg/dl)	.5
	(29)	Alanine Aminotransferase (IU/L)	441
	(29)	Alkaline Phosphatase (IU/L)	119
	(29)	Aspartate Aminotransferase (IU/L)	2456
	(29)	Bilirubin (mg/dl)	.7
	(36)	Alanine Aminotransferase (IU/L)	47
	(36)	Alkaline Phosphatase (IU/L)	107
	(36)	Aspartate Aminotransferase (IU/L)	76
	(36)	Bilirubin (mg/dl)	.5

Assessment: We assessed this case as unlikely or indeterminate for DILI due to VDA. The latency is compatible with DILI, and there is a positive dechallenge. However, resolution was too rapid (within 7 days) and AST markedly higher than ALT, raising the possibility of myopathy. Rapidly resolving congestive heart failure also competes. Sponsor's response to information request suggests no co-occurring ischemic events were being investigated.

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/s/

PAUL H HAYASHI
03/08/2024 05:12:24 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Memorandum: Review of Japanese postmarketing safety data

Date:	March 1, 2024
Reviewers:	Wei Liu, PhD, MSc Division of Epidemiology I (DEPI I) Office of Surveillance and Epidemiology (OSE) Kate Gelperin, MD, MPH DEPI I, OSE
Team Leader:	Steven Bird, PharmD, PhD DEPI I, OSE
Associate Director:	Kira Leishear, PhD, MS DEPI I, OSE
Subject:	Review of Japanese postmarketing safety data
Drug Name:	Vafseo™ Tablets 150 mg / 300 mg (Vadadustat)
Application Type/Number:	NDA 215192
Sponsor:	Akebia Therapeutics, Inc
TTT #:	2023-6571

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review follows a request from the Division of Non-malignant Hematology (DNH) to the Division of Epidemiology-1 (DEPI-1) and the Drug-Induced Liver Injury (DILI) Team in the Division of Hepatology and Nutrition (DHN) to review Japanese postmarketing safety data focusing on drug-induced liver injury (DILI) associated with vadadustat (VAFSEO™), a hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor proposed for the treatment of anemia associated with chronic kidney disease (CKD). The original NDA submission received a Complete Response (CR) on March 29, 2021; however, based on FDA's response to a formal dispute resolution request and suggestion for an appropriate path forward, with a focus on any reports of serious DILI in Japanese postmarketing safety data, the applicant resubmitted the NDA on September 27, 2023, seeking an indication for vadadustat in dialysis-dependent (DD) patients only.

Vadadustat was approved for marketing in Japan in June 2020 for the treatment of renal anemia due to CKD in both DD and non-dialysis dependent (NDD) adult patients. Japan is the only country where vadadustat is currently marketed. Based on sales data, the applicant estimates that more than (b) (4) patients in Japan have been treated with vadadustat. As required for all new drugs approved in Japan, the sponsor 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 postmarketing surveillance (PMS) observational study (VIOLET) to evaluate the safety and efficacy of long-term administration of vadadustat. VIOLET is a prospective, single-arm long-term surveillance study to evaluate the safety and efficacy of vadadustat. The program is designed to include 2,000 CKD patients. Although a final clinical study report is not currently available, the applicant provided an English translation of the interim VIOLET Study Data Summary which describes data collected from November 24, 2020 (study start date) through June 28, 2023. A total 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. Treatment was discontinued prematurely in 528 (28.6%) patients. The main reasons for treatment discontinuation were adverse events/adverse drug reactions (AEs/ADRs) in 162 patients (8.8%), drug ineffective in 99 patients (5.4%), and "hospital transfer" in 94 patients (5.1%). Hepatobiliary AEs/ADRs from the VIOLET study, including two that were classified as serious and three with clinical laboratory data consistent with Hy's Law (i.e., ALT or AST >3x ULN and bilirubin >2x ULN) were adjudicated by the DHN DILI team and were considered to be confounded by concomitant medications and herbal therapies.

(b) (4)

1 INTRODUCTION

1.1 REGULATORY BACKGROUND

Vadadustat (VAFSEO™) is a hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor which was originally proposed to be indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis. The original NDA submission received a Complete Response (CR) on March 29, 2021. The specific deficiencies highlighted by the review team include: 1) increased risk of major adverse cardiovascular events (MACE), 2) increased risk of thromboembolic events, and 3) a concerning drug-induced liver injury (DILI) event and an imbalance in the incidence of alanine aminotransferase (ALT) elevations.

Akebia (the Applicant) submitted a formal dispute resolution request (FDRR) for the CR which was denied by the Center for Drug Evaluation and Research (CDER) on May 26, 2023. Per the FDA's Formal Dispute Resolution Guidance, Dr. Peter Stein, Director of CDER's Office of New Drugs (OND) provided a full review of the materials submitted by the Applicant in support of their appeal, and reviews, meeting minutes, and decision memoranda prepared by FDA staff. Based on his review, Dr. Stein agreed with the decision made by the review team, but he also pointed out that there is an appropriate path forward for the Applicant to consider. Specifically, for the DILI-related deficiency, Dr. Stein wrote "*I conclude that there is a signal for DILI, but that it appears to be modest in intensity, suggesting that it is potentially manageable with appropriate monitoring. Additional post-market experience would be highly valuable in confirming that DILI will be unusual event post-approval. You have referred to data from Japan reflecting an extensive experience with vadadustat – these additional data may prove valuable in further assessing the risk of DILI with vadadustat.*"[a,b]

A Type A End of Dispute Meeting between the Applicant and FDA was held on July 17, 2023 to discuss the Japanese postmarketing safety data that are available to address the DILI deficiency in the CR letter as well as the structure of NDA resubmission.

Subsequently, the Applicant submitted an official response pertaining to the CR and resubmission of the NDA on September 27, 2023. For the resubmission, the Applicant is seeking an indication for vadadustat only in the dialysis patients. The Division of Non-malignant Hematology (DNH) consulted the Drug-Induced Liver Injury (DILI) Team in the Division of Hepatology and Nutrition (DHN) and the Division of Epidemiology I (DEPI-I) in the Office of Surveillance and Epidemiology (OSE) to review the Japanese postmarketing safety data and provide an analysis and recommendations regarding the DILI signal.

1.2 JAPANESE POSTMARKETING SAFETY DATA

Vadadustat was approved for marketing in Japan in June 2020 for the treatment of renal anemia due to CKD in both dialysis dependent and non-dialysis dependent adult patients. Vadadustat was launched in Japan in August 2020 by Akebia's development partner Mitsubishi Tanabe Pharma Corporation (MTPC). Based on numbers of tablets sold, average daily dose and number of days on treatment,

[a] Peter Stein. Formal Disput Resolution Appeal. May 26, 2023. NDA 215192 DARRTS Reference # 5180576.

[b] Japan is the only country where vadadustat is currently marketed.

MTPC estimates that more than (b) (4) CKD patients have been exposed to vadadustat as of data lock Jun 28, 2023.[c]

Akebia's Resubmission to NDA 215192 (vadadustat tablets) included summary analyses of postmarketing safety data from Japan which are described below as excerpted from the application.[d]

As required for all new drugs approved in Japan, MTPC created and maintains a local risk management plan (J-RMP) for vadadustat 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 collection of spontaneous adverse events / adverse drug reactions (AEs/ADRs), data generation from a post-marketing surveillance (PMS) observational study, and submission of aggregate data and other safety updates in periodic safety update reports (PSURs).

1.2.1 Early Post-marketing Phase Vigilance (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 and are not described further in this review. No new safety signals were identified from the EPPV and there were no reports of hepatic failure, liver transplant, or death due to DILI associated with vadadustat.[e]

1.2.2 Pharmacovigilance (Postmarketing Spontaneous Reports and PSURs)

During the reporting period from launch in Japan to Jun 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.[f]

There have been five Japan PSURs since approval of vadadustat (Vafseo) in Japan (PSUR#1: 29 Jun 2020 to 28 Dec 2020; PSUR#2: 29 Dec 2020 to 28 Jun 2021; PSUR#3: 29 Jun 2021 to 28 Dec 2021; PSUR#4: 29 Dec 2021 to 28 Jun 2022; and PSUR#5: 29 JUN 2022 to 28 Jun 2023). MTPC submitted PSURs to PMDA according to local regulations. 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.

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[c] \\CDSESUB1\EVSPROD\nda215192\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\safety-update-report.pdf (Safety Update Report)

[d] \\CDSESUB1\EVSPROD\nda215192\0046\m1\us\12-cov-let\cover-letter.pdf (Cover Letter/ NDA 215192/ vadadustat tablets/ resubmission/ Akebia)

[e] \\CDSESUB1\EVSPROD\nda215192\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\sur-appendix1.pdf (Vadadustat EPPV Report)

[f] \\CDSESUB1\EVSPROD\nda215192\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\sur-appendix2.pdf (Vadadustat Postmarketing Adverse Reactions Table/Listing/Figure)

1.2.3 Post-marketing Surveillance (PMS) Observational Study - VIOLET

The vadadustat PMS (observational surveillance study: post-marketing surveillance of **V**adadustat in patients with anem**I**a in chr**O**nic kidney disease for **L**ong-term **E**fficacy and safe**T**y [VIOLET]) is being conducted to evaluate the safety and efficacy of long-term administration of vadadustat in routine clinical settings in patients with renal anemia. The vadadustat PMS is designed to include 2,000 CKD patients (including ≥ 500 non-dialysis dependent [NDD] patients, ≥ 500 dialysis-dependent [DD] patients, and ≥ 100 peritoneal dialysis [PD] patients) at registration to ensure that at least 1,000 participants complete the observation period of 2 years (Appendix 6.2).

The PMS collects patient background characteristics, dialysis type and duration, treatment status (vadadustat and concomitant medications), AEs, and clinical laboratory test data. Study registration began November 24, 2020 and has fully enrolled. Follow-up per protocol is ongoing.

2 REVIEW MATERIALS

- New Drug Application (NDA) 215192/ vadadustat tablets/ RESUBMISSION/ 27 Sept 2023/ Safety Update Report. EDR Location: \\CDSESUB1\EVSPROD\nda215192\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\safety-update-report.pdf
- Vadadustat Japan VIOLET PMS Study - interim data summary (June 28, 2023 datacut). EDR Location: \\CDSESUB1\EVSPROD\nda215192\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\sur-appendix3.pdf
- Response to FDA's Information Request (IR) dated December 6, 2023. Submitted by Akebia on January 11, 2024. EDR Location: \\CDSESUB1\evsprod\NDA215192\0052
- Response to FDA's Information Request (IR) dated January 31, 2024. Submitted by Akebia on February 7, 2024. EDR Location: \\CDSESUB1\EVSPROD\nda215192\0054\m1\us\111-info-amend\clin-info-amend.pdf
- Response to FDA's Information Request (IR) dated February 15, 2024. Submitted by Akebia on February 21, 2024. EDR Location: \\CDSESUB1\EVSPROD\nda215192\0057\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\vafseo-english.pdf

3 REVIEW RESULTS

3.1 PHARMACOVIGILANCE - POSTMARKETING SPONTANEOUS REPORTS

During the period from vadadustat launch in Japan to June 28, 2023, a total of 4,159 AEs/ADRs in 2,793 unique patients were received by MTPC. Of these, 1,070 AEs/ADRs were considered serious, and 201 were assessed as related to vadadustat by the reporter. Of the 1,070 SAEs, 306 cases resulted in a fatal outcome. There were 3,089 non-serious AEs/ADRs reported during the period (Appendix 6.1). The Applicant identified 45 postmarketing spontaneous reports of hepatobiliary AEs/ADRs, of

which 13 were classified as serious.[g] Hepatobiliary cases were reviewed and adjudicated by Drs. Eileen Navarro Almario and Paul Hayashi for the Drug-induced Liver Injury Team, Division of Hepatology and Nutrition (DHN DILI team), and are described in their review. The DHN DILI team concluded that the cases "are confounded by herbal and U.S. unapproved drug product use. The surveillance program, however, demonstrates feasibility of liver monitoring in the setting of anemia of CKD, and supports considerations for safe use in the DD CKD population."

3.2 VIOLET PMS STUDY - INTERIM RESULTS

3.2.1 Study design and status

The VIOLET study is a prospective, multicenter, single-arm long-term surveillance study to evaluate the safety and efficacy of long-term use of vadadustat in actual clinic settings in patients with renal anemia, including NDD, DD, and PD patients. The VIOLET study is being conducted by Akebia's partner Mitsubishi Tanabe Pharma Corporation (MTPC) and is currently ongoing. Written informed consent is obtained prior to enrollment. The primary data source is electronic medical records, with an electronic data capture system utilizing the internet. Investigators were instructed to use Case Report Forms (CRF) to collect patient information 3 months before treatment initiation (including pre-treatment information and patient characteristics), 1 month, 2 months, 3 months, 6 months, 1 year, and 2 years after the start of treatment.

A final clinical study report is not currently available from MTPC; however, Akebia provided an English translation of the interim VIOLET Study Data Summary which describes data collected from November 24, 2020 (study start date) through June 28, 2023. Of the 431 sites currently participating in the VIOLET Study, 310 facilities also contributed data to the EPPV (August 2020 to February 2021). As a result of this overlapping time period, 41 patients simultaneously contributed to both the EPPV and the VIOLET Study. From November 24, 2020 through June 28, 2023, there were a total of 2,262 patients registered with the PMS from 431 registered facilities. Of these, 1,882 were enrolled and 1,847 patients were included in the safety analysis population: 1,233 NDD, 142 PD, and 472 HD.[h]

3.2.2 Patient demographics and clinical characteristics

During the reporting period, 2,262 patients were enrolled from 431 sites in Japan. A total of 1,847 cases were included in the safety analysis (Appendix 6.3), including 1,233 NDD, 142 PD, and 472 HD patients. Of these, 54% were male. The mean age at the time of vadadustat initiation was 74.2 years. Within the subgroup of 614 DD patients, 65% were male and the mean age at the start of treatment was 67.7 years. The mean dialysis period was 5.23 years (see Table 1 below for more details).

[g] NDA215192 (215192 - 0046 - (46) - 2023-09-27 - ORIG-1 /Multiple Categories/Subcategories) - Safety Update Report - Table 31.1p (#5)

[h] VIOLET Study – interim report (June 28, 2023 datacut) \\CDSESUB1\EVSPROD\nda215192\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\sur-appendix3.pdf

Table 1: Baseline demographic and clinical characteristics

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)

3.2.3 Pre-existing Conditions

Patient baseline characteristics were identified in the VIOLET study case report form, including gender, age, dialysis-dependence, duration of renal anemia, selected clinical laboratory parameters, history of adverse drug reactions, allergy, alcohol use, smoking history, "complications" and past medical history, concomitant medications, and switched drugs. The term "complications" (as used in the case report form and the interim report) refers to "all diseases that are currently occurring at the time of the start of administration of this drug," and included the following conditions:

- Thromboembolism (n=233; 12.6%), including cerebral infarction (n=110), myocardial infarction (n=43), and "other conditions" (n=93)
- Cardiovascular disease, not including thromboembolism (n=140; 7.6%)
- Hypertension (n=950; 51.4%)
- Diabetes mellitus (n=159; 8.6%)
- Malignant tumor (n=89; 4.8%)
- Proliferative diabetic retinopathy (n=145; 7.9%)
- Macular edema (n=20; 1.1%)
- Exudative age-related macular degeneration (n=4; 0.2%)
- Retinal vein occlusion (n=6; 0.3%)
- Liver function impairment[i] (n=75; 4.1%)

3.2.4 Extent of exposure

Table 2 describes dose and duration of vadadustat administration in the overall safety population (n=1,847), and in the dialysis-dependent (DD) subpopulation (n=614). The mean dosing period in the overall safety analysis was 201.8 days.

[i] Note: The definition of baseline "liver function impairment" was not described in the report.

Administration of vadadustat was discontinued prematurely in 528 (28.6%) patients. The main reasons for discontinuation were adverse events / adverse drug reactions (AEs/ADRs) in 162 patients (8.8%), drug ineffective in 99 patients (5.4%), and "hospital transfer" in 94 patients (5.1%). The mean dosing period for the 614 DD patients was 175.4 days. Of the 614 DD patients, 213 (34.7%) discontinued treatment because of drug ineffective (35.7%), AEs/ADRs (28.6%), or hospital transfer (11.7%).

Table 2: Dose and duration of vadadustat exposure

	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.

3.2.5 Adverse Events / Adverse Reactions

Among the 1,847 patients included in the safety analysis, adverse events / adverse drug reactions (AEs/ADRs) were reported in 202 patients (10.9%), of which 63 (3.4%) were classified as serious adverse events (SAEs). A total of ten AEs/ADRs resulting in death were reported (0.54%). (*Note: the terms adverse event and adverse reaction were used interchangeably by the Applicant in the interim study report.*)

Table 3: AEs/ADRs with a Fatal Outcome

	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

3.2.6 Hepatobiliary AEs/ADRs

The Applicant conducted a search of AEs/ADRs from the VIOLET study using the Standardised MedDRA Query (SMQ) "Drug- Related Hepatic Disorders - Comprehensive Search." Eleven hepatobiliary AEs/ADRs were identified in 9 patients (0.5%). One case of "Hepatic function abnormal" and one case of "Congestive hepatopathy" were classified as serious (Table 3). Hepatobiliary cases were reviewed and adjudicated by the DHN DILI team, and are described in their review.

Table 4: Hepatobiliary AEs/ADRs (SMQ/PT)

	Total (n=1,847)
No. of patients with hepatobiliary AEs/ADRs (MedDRA SMQ search)	9 (0.5%)
Alanine aminotransferase increased (PT)	1
Aspartate aminotransferase increased (PT)	2
Gamma-glutamyl transferase increased (PT)	1
Hepatic function abnormal (PT)	3
Hyperbilirubinemia (PT)	1
Liver disorder (PT)	1
Hepatic enzyme increased (PT)	1
Congestive hepatopathy (PT)	1

Source: Vadadustat Japan VIOLET Study Interim Results. June 28, 2023. Attachments 1-6, 1-18, and 1-21.

In addition, the Applicant reviewed available clinical laboratory data collected by MTPC from patients enrolled in the VIOLET study to identify cases with ALT or AST >3x the upper normal limit (ULN)

and bilirubin >2x ULN (potential Hy's Law cases). Three patients were identified based on clinical laboratory criteria but were considered by Akebia to have non-hepatic AEs/ADRs. These cases were assessed by the DHN DILI Team and are described in their review. Although all three cases had a fatal outcome, they were confounded by multiple concomitant medications and herbal therapies, and serious medical conditions including: 1) atypical hemolytic uremic syndrome (attributed to clopidogrel use) and invasive bronchopulmonary aspergillosis (JP-AKEB-22-021063/ 00002-002); 2) pancreatic cancer (AKE-2021- 1075/ 00035-007); and 3) pneumonia and heart failure (JP-AKEB-22-020921/ 00106-004).

3.2.7 Vadadustat discontinuation due to AE/ADR or hospital transfer

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 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%), as shown in Appendix 6.4.

In addition, 94 patients discontinued vadadustat treatment due to "hospital transfer." Of these, 19 (20%) patients had an associated AE/ADR (see Appendix 6.5). Hepatobiliary disorder was reported for one patient who discontinued vadadustat due to hospital transfer. In response to an Information Request, Akebia indicated that "hospital transfer" is often an administrative reason for study discontinuation; however, some patients may have associated AEs/ADRs.

(b) (4)

[redacted]

4 DISCUSSION

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 appear 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. The VIOLET PMS Study and postmarketing surveillance activities are conducted under contracts between the MTPC and Japanese medical institutions in accordance with local laws and regulations. These postmarketing safety monitoring activities are unique to Japan. The establishment of such infrastructure and reporting requirements may encourage physicians to contribute to pharmacovigilance activities including collection and submission of high-quality data.

4.1 STRENGTHS OF JAPANESE POSTMARKETING SAFETY DATA IN THIS REVIEW

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan is a robust health authority with regulations and practices regarding postmarketing safety surveillance comparable to those in the

United States. Japan is a founding member of the International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH). ICH was established in 1990 through cooperation of regulators and pharmaceutical industry representatives from three regions: United States, European Union, and Japan. The primary purpose of ICH is to improve efficiency of new drug development and registration processes and to promote public health. This is accomplished through development of harmonized, technical guidelines and standards that are implemented by regulatory authorities. 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.

4.2 LIMITATIONS OF JAPANESE POSTMARKETING SAFETY DATA IN THIS REVIEW

It is important to note that the Applicant did not conduct additional analyses of the safety data in the VIOLET PMS Study interim report that could facilitate comprehensive identification of all AESIs (adverse events of special interest). Because MedDRA PTs are very granular, similar disease conditions of interest may be coded with different PTs in different SOCs. In order to identify accurate case counts for AESIs, additional analyses with pre-specified case definition and comprehensive MedDRA search strategies are necessary. In the absence of accurate case counts, calculation of incidence for AESIs is not clinically meaningful.

Other limitations include:

- Translation from Japanese language to English was not of high quality (e.g., the category name from the VIOLET Study case report form describing baseline pre-treatment conditions was translated as “complications” which is not an accurate term for a pre-existing condition).
- VIOLET interim study results may not have undergone similar quality checks as would be expected in a final study report (e.g., discrepancy in some case counts depending on MedDRA search strategy, potential coding errors)
- Clinical details for hepatobiliary SAEs were sparse and were not provided for other SAEs.
- A large proportion (n=379; 17%) of enrolled patients were not included in the safety analysis (Appendix 6.3). It is unclear whether selection bias could be an issue.
- The estimated number of patients exposed to vadadustat in Japan is calculated based on sales data. Although this method is commonly used to estimate exposure to marketed drugs, it is not known how much of the vadadustat sold in Japan (e.g., to pharmacies) was actually prescribed for and taken by a patient.
- Definitions of Adverse Events of Special Interest (AESIs) were not pre-specified and were not described in the interim study report.
- Accurate case counts for AESIs cannot be determined based solely on MedDRA PTs in the absence of appropriate case definitions (including MedDRA search strategy) and case review. This limitation precludes calculation of reliable estimates of incidence of AESIs from the VIOLET study interim report.
- A large proportion (n=94; 5.1%) of patients in the VIOLET study discontinued vadadustat due to “hospital transfer” which is described as an administrative reason in Akebia’s IR response; however, adverse events were also reported for some of these patients consistent with potential underreporting of AEs/ADRs as a reason for study discontinuation.

5 CONCLUSION

The estimation of incidence of AESIs in the VIOLET PMS 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. The number of hepatobiliary SAEs reported during marketed experience in Japan appears small based on available data. DEPI defers to the DHN DILI team for hepatobiliary case adjudication, and concurs with their conclusion that the cases "are confounded by herbal and U.S. unapproved drug product use. The surveillance program, however, 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, it is reasonable to conclude that the safety profile of vadadustat is consistent with product labeling in Japan (Appendix 6.6).

6 APPENDICES

6.1 POSTMARKETING SPONTANEOUS REPORTS - JAPAN

Akebia Therapeutics, Inc.
Post-Marketing (Japan)

Table 30.1.1p
Overall Summary of Adverse Events for Post-Marketing in Japan

Category	n
Any AEs	2793
Any Serious AEs	824
Any AEs with Reported Causality (Related) [1]	1008
Any AEs with Company Causality (Related) [1]	996
Any AEs Leading to Product Discontinuation	1175
Any AEs Leading to Death	306

Source code: ...\Post-Marketing (Japan)\Tables\Production\333_t_postae.sas (11JUL2023 16:38)

Source: Safety Update Report Appendix 2 – Vafseo Postmarketing TLFs – Table 30.1.1p
\\CDSESUB1\EVSPROD\nda215192\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\anemia-chronic-kidney-disease\5353-rep-analys-data-more-one-stud\safety-update-resub\sur-appendix2.pdf

6.2 VIOLET PMS STUDY - PROTOCOL

1) Study objective

To evaluate the safety and efficacy of long-term use of Vadadustat in actual clinic settings in patients with renal anemia at non-dialysis, peritoneal dialysis, and hemodialysis stages.

2) Study methods

a. Design

This is a prospective, multicenter, single-arm long-term surveillance/survey study focusing on events of particular interest with Vadadustat treatment (refer to section d for further explanation).

b. Setting

The survey is conducted at about 400 facilities, mainly those with nephrology, internal medicine, dialysis, or urology. Registration Form and Case Report Forms are collected using the Fujitsu "PostMaNet" Electronic Data Capture (EDC) system.

c. Study population selection and follow-up

Patients taking Vadadustat for the first time for renal anemia at all survey sites in Japan, excluding those on the waiting list for kidney transplantation, are enrolled in the study. Written informed consent should be obtained from participants prior to the administration of survey activities.

Each participant should be observed for 2 years. The investigators should enter the information on all registered participants 3 months before, 1 month, 2 months, 3 months, 6 months, 1 year, and 2 years after the start of treatment. The observation period for each participant terminates when she/he discontinues treatment, withdraws the informed consent, or at the end of the observation period (i.e., 2 years after treatment initiation), whichever comes first.

d. Safety outcomes of interest

Primary outcomes of interest include hepatic disorder, thromboembolism, hypertension.

Secondary outcomes of interest include cardiovascular events, malignant tumor, retinal hemorrhage, progression of disease in patients with autosomal dominant polycystic kidney disease (ADPKD).

e. Covariates

The study is conducted using primarily secondary data (i.e., information already collected in the electronic medical records). Information to be collected from each individual include demographics, Vadadustat use (e.g., dosage, number of daily dose, duration of treatment), medical history (e.g., stage of chronic kidney disease defined by the estimated glomerular filtration rate [eGFR], starting time of dialysis, onset time of renal anemia, other complications such as thromboembolism, hypertension, diabetes), treatment history (especially drugs for the treatment of renal anemia before switching to Vadadustat such as erythropoiesis-stimulating agent [ESA], other HIF-PH inhibitors, iron-preparations), other medication use before and during the observation period, laboratory tests (e.g., liver function tests, red blood cell count, hematocrit, serum ferritin, serum iron) routinely collected through clinical visits and updated at each patient encounter.

f. Study period and sample size

The survey registration period lasts from November 2020 through November 2022; the survey period starts in November 2020 and ends in November 2024 (so those patients enrolled in November 2022 will have two years of follow-up to capture the outcomes).

The number of participants for registration is 2,000 which includes ≥500 each at non-dialysis, hemodialysis stages, and ≥100 in the peritoneal dialysis stage. The estimated benchmark incidence of hepatic function disorder based on the clinical studies conducted in Japan and elsewhere is 0.3% (i.e., 14 in approximately 4,500 subjects). Hence, the minimum number of patients needed to detect one or more events that can occur with a frequency of 0.3% with a probability of 95% is 998. Considering the degree of drop-outs, the final sample size is set to be 2,000 to ensure that there will be at least 1,000 patients who might have received Vadadustat continuously for 2 years.

g. Statistical analyses

The statistical analysis will be mainly descriptive in nature. Summary statistics will be calculated for numerical data and ratios will be calculated for categorical data. For hepatic function disorder, the incidence rate and 95% confidence intervals should be calculated. Subgroup analyses will be conducted in the search of potential effect modifiers such as patient background factors.

6.3 CASE DISPOSITION

Enrolled sites	431	sites
Enrolled cases	2262	cases

Fixed questionnaire sites	392	sites
Fixed questionnaire cases	1883	cases
Questionnaire (3 months)	1883	cases
Questionnaire (6 months)	1122	cases
Questionnaire (12 months)	643	cases
Questionnaire (24 months)	31	cases
Questionnaire regarding presence or absence of malignant tumor onset (24 months)	15	cases

Subjects excluded from safety analysis *1	36	cases
Cases with a violation of enrollment criteria	4	cases
Cases not treated	32	cases
Cases with non-evaluable adverse event	15	cases

Subjects included in safety analysis	1847	cases
Non-dialysis-dependent	1233	cases
Peritoneal dialysis-dependent	142	cases
Hemodialysis-dependent	472	cases

Subjects excluded from efficacy analysis *1	36	cases
Cases not evaluable for efficacy *2	36	cases

Subjects included in efficacy analysis	1811	cases
Non-dialysis-dependent	1198	cases
Peritoneal dialysis-dependent	142	cases
Hemodialysis-dependent	471	cases

*1 The breakdown of the number of excluded cases uses overlapping aggregation.
*2 Cases in which hemoglobin levels were not measured for at least one time point, respectively, before and after administration of this Drug

Source of data: Vadadustat Japan VIOLET Study Interim Results. June 28, 2023. Page 2.

6.4 VIOLET STUDY - VADADUSTAT TREATMENT DISCONTINUATION DUE TO AE/ADR

System Organ Class (SOC) Preferred Term	N=1847 n (%)
Blood and lymphatic system disorders (SOC)	4 (0.2)
Anaemia	2 (0.1)
Atypical haemolytic uraemic syndrome	1 (0.1)
Disseminated intravascular coagulation	1 (0.1)
Cardiac disorders (SOC)	22 (1.2)
Aortic valve stenosis	2 (0.1)
Arrhythmia	1 (0.1)
Cardiac failure	3 (0.2)
Cardiac failure acute	2 (0.1)
Cardiac failure chronic	6 (0.3)
Cardiac failure congestive	4 (0.2)
Cardiac tamponade	1 (0.1)
Cardio-respiratory arrest	1 (0.1)
Myocardial infarction	1 (0.1)
Palpitations	2 (0.1)
Congenital, familial and genetic disorders (SOC)	1 (0.1)
Congenital cystic kidney disease	1 (0.1)
Ear and labyrinth disorders (SOC)	2 (0.1)
Tinnitus	1 (0.1)
Vertigo	1 (0.1)
Eye disorders (SOC)	2 (0.1)
Diabetic retinal oedema	1 (0.1)
Retinal haemorrhage	1 (0.1)
Gastrointestinal disorders (SOC)	37 (2)
Abdominal discomfort	6 (0.3)
Constipation	1 (0.1)
Defaecation urgency	1 (0.1)
Diarrhoea	10 (0.5)
Dyspepsia	1 (0.1)
Faeces soft	2 (0.1)
Gastrointestinal haemorrhage	3 (0.2)
Ileus	1 (0.1)
Mallory-Weiss syndrome	1 (0.1)
Melaena	1 (0.1)
Nausea	15 (0.8)
Vomiting	5 (0.3)
General disorders and administration site conditions (SOC)	12 (0.6)
Death	1 (0.1)

Face oedema	1 (0.1)
Feeling abnormal	1 (0.1)
Feeling hot	1 (0.1)
Malaise	2 (0.1)
Oedema	2 (0.1)
Oedema peripheral	1 (0.1)
Pyrexia	1 (0.1)
Sudden death	2 (0.1)
Hepatobiliary disorders (SOC)	8 (0.4)
Budd-Chiari syndrome	1 (0.1)
Cholecystitis	1 (0.1)
Congestive hepatopathy	2 (0.1)
Hepatic function abnormal	2 (0.1)
Liver disorder	2 (0.1)
Immune system disorders (SOC)	1 (0.1)
Type IV hypersensitivity reaction	1 (0.1)
Infections and infestations (SOC)	19 (1)
Bacteraemia	1 (0.1)
Bronchopulmonary aspergillosis	1 (0.1)
COVID-19	3 (0.2)
Hepatic cyst infection	1 (0.1)
Herpes zoster	1 (0.1)
Peritonitis	1 (0.1)
Pneumonia	3 (0.2)
Pneumonia aspiration	7 (0.4)
Sepsis	3 (0.2)
Injury, poisoning and procedural complications (SOC)	5 (0.3)
Extradural haematoma	1 (0.1)
Fall	1 (0.1)
Radius fracture	1 (0.1)
Shunt occlusion	2 (0.1)
Spinal compression fracture	1 (0.1)
Investigations (SOC)	17 (0.9)
Alanine aminotransferase increased	1 (0.1)
Aspartate aminotransferase increased	2 (0.1)
Blood creatine phosphokinase increased	1 (0.1)
Blood creatinine increased	2 (0.1)
Blood iron decreased	1 (0.1)
Blood lactate dehydrogenase increased	2 (0.1)
Blood pressure decreased	2 (0.1)
Blood pressure increased	2 (0.1)
Fibrin degradation products increased	1 (0.1)

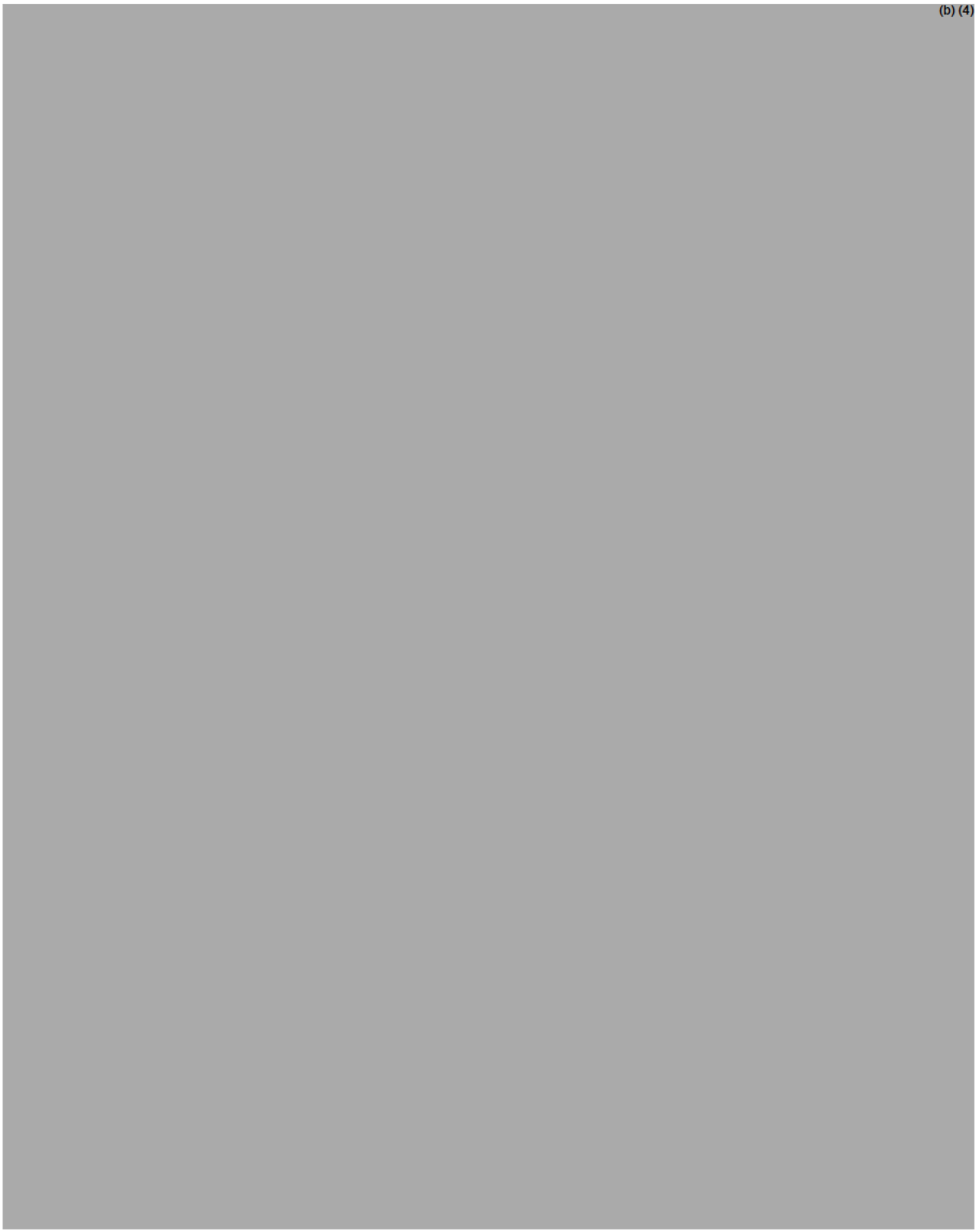
Gamma-glutamyltransferase increased	1 (0.1)
Haematocrit increased	1 (0.1)
Haemoglobin increased	3 (0.2)
Hepatic enzyme increased	1 (0.1)
Iron binding capacity total increased	1 (0.1)
Iron binding capacity unsaturated increased	1 (0.1)
Platelet count decreased	1 (0.1)
Protein urine present	1 (0.1)
Weight decreased	2 (0.1)
Weight increased	1 (0.1)
Metabolism and nutrition disorders (SOC)	20 (1.1)
Cachexia	1 (0.1)
Decreased appetite	11 (0.6)
Dehydration	3 (0.2)
Hypercalcaemia	1 (0.1)
Hyperkalaemia	1 (0.1)
Hypophagia	1 (0.1)
Marasmus	6 (0.3)
Musculoskeletal and connective tissue disorders (SOC)	5 (0.3)
Arthralgia	1 (0.1)
Back pain	1 (0.1)
Musculoskeletal discomfort	1 (0.1)
Osteoarthritis	1 (0.1)
Osteoporosis	1 (0.1)
Pain in extremity	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	10 (0.5)
Bladder cancer	1 (0.1)
Bladder neoplasm	1 (0.1)
Colon cancer	1 (0.1)
Gastric cancer	2 (0.1)
Haemangioma	1 (0.1)
Hepatic cancer	1 (0.1)
Pancreatic carcinoma	1 (0.1)
Rectal cancer	1 (0.1)
Small cell lung cancer	1 (0.1)
Nervous system disorders (SOC)	13 (0.7)
Cerebral haemorrhage	1 (0.1)
Cerebral infarction	3 (0.2)
Dementia Alzheimer's type	1 (0.1)
Dizziness	5 (0.3)
Dysarthria	1 (0.1)

Headache	1 (0.1)
Hypoaesthesia	1 (0.1)
Limbic encephalitis	1 (0.1)
Renal and urinary disorders (SOC)	8 (0.4)
Acute kidney injury	1 (0.1)
Azotaemia	1 (0.1)
Chronic kidney disease	1 (0.1)
Pollakiuria	2 (0.1)
Renal failure	2 (0.1)
Renal impairment	1 (0.1)
Respiratory, thoracic and mediastinal disorders (SOC)	5 (0.3)
Acute respiratory failure	1 (0.1)
Cough	1 (0.1)
Hypoxia	1 (0.1)
Pleural effusion	2 (0.1)
Skin and subcutaneous tissue disorders (SOC)	16 (0.9)
Dermatitis allergic	1 (0.1)
Drug eruption	3 (0.2)
Erythema multiforme	1 (0.1)
Hangnail	1 (0.1)
Pruritus	2 (0.1)
Rash	6 (0.3)
Skin mass	1 (0.1)
Urticaria	1 (0.1)
Vascular disorders (SOC)	4 (0.2)
Aortic dissection	1 (0.1)
Circulatory collapse	1 (0.1)
Deep vein thrombosis	1 (0.1)
Iliac artery stenosis	1 (0.1)

6.5 VIOLET STUDY - VADADUSTAT TREATMENT DISCONTINUATION DUE TO HOSPITAL TRANSFER

System Organ Class (SOC) Preferred Term	N=94 n (%)
AE/ADR Not Reported	75 (79.8)
Blood and lymphatic system disorders (SOC)	2 (2.1)
Anaemia	1 (1.1)
Iron deficiency anaemia	1 (1.1)
Cardiac disorders (SOC)	3 (3.2)
Acute myocardial infarction	1 (1.1)
Cardiac failure	2 (2.1)
Gastrointestinal disorders (SOC)	4 (4.3)
Gastric ulcer	1 (1.1)
Intestinal obstruction	1 (1.1)
Large intestine perforation	1 (1.1)
Nausea	2 (2.1)
General disorders and administration site conditions (SOC)	3 (3.2)
Generalised oedema	1 (1.1)
Oedema	1 (1.1)
Oedema peripheral	1 (1.1)
Hepatobiliary disorders (SOC)	1 (1.1)
Hyperbilirubinaemia	1 (1.1)
Infections and infestations (SOC)	2 (2.1)
COVID-19	1 (1.1)
Peritonitis	1 (1.1)
Investigations (SOC)	1 (1.1)
Low density lipoprotein decreased	1 (1.1)
Metabolism and nutrition disorders (SOC)	3 (3.2)
Dehydration	1 (1.1)
Diabetic complication	1 (1.1)
Fluid retention	1 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (1.1)
Lung neoplasm malignant	1 (1.1)
Nervous system disorders (SOC)	1 (1.1)
Transient ischaemic attack	1 (1.1)
Renal and urinary disorders (SOC)	6 (6.4)
Nephrotic syndrome	1 (1.1)
Renal failure	1 (1.1)
Renal impairment	4 (4.3)
Skin and subcutaneous tissue disorders (SOC)	1 (1.1)
Eczema	1 (1.1)

6.6 VAFSEO (VADADUSTAT) LABEL – JAPAN (ENGLISH TRANSLATION)



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STEVEN BIRD
03/04/2024 11:22:55 AM

KIRA N LEISHEAR WHITE
03/04/2024 11:24:39 AM

4FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 29, 2024

To: Carleveva Thompson, MS, Senior Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Melissa Khashei, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for VAFSEO® (vadadustat) tablets, for oral use

NDA: 215192

Background:
In response to DNH's consult request dated January 24, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for VAFSEO® (vadadustat) tablets, for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 16, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on February 27, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on March 28, 2021, we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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MELISSA KHASHEI
02/29/2024 11:13:17 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 27, 2024
To:	Carleveva Thompson, MS Senior Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, WOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VAFSEO (vadadustat) tablets
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215192
Applicant:	Akebia Therapeutics, Inc.

1 INTRODUCTION

On September 27, 2023, Akebia Therapeutics, Inc. resubmitted for the Agency's review a proposed New Drug Application (NDA) 215192 for VAFSEO (vadadustat) tablets in response to the Agency's Complete Response (CR) letter dated March 29, 2022. With this resubmission, the Applicant proposes an indication for VAFSEO (vadadustat) tablets for the treatment of anemia associated with chronic kidney disease in adults on dialysis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on January 24, 2024 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VAFSEO (vadadustat) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft VAFSEO (vadadustat) tablets MG received on September 27, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 20, 2024.
- Draft VAFSEO (vadadustat) tablets Prescribing Information (PI) received on September 27, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 20, 2024.
- Approved JESDUVROQ (daprodustat) comparator labeling dated February 1, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MARIA T NGUYEN
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DMPP-OPDP review of vadadustat (VAFSEO) NDA 215192 MG

MELISSA KHASHEI
02/27/2024 08:19:47 AM

BARBARA A FULLER
02/27/2024 08:31:11 AM

LASHAWN M GRIFFITHS
02/27/2024 08:47:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
And Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Memorandum

Date: 2/7/24 **Date Consulted:** 1/25/24

From: Jane Liedtka, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Carleveva Thompson, Regulatory Project Manager (RPM)
Division of Non-Malignant Hematology (DNH)

Drug: Vafseo (vadadustat)

NDA: 215192

Applicant: Akebia Therapeutics

Subject: Input for the Post-Marketing Requirement (PMR) Template for a Descriptive Pregnancy Safety Study (DPSS)

Indication: Vafseo is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia associated with chronic kidney disease in adults on dialysis.

BACKGROUND

- On 3/29/21 the applicant submitted a Class 2 resubmission to the Complete Response (CR) that was issued for NDA 215192.

- On 1/25/24, DNH consulted DPMH to review the attached PMR development template for a PMR for a DPSS for Vafseo and to provide advice on the PMR language and template.

REVIEW

The PMR template (see Appendix A) was reviewed and determined to be correctly filled out for a DPSS. Milestone dates were recommended by DPMH as seen in Section B, Question #2.

In addition to the PMR, DPMH is recommending a requested pharmacovigilance for Vafseo use in females of reproductive potential. DPMH previously participated in the review of another drug in the same class, Jesduvroq. Jesduvroq[1,2] (daprodustat), NDA 216951, approved on 2/1/23, has the same list of potential safety concerns and same indication as Vafseo. A PMR for a DPSS was included in the approval letter for Jesduvroq. In addition, in the section of the approval letter titled REQUESTED PHARMACOVIGILANCE, was the following request:

> We also request that, in the narrative portion of your annual PADER, you submit annual reports of Jesduvroq utilization rates, including use in the non-dialysis dependent population and among females of reproductive potential (i.e., females aged 15 to 50 years) calculated cumulatively from the initial U.S. approval date annually through the 5th year following the initial U.S. approval date.

Reviewer's Comments
This additional request is designed to alert the Agency to the extent of use amongst females of reproductive potential (both off and on label use). If use in this population is significantly greater than expected, this could be considered a new safety signal that would trigger FDAAA and would result in the Agency issuing a PMR for a Pregnancy Registry to replace the DPSS.

DISCUSSION/CONCLUSIONS

1. DPMH agrees with the decision to issue a postmarketing requirement (PMR) Descriptive Pregnancy Safety Study to follow-up on maternal and infant outcomes of vadadustat-exposed pregnancies. See Appendix A for input on PMR template.
2. DPMH recommends including REQUESTED PHARMACOVIGILANCE in the Vafseo approval letter that states,

   > In the narrative portion of your annual PADER, you submit annual reports of Vafseo utilization rates, to include use in the non-dialysis dependent

[1] DPMH's PLLR Review of JESDUVROQ (daprodustat), NDA 216951. Jane Liedtka M.D., 12/1/22. DARRTS Reference ID # 5086969.
[2] DPMH consult reviews of JESDUVROQ, NDA 216951 was part of the materials reviewed, but was not relied upon for the purposes of the recommendations.

population among females of reproductive potential (i.e., females aged 15 to 50 years) calculated cumulatively from the initial U.S. approval date annually through the 5th year following the initial U.S. approval date.

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JANE E LIEDTKA
02/07/2024 12:09:37 PM

TAMARA N JOHNSON
02/08/2024 10:04:43 AM

LYNNE P YAO
02/14/2024 04:43:08 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 22, 2024
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 215192
Product Name, Dosage Form, and Strength:	Vafseo (vadadustat) tablets, 150 mg, 300 mg and 450 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Akebia Therapeutics, Inc. (Akebia)
FDA Received Date:	September 27, 2023, October 12, 2023
TTT ID #:	2023-6572
DMEPA 2 Safety Evaluator:	Sue Black, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1. REASON FOR REVIEW

As part of the approval process of the 505 (b)(1) class II resubmission for Vafseo (vadadustat) tablets, we reviewed the proposed Vafseo Prescribing Information (PI), Medication Guide (MG), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On March 29, 2021, Akebia submitted NDA 215192 seeking licensure for Vafseo. DMEPA completed a label and labeling review for this application on August 27, 2021[a]. We concluded that the proposed PI, container labels, and carton labeling were unacceptable from a medication error perspective and the MG was acceptable from a medication error perspective; however, our comments were not communicated to the Applicant at that time. The application received a Complete Response (CR) letter[b] on March 29, 2022 due to clinical and statistical issues. The letter stated that we reserve comment on the proposed labels and labeling until the application is otherwise adequate. On September 27, 2023, Akebia submitted a response to the CR letter.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

[a] DeGraw, S. Label and Labeling Review for Vafseo (NDA 215192). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 AUG 27. TTT ID No.: 2021-644.

[b] Thompson, C. Complete Response Letter for NDA 215192. Silver Spring (MD): FDA, CDER, OCHEN (US); 2022 MAR 29. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80653286.

We performed a risk assessment of the proposed container labels, carton labeling, PI, and MG for Vafseo to identify deficiencies that may lead to medication errors and other areas of improvement.

We note that the proposed Vafseo PI and MG were updated from previously submitted, therefore, some of our previous recommendations[c] no longer apply. Our evaluation of the proposed Vafseo PI and MG identified areas of vulnerability that may lead to medication errors. We provide our recommendations in Section 4.1 for Division to improve the clarity of information (e.g., revising dosing information, including the route of administration, replacing symbols with their intended meaning, removing trailing zeros), to add a new section for important dosing information, to add the statement "VAFSEO should be swallowed whole. Tablets should not be cut, crushed, or chewed.", to include tablet information in Section 16 and to revise storage information to be consistent with container labels and carton labeling.

We note that no new Vafseo container labels and carton labeling were received with this resubmission. The Applicant confirmed that the container labels and carton labeling are the same as previously submitted on March 29, 2021. Therefore, we re-reviewed the container labels and carton labeling submitted on March 29, 2021. Our evaluation of the proposed Vafseo container labels and carton labeling identified areas of vulnerability that may lead to medication errors. We provide our recommendations in Section 4.2 for the Applicant to revise the color scheme of the 300 mg strength, dosage and MG statements, increase prominence of established name, de-bold the "Rx only" statement, clarify the format of the expiration date and add a "Swallow tablets whole. Do not cut, crush, or chew tablets." In addition, we provide recommendations in Section 4.2 for the Applicant to revise the strength statement on and add storage statement to the professional sample pack.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, MG, container labels, and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the Division in Section 4.1 and recommendations for Akebia in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Prescribing Information

1. Highlights of Prescribing Information

a. Dosage and Administration

i. We recommend revising the fourth bullet point (b) (4)

(b) (4)

[c] DeGraw, S. Label and Labeling Review for Vafseo (NDA 215192). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 AUG 27. TTT ID No.: 2021-644.

ii. We recommend [redacted] (b) (4) appear as "The recommended starting dose is 300 mg orally once daily, with or without food." for clarity.
iii. We recommend revising the fifth bullet point to improve clarity. Revise to read "Adjust dose in increments of 150 mg to achieve or maintain hemoglobin levels (10 g/dL to 11 g/dL). Doses may range from 150 mg to a maximum of 600 mg."
iv. We recommend revising the order of the bullets and referenced sections for increased readability and clarity. For example, revise to:

---------- **DOSAGE AND ADMINISTRATION** ----------

- The recommended starting dose is 300 mg orally once daily, with or without food. (2.2 and 2.3)
- Monitor hemoglobin levels when initiating or adjusting dose. (2.1 and 2.4)
- Measure ALT, AST, and bilirubin prior to the initiation of VAFSEO and monthly after initiation for the first 3 months and then monitor as clinically indicated. (2.1 and 2.4)
- Increase the dose no more frequently than once every 4 weeks. Decreases in dose can occur more frequently. (2.4)
- Adjust dose in increments of 150 mg to achieve or maintain hemoglobin levels (10 g/dL to 11 g/dL). Doses may range from 150 mg to a maximum of 600 mg. (2.4)

B. Full Prescribing Information

1. Dosage and Administration Section
   a. We recommend including the abbreviation for hemoglobin in Section 2.1 *Pre-Treatment and On-Treatment Evaluations of Anemia, Iron Stores, and Liver Tests* as this abbreviation alone is used frequently in the subsequent sections. For example, revise to: "Measure hemoglobin (Hb) at baseline and as direction in section 2.3."
   b. As currently presented, there is no section for important dosing information and no statement indicating the tablet should be swallowed whole. We recommend adding a Section 2.2 Important Dosing Information and relocating the information "VAFSEO is administered orally once daily with or without food and can be taken at any time before, during, or after dialysis." and information within Section 2.5 Missed Dose to this section. In addition, as this is a film-coated tablet, we recommend adding the statement "VAFSEO should be swallowed whole. Tablets should not be cut, crushed, or chewed." to this section. For example, revise to:

2.2 Important Dosing Information

Individualize dosing and use the lowest dose of VAFSEO sufficient to reduce the need for red blood cell transfusions. Do not target a hemoglobin level higher than 11 g/dL.

VAFSEO can be taken with or without food.

VAFSEO should be swallowed whole. Tablets should not be cut, crushed, or chewed.

VAFSEO can be administered without regard to the timing or type of dialysis [see Clinical Pharmacology (12.3)].

If a dose of VAFSEO is missed, it should be taken as soon as possible, unless it is the same day as the next dose. In this case, the missed dose should be skipped, and the next dose taken at the usual time. Double-doses should not be taken to make-up for a missed dose.

c. As currently presented in the Recommended Starting Dose section, it is not clear the first recommended dosage statement refers to adults not being treated with an ESA and what dose amount is meant by the statement "one dose higher". In addition, the route of administration is missing, symbols (e.g., ≥) are present, the Hb level contains a trailing zero (e.g., 9.0 g/dL). For clarity, we recommend adding a subheader to clarify the dosing information, clarifying "one dose higher", including the route of administration, replacing symbols with its intended meaning and removing the trailing zero. For example, revise to:

2.3 Recommended Starting Dose of VAFSEO

Adults Not Being Treated with an ESA

The recommended starting dose is 300 mg orally once daily with or without food and can be taken at any time before, during, or after dialysis.

Adults Being Switched from an ESA

When converting from an ESA to VAFSEO, the recommended starting dose is 300 mg orally once daily.

(b) (4)

(b) (4) Taking into account the gradual rise in Hb with VAFSEO, rescue therapy in the form of RBC transfusion or ESA treatment may be considered during the transition phase if Hb values fall below 9 g/dL or response is considered not acceptable. Patients receiving RBC transfusions are recommended to continue VAFSEO treatment during the transfusion period. VAFSEO should be paused for those patients receiving temporary ESA rescue treatment and may be resumed when Hb levels are greater than or equal to 10 g/dL. Depending on the ESA employed, the pause in VAFSEO treatment should be extended to:

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

Following ESA rescue, VAFSEO should be resumed at the prior dose or with a dose that is 150 mg greater than prior dose, with subsequent titration according to the dose titration guidelines given below in this section.

d. As currently presented the Monitoring and Dose Titration section contains symbols (e.g., >, x) and unspecified abbreviations (e.g., ULN). In addition, the dosage adjustment statements are unclear. For clarity, we recommend replacing symbols and abbreviations with their intended meanings and revising the dosage adjustment statements. For example, revise to:

2.4 Monitoring Response to Therapy and Dose Adjustment

Following initiation of therapy and after each dose adjustment, monitor hemoglobin (Hb) levels, every two weeks until stable, then monitor at least monthly [see Warnings and Precautions (5.1)].

(b) (4)

Dose Titration

Increase the dose no more frequently than once every 4 weeks. Decreases in dose can occur more frequently.

Adjust dose in increments of 150 mg to achieve or maintain Hb levels within 10 g/mL to 11 g/dL. Doses may range from 150 mg to a maximum of 600 mg. When adjusting the dose, consider the patient's clinical condition, Hb variability, Hb rate of rise and rate of decline, and VAFSEO 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 VAFSEO 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.

Treatment with VAFSEO should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in hemoglobin level is not achieved. Alternative explanations for an inadequate response should be sought and treated before restarting therapy.

e. We recommend retitling the header from (b) (4) (b) (4) to "2.5 Dosage Adjustments Due to Drug Interactions".

2. Dosage Forms and Strengths
   a. We recommend revising (b) (4) to read "…following strengths" in the dosage form statement for clarity.

3. How Supplied/Storage and Handling Section
   a. We recommend the revising the How Supplied section to include the tablet descriptions. Revise as follows:

How Supplied

VAFSEO film-coated tablets are available in the following strengths and packages:

Tablet Strength	Tablet Shape/Color	Tablet Markings	Pack size	NDC
150 mg	Round/white	"VDT" and "150"	60 count bottle	59922-641-60
300 mg	Oval/yellow	"VDT" and "300"	60 count bottle	59922-642-60
450 mg	Oval/pink	"VDT" and "450"	60 count bottle	59922-643-60

   b. We recommend revising the storage statement to reflect USP controlled room temperature and to be consistent with the storage statement on the container labels and carton labeling. Revise to read "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]."

C. Medication Guide

1. As currently presented, there is no statement indicating that tablets should be swallowed whole. As this is a film-coated tablet, we recommend adding the following warning statements: "VAFSEO should be swallowed whole. Tablets should not be cut, crushed, or chewed." as a separate bullet ." after the statement "You may take VAFSEO with or without food."

4.2 RECOMMENDATIONS FOR AKEBIA THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA Supplement:

A. General Comments (Container labels & Carton Labeling)

1. The 300 strength is not clearly differentiated due to the similarity between the (b) (4) color which also overlap with the (b) (4) font color used for the proprietary name. Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. We recommend revising the color scheme of the 300 mg strength such that the strength and the proprietary name appear in their own unique color that do not overlap.
2. The "Rx only" statement appears more prominent than other critical information on the principal display panel. The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel. We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). De-bold the font used for "Rx Only" statement wherever the font is bolded.
3. We recommend revising the statement of dosage statement to read, "Recommended Dosage: See Prescribing Information."
4. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for

Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

5. As currently presented, the Medication Guide statement is inconsistent between the container labels, carton labeling and the professional sample. We recommend revising the Medication Guide statement so it describes how the Medication Guide is provided and to be consistent across all labels and labeling. For example, revise all Medication Guide statements to read "Dispense with the enclosed Medication Guide" or "Dispense with the accompanying Medication Guide". Ensure this is present on all labels and labeling, including the 150 mg container (bottle) label if space allows.
6. As currently presented, the statement "Swallow tablets whole. Do not split, chew, or crush tablets" is missing. To minimize wrong administration errors, we recommend adding the following warning statement to the side or back panel below the dosage statement: "Swallow tablets whole. Do not cut, crush, or chew tablets."

B. Carton Labeling

1. As currently presented, the established name lack prominence on the principal display panel. The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). We recommend increasing the prominence of the established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). We recommend bolding the established name on the carton labeling for consistency with the container labels and for prominence.

C. Professional Sample Blister Pack

1. As currently presented, the strength statement is separated into 2 lines. To prevent confusion and increase prominence of this information, we recommend revising the strength statement on the principal display panel to ensure that "300 mg per tablet" is presented on the same line within the strength box.
2. As currently presented, the storage statement is missing on the back panel of the blister pack. To prevent deteriorated drug medication errors, we recommend adding a storage statement to the back panel in alignment with the storage statement on the container labels and carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vafseo received on September 27, 2023 from Akebia Therapeutics, Inc.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Vafseo</th></tr>
<tr><td>Initial Approval Date</td><td>NA</td></tr>
<tr><td>Active Ingredient</td><td>vadadustat</td></tr>
<tr><td>Indication</td><td>Treatment of anemia associated with chronic kidney disease in adults on dialysis.</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>tablets</td></tr>
<tr><td>Strength</td><td>150 mg, 300 mg and 450 mg</td></tr>
<tr><td>Dose and Frequency</td><td>• Administer orally once daily, with or without food.
• Monitor hemoglobin levels when initiating or adjusting dose.
• The recommended starting dose is 300 mg once daily.
• Measure ALT, AST, and bilirubin prior to the initiation of VAFSEO and monthly after initiation for the first (b) (4) months and then monitor as clinically indicated. Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently.
• Adjust dose in increments of 150 mg within the range of 150 mg to 600 mg to achieve or maintain hemoglobin levels (10 to 11 g/dL).</td></tr>
<tr><td>How Supplied</td><td>VAFSEO film-coated tablets are available in the following strengths and packages:<table><tr><th>Tablet Strength</th><th>Pack size</th><th>NDC</th></tr><tr><td>150 mg</td><td>60 count bottle</td><td>59922-641-60</td></tr><tr><td>300 mg</td><td>60 count bottle</td><td>59922-642-60</td></tr><tr><td>450 mg</td><td>60 count bottle</td><td>59922-643-60</td></tr></table></td></tr>
<tr><td>Storage</td><td>Store at 15°C to 30°C (59°F to 86°F). Keep out of reach of children.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 17, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, 215192. Our search identified one previous review[d], and we considered our previous recommendations to see if they are applicable for this current review.

[d] DeGraw, S. Label and Labeling Review for Vafseo (NDA 215192). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 AUG 25. TTT ID No.: 2021-644.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Vafseo labels and labeling submitted by Akebia Therapeutics, Inc.

- Container label received on March 29, 2023
- Carton labeling received on March 29, 2023
- Prescribing Information (Image not shown) received on September 27, 2023, available from \\CDSESUB1\EVSPROD\nda215192\0046\m1\us\114-label\1141-draft-label\proposed.pdf
- Medication Guide (Image not shown) received on September 27, 2023, available from \\CDSESUB1\EVSPROD\nda215192\0046\m1\us\114-label\1141-draft-label\medguide-pdf.pdf

F.2 Label and Labeling Images

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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NICOLE F IVERSON
01/23/2024 04:48:44 PM

Division of Cardiology and Nephrology Consult

Date: July 15, 2022
NDA # and Product: 215192 Vadadustat
From: Rekha Kambhampati, Medical Officer, Division of Cardiology and Nephrology (DCN)
Through: Mary Ross Southworth, Deputy Division Director for Safety, DCN
Aliza Thompson, Deputy Director, DCN
To: Carleveva Thompson, Consumer Safety Officer, Division of Non-malignant Hematology
Subject: Input on safety considerations for the DD-CKD population

Background

Vadadustat is a synthetic, orally bioavailable, small molecule inhibitor of hypoxia-inducible factor (HIF) prolyl-hydroxylases that is being developed for the treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis.

On March 29, 2021, the Division of Non-malignant Hematology (DNH) received a new NDA for vadadustat with the proposed indication of "treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis." On February 16, 2022, the Division of Cardiology and Nephrology (DCN) provided input on key renal safety findings in the pivotal trials evaluating the non-dialysis dependent chronic kidney disease (NDD-CKD) and DD-CKD populations. On March 29, 2022, DNH issued a Complete Response Letter, citing an unfavorable benefit-risk assessment of vadadustat for both the NDD-CKD and DD-CKD populations. The Complete Response Letter noted that for vadadustat compared to darbepoetin, there was a higher use of erythropoietin stimulating agent (ESA) rescue therapy for worsening anemia for both the NDD-CKD and DD-CKD populations and a higher incidence of red blood cell transfusion rescue in the DD-CKD population. The Complete Response Letter also cited the following safety concerns for vadadustat compared to darbepoetin: increased risk of MACE for the NDD-CKD population, concern for a signal for adjudicated thromboembolic events (including vascular access thrombosis (VAT)) for the DD-CKD population, and concern for a signal for drug-induced liver injury (DILI) in patients with CKD.

On June 6, 2022, the Applicant requested an End of Review Conference to discuss the contents of the Complete Response Letter. In its Briefing Package, the Applicant noted that they plan to pursue an indication only in the "dialysis-dependent CKD population" at this time. The Applicant does not plan on conducting additional clinical trials. The Briefing Package included proposed amendments to draft labeling, including increased monitoring of liver enzymes after initiation of vadadustat, and also included data on the total number of VAT events for vadadustat versus darbepoetin for the DD-CKD population in the pivotal trials. On July 8, 2022, DNH consulted DCN to opine on: (1) the feasibility of the proposed laboratory monitoring in a dialysis setting, and (2) the clinical relevance of the VAT signal in the DD-CKD population.

Material Reviewed

1) End of Review Conference Meeting Request and Briefing Package dated June 6, 2022

Consult Question 1:

From a nephrologist's clinical point of view, please comment on the feasibility of the hepatic monitoring proposal. The team had concerns that patients may not be able to comply with the additional laboratory

monitoring for a variety of reasons, including dialysis facilities may not be reimbursed for enhanced monitoring. Are these concerns valid?

DCN Response to Question 1:

In the Complete Response Letter dated March 29, 2022, DNH raised concern for a "clinically significant risk for drug-induced liver injury (DILI) with the use of vadadustat in patients with CKD." In the Briefing Package dated June 6, 2022, the Applicant proposed amending the vadadustat draft labeling to recommend (b) (4) As rationale for their monitoring schedule, (b) (4) (b) (4)

Regarding the clinical feasibility of the proposed laboratory measurements, we note that clinical staff in dialysis units in the U.S. routinely collect laboratory assessments monthly, interpret results, and modify care accordingly. Questions about related costs or compliance are beyond the scope of our expertise.

Consult Question 2:

An increased risk of VAT was observed in the vadadustat group compared to the darbepoetin alpha group in patients with DD-CKD. We believe that the increase risk of VAT is clinically relevant and can lead to serious complications including loss of vascular access. Do you agree with this assessment? The impact of VAT on clinical care in patients with DD-CKD would be appreciated from the clinical perspective of a nephrologist.

DCN Response to Question 2:

The Applicant is proposing pursuing the following indication: "VAFSEO is indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis." The Applicant states that limiting the indication to DD-CKD patients "removes the risk of MACE observed in the NDD-CKD population and provides a patient population where there is enhanced monitoring and pharmacovigilance."

In the consult review dated February 16, 2022, DCN noted an increased risk of access-related thrombosis events for the vadadustat versus darbepoetin arms for the pooled DD-CKD population based on analyses conducted by DNH. DCN stated that AV-access thrombosis is a clinically important finding in this population and that patients on hemodialysis rely heavily on a functional access as their "lifeline." In their Briefing Package dated June 6, 2022, the Applicant acknowledged the Agency's time-to-first-event analyses for vascular access thrombosis (VAT) events and provided additional analyses assessing total VAT events. The Applicant noted that their time-to-multiple VAT events analysis, which yielded a HR of 1.0 (95% CI: 0.8, 1.2) for vadadustat compared to darbepoetin, is "more informative in assessing the risk of fistula or graft abandonment, the major clinical consequences of a VAT." The Applicant further noted that the incidence of fistula/graft abandonment events for the DD-CKD population in the pivotal trials was similar between treatment groups (3.8% vadadustat vs 4.4% darbepoetin).

In principle, when evaluating whether and to what extent a drug may increase the risk of VAT, it is reasonable to consider not just the time-to-first event, but also the total number of events and

incidence of AV fistula or graft abandonment. That said, without a better understanding of the data and these analyses, it is difficult to comment further on these particular findings.

We agree that VAT can result in fistula/graft abandonment and that loss of access can have dire clinical consequences for this population (i.e., DD-CKD patients), which relies on their access for survival. We also note that VAT events that do not result in access abandonment can result in a temporary inability to use the access point. ESKD patients rely on their dialysis to treat a variety of conditions, including toxin buildup, electrolyte imbalances, and fluid retention. Often, access-related thrombosis events result in missed or inadequate dialysis sessions, which can put the patient at risk for acute events, such as fluid overload and cardiac arrhythmias. However, an increase in the risk of VAT may be acceptable to some patients if the absolute increase in risk is not large, one could identify a population at lower baseline risk for such events, and the therapy offered other advantages over existing agents (e.g., benefit of an oral agent for patients on home dialysis).

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/s/

REKHA KAMBHAMPATI
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MARY R SOUTHWORTH
07/15/2022 12:00:56 PM

ALIZA M THOMPSON
07/15/2022 12:03:41 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 28, 2022

To: Carleveva Thompson, MS, Regulatory Project Manager,
Division of Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DNH

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Consult Request for VAFSEO™ (vadadustat) tablets, for oral use

NDA: 215192

This memo is in response to DNH's labeling consult request dated April 26, 2021. DNH has communicated by electronic mail (Carleveva Thompson) that a Complete Response (CR) Action is planned for this application. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DNH submit a new consult request during the subsequent review cycle. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

REBECCA A FALTER
02/28/2022 10:41:53 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	February 24, 2022
To:	Carleveva Thompson, MS Regulatory Project Manager **Division of Nonmalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	VAFSEO (vadadustat) [AKB-6548]
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215192
Applicant:	Akebia Therapeutics, Inc.

1 INTRODUCTION

On March 29, 2021, Akebia Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 215192 for VAFSEO (vadadustat) [AKB-6548] tablets, for the proposed indication for the treatment of anemia associated with chronic kidney disease in adult patients on dialysis and not on dialyisis. On August 12, 2021, the Division of Nonmalignant Hematology (DNH) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for VAFSEO (vadadustat) [AKB-6548] tablets.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for VAFSEO (vadadustat) [AKB-6548].

2 CONCLUSIONS

Due to outstanding deficiencies, DNH plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON R MILLS
02/24/2022 01:44:34 PM

Division of Cardiology and Nephrology Consult

Date: February 16, 2022
From: Rekha Kambhampati, Medical Officer
Division of Cardiology and Nephrology
Through: Aliza Thompson, Deputy Director
Division of Cardiology and Nephrology
To: May Zuwannin, Consumer Safety Officer, Division of Non-Malignant Hematology
Subject: Evaluation of key renal safety findings in the NDD-CKD and DD-CKD populations (NDA 215192 Vadadustat)

Background

Vadadustat is a synthetic, orally bioavailable, small molecule inhibitor of hypoxia-inducible factor (HIF) prolyl-hydroxylases that is being developed for the treatment of anemia associated with non-dialysis dependent chronic kidney disease (NDD-CKD) and dialysis-dependent chronic kidney disease (DD-CKD). By stabilizing and increasing cellular levels of HIF, vadadustat is thought to stimulate erythropoietin expression and heighten the oxygen-carrying capacity of the blood via improved production of hemoglobin and red blood cells. In clinical studies in healthy adult male subjects and male and female CKD patients, vadadustat has also been shown to increase iron utilization by decreasing hepcidin and increasing total iron binding capacity (TIBC) levels, which is thought to enable iron transport mechanisms to enhance the terminal steps of erythropoiesis.

On March 29, 2021, the Division of Non-malignant Hematology (DNH) received a new NDA for vadadustat with the proposed indication of "treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis." In support of the proposed indication the Applicant conducted trials AKB-6548-CI-0014 and AKB-6548-CI-0015 in patients with NDD-CKD, and trials AKB-6548-CI-0016 and AKB-6548-CI-0017 in patients with DD-CKD.

During their safety review, the DNH team noted a higher incidence of acute kidney injury and hyperphosphatemia adverse events in the vadadustat arm compared to the darbepoetin arm in the NDD-CKD population (trials 0014 and 0015)[1]. They also noted a higher incidence of thromboembolic and access-related thrombosis adverse events in the vadadustat arm compared to the darbepoetin arm in the DD-CKD population (trials 0016 and 0017). DNH has asked the Division of Cardiology and Nephrology (DCN) to assist with interpretation of the clinical relevance of the renal findings. DNH has also asked DCN to comment on "the potential impact of either of these treatments (i.e. vadadustat and darbepoetin) on fistula maturation and AV fistula stenosis and the clinical importance of the results in relation to the benefit-risk evaluation."

Materials Reviewed

- Clinical Study Protocols for Study AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0016, and AKB-6548-CI-0017
- Clinical Study Reports for Study AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0016, and AKB-6548-CI-0017
- Proposed draft label

[1] Analyses were based on individual preferred terms (PTs).

- Key safety analyses (see Appendix)

Consult Questions

Question 1

During our safety analysis, we identified higher incidence of acute kidney injury and hyperphosphatemia in the vadadustat arm, compared to the darbepoetin alpha arm, in the NDD-CKD population. This finding was also noted in the applicant's submission. Please review the relevant section of this NME application[2] and provide us with your opinion in relation to the relevance and significance of these potential renal-based safety signals, in the context of a population with moderate-severe chronic kidney disease.

DCN Response to Question 1

AKI

According to DNH's analyses, there was a slight imbalance in the incidence of AKI TEAEs (narrow FMQ) for the vadadustat (8.0%) versus darbepoetin (7.2%) arm for the pooled NDD-CKD population (Table 1), and the incidence of SAEs associated with AKI (narrow FMQ) was similar in the two arms (4.9% vadadustat vs 4.4% darbepoetin) (Table 1). We also note that the active comparator, darbepoetin, is not known to carry a risk of AKI[3]. Based on these data and this information, we do not believe there is an obvious signal for AKI.

Hyperphosphatemia

According to DNH's analyses, there was a slight imbalance in the incidence of hyperphosphatemia TEAEs (grouped query) for the vadadustat (6.3%) versus darbepoetin (5.5%) arm for the pooled NDD-CKD population; most cases were mild to moderate in severity for both arms (Table 2). In contrast, the proportion of patients with a new incidence of clinically significant serum phosphate elevation (i.e., serum phosphate >6 mg/dL) was lower in the vadadustat (14.4%) as compared to the darbepoetin (16.1%) arm (Table 3). Based on these data, we do not believe there is an obvious signal for hyperphosphatemia.

Question 2

In addition, during your safety analysis, we confirmed the Applicant's identified safety signal of venous thromboembolism in the DD-CKD population, with a higher prevalence in Access-related VTE[4]. Please comment on the clinical importance of this findings in the benefit-risk evaluation.

DCN Response to Question 2

According to the Applicant's analyses (adjudicated data), there was an increased risk of thromboembolism events for the vadadustat versus darbepoetin arm for the pooled DD-CKD population (HR 1.20, 95% CI: 0.96, 1.50) (Figure 1), and there was an increased risk of access-related thrombosis events for the vadadustat versus darbepoetin arm for the pooled DD-CKD population (HR 1.28, 95% CI: 1.00, 1.63) (Figure 1). On-treatment[5] analyses of access-related thrombosis TEAEs (grouped query (narrow)) conducted by DNH were consistent with the Applicant's analyses (HR 1.12 for vadadustat

[2] After further discussion with DNH, it was agreed that DNH would provide DCN with specific analyses to review and provide input on

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103951s5378lbl.pdf

[4] DNH clarified that "access-related VTE" refers to access-related thrombosis

[5] On-treatment: patients were followed until the date of last contact or date of event

compared to darbepoetin, 95% CI: 0.92, 1.37) (Figure 3). A sensitivity analysis (on-treatment+7)[6] of access-related thrombosis TEAEs conducted by DNH was consistent with the on-treatment analysis (Figure 3).

According to additional analyses by DNH, there was a slight imbalance in the incidence of AV-access complications (EMQ) for the vadadustat (13.0%) versus darbepoetin (12.0%) arms for the pooled DD-CKD population (Table 4).

Generally speaking, patients with end-stage kidney disease (ESKD) depend on their dialysis for survival and those on hemodialysis rely heavily on a functional access as their "lifeline." Therefore, AV access thrombosis is a clinically important finding in this population. Analyses of access-related thrombosis events are concerning for a signal for vadadustat compared to darbepoetin. We also note that the active comparator, darbepoetin, is known to carry a risk of AV graft thrombosis[7]. If vadadustat is approved, we recommend that labeling adequately describe the risk of AV- access thrombosis.

Question 3

Lastly, please comment on the potential impact of either treatments (i.e. vadadustat and darbepoetin) on fistula maturation and AV fistula stenosis and the clinical importance of the results in relation to the benefit-risk evaluation.

DCN Response to Question 3

According to DNH's analyses, the risk of AV-access stenosis events (grouped query) was lower in the vadadustat versus darbepoetin arm (HR 0.80, 95% CI: 0.61, 1.06) (Figure 3), and the incidence of AV-access stenosis TEAEs (grouped query) was slightly lower in the vadadustat (4.4%) versus the darbepoetin (5.5%) arm (Table 7). Primary AV fistula failure (i.e., an AV fistula that is never usable or fails within the first three months of its use) is common in dialysis patients and vascular access stenosis is also common. We do not believe the aforementioned findings are particularly notable or readily interpretable.

[6] On-treatment+7: patients were followed until the date of last contact, date of event, or 7 days after the last dose
[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103951s5378lbl.pdf

Appendix

Overview of Studies

Study 0014 (NDD-CKD), 0015 (NDD-CKD), 0016 (DD-CKD), and 0017 (DD-CKD) were identical in design except for eligibility criteria. All four studies were randomized, open-label, sponsor-blinded, active-controlled, phase 3 studies evaluating oral vadadustat compared to darbepoetin for the correction of anemia and maintenance of hemoglobin.

Study 0014 and 0015 each enrolled adult patients with eGFR ≤60 mL/min/1.73 m^2 (CKD-EPI), serum ferritin ≥100 ng/mL, and transferrin saturation (TSat) ≥20%. The hemoglobin threshold for enrollment was <10 g/dL for Study 0014 and either between 8 and 11 g/dL (US sites) or between 9 and 12 g/dL (sites outside of US) for Study 0015.

Study 0016 and 0017 enrolled adult patients on incident dialysis (defined as the initiation of chronic maintenance peritoneal or hemodialysis within 16 weeks (for Study 0016) or 12 weeks (for Study 0017) prior to Screening) who had a hemoglobin between 8 and 11 g/dL, serum ferritin ≥100 ng/mL, TSat ≥20%, and folate and vitamin B12 measurements greater than the "lower limit of normal" during screening.

All four studies excluded patients with anemia due to a cause other than CKD or with active bleeding or recent blood loss, history of DVT or pulmonary embolism within 12 weeks prior to randomization, as well as patients receiving any ESA or a red blood cell transfusion within eight weeks prior to randomization. In addition, studies 0016 and 0017 excluded patients anticipated to recover renal function and no longer require dialysis.

Patients in both studies were randomized 1:1 to either oral vadadustat or subcutaneous darbepoetin with the dose titrated during the treatment period to a target hemoglobin range of 10-12 g/dL. After completion of the 52 week treatment period, patients entered the Long-Term Treatment Period to assess long-term safety; patients continued study medication (either vadadustat or darbepoetin) from Week 53 until study completion. The studies were event driven; the end-of-study (EOS) for the two NDD-CKD studies occurred once 631 MACE events were recorded (both studies combined) and all enrolled patients had the opportunity to have their Week 36 visit. EOS was similarly defined for the two DD-CKD studies.

The primary efficacy endpoint for each study was the mean change in hemoglobin between baseline and the primary evaluation period (Weeks 24 to 36).

Primary Review Team Approach to the Safety Analyses[8]

The primary team conducted both frequency-based and exposure-adjusted safety analyses pooled for the NDD-CKD (studies 0014 and 0015) and DD-CKD (studies 0016 and 0017) populations. Unless otherwise specified, analyses of TEAEs were based on individual PTs.

Thromboembolic events (TE) were assessed for the pooled DD-CKD population in two ways: based on the Applicant's pre-specified adjudication data and the Agency's own definition using PT terms. The Applicant defined TE as arterial thrombosis (ATE), deep vein thrombosis (DVT), pulmonary embolism (PE) and vascular access thrombosis (VAT). Potential cases were adjudicated by the adjudication

[8] Source: NDA 215192 Integrated Review draft

committee. The Agency independently assessed the risk of TE (narrow), defined using PT terms relevant to venous thrombosis (VTE) and ATE. In addition, the Agency assessed the risk of TE (broad) in a more comprehensive way by adding non-fatal MI, non-fatal stroke, arteriovenous connection stenosis, transient ischemic attack and thrombosis-related death to the narrow definition of TE. Other thrombosis-related adverse events, such as transient ischemic attack, arteriovenous connection stenosis, and thrombosis-related death, were assessed separately.

The Applicant's and primary review team's analyses both used "on-study" data, which followed patients until the date of last contact or date of event, for all primary analyses. In order to take difference in duration of drug exposure between arms into consideration, FDA conducted additional sensitivity analyses using "on-treatment+7" data, which followed patients until the date of last contact, date of event, or 7 days after the last dose.

DCN Approach to the Consult Questions

We reviewed key safety analyses conducted by DNH and the Applicant. We also recommended additional safety analyses by treatment arm to further analyze whether a signal exists for each of the concerns from DNH, as listed below:

1. Standard FDA Kidney Injury Follow-On Guide (pooled NDD-CKD population)
2. Analysis of hyperphosphatemia TEAEs based on the pooling of PTs blood phosphorus increased and hyperphosphatemia (pooled NDD-CKD population)
3. Proportion of patients with a new incidence of a clinically significant serum phosphorus elevation (i.e., >6 mg/dL) (pooled NDD-CKD population)
4. Proportion of patients with each type of access at baseline (e.g., AV fistula, AV graft, catheter) in the pooled DD-CKD population by treatment arm
5. Analysis of dialysis-access related TEAEs based on the "Embolic and thrombotic events, vessel type unspecified and mixed and arterial venous" SMQ (pooled DD-CKD population)
6. Analysis of dialysis-access related TEAEs based on the "AV fistula thrombosis/occlusion/malfunction/stenosis" Ellis Medical Query (EMQ)
7. Analysis of hyperkalemia TEAEs based on the pooling of PTs blood potassium increased and hyperkalemia (pooled NDD-CKD population)
8. Proportion of patients with a new incidence of a clinically significant serum potassium elevation (i.e., >6 mmol/L) (pooled NDD-CKD population)

In addition to the analyses requested by DCN, the primary review team also conducted the following analyses by treatment arm for the DD-CKD population based on custom grouped queries of pooled PTs (see below for details of each grouped query): access-related thrombosis events, access-unrelated thrombosis events, arteriovenous connection stenosis events, and arterial thrombosis events.

Key Renal Safety Analyses

Acute Kidney Injury

Table 1. Adverse Events by AKI FMQ (Narrow) and Preferred Term Occurring in ≥2% of Patients, Safety Population, Trials 0014 and 0015 (NDD-CKD)

AKI FMQ (Narrow) Preferred Term	Vadadustat N=1739 n (%)	Darbepoetin N=1732 n (%)	Risk Difference (%) (95% CI)
Any AEs	139 (8.0)	124 (7.2)	0.8 (-0.9, 2.6)
Acute kidney injury	120 (6.9)	109 (6.3)	0.6 (-1.0, 2.3)
Any serious AEs	86 (4.9)	77 (4.4)	0.5 (-0.9, 1.9)
Acute kidney injury	76 (4.4)	72 (4.2)	0.2 (-1.1, 1.6)
Any fatal AEs	4 (0.2)	5 (0.3)	-0.1 (-0.4, 0.3)
Any AE with outcome of drug discontinuation	3 (0.2)	1 (0.06)	0.1 (-0.1, 0.3)

Source: Kidney Injury Follow-On Guide; adae.xpt; Software: R
Treatment-emergent adverse events defined as an adverse event (AE) that begins (or a pre-existing AE that worsens) on or after the first dose.
Includes the AKI FMQ related MedDRA preferred terms that are present in the adae.xpt dataset.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; AKI, acute kidney injury; CI, confidence interval; FMQ, FDA medical query; N, number of patients in group; n, number of patients meeting criteria

Hyperphosphatemia

Table 2. Hyperphosphatemia Treatment-Emergent Adverse Events, Safety Population, Pooled Trials 0014 and 0015 (NDD-CKD)

Event Assessment	Vadadustat N=1739 n (%)	Darbepoetin N=1732 n (%)	Risk Difference (%) (95% CI)
Any AE in group	110 (6.3)	95 (5.5)	0.8 (-0.7, 2.4)
Blood phosphorus increased	4 (0.2)	2 (0.1)	0.1 (-0.2, 0.4)
Hyperphosphatemia	106 (6.1)	93 (5.4)	0.7 (-0.8, 2.3)
Maximum severity			
Severe	1 (0.06)	0	0.1 (-0.1, 0.2)
Moderate	61 (3.5)	43 (2.5)	1.0 (-0.1, 2.2)
Mild	48 (2.8)	52 (3.0)	-0.2 (-1.4, 0.9)
Serious	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)

Source: FDA Clinical Data Scientist

Analysis based on the following pooled PTs: blood phosphorus increased, hyperphosphataemia

Table 3. Proportion of Patients with a New Incidence of a Clinically Significant Serum Phosphate Elevation, Safety Population, Pooled Trials 0014 and 0015 (NDD-CKD)

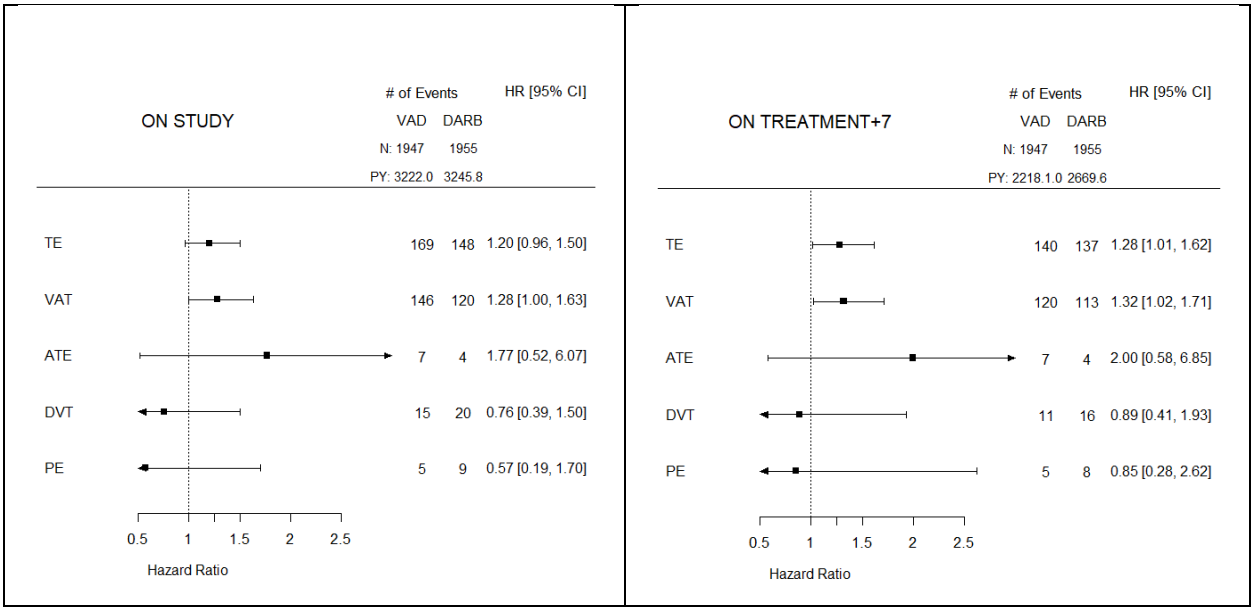
Parameter	Vadadustat N=1739 n (%)	Darbepoetin N=1732 n (%)
Phosphate (mg/dL)	251 (14.4)	278 (16.1)

Source: FDA Clinical Data Scientist

New incidence defined as patients who had a serum phosphate ≤6 mg/dL at baseline and >6 mg/dL at any time post-baseline

Dialysis Access-Related Events

Figure 1. Risk of Thromboembolic Event and Sub-Outcomes Based on Adjudicated Data (DD-CKD)

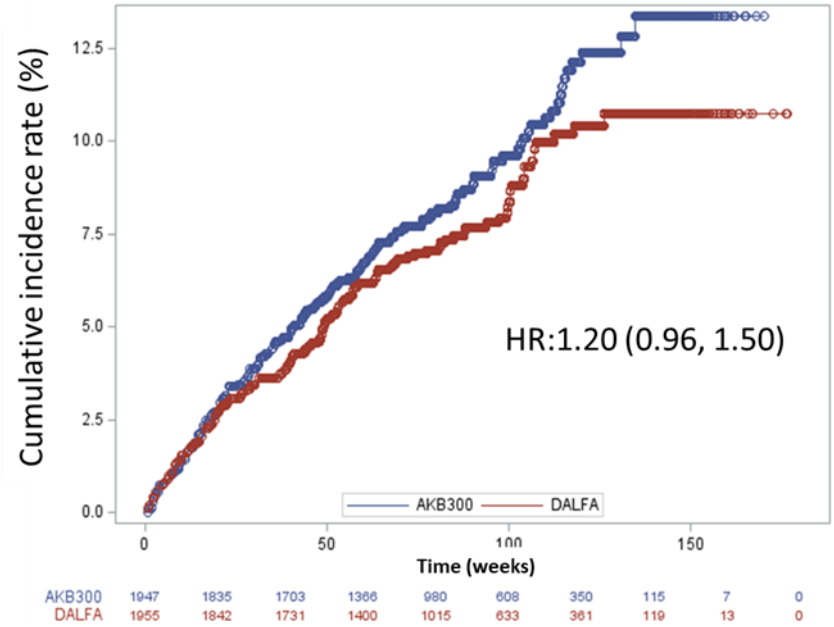


Source: FDA statistical reviewer; adtte.xpt, adadj.xpt, adsl.xpt datasets from INNO2VATE program

The on-study analysis followed patients until the date of last contact or date of event; the on-treatment + 7 analysis followed patients until the date of last contact, date of event, or 7 days after the last dose

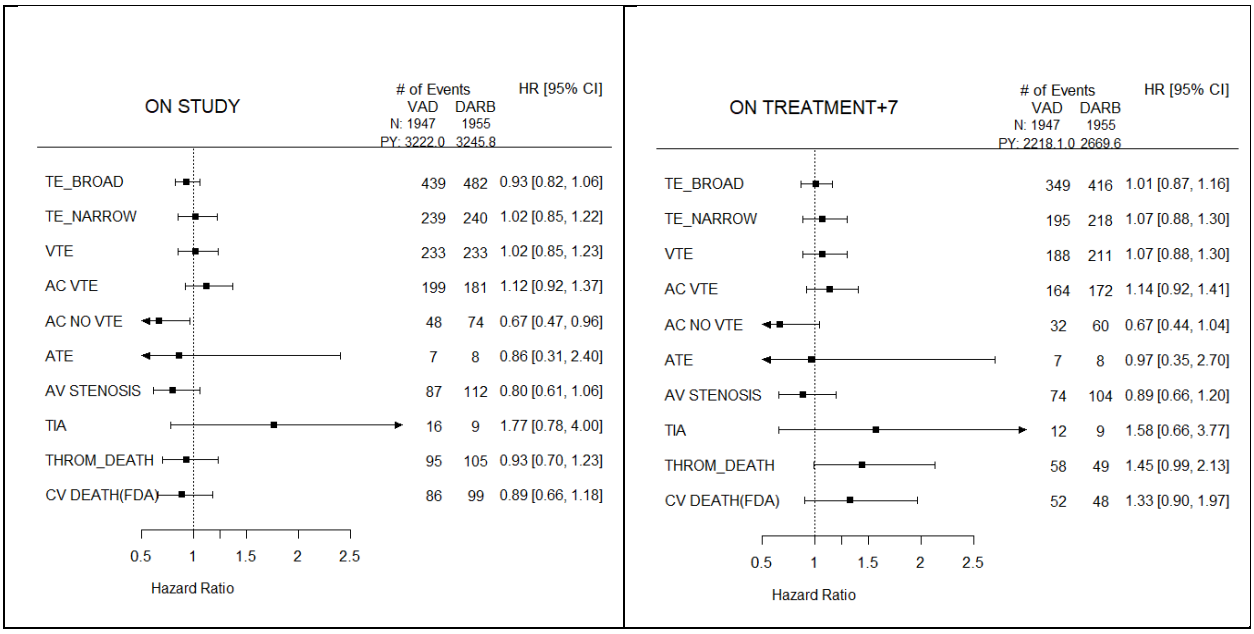
Abbreviations: TE, applicant's adjudicated thromboembolic events including arterial thrombosis, deep vein thrombosis, pulmonary embolism and vascular access thrombosis; VAT, vascular access thrombosis; ATE, arterial thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; HR, hazard ratio; CI, confidence interval; VAD, vadadustat; DARB, darbepoetin alpha; 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 2. Cumulative Incidence Rate of Thromboembolic Events (Adjudicated Data) (DD-CKD)



Source: FDA statistical reviewer; ae.xpt, adsl.xpt datasets from INNOVATE program

Figure 3. Risk of Thromboembolic Event and Sub-Outcomes Using the Agency's Definition (DD-CKD)



Source: FDA statistical reviewer; ae.xpt, adsl.xpt datasets from INNO2VATE program

The on-study analysis followed patients until the date of last contact or date of event; the on-treatment + 7 analysis followed patients until the date of last contact, date of event, or 7 days after the last dose

Abbreviations: TE_BROAD, FDA's broad definition of TE; TE_NARROW, FDA's narrow 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 alpha; 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.

Table 4. Dialysis Access-Related Adverse Events by AV fistula thrombosis/occlusion/malfunction/stenosis EMQ Occurring in ≥2% of Patients, Safety Population, Pooled Trials 0016 and 0017 (DD-CKD)

Event Assessment	Vadadustat N=1947 n (%)	Darbepoetin N=1955 n (%)	Risk Difference (%) (95% CI)
Any AE in group	254 (13.0)	234 (12.0)	1.1 (-1.0, 3.2)
Arteriovenous fistula site complication	54 (2.8)	61 (3.1)	-0.3 (-1.4, 0.7)
Arteriovenous fistula thrombosis	114 (5.9)	89 (4.6)	1.3 (-0.1, 2.7)
Arteriovenous graft thrombosis	43 (2.2)	43 (2.2)	0.0 (-0.9, 0.9)
Maximum severity			
Severe	26 (1.3)	36 (1.8)	-0.5 (-1.3, 0.3)
Moderate	152 (7.8)	122 (6.2)	1.6 (-0.0, 3.2)
Mild	76 (3.9)	76 (3.9)	0.0 (-1.2, 1.2)
Serious	103 (5.3)	84 (4.3)	1.0 (-0.3, 2.3)
Resulting in discontinuation	0	0	0 (0, 0)

Source: FDA Clinical Data Scientist

Table 5. Dialysis Access-Related Adverse Events by Embolic and thrombotic events, vessel type unspecified and mixed and arterial venous SMQ Occurring in ≥2% of Patients, Safety Population, Pooled Trials 0016 and 0017 (DD-CKD)

Event Assessment	Vadadustat N=1947 n (%)	Darbepoetin N=1955 n (%)	Risk Difference (%) (95% CI)
Any AE in group	227 (11.7)	220 (11.3)	0.4 (-1.6, 2.4)
Arteriovenous fistula thrombosis	114 (5.9)	89 (4.6)	1.3 (-0.1, 2.7)
Arteriovenous graft thrombosis	43 (2.2)	43 (2.2)	0.0 (-0.9, 0.9)
Vascular access site thrombosis	34 (1.7)	40 (2.0)	-0.3 (-1.2, 0.6)
Maximum severity			
Severe	48 (2.5)	62 (3.2)	-0.7 (-1.7, 0.3)
Moderate	128 (6.6)	108 (5.5)	1.0 (-0.4, 2.5)
Mild	47 (2.4)	45 (2.3)	0.1 (-0.8, 1.1)
Serious	128 (6.6)	117 (6.0)	0.6 (-0.9, 2.1)
Resulting in discontinuation	0	1 (0.05)	-0.1 (-0.2, 0.0)

Source: FDA Clinical Data Scientist
Displaying results of renal-related PTs

Table 6. Dialysis Access-Related Adverse Events by Customized Grouped Query Occurring in ≥2% of Patients, Safety Population, Pooled Trials 0016 and 0017 (DD-CKD)

Event Assessment	Vadadustat N=1947 n (%)	Darbepoetin N=1955 n (%)	Risk Difference (%) (95% CI)
AE grouping related to AESI	197 (10.1)	175 (9.0)	1.2 (-0.7, 3.0)
Arteriovenous fistula thrombosis	114 (5.9)	89 (4.6)	1.3 (-0.1, 2.7)
Arteriovenous graft thrombosis	43 (2.2)	43 (2.2)	0.0 (-0.9, 0.9)
Vascular access site thrombosis	34 (1.7)	40 (2.0)	-0.3 (-1.2, 0.6)
Maximum severity			
Severe	29 (1.5)	36 (1.8)	-0.4 (-1.2, 0.5)
Moderate	125 (6.4)	99 (5.1)	1.4 (-0.1, 2.8)
Mild	43 (2.2)	40 (2.0)	0.2 (-0.7, 1.1)
Serious	95 (4.9)	83 (4.2)	0.6 (-0.7, 1.9)
Resulting in discontinuation	0	0	0 (0, 0)

Source: FDA Clinical Data Scientist
Analysis based on the following pooled PTs: 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

Table 7. Arteriovenous Connection Stenosis Treatment-Emergent Adverse Events by Customized Grouped Query Occurring in ≥2% of Patients, Safety Population, Pooled Trials 0016 and 0017 (DD-CKD)

Event Assessment	Vadadustat N=1947 n (%)	Darbepoetin N=1955 n (%)	Risk Difference (%) (95% CI)
AE grouping related to AESI	86 (4.4)	108 (5.5)	-1.1 (-2.5, 0.3)
Arteriovenous fistula site stenosis	56 (2.9)	75 (3.8)	-1.0 (-2.1, 0.2)
Maximum severity			
Severe	3 (0.2)	10 (0.5)	-0.4 (-0.7, 0.0)
Moderate	58 (3.0)	70 (3.6)	-0.6 (-1.7, 0.5)
Mild	25 (1.3)	28 (1.4)	-0.1 (-0.9, 0.6)
Serious	9 (0.5)	18 (0.9)	-0.5 (-1.0, 0.1)
Resulting in discontinuation	0	0	0 (0, 0)

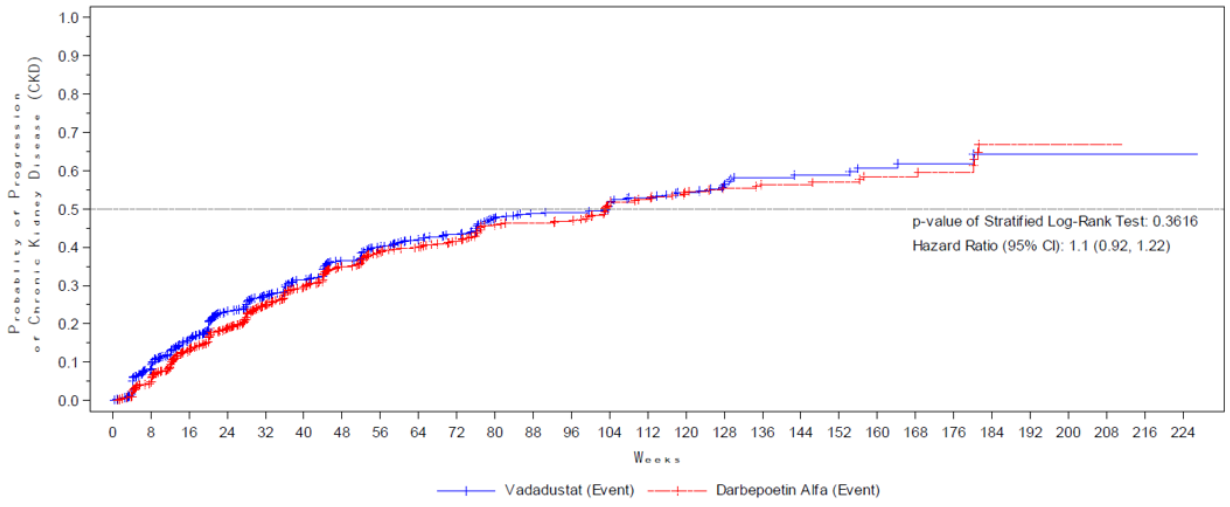
Source: FDA Clinical Data Scientist

Analysis based on the following pooled PTs: 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

Accelerated Loss of Renal Function

We also assessed for accelerated loss of renal function with vadadustat compared to darbepoetin. An analysis of the time to progression of chronic kidney disease conducted by the Applicant was similar for the two arms for both Study 0014 (Figure 4) and 0015 (Figure 5); there was no obvious signal for accelerated loss of renal function with vadadustat compared to darbepoetin.

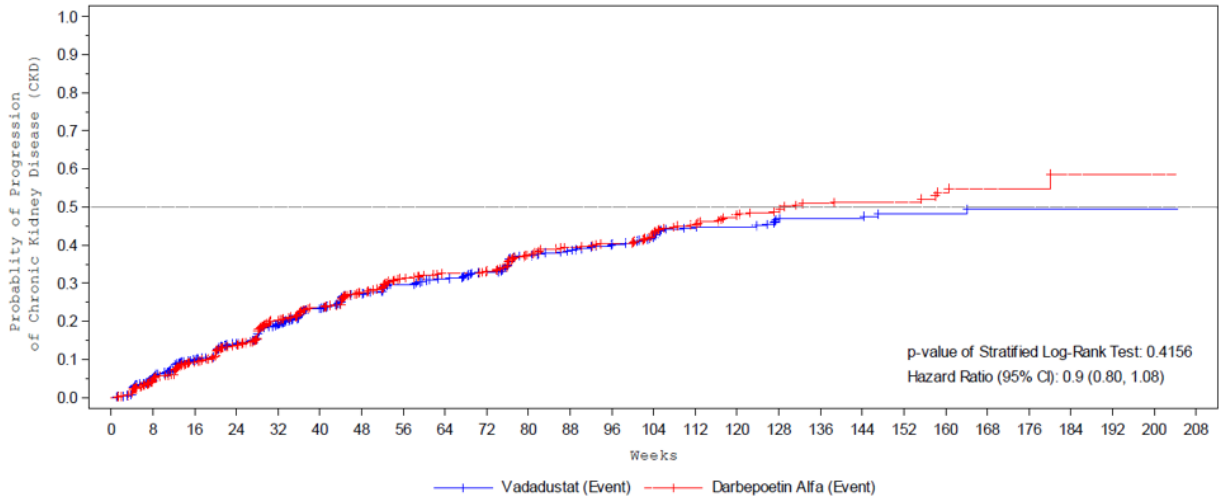
Figure 4. Cumulative Incidence of Progression of Chronic Kidney Disease, Safety Population, Trial 0014 (NDD-CKD)



Source: Applicant, Clinical Study Report, Trial AKB-6548-CI-0014, Fig 14.2.3.2

Progression of CKD was defined as experiencing 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)

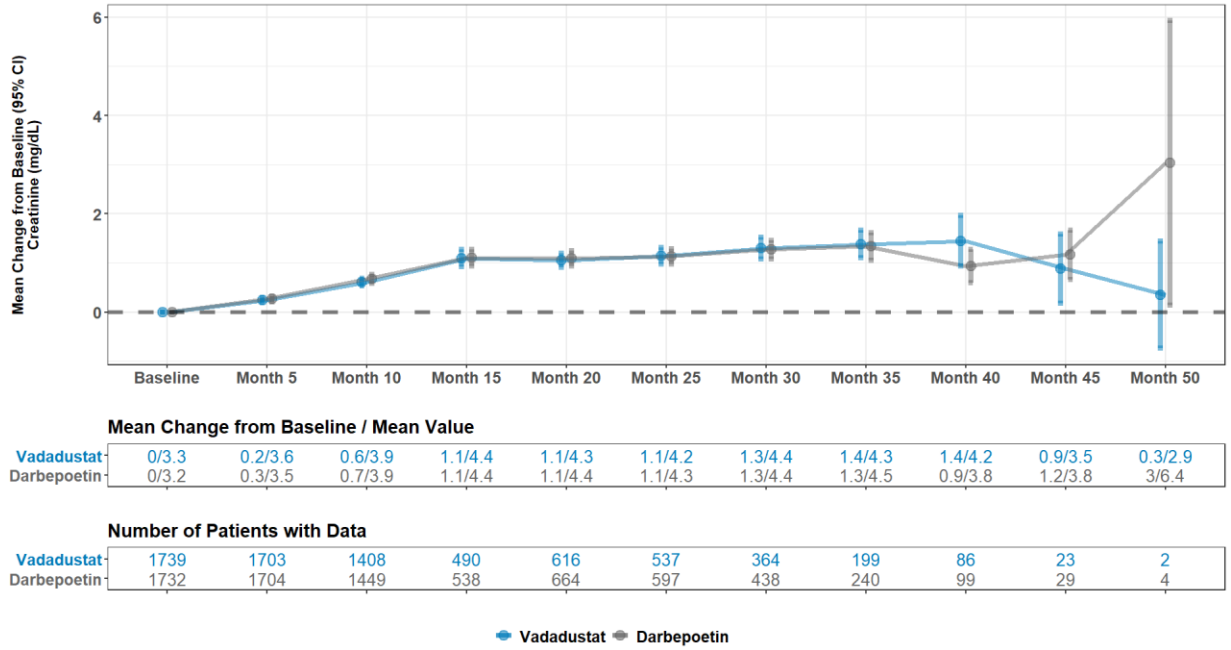
Figure 5. Cumulative Incidence of Progression of Chronic Kidney Disease, Safety Population, Trial 0015 (NDD-CKD)



Source: Applicant, Clinical Study Report, Trial AKB-6548-CI-0014, Fig 14.2.3.2
Progression of CKD was defined as experiencing any of the following: transition to chronic dialysis, or receipt of a kidney transplant, or eGFR <15 mL/min/1.73 m^2 and confirmed by another measurement with a GFR <15 mL/min/1.73 m^2, 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)

Figure 6. Mean Creatinine (mg/dL) Change From Baseline Over Time, Safety Population, Trials 0014 and 0015 (NDD-CKD)



Source: Kidney Injury Follow-On Guide; adlb.xpt; Software: R
Abbreviations: CI, confidence interval

Hyperkalemia

Table 8. Hyperkalemia Treatment-Emergent Adverse Events, Safety Population, Pooled Trials 0014 and 0015 (NDD-CKD)

Event Assessment	Vadadustat N=1739 n (%)	Darbepoetin N=1732 n (%)	Risk Difference (%) (95% CI)
Any AE in group	196 (11.3)	231 (13.3)	-2.1 (-4.3, 0.1)
Blood potassium increased	9 (0.5)	15 (0.9)	-0.3 (-0.9, 0.2)
Hyperkalemia	189 (10.9)	221 (12.8)	-1.9 (-4.0, 0.3)
Maximum severity			
Death	0	1 (0.06)	-0.1 (-0.2, 0.1)
Life-threatening	0	0	0 (0, 0)
Severe	28 (1.6)	18 (1.0)	0.6 (-0.2, 1.3)
Moderate	87 (5.0)	106 (6.1)	-1.1 (-2.6, 0.4)
Mild	81 (4.7)	106 (6.1)	-1.5 (-3.0, 0.0)
Serious	33 (1.9)	37 (2.1)	-0.2 (-1.2, 0.7)
Resulting in discontinuation	2 (0.1)	1 (0.06)	0.1 (-0.1, 0.3)

Source: Clinical Data Scientist
Analysis based on the following pooled PTs: blood potassium increased, hyperkalaemia

Table 9. Proportion of Patients with a New Incidence of a Clinically Significant Serum Potassium Elevation, Safety Population, Pooled Trials 0014 and 0015 (NDD-CKD)

Parameter	Vadadustat N=1739 n (%)	Darbepoetin N=1732 n (%)
Potassium (mEq/L)	147 (8.5)	188 (10.9)

Source: FDA Clinical Data Scientist

New incidence defined as patients who had a serum potassium ≤6 mEq/L at baseline and >6 mEq/L at any time post-baseline

Preferred Terms Making Up Key Grouped Queries

Hyperphosphatemia

blood phosphorus increased, hyperphosphatemia

Hyperkalemia

blood potassium increased, hyperkalaemia

Access-Related Thrombosis

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

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

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Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	215192
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Vadadustat
Indication	Anemia in CKD
Applicant	Akebia Therapeutics, Inc.
Requesting Division	Division of Non-malignant Hematology (DNH); May Zuwannin, RPM
Primary Reviewer	Ling Lan, MD, PhD, Clinical Analysist, DILI Team, DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Feb 5, 2021

Context: Vadadustat (VDA) is an orally delivered, small molecule inhibitor of hypoxia inducible factor prolyl-hydroxylase (HIF-PH). HIF-1 and HIF-2 are transcriptional factors that facilitate adaptation to hypoxia by regulating expression of erythropoietin (EPO), transferrin and other genes involved with erythropoiesis and iron utilization. VDA's inhibitory properties are postulated to stimulate erythropoiesis pathways associated with chronic hypoxia. The sponsor submitted an NDA for VDA use in anemia associated with chronic kidney disease. There was a hepatotoxicity signal identified early in their drug development program, but also a potential Hy's Law case in a phase 3 trial. The Division of Non-malignant Hematology (DNH) asked the DILI Team to give opinion on the "type, severity and significance of any potential hepatotoxicity safety signals." The DILI Team took part in the Late Cycle conference with the sponsor on Nov 18, 2021. The sponsor presented the one subject with DILI, jaundice and high transaminases but suggested it was not a Hy's Law case.

Executive Summary: We believe there is a significant hepatotoxicity risk with VDA. In the Integrated Safety Summary datasets, there is one case which we meets Hy's Law criteria and at least seven cases of probable DILI due to VDA in Temple's Corollary, five of which had significant elevations in ALT (over 10x upper limit of normal). The exposed population is large at over 4000 subjects, so the overall rates of injury are low. Nevertheless, such low rates may still generate significant cases of liver injury if this drug is used widely. If the need is high, advantages obvious and efficacy clear for VDA, then we can work with DNH to produce a risk mitigation strategy for post-approval use. Our full assessment and recommendations are in Section 5.0.

Consultation Sections:

Section 1.0 – Rationale (target disease and mechanism of action)
Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.

Abbreviations:
AP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BEC: Blinded Evaluation Committee (for liver related AEs)
CKD: chronic kidney disease
CPK: creatinine phosphokinase
DB: direct bilirubin
DD: dialysis dependent
DILI: drug-induced liver injury
EPO: erythropoietin
ESA: erythropoiesis-stimulating agent (e.g., darbepoetin)
IDMC: Independent Data Monitoring Committee
GFR: glomerular filtration rate
GGT: gamma-glutamyl transferase
Hb: hemoglobin
HDS: herbal/dietary supplement
HAC: Hepatology Assessment Committee
HIP: hypoxia inducible factor
HIF-PH: hypoxia inducible factor prolyl-hydroxylase
IP: investigational product
LDH: lactate dehydrogenase
MACE: major adverse cardiovascular event
NDD: non-dialysis dependent
PEP: primary efficacy period
SEP: secondary efficacy period
TB: total bilirubin
VDA: Vadadustat

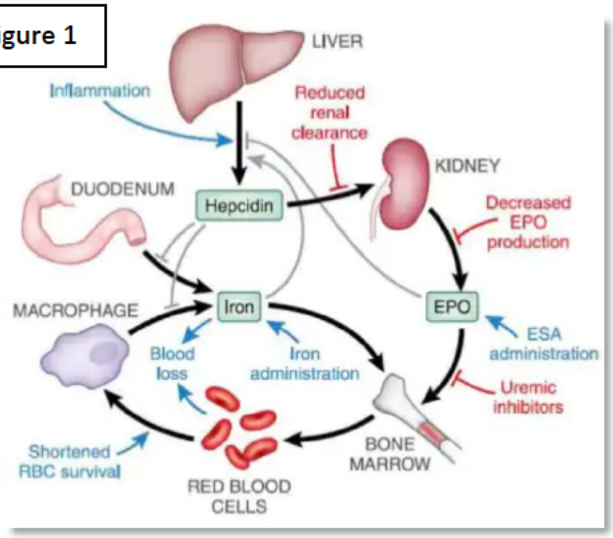
1.0 Rationale

1.1 Disease: Anemia is common in patients with chronic kidney disease (CKD) and inversely related to glomerular filtration rate (GFR).[1] The prevalence of anemia rises from 1% in those with GFR $\geq$ 60 mL/min/1.73 m^2 to 33-67% when GFR falls to $\leq$15.[2] The pathophysiology of anemia in CKD includes

[1] UpToDate Treatment of anemia in nondialysis chronic kidney disease - UpToDate (Accessed Nov 7, 2021)
[2] Astor BC, et al. Arch Intern Med (2002)

uremic inhibitors, reduced renal clearance of hepcidin, and reduction of erythropoietin (EPO) production by the kidney (Figure 1).[3] Hepcidin decreases iron absorption and trafficking, thus its lack of clearance can contribute to iron deficiency.

Figure 1



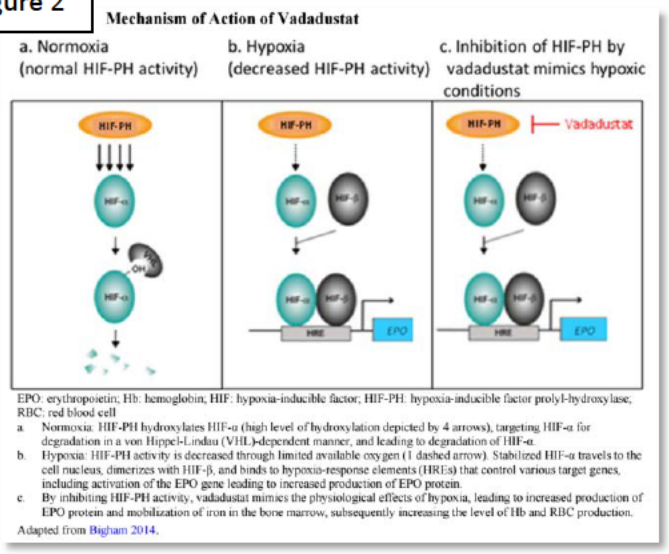
Treatment consists of iron, erythropoiesis-stimulating agents (ESAs) and red blood cell transfusions. ESAs are delivered subcutaneously or intravenously. There are no approved oral agents.

1.2 Rationale: Vadadustat (VDA) is an oral, small molecule inhibitor of hypoxia inducible factor prolyl-hydroxylase (HIF-PH). HIF-1 and HIF-2 are transcriptional factors that facilitate adaptation to hypoxia by regulating expression of erythropoietin (EPO), transferrin and other genes involved with erythropoiesis and iron utilization. HIFs consist of a constitutively expressed beta unit (HIF-beta) and a short half-life (5 minutes) alpha unit. The alpha unit (HIF-alpha) is degraded quickly when HIF-PH hydroxylases HIF-alpha prolines which signals proteasomal destruction. Under hypoxia, HIF-PH decreases thus leading to less destruction of HIF-alpha. Longer lasting HIF-alpha can then translocate to the nucleus in greater amounts to dimerize with HIF-beta. The complete HIF protein can then bind hypoxia response elements and activate transcription of targeted genes.

Thus, inhibition of HIF-PH is expected to mimic hypoxia conditions that allow increased HIF-alpha/beta downstream effects including increase in red blood cell production thus treating anemia associated with chronic kidney disease (CKD) (Figure 2).

[3] Babbitt JL et al. JASN (2016)

Figure 2



EPO: erythropoietin; Hb: hemoglobin; HIF: hypoxia-inducible factor; HIF-PH: hypoxia-inducible factor prolyl-hydroxylase; RBC: red blood cell

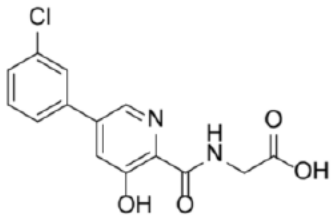
a. Normoxia: HIF-PH hydroxylates HIF-α (high level of hydroxylation depicted by 4 arrows), targeting HIF-α for degradation in a von Hippel-Lindau (VHL)-dependent manner, and leading to degradation of HIF-α.
b. Hypoxia: HIF-PH activity is decreased through limited available oxygen (1 dashed arrow). Stabilized HIF-α travels to the cell nucleus, dimerizes with HIF-β, and binds to hypoxia-response elements (HREs) that control various target genes, including activation of the EPO gene leading to increased production of EPO protein.
c. By inhibiting HIF-PH activity, vadadustat mimics the physiological effects of hypoxia, leading to increased production of EPO protein and mobilization of iron in the bone marrow, subsequently increasing the level of Hb and RBC production.

Adapted from Bigham 2014.

2.0 ADME data

2.1 Structure (Figure 3):

Figure 3



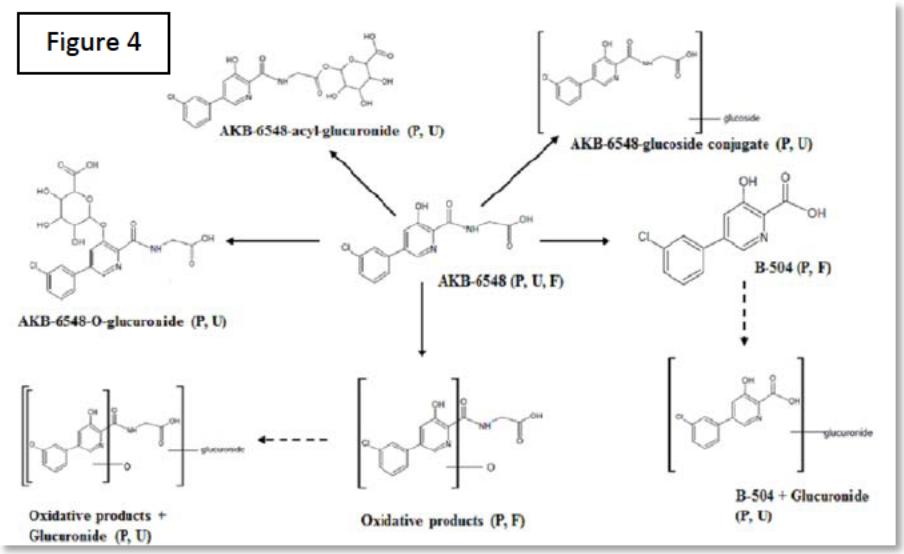
Vadadustat has no chiral centers

2.2 Absorption: VDA absorption is rapid with median time to maximum plasma levels falling between 1 and 4 hours in both healthy and CKD subjects.

2.3 Distribution: VDA is highly albumin bound in human plasma (>99%) without concentration dependence up to 100 ug/ml. The binding was similar between healthy and CKD subjects.

2.4 Metabolism: VDA is hepatically metabolized to multiple primary and secondary metabolites (Figure 4). However, in vitro microsomal incubations with human, rat, dog and monkey hepatocytes suggest CYPs are not involved. However, phase II metabolism (i.e., glucuronidation) does occur via UGT1A1, 1A7, 1A8 and 1A9. VDA and VDA-O-glucuronide are the major circulating forms, and the latter is pharmacologically inactive.

Figure 4



2.5 Excretion: While excretion via bile and feces are the major routes in rats and dogs, urinary elimination of drug and metabolites is primary in humans (59% urine; 27% feces). Most of the urine metabolite is DAD-O-glucuronide. Less than 1% is unchanged VDA.

2.6 Summary PK data based on Phase 1 and 2 studies (Table 1). NDA215192 (215192 - 0026 - (26) - 2021-11-03 - ORIG-1 /Quality/Response To Information Request) - Vadadustat Dosing Rationale for Planned Phase 3 Studies (DD-CKD) (#6)

Table 1 **Summary Vadadustat PK Parameters Derived from the Integrated PPK Model Developed with Phase 2a PK data**

Summary of PK Parameter Estimates by Subject Type

Statistic	CL (L/hr)	K (/hr)	$t_{1/2}$ (hr)	V (L)	KA (/hr)	Lag Time (hr)
Healthy Subjects						
Median	1.59	0.146517	4.74	11.0	0.827	0.399
Minimum	0.786	0.103	3.23	7.64	0.259	0.397
Maximum	2.84	0.215	6.74	14.1	2.52	0.408
Patients						
Median	1.11	0.0986	7.03	11.3	0.491	0.400
Minimum	0.512	0.0593	3.83	7.65	0.118	0.400
Maximum	2.84	0.181	11.7	15.7	4.33	0.516

Source: Report AKB-6548-CP-0001

3.0 Non-clinical data

3.1 In vitro data:

3.1.1 Transporters: In vitro VDA inhibited BCRP, OAT P1B1, OAT1 and OAT3. There is no mention of other transporter inhibition in the Non-Clinical overview.

3.1.2 Cytochrome testing: VDA is not extensively metabolized by the cytochrome p450 system based on microsome studies. Therefore,

"P450-based phenotyping assays were not conducted." VDA does inhibit CYP2B6, 2C8 and 2C9.

3.2 Animal data: Overall, no liver histopathology or liver chemistry changes are mentioned in the Nonclinical Overview (Module 2.4), under section 4.0. Main toxicities in their Wistar rat and Beagle dog studies involved thrombosis formation and increased hematopoiesis.

3.2.1 Beagle Dog 9-month oral exposure: Dosing was 10, 25 and 50 mg/kg/day by oral gastric lavage. One dog died on the 50 mg/kg/day dose but not due to liver injury. This dog had polycythemia. No study drug effects on clinical chemistries in the other surviving dogs were seen. No liver histopathology is mentioned. The NOAEL was 25 mg/kg/d for females and 50 mg/kg/d for males. These correspond to a 0.07 to 0.11 fold difference compared to the 600 mg/d given in NDD and DD trials.

3.2.2 Wistar rat 90-day exposure study: Similar to the dogs, rats had toxicities related to thromboses and increased hematopoiesis primarily. No liver chemistry elevations or histopathology of note are mentioned. The NOAEL was 40 mg/kg/d corresponding to 0.34 and 0.51 fold difference in the NDD and DD subjects.

4.0 Clinical data:

4.1 In class or near class data: Several HIF-PHIs are in development for the treatment of anemia and chronic kidney disease, but none are approved in the US or Europe. Roxadustat was approved in China and Japan in 2008. In July 2021, the FDA did not approve Roxadustat for the treatment of anemia associated with chronic kidney disease due to lack of acceptable risk and benefit. The EMA approved Roxadustat in August 2021. The DHN DILI Team consulted on the Roxadustat NDA (213805) in Mar 2021. While bland cholestasis was seen in the application, it could not be clearly attributed to the DILI. There were no Hy's Law cases, and the DILI Team did not feel that hepatotoxicity risk high enough to hold up approval. Other non-hepatic factors weighed on the FDA's decision.

4.2 Studies: Clinical studies for this drug development program are listed in Table 2.

Table 2 **Vadadustat Clinical Program Overview**

Study #	Phase/Name	Population	Dose Range	Subjects Randomized	Treatment Duration
Studies in Subjects with NDD-CKD					
AKB-6548-CI-0014	Phase 3/ PRO$_2$TECT	NDD-CKD	150 to 600 mg QD	1761	≥36 weeks
AKB-6548-CI-0015	Phase 3/ PRO$_2$TECT	NDD-CKD	150 to 600 mg QD	1750	≥36 weeks
AKB-6548-CI-0003	Phase 2a	NDD-CKD	500 mg	22	Single Dose
AKB-6548-CI-0004	Phase 2a	NDD-CKD	200 to 700 mg QD	10	28 Days
AKB-6548-CI-0005	Phase 2a	NDD-CKD	240 to 630 mg QD	91	42 days
AKB-6548-CI-0007	Phase 2b	NDD-CKD	150 to 600 mg QD	209	20 weeks
AKB-6548-CI-0021	Phase 2	NDD-CKD	150 to 300 mg QD	51	16 weeks
MT-6548-J01	Phase 3	NDD-CKD	150 to 600 mg QD	304	52 weeks
Studies in Subjects with DD-CKD					
AKB-6548-CI-0016	Phase 3/ INNO$_2$VATE	DD-CKD	150 to 600 mg QD	369	≥36 weeks
AKB-6548-CI-0017	Phase 3/ INNO$_2$VATE	DD-CKD	150 to 600 mg QD	3554	≥36 weeks
AKB-6548-CI-0009	Phase 1	ESRD	450 mg given as 2 single doses	12	3 days
AKB-6548-CI-0011	Phase 2	DD-CKD	300 to 450 mg QD, 450 mg TIW	94	16 weeks
AKB-6548-CI-0022	Phase 2	DD-CKD	150 to 600 mg QD	60	16 weeks
MT-6548-J02	Phase 3	DD-CKD	150 to 750 mg QD	42	24 weeks
MT-6548-J03	Phase 3	DD-CKD	150 to 600 mg QD	323	52 weeks
MT-6548-J04	Phase 3	DD-CKD	150 to 600 mg QD	24	24 weeks
404-201-00012/ AKB-6548-CI-0036[a]	Phase 3b	DD-CKD	150 to 900 mg QD 150 to 1200 mg TIW	300 (planned)	52 weeks (planned)
AKB-6548-CI-0025	Phase 2/ FO$_2$RWARD-2	DD-CKD	150 to 900 mg QD and TIW	165	≥20 weeks
AKB-6548-CI-0034	Phase 1b	DD-CKD	600 to 900 mg QD	46	10 days
Studies in Healthy Subjects					
AKB-6548-CI-0001	Phase 1a	HS	80 to 1200 mg	48	Single Dose
AKB-6548-CI-0002	Phase 1b	HS	500 to 900 mg QD	34	10 days
AKB-6548-CI-0006	Phase 1	HS	315 mg	8	Single Dose
AKB-6548-CI-0008	Phase 1	HS	650 mg	6	Single Dose
AKB-6548-CI-0010	Phase 1	HS	600 to 1200 mg	50	Single Dose
AKB-6548-CI-0012	Phase 1	HS	450 mg given as 2 single doses	10	Single Dose
AKB-6548-CI-0013	Phase 1	HS	150 mg given as 3 single doses	18	Single Dose
AKB-6548-CI-0019	Phase 1	HS	600 mg QD	12	7 days
AKB-6548-CI-0020	Phase 1	HS	150 to 600 mg QD	48	10 days
AKB-6548-CI-0024	Phase 1	Hepatic Impaired and HS	450 mg	16	Single Dose
AKB-6548-CI-0027	Phase 1	HS	150 mg given as 2 single doses	50	Single Dose
AKB-6548-CI-0028	Phase 1	HS	450 mg given as 3 single doses	54	Single Dose
AKB-6548-CI-0029	Phase 1	HS	300 mg given as 2 single doses	40	Single Dose
AKB-6548-CI-0030	Phase 1	HS	600 mg QD	134	8 days
AKB-6548-CI-0031	Phase 1	HS	600 mg QD on Days 13 to 19	62	19 days
AKB-6548-CI-0033	Phase 1	HS	300 mg	20	Single Dose
AKB-6548-CI-0037	Phase 1	HS	300 mg given as 4 single doses	54	Single Dose
MT-6548-J05	Phase 3	HS	150 mg given as 3 or 2 single doses	61	Single Dose

DD-CKD: dialysis-dependent chronic kidney disease; ESRD: end-stage renal disease; HS: healthy subjects; NDD-CKD: non-dialysis-dependent chronic kidney disease; QD: once daily; TIW: 3 times weekly.
a Study AKB-6548-CI-0036 is ongoing
Source: Module 5.2

4.3 Safety populations. Both dialysis dependent (DD) and non-dialysis dependent (NDD) studies are included. For this consult report we focused on the larger

Phase 3 pivotal studies. For all these trials, VDA is begun at 300 mg/d and titrated in 150 mg/d increments to 600 mg/d maxiumum. In the figures below, 0 to 52 weeks is the "correction and maintenance period". PEP is primary efficacy period, and SEP is secondary efficacy period. Primary efficacy endpoint is change in average Hb over weeks 24-36. Primary safety endpoint is MACE at any time. Subjects are randomized, without later cross-over or OLE, to VDA or darbepoetin. All figures include enrollment numbers and completion numbers at various stages.

4.3.1 DD-CKD Studies (Table 3)

Table 3

Number of Subjects by Study - DD-CKD Population (Safety Population)

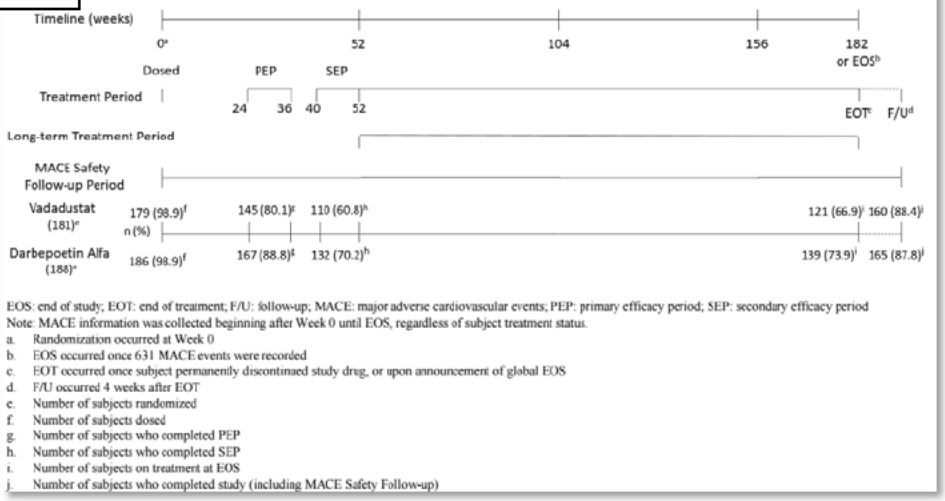
Study	Vadadustat	IV ESA	Placebo	Total
CI-0009[a]	12	0	0	12
CI-0011[b]	94	0	0	94
CI-0016[c]	179	186[e]	0	365
CI-0017[c]	1768	1769[e]	0	3537
CI-0022[b,d]	51	0	15	60
CI-0025[b]	134	41[f]	0	175
CI-0034[a]	37	7	0	44
MT-6548-J02[c]	42	0	0	42
MT-6548-J03[c]	162	161[e]	0	323
MT-6548-J04[c]	24	0	0	24
Total	2503	2164	15	4676[g]

CSR: clinical study report, DD-CKD: dialysis-dependent chronic kidney disease, ISS: Integrated Summary of Safety, IV ESA: intravenous erythropoiesis-stimulating agent either darbepoetin alfa or epoetin alfa.
a. Phase 1 study.
b. Phase 2 studies.
c. Phase 3 studies.
d. For Study CI-0022, there were 2 treatment periods where 6 subjects who received placebo in the first treatment period were switched to vadadustat during the second treatment period. These 6 subjects were included in both the placebo and vadadustat columns, while only counted once in the total column.
e. Subjects received darbepoetin alfa
f. Subjects received epoetin alfa
g. Numbers add up vertically to total 4676 but not horizontally due to CI-0022 dose switch
Source: ISS Table 14.1.1.1a, CSR 0025 Table 14.1.1.1a and Table 14.1.1.2a, CSR 0034 Table 14.1.1

Study CI-0016: Inno2vate-Correction/Conversion—Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction of Maintenance Treatment of Anemia in Subjects with Incident Dialysis-Dependent Chronic Kidney Disease (DD-CKD). Subjects have initiated dialysis within 16 weeks of screening. Study schematic with enrollment numbers across time is shown below (Figure 5).

Clinical Study Report: AKB-6548-CI-0016
Date: 18 December 2020

Figure 5 **Timeline of Activities for INNO$_2$VATE Studies**

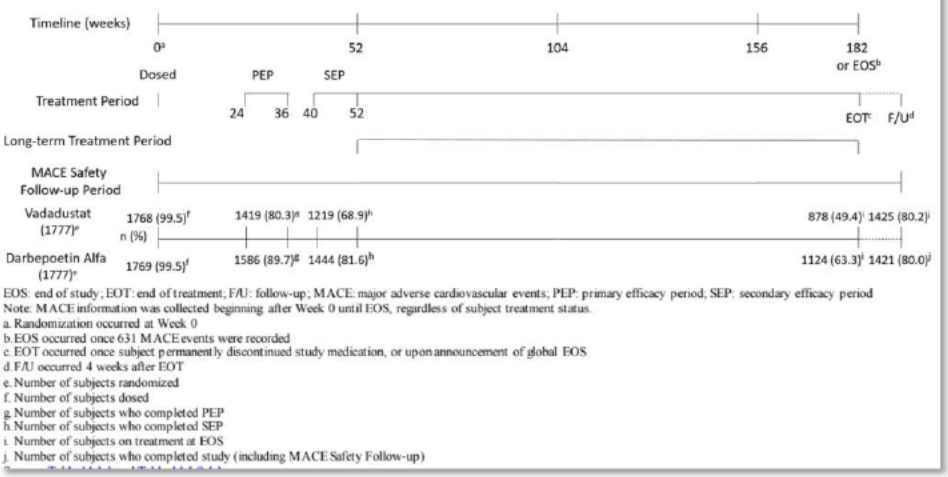


EOS: end of study; EOT: end of treatment; F/U: follow-up; MACE: major adverse cardiovascular events; PEP: primary efficacy period; SEP: secondary efficacy period
Note: MACE information was collected beginning after Week 0 until EOS, regardless of subject treatment status.
a. Randomization occurred at Week 0
b. EOS occurred once 631 MACE events were recorded
c. EOT occurred once subject permanently discontinued study drug, or upon announcement of global EOS
d. F/U occurred 4 weeks after EOT
e. Number of subjects randomized
f. Number of subjects dosed
g. Number of subjects who completed PEP
h. Number of subjects who completed SEP
i. Number of subjects on treatment at EOS
j. Number of subjects who completed study (including MACE Safety Follow-up)

Study CI-0017: Inno2vate-Conversion—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 Dialysis-Dependent Chronic Kidney Disease (DD-CKD). Subjects were all on ESAs for at for at least 6 weeks prior to screening (Figure 6).

Clinical Study Report: AKB-6548-CI-0017
Date: 07 Dec 2020

Figure 6 **Timeline of Activities for INNO$_2$VATE Studies**



EOS: end of study; EOT: end of treatment; F/U: follow-up; MACE: major adverse cardiovascular events; PEP: primary efficacy period; SEP: secondary efficacy period
Note: MACE information was collected beginning after Week 0 until EOS, regardless of subject treatment status.
a. Randomization occurred at Week 0
b. EOS occurred once 631 MACE events were recorded
c. EOT occurred once subject permanently discontinued study medication, or upon announcement of global EOS
d. F/U occurred 4 weeks after EOT
e. Number of subjects randomized
f. Number of subjects dosed
g. Number of subjects who completed PEP
h. Number of subjects who completed SEP
i. Number of subjects on treatment at EOS
j. Number of subjects who completed study (including MACE Safety Follow-up)

4.3.2 NDD-CKD subject trials (Table 4)

Table 4 **Number of Subjects by Study - NDD-CKD Population (Safety Population)**

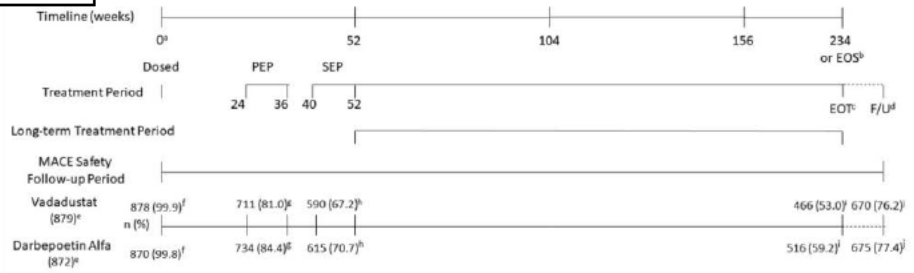
Study	Vadadustat	Darbepoetin Alfa	Placebo	Total
CI-0003[a]	22	0	0	22
CI-0004[a]	10	0	0	10
CI-0005[a]	72	0	19	91
CI-0007[a]	138	0	72	210
CI-0014[b]	878	870	0	1748
CI-0015[b]	861	862	0	1723
CI-0021[a]	51	0	14	51
MT-6548-J01[b]	151	153	0	304
Total	2183	1885	105	4159

NDD-CKD: non-dialysis-dependent chronic kidney disease.
For Study CI-0021, there are 2 study periods and placebo subjects were switched to take vadadustat in the second period. The placebo subjects were counted into both the vadadustat and placebo columns but only once in the total column.
a. Phase 2 studies.
b. Phase 3 studies.
Source: Integrated Summary of Safety Table 14.1.1.1b

Study CI-0014: Prot2tect-Correction-- Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD). Subjects cannot have been on any ESAs for 8 weeks prior to enrollment. Study schematic with enrollment numbers across time is shown (Figure 7). Primary efficacy endpoint is change in average Hgb during weeks 24 to 36 (PEP). Primary safety endpoint is MACE at any time during the study.

Clinical Study Report: AKB-6548-CI-0014
Date: 14 Jan 2021

Figure 7 **Study Periods for PRO$_2$TECT Studies**



EOS: end of study; EOT: end of treatment; F/U: Follow-up; MACE: major adverse cardiovascular event; PEP: primary efficacy period; SEP: secondary efficacy period
Note: MACE information was collected beginning after Week 0 until EOS, regardless of subject treatment status.
a Randomization occurred at Week 0
b EOS occurred once 631 MACE events were recorded
c EOT occurred once subject permanently discontinued study drug, or upon announcement of global EOS.
d F/U occurred 4 weeks after EOT
e Number of subjects randomized
f Number of subjects dosed
g Number of subjects who completed PEP
h Number of subjects who completed SEP
i Number of subjects on treatment at EOS
j Number of subjects who completed study (including MACE Safety Follow-up)

Study CI-0015: Pro2tect-Conversion—Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD). Design is identical to CI-0014. Primary endpoints are similar in terms of Hgb change but subjects are randomized to conversion to VDA from available ESAs. Thus, all subjects are on ESAs prior to screening.

4.3.3 Hepatic Impairment Study (CI-0024): Subjects with normal and moderate hepatic dysfunction (Child Pugh B) were studied. AUCs were slightly higher and half-life 33% longer in subject with moderate hepatic dysfunction. Other parameters and volume of distribution were not different (Table 5).

Table 5 **CI-0024—Mean (%CV) Pharmacokinetic Parameters of Vadadustat Following a Single-Dose of 450 mg Vadadustat to Subject With Normal Hepatic Function and Subjects With Moderate Hepatic Impairment**

Parameter	Group 1 Moderate Hepatic Impairment (N = 8)	Group 2 Normal Hepatic Function (N = 8)
t_{max}, h	2.00 (1.00, 4.00)	2.50 (1.50, 6.00)
C_{max}, µg/mL	52.9 (22.2)	52.6 (28)
$AUC_{0\text{-last}}$, µg·h/mL	432 (35.4)	395 (18.2)
$AUC_{0\text{-}\infty}$, µg·h/mL	436 (35.6)	397 (18.1)
$t_{½}$, h	7.75 (32.6)	5.81 (24.5)
CL/F, L/h	1.15 (33.7)	1.17 (22)
Vd/F, L	12.3 (32.6)	9.57 (19.6)

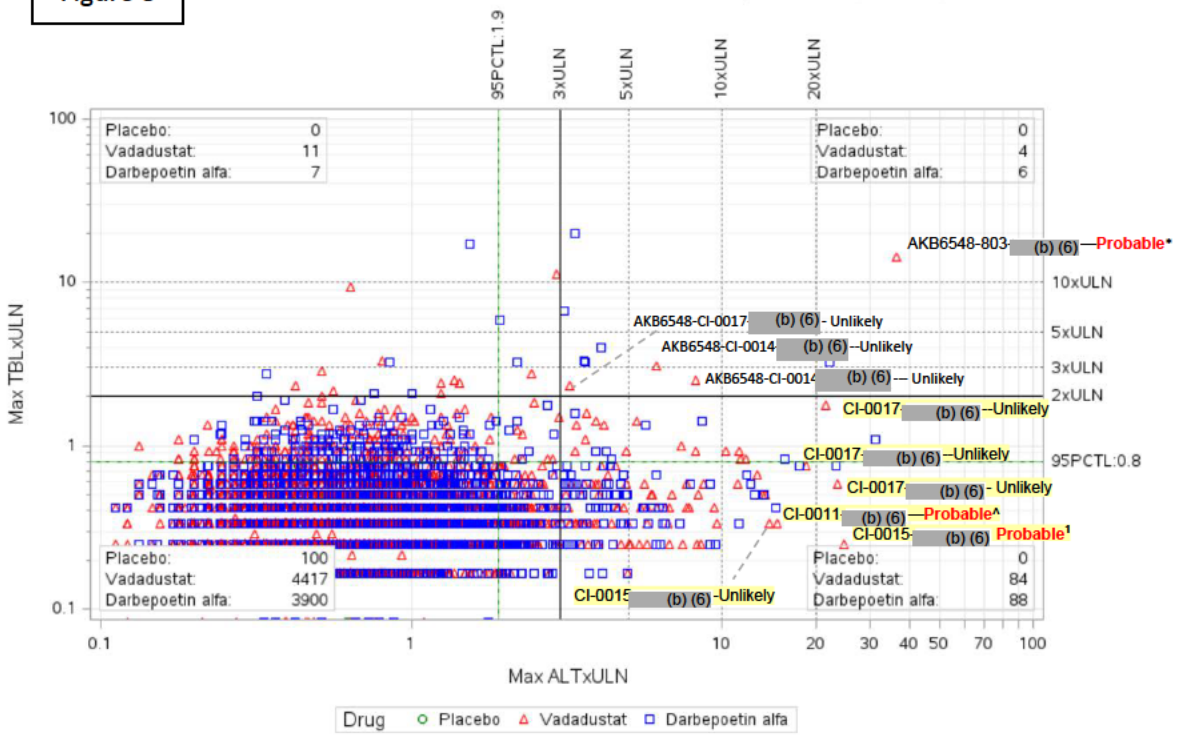
$AUC_{0\text{-}\infty}$: area under the plasma time concentration curve from time 0 to infinity; $AUC_{0\text{-last}}$: area under the plasma time concentration curve from time 0 to the last measurable concentration; CL/F: apparent clearance following oral administration; C_{max}: maximal plasma concentration; CV: coefficient of variation; N: number of subjects; $t_{½}$: half life; t_{max}: time to maximal plasma concentration; Vd/F: apparent volume of distribution
t_{max} is expressed as median (minimum, maximum).

4.4 eDISH, liver enzyme elevation shift tables, and case level analyses

4.4.1 Hepatocellular scatter plots (eDISH)

4.4.1.1 Maximum TB by maximum ALT (Figure 8)

Figure 8 **100 on Placebo : 4,516 on Vadadustat : 4,001 on Darbepoetin alfa (N: 8,617)**



*HAC assessment: 6 probable

^HAC assessment: No assessment provided
[1]HAC assessment: 3 probable, 2 possible

All cases in Temples Corollary with ALT greater than 5x ULN were assessed individually. Due to crowding of data points on the ALT scatter plot, the remaining case assessments are shown in tabular format (Table 6)

Table 6: DILI Team and HAC case level assessments of cases with ALT >5x ULN and TB <2x ULN. The first 7 cases listed had ALT >10x ULN.

Case	DILI Team assessment	HAC
CI-0017 (b) (6)	Possible	1 possible, 3 unlikely*
CI-0014	Unlikely	All unlikely
CI-0016	Unlikely	All unlikely
CI-0014	Probable	4 probable
CI-0014	Probable	3 probable; 3 strong possible; 1 indeterminant
CI-0016	Probable	2 probable; 3 strong possible; 2 weak possible; 1 indeterminant
CI-0017	Unlikely	2 probable; 1 strong possible; 1 indeterminant
CI-0017	Possible	1 probable; 4 weak possible; 1 unlikely
CI-0015	Unlikely	All unlikely
CI-0017	Unlikely	1 strong possible; 3 unlikely
CI-0017	Unlikely	1 probable; 3 weak possible
CI-0014	Possible	1 probable, 3 strong possible, 4 weak possible
CI-0014	Unlikely	Weak possible 3; 1 unlikely
CI-0017	No narrative	No assessments
CI-0014	Unlikely	All unlikely
CI-0015	Probable	3 probable
CI-0014	Indeterminant	1 probable, 2 strong possible, 1 weak possible
CI-0034	Probable	4 probable 2 strong possible, 1 weak possible
CI-0017	Unlikely	1 strong possible; 3 unlikely
CI-0015	Unlikely	1 probable, 1 strong possible, 2 unlikely
CI-0014	Possible	4 probable, 1 strong possible, 2 weak possible, 1 unlikely, 1 indeterminant
CI-0014	Unlikely	1 strong possible; 3 unlikely
CI-0014	unlikely	2 probable, 1 strong possible, 1 weak possible
CI-0017	Possible	2 strong possible, 1 weak possible, 1 unlikely
CI-0014	unlikely	3 probable, 1 strong possible
CI-0016	unlikely	3 probable, 1 strong possible
CI-0015	Possible	1 probable, 2 strong probable, 2 weak probable, 1 Unlikely
CI-0017	Possible	1 probable, 2 strong probable, 1 weak probable
CI-0015	Unlikely	3 probable, 1 unlikely
CI-0014	Unlikely	1 P, 1 SP, 1 WP, 1 U
CI-0016	Unlikely	4 Unlikely
CI-0017	No narrative	Not available
CI-0015	Unlikely	1 P, 2 WP, 1 U
CI-0015	No narrative	Not available.
CI-0017	Indeterminant	1 P, 2 SP
CI-0017	No narrative	Not available
CI-0014	Unlikely	4 Unlikely
CI-0017	No narrative	Not available

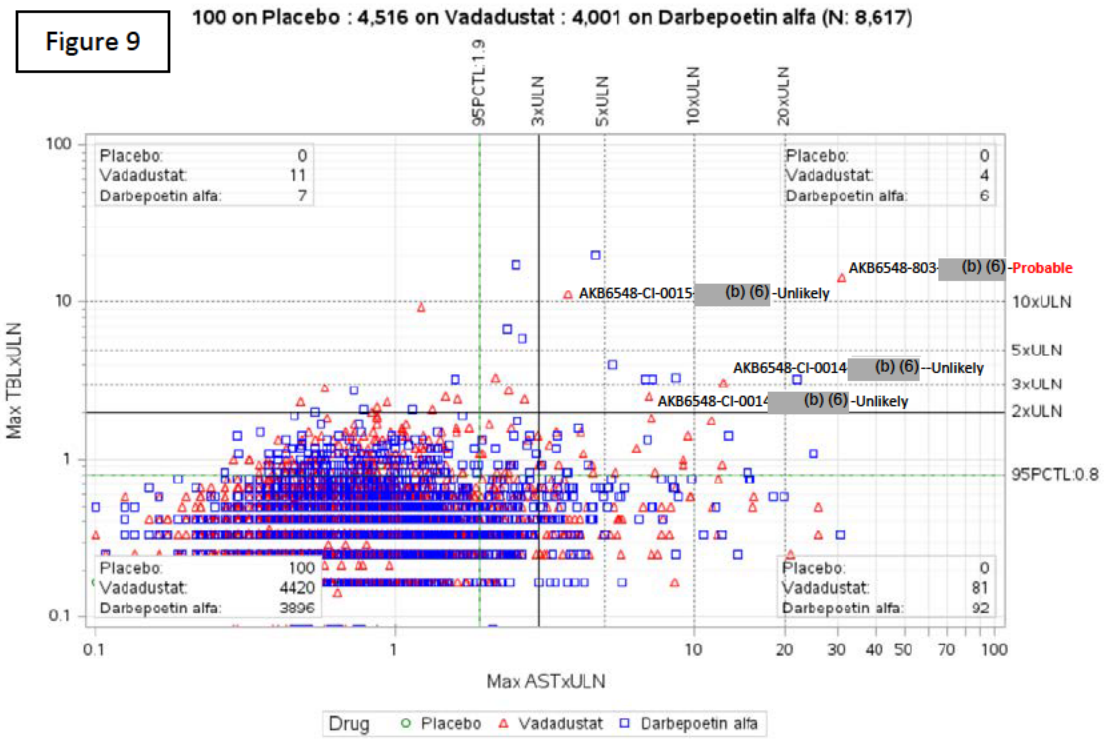
*Three HAC reviewers may have misread the data of DILI onset which occurred before the subject presented with heart failure.

4.4.1.2 Maximum TB by maximum AST:

Only one case in Hy's Law quadrant was considered probable DILI (Figure 9). This subject is the same subject seen Hy's Law quadrant of the ALT scatter plot (Figure

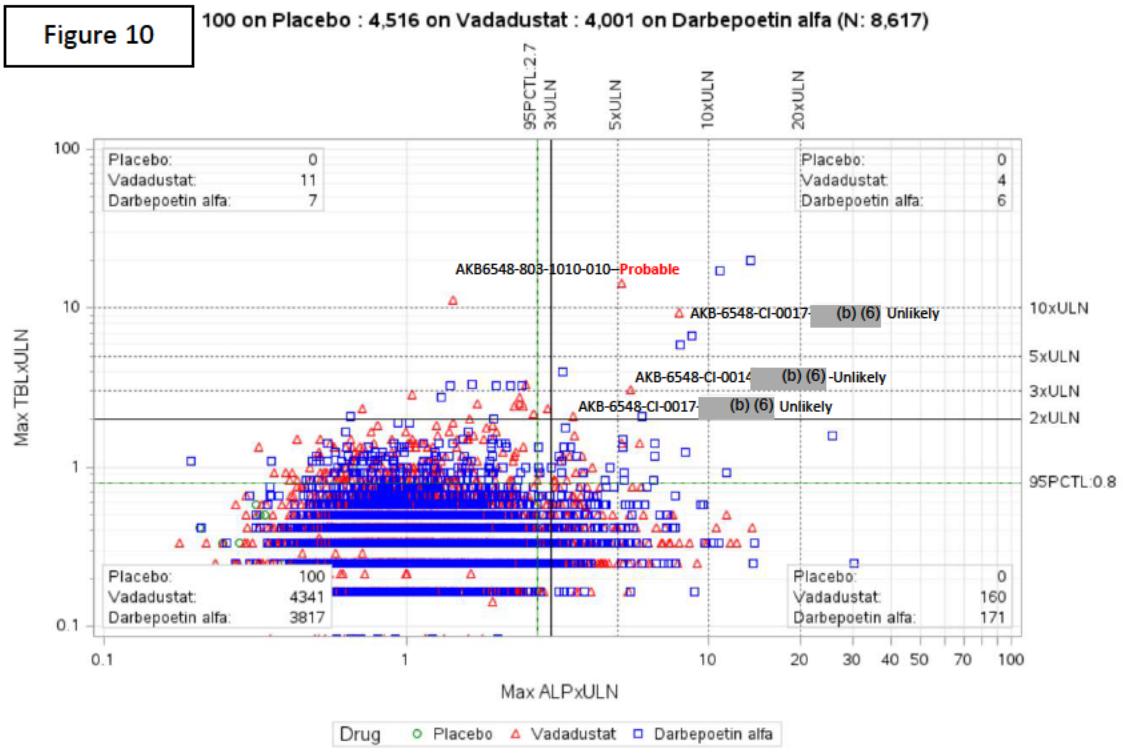
8) and discussed in detail below (Section 4.5.2). We did not do case level analyses for the Temple's Corollary cases in this AST scatterplot.

Figure 9



4.4.2 Cholestatic scatter plot or maximum TB by maximum AP (Figure 10): There was only one case in the right upper quadrant with AP >2x ULN and jaundice. This case is the same as the probable DILI case in the ALT and AST scatter plots (Figures 8 and 9)

Figure 10



4.4.3 Categories of abnormal transaminases and bilirubin from the pooled safety population are provided by the sponsor (Table 7).

Table 7 **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)

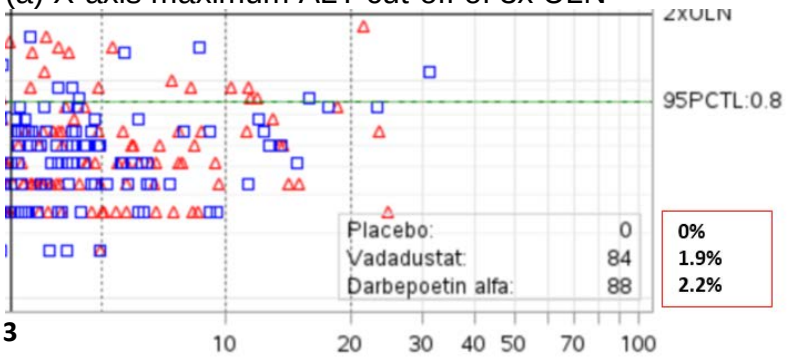
CKD: dialysis-dependent chronic kidney disease; N: number of subjects; n: number of subjects with events; N1: Number of subjects with any non-missing post-baseline assessments; ULN: upper limit of normal.
If there were assessments falling into different categories of criteria for a subject, then the subject was counted in the worst category only.
Source: Integrated Summary of Safety Table 14.3.5.8c

4.4.4 Abnormal transaminases by different maximum ALT cut-offs: While the number of cases in Temple's Corollary quadrant (eDISH, Figure 11 a) were the same between arms, there appeared to be a shift

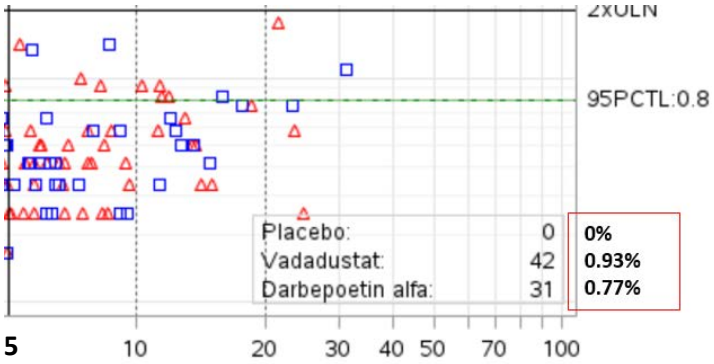
toward higher ALT levels for active arm cases (red triangles). To assess this appearance, we set the ALT cut-offs at >5x ULN, >8x ULN and >10x ULN in succession for the right lower quadrant, rather than bound categories of ALT levels (Figure 11 c-d).

Figure 11: Maximum TB versus maximum ALT scatterplots (eDISH) in x ULN. Only right lower quadrants shown using different maximum ALT cut-offs. Tallies and percentages reflect only subjects in the eDISH right lower quadrants shown.

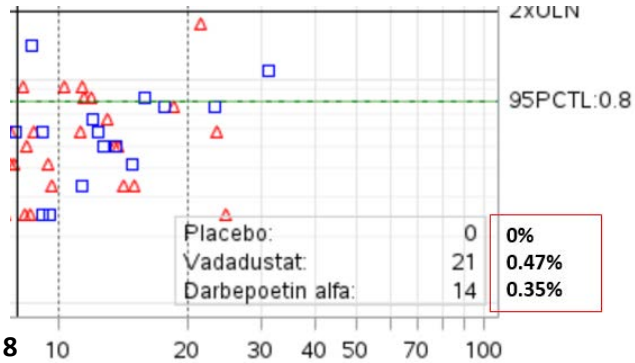
(a) X-axis maximum ALT cut-off of 3x ULN



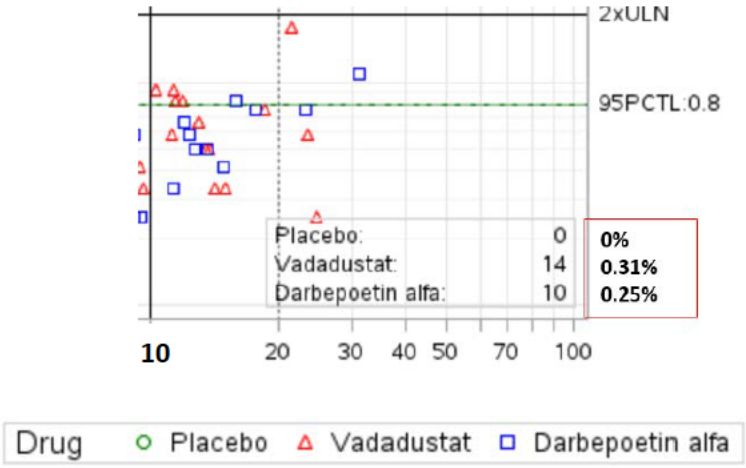
(b) X-axis maximum ALT cut-off of 5x ULN



(c) X-axis maximum ALT cut-off of 8x ULN



(d) X-axis maximum ALT cut-off of 10x ULN



4.5 Case level analysis by DILI team

4.5.1 Summary data for the 8 probable DILI cases with ALT >5x ULN are shown (Table 8).

Table 8

ID	Causality Score*	Study	Age (yr)	Sex	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak (ALT)^	R value peak (AST)^	Washout 50% ALT (da)	Washout 50% AST (da)	Washout ALT normal (da)	Washout AST normal (da)	Washout ALP normal (da)	Washout bilirubin normal (da)
(b) (6)	3	AKB-6548-CI-0034	31	M	Black AA	No	9	0	332	136	124	0.41	8.19	3.35	23	23	NA	30		
	3	AKB-6548-CI-0015	56	F	Black AA	No	27	-4	816	646	130	0.29	19.20	15.20	15	15	28	28		
	3	AKB-6548-CI-0007	69	F	White	Yes	56	-29	1166	1045	631	17.3	5.65	5.07	16	13	128	126	120	41
	3	AKB-6548-CI-0014	79	M	White	No	29	-7	487	169	130	0.99	11.46	3.98	30	30	30	30		
	3	AKB-6548-CI-0016	50	M	White	No	168	-28	469	274	349	0.94	4.11	2.40	28	28	87	28	87	
	3	AKB-6548-CI-0011	70	F	White	No	56	-1	480	879	202	0.4	7.27	13.31	16	16	16	16	16	
	3	AKB-6548-CI-0014	74	F	White	No	81	-197	297	187	130	0.4	6.99	4.40	12	14	26	21		
	3	AKB-6548-CI-0015	68	M	White	No	111	-10	218	110	135	0.6	4.94	2.49	14	14	41	14		
		Mean	*62.1*				*67*	*-35*	*533*	*431*	*229*	*2.7*	*8.5*	*6.3*	*19*	*19*	*51*	*37*		
		Std Dev	*14.7*				*49*	*62*	*293*	*348*	*158*	*5.5*	*4.6*	*4.7*	*6*	*6*	*38*	*34*		
		Median	*68.5*				*56*	*-9*	*475*	*231*	*133*	*0.5*	*7.1*	*4.2*	*16*	*16*	*30*	*28*		
		Max	*79*				*168*	*0*	*1166*	*1045*	*631*	*17.3*	*19.2*	*15.2*	*30*	*30*	*128*	*126*		
		Min	*31*				*9*	*-197*	*218*	*110*	*124*	*0.3*	*4.1*	*2.4*	*12*	*13*	*16*	*14*		

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^R-value (transaminase/ULN ÷ AP/ULN) estimates are based on peak enzyme values within 30 days of each other and the following ULNs: ALT 34, AST 34, AP 104

**R-values for this case, using peak enzyme values within 30 days of each other and local ULNs (ALT 33, AST 35, AP 123), are 6.89 by ALT and 5.82 by AST.

4.5.2 Case-by-case analyses by DILI Team: Three cases of probable DILI due to study drug are discussed in detail including the subject falling in Hy's Law quadrant.

Case (b) (6) (Study AKB-6548-CI-0007)

Summary: This is a 69-year-old woman with high transaminases starting about 4 weeks after start of VDA. She became jaundiced.

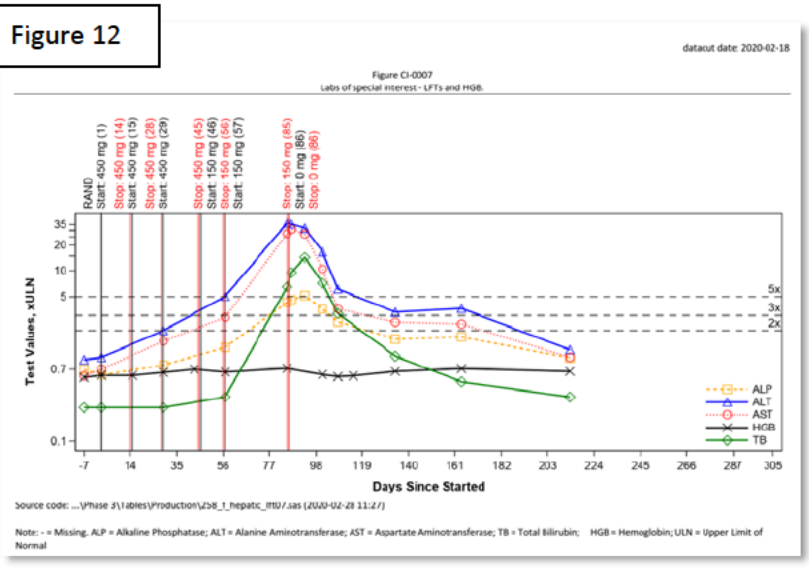
She had multiple medical problems including diabetes, hyperlipidemia, acute kidney injury, CKD and hypertension, but was not on dialysis. She was status post cholecystectomy. Medications included benazepril/HCTZ, saxagliptin (b) (6) start), simvastatin ((b) (6) start; dose lowered 40 to 20 mg (b) (6)), glipizide, HCTZ, linagliptin (start (b) (6)

(b) (6) chlorthalidone ((b) (6) start). No herbal/dietary supplements (HDS).

She started VDA 450 mg/d on (b) (6). Her liver tests were normal. At week 4, her ALT and AST climbed to 64 and 51. By week 8 (b) (6)), they were 161 and 97. VDA dose was decreased to 150 mg/d. Simvastatin had already been decreased on (b) (6). ALT and AST kept climbing to 1166 and 1045 respectively, between (b) (6) (b) (6). VDA and several other medications including simvastatin and linagliptin were all stopped. TB 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 HDS. Ultrasound was unremarkable. Hepatitis A-E tests were negative. IgG level was normal, and ANA was negative. No liver biopsy was done. Liver enzymes and bilirubin quickly fell by 50% but took several weeks to return to normal (Figure 12).

Assessment: We assessed this case as probable DILI due to VDA. This case is important because it is the only one in Hy's Law quadrant that is causally linked to VDA. 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. No tests for EBV or CMV, but she had no symptoms. Sponsor's HAC considered this case "probable" DILI due to VDA. Though the AP 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) nR values > 5 using (Table 8).[4]

Figure 12



[4] Robles-Diaz M, et al. Gastroenterology 2014

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Case [redacted] (b) (6) (Study AKB-6548-CI-0015)

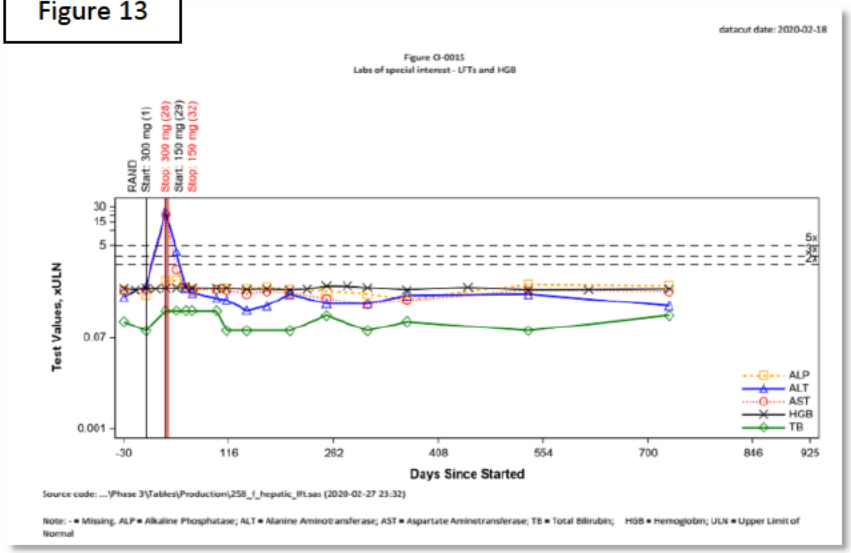
Summary: This is a 56-year-old Black woman with elevation in transaminases without jaundice occurring 4 weeks after VDA start (300 mg/d).

She had a history of hepatitis B, diabetes mellitus, hyperlipidemia, hypertension and CKD-anemia. She had normal liver tests at baseline. She started valsartan as the only new medication in the prior 6 months [redacted] (b) (6) and continued thru event).

She started VDA on [redacted] (b) (6) at 300 mg/d. At her 4-week visit she had asymptomatic elevation of ALT and AST (816 U/L and 646 U/L) without bilirubin or AP rise. She denied illicit drug use, new medications, or HDS use. Evaluation testing included HBsAg (-), anti-HBc (+) and anti-HBs (-), HCV Ab (-) and HIV (-). No imaging or other testing noted. VDA was stopped with rapid decline in liver tests to normal (Figure 13).

Assessment: This is probable DILI due to VDA. 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.

Figure 13



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Case [redacted] (b) (6) (Study AKB-6548-CI-0016)

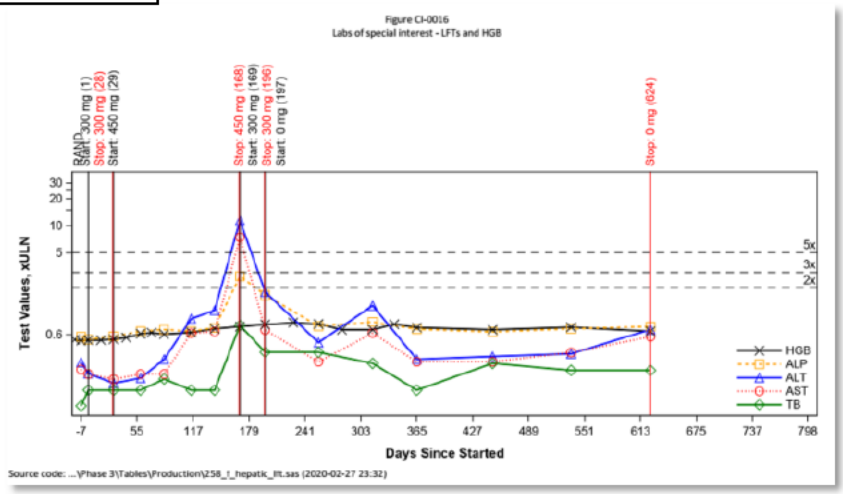
Summary: This is a 50-year-old Caucasian man enrolled in [redacted] (b) (6) who had elevation in transaminases without jaundice 24 weeks after starting VDA 300 mg/d.

The subject had DM, HTN, NYHA II heart failure, "hepatosis" and CAD 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/d. ALT and AST rose further to 469 and 274. AP also rose to 349 U/L. VDA was stopped on [redacted] (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 (Figure 14). 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 VDA 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

Figure 14



4.5.3 Summary of case-by-case analyses by sponsor: The sponsor had two hepatology assessment committees (HAC) with different members adjudicate liver injury cases for likelihood of DILI. The first unblinded HAC found more subjects with probable and possible DILI due to VDA in the active arm while the second blinded HAC found no difference between arms (Tables 9 and 10).

Table 9 **Summary of Subjects who Underwent Unblinded Assessment of Hepatic Events**

Event Type	Causal Relationship to Drug	Vadadustat N=4515 n (%)	Comparator[a] N=4001 n (%)
SAEs[b]	Probable	1 (0.02%)	0
	Possible	10 (0.22%)	0
	Unrelated	24 (0.53%)	23 (0.57%)
	Unlikely	12 (0.27%)	7 (0.17%)
	Not a hepatic event	9 (0.20%)	8 (0.20%)
	Insufficient information to assess	0	0
AEs/Labs	Probable	0	0
	Possible	11 (0.24%)	1 (0.02%)
	Unrelated	16 (0.35%)	35 (0.87%)
	Unlikely	35 (0.78%)	45 (1.12%)
	Not a hepatic event	1 (0.02%)	2 (0.05%)
	Insufficient information to assess	1 (0.02%)	4 (0.10%)
Total		120	125

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAE: serious adverse event; ULN: upper limit of normal.
a Comparator is darbepoetin alfa or epoetin alfa.
b New elevation in ALT or AST >3 × ULN, with or without elevation of total serum bilirubin >2 × ULN was considered a SAE with medical significance.
Note: If the expert committee is unable to make the diagnosis of a hepatic event, or neither causality nor severity can be assessed, they may adjudicate the case as Not Assessable. Events assessed as 'Not assessable' by expert committee are excluded from this table
Note: If subject met >1 criteria, the subject counted as SAE.
Source: Post-text Table 7ub

Table 10 **(Blinded Evaluation)**
Summary of BEC Drug Relationship Assessment of Hepatic Events

Event Type	Causal Relationship to Drug	Vadadustat N=4515 n (%)	Comparator[a] N=4001 n (%)
SAEs[b]	Probable	15 (0.33%)	14 (0.35%)
	Possible	32 (0.71%)	27 (0.67%)
	Unrelated	24 (0.53%)	14 (0.35%)
	Unlikely	10 (0.22%)	15 (0.37%)
	Not a hepatic event	17 (0.38%)	15 (0.37%)
	Insufficient information to assess	0	1 (0.02%)
AEs/Labs	Probable	16 (0.36%)	24 (0.60%)
	Possible	19 (0.42%)	29 (0.72%)
	Unrelated	10 (0.22%)	11 (0.27%)
	Unlikely	8 (0.18%)	11 (0.27%)
	Not a hepatic event	4 (0.09%)	6 (0.15%)
	Insufficient information to assess	3 (0.07%)	1 (0.02%)
Total		158	168

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAE: serious adverse event; ULN: upper limit of normal.
a Comparator includes darbepoetin alfa or epoetin alfa
b New elevation in ALT or AST >3 × ULN, with or without elevation of total serum bilirubin >2 × ULN was considered a SAE with medical significance.
Note: If the expert committee is unable to make the diagnosis of a hepatic event, or neither causality nor severity can be assessed, they may adjudicate the case as Not Assessable. Events assessed as 'Not assessable' by the expert committee are excluded from this table.
Note: If subject met >1 criteria, the subject counted as SAE.
Source: Post-text Table 7

5.0 Assessment & Recommendations

5.1 Assessment:

Vadadustat (VDA) is an orally delivered, small molecule inhibitor of hypoxia inducible factor prolyl-hydroxylase (HIF-PH). HIF-1 and HIF-2 are transcriptional factors that help adaptation to hypoxia by regulating expression of erythropoietin (EPO), transferrin and other genes involved with erythropoiesis and iron utilization. The sponsor is seeking approval for use in anemia associated with chronic kidney disease.

In vitro studies suggest VDA is hepatically metabolized by not by the cytochrome p450 system to any significant degree. Rather, VDA undergoes phase II metabolite formation including glucoronidated and glycosylated compounds. In humans, the major route of metabolite elimination is urinary (59%). VDA inhibits BCRP, but not BSEP. VDA median half lives in healthy volunteers and patients were 4.7 and 7.0 hours, respectively. Long-term exposure in animals (9-month Beagle dog; 3-month Wistar rat) did show significant liver histopathology.

Over 4000 subjects were exposed to VDA across this NDA. Control arms primarily received erythropoiesis-stimulating agents. In the integrated summary of safety datasets, liver injury attributable to VDA was seen with one case in Hy's Law quadrant that was probable DILI due to VDA. The subject recovered. There is disagreement between the DILI Team and the sponsor about whether this case meets Hy's Law.

The sponsor suggests this case does not meet Hy's Law due to the elevated alkaline phosphatase (AP). We do not agree. While the peak AP was >2x ULN, we feel this subject had predominant hepatocellular injury with jaundice and therefore meets Hy's Law. The ALT and AST were both over 1000 and total bilirubin 17.3 mg/dL suggesting significant hepatocellular injury. The 2009 FDA guidance does not set an absolute AP cut-off for Hy's Law, but many use a cut-off of < 2x ULN. More recent data suggest this AP cut-off erodes accuracy for identifying hepatocellular DILI at risk of acute liver failure. A validated, modified Hy's Law criterion using the ratio of AP to transaminase elevation (nR-value) improves identification of patients at risk of poor outcome.[5],[6] We find this criterion useful in cases where AP rises to >2-3x ULN with remarkably high transaminases (e.g., >900-1000) and severe jaundice. By nR-value criterion, this subject had hepatocellular DILI with a risk of poor outcome, fulfilling Hy's Law.

There were also seven cases of probable DILI due to VDA with ALT levels > 5x ULN with five having levels > 10x ULN. 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) (Section 4.5.1, Table 8). One subject had mild injury and developed tolerance as VDA was continued and enzyme elevations resolved. Injury pattern was mostly hepatocellular (median R-value$_{ALT}$ 7.1, range 4.1 to 19.2). Two cases had mixed injuries (R-values 4.1 and 4.9).

Transaminase elevations were not statistically different between active and control arms by usual category counts (i.e., 3-5 x ULN, 5-10 x ULN etc.). However, there were numerically and proportionately more active arm cases in the higher ALT categories (e.g., >5x ULN, >8x ULN and >10x ULN) compared to control arm.

The sponsor had two hepatology assessment committees (HAC) assess the liver related AEs and SAEs for attribution to VDA. The first was unblinded, the second blinded. The unblinded HAC found increased attribution to VDA in the treatment arm compared to control, while the blinded HAC did not. Knowledge of medications taken is core to DILI causality accuracy, particularly when the control medication has known, low DILI potential. We

[5] Robles-Diaz M, et al. Gastroenterology 2014

[6] Bessone F, et al. Sem Liv Dis 2019

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.

Overall, we see a concerning liver injury signal that may rarely lead to acute liver failure and death. The exposed sample set is quite large, so approval and marketing might be manageable, if the need is high, advantages significant and efficacy clear for this drug. If approved, a risk mitigation strategy and/or significant labeling would be needed. Exclusions for certain liver disorders, baseline liver tests, and monitoring of liver tests in the first few months will likely be needed.

5.2 Recommendations if NDA is approved:

a) If approved, label for hepatotoxicity risk and give strong consideration for a specific PMR plan for evaluation of hepatotoxicity.
b) Baseline and monitoring of liver tests should be done during the first several months of use.
c) Use in patients with cirrhosis or active, acute liver disease should be discouraged.

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CDER/OND

_____

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/s/

PAUL H HAYASHI
02/07/2022 04:56:47 PM

CLINICAL INSPECTION SUMMARY

Date	September 7, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Fadi Nossair, M.D., M.S., Medical Officer Albert Deisseroth, M.D., Ph.D., Deputy Division Director Ann Farrell, M.D., Division Director May Metanuj Zuwannin, Project Manager Division of Nonmalignant Hematology (DNH) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
NDA	NDA 215192
Applicant	Akebia Therapeutics, Inc.
Drug	Vafseo™ (vadadustat)
NME	Yes
Division Classification	Inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIFPHs)
Proposed Indication	Treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis
Review Type	Standard
Consultation Request Date	May 14, 2021
Summary Goal Date	September 10, 2021
Action Goal Date	March 29, 2022
PDUFA Date	March 29, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from four studies (AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0016, and AKB-6548-CI-0017) were submitted to the Agency in support of a New Drug Application 215192 for the drug vadadustat, proposed for treatment of anemia in adult patients with chronic kidney disease on dialysis and not on dialysis. Three clinical investigators (Harold Hubert, M.D., Pablo Pergola, M.D., and Ahmed M. Awad, D.O.) were inspected in support of NDA 215192. Akebia Therapeutics, Inc. (sponsor) was also inspected for monitoring and oversight of the above four studies.

Based on these inspections, the conduct of the above studies appears to be adequate. The study data derived from the above three clinical investigator sites are considered reliable.

Monitoring and oversight of Studies AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0016 and AKB-6548-CI-0017 by Akebia Therapeutics, Inc. were considered adequate. The study data submitted to the Agency for assessment appeared acceptable in support of the proposed indication.

II. BACKGROUND

Vadadustat is being developed as an inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIFPHs) for the treatment of anemia associated with chronic kidney disease (CKD). The sponsor claims vadadustat offers the potential of flexible oral dosing that is easier to titrate than injectable erythropoiesis-stimulating agents (ESAs). Vadadustat could potentially enhance iron metabolism and transport since hypoxia-inducible factors downregulate the iron absorption regulator hepcidin and upregulate the iron-mobilizing regulators ferroportin and transferrin (and its receptor), thereby enhancing erythropoietin responsiveness. The Applicant proposes vadadustat for the correction or maintenance treatment of anemia in adult patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) or dialysis-dependent chronic kidney disease (DD-CKD).

Four large randomized clinical trials were submitted in support of the applicant's NDA. For this NDA under the PDUFA program review, CDER DNH requested three clinical study investigator sites for inspection in the submitted study protocols (Study AKB-6548-CI-0014, Study AKB-6548-CI-0015, Study AKB-6548-CI-0016 and Study AKB-6548-CI-0017). The sites enrolled large numbers of patients and greater efficacy compared to other study sites. DNH also requested sponsor inspections.

Study AKB-6548-CI-0014

Study AKB-6548-CI-0014 was a Phase 3, randomized, open-label, sponsor-blinded, active-controlled, global, multicenter study of the efficacy and safety of vadadustat versus darbepoetin alfa for the correction of anemia and maintenance of hemoglobin 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 hemoglobin (Hb) in subjects with anemia secondary to NDD-CKD.

The primary efficacy endpoint was to assess the change in average hemoglobin between Baseline and the primary efficacy period (Weeks 24 to 36). The primary safety endpoint was time to the first adjudicated major adverse cardiovascular events (MACE), defined as all-cause mortality, non-fatal myocardial infarction (MI), or non-fatal stroke.

Study AKB-6548-CI-0014 was a multicenter study. Of the subjects randomized, 1748 subjects were included in the safety population, and 1723 subjects were included in the Full Analysis Set (FAS) population. The calendar date of first subject consent was on (b) (6). The calendar date of last subject's last visit was on (b) (6)

Study AKB-6548-CI-0015

Study AKB-6548-CI-0015 was a Phase 3, randomized, open-label, sponsor-blinded, active-controlled, global, multicenter study of vadadustat versus darbepoetin alfa for maintenance treatment of anemia after conversion from current ESA therapy 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 maintenance treatment of anemia in subjects with NDD-CKD after conversion from current erythropoiesis-stimulating agents (ESA) therapy.

The primary efficacy endpoint was to assess the change in average hemoglobin between baseline and the primary efficacy period (PEP) (Weeks 24 to 36).

Study AKB-6548-CI-0015 was a multicenter study. The actual number of subjects enrolled was 1725 study subjects at 328 investigative sites in 26 countries. Of the subjects randomized, 1723 subjects were included in the safety population, and 1710 subjects were included in the Full Analysis Set (FAS) population. The calendar date of first subject consent was on (b) (6). The calendar date of last subject's last visit was on (b) (6)

Study AKB-6548-CI-0016

Study AKB-6548-CI-0016 was a Phase 3, randomized, open-label, sponsor-blinded, active-controlled, global, multicenter study of the efficacy and safety of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia after correction of hemoglobin or conversion from current erythropoiesis-stimulating agent (ESA) in adult subjects with incident dialysis (initiation of chronic maintenance peritoneal or hemodialysis within 16 weeks prior to Screening).

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

The primary efficacy endpoint was to assess the change in average hemoglobin between baseline and the primary efficacy period (Weeks 24 to 36).

Study AKB-6548-CI-0016 was a multicenter study. Approximately 140 investigative sites in North America, Latin America, Europe, and Asia Pacific participated in this study's enrolment. The actual number of subjects enrolled was 369 at 83 centers in 10 countries. Of the subjects randomized, 365 were included in the safety population and 364 were included in the Full Analysis Set (FAS) population. The calendar date of first subject consent was on (b) (6) The calendar date of last subject's last visit was on (b) (6).

Study AKB-6548-CI-0017

Study AKB-6548-CI-0017 was a Phase 3, randomized, open-label, sponsor-blinded, active-controlled, global, multicenter study of the safety and efficacy of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in subjects with DD-CKD (either peritoneal dialysis or hemodialysis) after conversion from erythropoiesis-stimulating agent (ESA) therapy.

The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with DD-CKD. The primary efficacy endpoint was to assess the change in average hemoglobin between baseline and the primary efficacy period (Weeks 24 to 36).

Study AKB-6548-CI-0017 was a multicenter study. Approximately 300 investigative sites in North America, Latin America, Europe, and Asia Pacific enrolled. The actual number of subjects enrolled was 3554 at 275 centers in 18 countries. Of the subjects randomized, 3537 subjects were included in the safety population, and 3514 subjects were included in the Full Analysis Set (FAS) population. The calendar date of first subject consent was on (b) (6). The calendar date of last subject's last visit was on (b) (6)

III. RESULTS (by site)

1. Harold Hubert, M.D.
1521 Anthony Road
Augusta, GA 30904

Inspection dates: July 13 to 16, 2021

For AKB-6548-CI-0014 (Site 10013), 74 subjects were consented and screened, and 25 subjects were enrolled and randomized into the study. Of the 25 randomized subjects, 15 subjects completed the study through Visit 13 and five subjects were followed to global study completion. Four (4) subjects died, and a single subject withdrew from the study.

For AKB-6548-CI-0017 (Site 10008), 142 subjects were consented and screened, 88 subjects were enrolled and randomized into the study. Of the 88 randomized subjects, 60 subjects completed the study through Visit 13 and 18 subjects were followed to global study completion. Ten subjects died.

For AKB-6548-CI-0014 (Site 10013), a total of 15 subject records were inspected during the site audit.

For AKB-6548-CI-0017 (Site 10008), a total of four study subject records were audited during FDA's inspection.

The following records were evaluated during the inspection: study subject eligibility; protocol-required procedures; concomitant (non-study) medications; serious adverse event reporting; study efficacy endpoints; patient clinical progress notes; electrocardiographic reports; central laboratory reports; protocol adherence, and study drug accountability.

The primary efficacy endpoint data were verified against the data line listings. No discrepancies in the endpoint data were noted. There was no under-reporting of serious adverse events.

A Form FDA 483 was issued for inadequate investigational drug disposition records. For example, the drug accountability for the following kits were not recorded in the master log timely for the following study subjects:

(b) (6)

Dr. Hubert responded to the 483 in a letter dated August 19, 2021 and explained that the study site had a log for Subject Drug Accountability and a log for Site Master Drug Accountability. The Subject Drug Accountability Log was the original source document per the sponsor. Study personnel acknowledged kit dispensation and kit return to and from the study subjects in real time, via their initials and date. The Site Master Drug Accountability Log was a compilation of all study kits received by the site (including kits returned by the subject, kits permanently quarantined due to a temperature excursion or physical damage to the kit, or kits destroyed onsite or returned to the destruction depot). At the conclusion of the study, a final IP reconciliation was conducted, and the Site Master Drug Accountability and Subject Drug Accountability Logs were completed. In all the above four subjects, the kits accountability had been appropriately and contemporaneously documented on the Subject Drug Accountability Log. The clinical investigator acknowledged late entries in the Site Master Drug Accountability Log in the above cases and will work on corrective action plans.

The clinical investigator's response was adequate, and the above inspectional observational results were not considered significant.

2. Pablo Pergola, M.D.
1123 North Main Avenue, Suite 120
San Antonio, TX 78212-4740

Inspection dates: July 13 to 22, 2021

For AKB-6548-CI-0014 (Site 10006), a total of 210 subjects were screened and consented, and 97 study subjects enrolled and randomized. There were 76 subjects who completed the study. Of those randomized, 15 died during the study and six patients were lot to follow-up.

For AKB-6548-CI-0015 (Site 10006), a total of 74 subjects were screened and consented, and 45 study subjects enrolled and randomized. Of the 45 study patients randomized, there were 36 subjects who completed the study. Nine study patients discontinued for the following reasons: 6 subjects died, two subjects lost to follow-up, and a single study patient withdrew consent.

For AKB-6548-CI-0017 (Site 10506), a total of 84 subjects were screened and consented, and 62 study subjects enrolled and randomized. There were 46 subjects who completed the study. Of the subjects randomized, 15 died and a single study patient withdrew consent.

The following regulatory documents were assessed: IRB approval letters and correspondence, monitoring reports, informed consent forms, subject medical records, financial disclosure reports, case report forms, subject questionnaires and diaries, dosing records, scans, independent reviewer imaging, site signature and responsibility logs, and site training documentation. The selected subjects' records were audited for eligibility, protocol adherence and adverse event reporting.

For AKB-6548-CI-0014 (Site 10006), a total of 20 subject records reviewed during the inspection.

For AKB-6548-CI-0015 (Site 10006), a total of 12 subject records reviewed during the inspection.

For AKB-6548-CI-0017 (Site 10506), a total of 12 subject records reviewed during the inspection.

Source records evaluated, as described, for the enrolled study patients were examined and verifiable, for primary endpoint data against the data line listings. No discrepancies were noted. There was no evidence of under-reporting of adverse events or protocol deviations.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. Ahmed M. Awad, D.O.
Clinical Research Consultants, LLC
3930 Washington St
Kansas City, MO 64111

Inspection dates: August 2 to 6, 2021

For Study AKB-6548-CI-0017 (Site 10304), there were 123 subjects were consented and screened, 73 subjects were enrolled and randomized. Of the 73 subjects who were randomized, and 46 study patients completed study treatment. Of the 27 study subjects who discontinued from the study, there were 18 deaths, five patients withdrew from the study, and four study subjects were lost to follow-up.

The study records audited at Dr. Awad's site included, in part, the following review: IRB approval letters and correspondence, site signature and responsibility logs, and site training documentation informed consent forms, monitoring reports, subject medical records, case report forms, study visit source documents, laboratory test results, dosing records, and investigational drug accountability records.

Source records at the site for the 22 enrolled and randomized study patients were examined and verifiable, for primary endpoint data against the data line listings. No discrepancies were observed. There was no evidence of under-reporting of adverse events.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Akebia Therapeutics, Inc.
245 First Street, Suite 1400
Cambridge, MA 02142

Inspection dates: August 5 to 12, 2021

The inspection assessed the application sponsor, Akebia Therapeutics, Inc., responsibilities for the following studies: AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0016 and AKB-6548-CI-0017.

The inspection included review of the trial master files, standard operating procedures (SOPs) related to the studies, site monitoring, handling of adverse events, data collection, and how the sponsor brought non-compliant sites into compliance. Information was also obtained concerning procedures for selection of clinical investigators, selection of monitors, monitoring procedures and frequency, contract services used, and other sponsor/monitor related activities.

Records for the following clinical study sites were evaluated: Sites 10006 and 10013 (Study AKB-6548-CI-0014), Site 10013 (Study AKB-6548-CI-0015), Site 10001 (Study AKB-6548-CI-0016) and Sites 10008, 10596 and 10304 (Study AKB-6548-CI-0017). The FDA audit found that these sites were monitored throughout the studies, and clinical investigators carried out their responsibilities according to the FDA regulatory requirements.

In general, the monitoring and oversight of Studies AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0016 and AKB-6548-CI-0017, respectively, by Akebia Therapeutics, Inc. appeared adequate. There were no objectionable conditions noted, and no Form FDA-483, Inspectional Observations, was issued.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
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MIN LU
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KASSA AYALEW
09/10/2021 09:58:24 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 25, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 215192
Product Name, Dosage Form, and Strength:	Vafseo (vadadustat) tablets 150 mg, 300 mg, 450 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Akebia Therapeutics (Akebia)
FDA Received Date:	March 29, 2021
OSE RCM #:	2021-644
DMEPA 2 Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Akebia Therapeutics submitted 505(b)(1) NDA 215192 for Vafseo (vadadustat) tablets on March 29, 2021. Vafseo is a hypoxia-inducible factor prolyl hydroxylase inhibitor proposed for the treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis. We evaluated the proposed container labels, carton labeling, Prescribing Information (PI), and Medication Guide for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, PI, and Medication Guide for Vafseo (vadadustat) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI, container labels, and carton labeling identified areas that can be modified to improve the clarity of the information presented. Our review of the Medication Guide determined it is acceptable from a medication error perspective at this time.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container labels, and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for Akebia in Section 4.2 below. We conclude the proposed Medication Guide is acceptable from a medication error perspective. We defer to Patient Labeling Team for recommendations for the Medication Guide.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. Highlights of Prescribing Information
   1. We recommend revising the second bullet point to remove [redacted] Revise to read "Increase the dose no more frequently than once every 4 weeks. Decreases in dose can occur more frequently."
   2. We recommend revising the fourth bullet point to improve clarity. Revise to read "Adjust dose in increments of 150 mg to achieve or maintain hemoglobin levels (10 to 11 g/dL). Doses may range from 150 mg to a maximum of 600 mg."

B. Dosage and Administration [2]
   1. Chronic Kidney Disease [2.1]
      a. We recommend revising the sub-heading title to read "Important Dosage Information", moving all pertinent information that is currently in subsection *2.2 Important Administration Instructions* up to this section to ensure this important information is not overlooked, and revising all statements to be in active voice.
      b. As currently presented, there is no statement indicating that tablets should be swallowed whole. As this is a film-coated tablet, we recommend adding the following warning statements: "Swallow tablets whole. Do not cut, crush, or chew."

         We recommend revising subsection 2.1 to read as follows:

Evaluate the iron status in all patients before and during treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%.

[redacted] causes of anemia (e.g., vitamin deficiency, other metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating VAFSEO.

[redacted]

2. Important Administration Instructions [2.2]
    a. We recommend revising the sub-heading title to read [redacted (b) (4)], [redacted (b) (4)]

    We recommend revising subsection 2.2 to read as follows:

[redacted (b) (4)]

3. Dosage Forms and Strengths [3]
    a. We recommend revising [redacted (b) (4)] to read "…following strengths" in the dosage form statement.

4. How Supplied/Storage and Handling [16]
    a. We recommend the revising the How Supplied section to include the tablet descriptions. Revise as follows:

How Supplied

VAFSEO film-coated tablets are supplied as follows:

Tablet Strength	Tablet Shape/Color	Tablet Markings	Package size	NDC
150 mg	round/white	"VDT" and "150"	60 count bottle	59922-641-60
300 mg	oval/yellow	"VDT" and "300"	60 count bottle	59922-642-60
450 mg	oval/pink	"VDT" and "450"	60 count bottle	59922-643-60

    b. We recommend revising the storage statement to reflect USP controlled room temperature and to be consistent with the storage statement on the container labels and carton labeling. Revise to read "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].

4.2 RECOMMENDATIONS FOR AKEBIA THERAPEUTICS

A. General Comments for All Labels and Labeling

1. On all labels, we note the (b) (4) font color used for the proprietary name "Vafseo" is the same (b) (4) color used to highlight the 300 mg strength. The use of the same color for the font for the proprietary name that is used to highlight one of the strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors. We recommend revising the font color for the proprietary name (e.g., black font) so it does not overlap with any of the colors utilized in highlighting the strengths.

2. We recommend revising the Medication Guide statement so it describes how the medication guide is provided and to be consistent across all labels and labeling. For example, revise all Medication Guide statements to read "Dispense with the enclosed Medication Guide" or "Dispense with the accompanying Medication Guide". Ensure this is present on all labels and labeling, including the 150 mg container (bottle) label if space allows.

3. We recommend adding the following warning statements to the back panel below the dosage statement: "Swallow tablets whole. Do not cut, crush, or chew."

4. As currently presented, the "Rx only" statement appears more prominent than critical information on the principal display panel on some of the labels. Therefore, we recommend de-bolding the font used for Rx only statement wherever the font is bolded.

B. Professional Sample Blister Pack

1. We recommend revising the strength statement on the principal display panel to ensure that "300 mg per tablet" is presented on the same line to prevent confusion.

2. To prevent deteriorated drug medication errors, we recommend adding a storage statement to the back panel in alignment with the storage statement on the container labels and carton labeling.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vafseo received on March 29, 2021 from Akebia Therapeutics.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Vafseo</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>vadadustat</td></tr>
<tr><td>Indication</td><td>Treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis and not on dialysis</td></tr>
<tr><td>Route of Administration</td><td>oral</td></tr>
<tr><td>Dosage Form</td><td>tablet</td></tr>
<tr><td>Strength</td><td>150 mg, 300 mg, 450 mg</td></tr>
<tr><td>Dose and Frequency</td><td>• Recommended starting dose is 300 mg once daily.
• Adjust dose in increments of 150 mg within the range of 150 mg to 600 mg to achieve or maintain hemoglobin levels (10 to 11 g/dL).
• Do not increase the dose more frequently than once every 4 weeks; decreases in dose can occur more frequently.</td></tr>
<tr><td>How Supplied</td><td>Film-coated tablets are available in the following strengths and packages:
<table>
<tr><th>Tablet Strength</th><th>Pack size</th><th>NDC</th></tr>
<tr><td>150 mg</td><td>60 count bottle</td><td>59922-641-60</td></tr>
<tr><td>300 mg</td><td>60 count bottle</td><td>59922-642-60</td></tr>
<tr><td>450 mg</td><td>60 count bottle</td><td>59922-643-60</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Store at 15°C to 30°C (59°F to 86°F)</td></tr>
</table>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,[a] along with post-market medication error data, we reviewed the following Vafseo labels and labeling submitted by Akebia Therapeutics on March 29, 2021:

- Container Labels
- Carton Labeling
- Profession Sample Label Blister Pack
- Prescribing Information (no image shown) \\CDSESUB1\evsprod\nda215192\0001\m1\us\114-label\1141-draft-label\proposed.docx
- Medication Guide (no image shown) \\CDSESUB1\evsprod\nda215192\0001\m1\us\114-label\1141-draft-label\medguide-word.docx

G.2 Labels and Labeling

Container Labels

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

STEPHANIE L DEGRAW
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HINA S MEHTA
08/27/2021 09:46:23 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-215192
Submission Number	001 (New NDA)
Submission Date	3/29/2021
Date Consult Received	5/5/2021
Drug Name	Vadadustat
Indication	Treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis.
Therapeutic dose	150 mg to 600 mg once daily (titrated)
Clinical Division	DNH

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 5/5/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND-102465 dated 04/26/2012 in DARRTS (link);
- Previous IRT review for IND-102465 dated 10/28/2013 in DARRTS (link);
- Previous IRT review for IND-102465 dated 12/15/2014 in DARRTS (link);
- Sponsor's clinical study protocol # AKB-6548-CI-0010 (SN0001; link);
- Sponsor's clinical study report # AKB-6548-CI-0010 (SN0001; link);
- Sponsor's statistical analysis plan # AKB-6548-CI-0010 (SN0001; link);
- Investigator's brochure V13 (SN0001; link);
- Sponsor's proposed product label (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0001; link).

1 SUMMARY

No significant QTc prolongation effect of vadadustat was detected in this QT assessment.

The effect of vadadustat was evaluated in Study AKB-6548-CI-0010. This was a randomized, partially double-blinded, placebo- and active- controlled, single-dose, 4-treatment, 4-period, 4-sequence crossover study in healthy subjects. The highest dose evaluated was 1200 mg single dose, which covers the high clinical exposure scenario (dialysis dependent CKD patients, Section 3.1). The study included moxifloxacin as active control and assay sensitivity was established using by time analysis.

The data were analyzed using by-time analysis as the primary analysis which did not suggest that vadadustat is associated with significant QTc prolonging effect (Section 4.3) – see Table 1 for overall results.

The findings of this analysis are further supported by the available exposure-response analysis (Section 4.5) and categorical analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Time (h)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Vadadustat 600 mg	24	1.2	(-1.1 to 3.6)
QTc	Vadadustat 1200 mg	8	3.3	(1.0 to 5.7)

For further details on the FDA analysis, please see Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Each Section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Vafseo does not prolong the QT interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Akebia Therapeutics is developing vadadustat for the treatment of anemia associated with chronic kidney disease (in adults on dialysis and not on dialysis). Vadadustat (AKB-6548, Vafseo; MW: 306.7) is a hypoxia-inducible factor prolyl-hydroxylase inhibitor. The

sponsor states that oral administration of vadadustat is expected to increase cellular levels of hypoxia-inducible factor thereby stimulating endogenous erythropoietin production, increasing iron mobilization, hemoglobin, and red blood cell production.

The product is formulated as an immediate-release film-coated tablet formulation containing 150, 300, and 450 mg vadadustat for oral administration. The proposed recommended dose includes titration to achieve or maintain hemoglobin levels (10 to 11 g/dL). The recommended starting dose is 300 mg once daily with dose adjustments in increments of 150 mg (not to increase more frequently than once every 4 weeks). The maximum recommended dose is 600 mg once daily.

The peak concentrations of ~72.5 µg/mL (Tmax: 1 to 4 h; half-life: ~9 h) were observed at steady state with the maximum proposed dose in patients who are dialysis dependent (600 mg once daily in dialysis dependent patients; Study # CI-0034). Relatively lower Cmax (~41 µg/mL; half-life: ~8 h) was observed in patients who are not dialysis dependent (Study # CI-0031; Extrapolated from 500 mg with sparse samples). The maximum studied dose is 1200 mg as a single dose (Cmax: ~112 µg/mL in healthy subjects; Study # CI-0001) and 900 mg once daily for 10 days (Cmax: ~82 µg/mL in healthy subjects, Study # CI-0002). Higher concentrations were observed in patient population (Cmax: ~113 µg/mL; dialysis dependent, Study # CI-0034; POP-PK). The sponsor highlights that no significant accumulation is expected at steady-state with the proposed maximum therapeutic dose (Cmax Racc: up to 1.4; Study # CI-0002).

The studies indicate that vadadustat is extensively metabolized forming glucuronide metabolite. Other minor metabolites include 7 oxidation metabolites (M5, M14, M20, M22, M23, M24, M26) as well as a metabolite formed by oxidation with glucuronide conjugation (M1, M2, M3, M6, M7, M12). The human mass balance study indicates that ~27% of the drug (as TR; <10% unchanged, potentially unabsorbed fraction) is excreted in feces, and ~59% (as TR; <1% unchanged) in urine (Study # CI-0008). No formal renal impairment study was conducted by the sponsor (POP-PK). The sponsor highlights that the exposures were similar between subjects with moderate hepatic impairment and subjects with normal hepatic function (Cmax: 52 vs. 50 µg/mL; Study # AKB-6548-CI-0024). The proposed label describes that there are no data in patients with severe hepatic impairment. Concomitant administration of vadadustat with an inhibitor of OAT1/OAT3 (probenecid: 500 mg Q12h and vadadustat: 300 mg QD) is expected to result in increased exposures of vadadustat (AUC: ~2-fold; Cmax: no change; Study # AKB-6548-CI-0029).

Previously, the sponsor proposed to characterize QT effects of their product in a thorough QT study (Protocol # AKB-6548-CI-0010; IND-102465). This was a phase-1, single-center, partially double-blinded, active- and placebo- controlled, randomized 4-way crossover study evaluating the QT effect of vadadustat in healthy subjects (n=49). The sponsor proposed to use single 600 mg (therapeutic) and 1200 mg (supratherapeutic) doses. Refer to previous IRT review in DARRTS (for IND-102465 dated 10/28/2013 and 12/15/2014). The peak concentration (Cmax: ~89 µg/mL) observed with highest dose studied (i.e., 1200 mg single dose) is expected to cover the high clinical exposure scenario (Cmax: ~72.5 µg/mL) associated with the maximum proposed dose at the steady state in patients (who are dialysis dependent).

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety. The expected peak concentrations of ~72.5 µg/mL (Free: ~2.4 µM; PPB: ~99%) at steady-state with once daily dosing of 600 mg offers ~12-fold margin (hERG: ~23% inhibition at ~28.9 µM).

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

Vadadustat excluded the 10 msec threshold at the supratherapeutic dose level of 1200 mg for ΔΔQTc.

Reviewer's comment: The sponsor's results are similar to reviewer's assessments. Please see Section 4.3

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm. Multiplicity control was adjusted at 3 time points using Hochberg procedure.

Reviewer's comment: The conclusion is similar to reviewer's assessment. Please see Section 4.3.1.1 for more details.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: The results are similar to reviewer's assessments. Please see Section 4.4 for more details.

3.2.3 Exposure-Response Analysis

The sponsor performed PK/PD analysis to explore the relationship between plasma concentration of vadadustat and ΔΔQTcF using a linear mixed-effects approach. The sponsor's analysis (Model 1) shows that there was a slight positive slope of 0.0233 msec per µg/mL (90% CI: 0.0036 to 0.043; statistically significant) for the relationship between ΔΔQTcF and plasma concentration of vadadustat. The model predicted ΔΔQTcF (upper confidence interval) values were below 10 msec at the mean peak concentrations (geomean Cmax ~89.3 µg/mL) for the highest dose studied (i.e., 1200 mg) following single oral administration. The sponsor highlights that the concentration-QT analysis supports the conclusion from the primary analysis that vadadustat does not have a clinically meaningful effect on cardiac repolarization.

Reviewer's comment: The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the highest proposed dose. The results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.

3.2.4 Safety Analysis

All treatment-emergent AEs (TEAEs) reported during the study were mild in severity.

There were no deaths, no serious AEs (SAEs), and no subjects were discontinued by the Investigator due to a TEAE.

The most frequently reported TEAEs following administration of vadadustat (>5%) and occurring at a markedly higher incidence than with placebo or moxifloxacin included nausea, diarrhea, abdominal pain, headache, and dizziness.

No AEs of Torsades de Pointes, sudden death, ventricular tachycardia, ventricular fibrillation or flutter, syncope, or seizures were reported. There were no clinically significant abnormalities in clinical laboratory data, vital signs data, ECG findings, or physical examination findings.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guideline occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTc for different treatment groups. The maximum ΔΔQTc values by treatment are shown in Table 2. The largest estimated confidence limits of both dosage levels are below 10 msec.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).

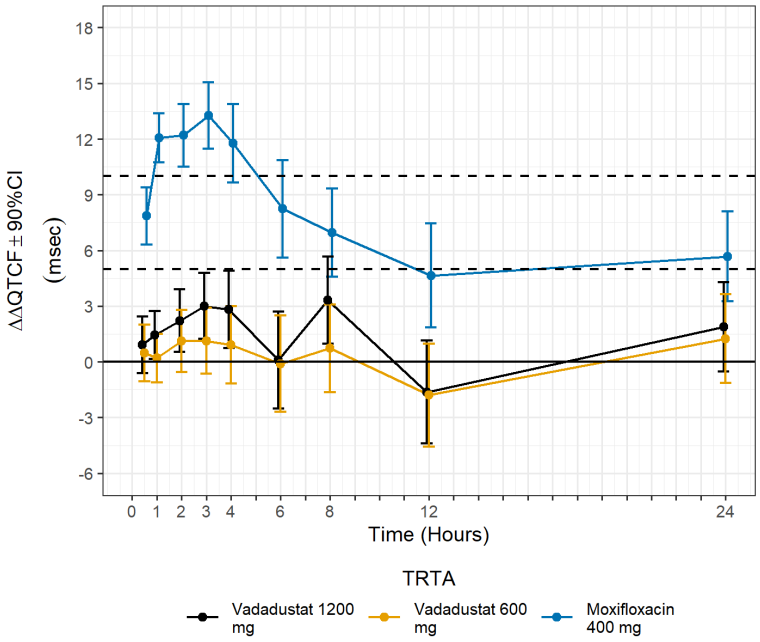


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Actual Treatment	N	Time (hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Vadadustat 1200 mg	49 / 47	8.0	3.3	(1.0 to 5.7)
Vadadustat 600 mg	49 / 48	24.0	1.2	(-1.1 to 3.6)

4.3.1.1 Assay sensitivity

The time-course of changes in ΔΔQTc is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 3).

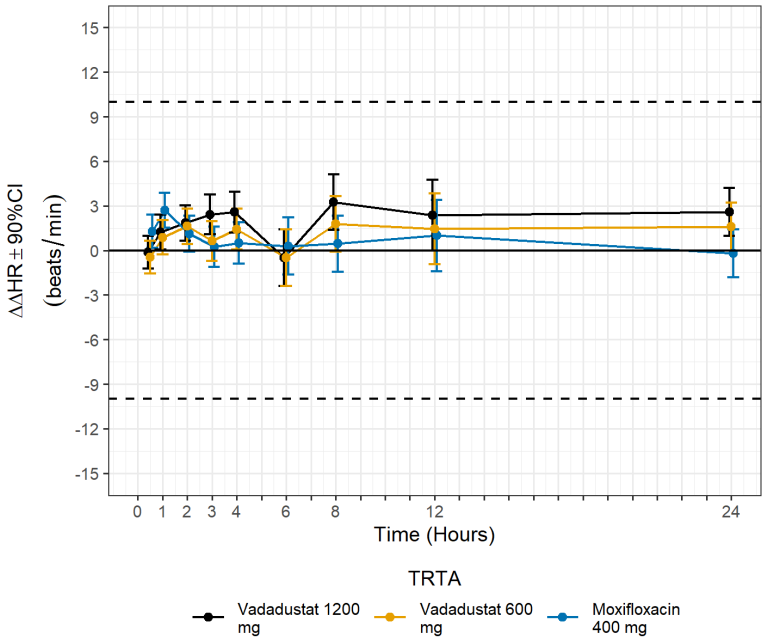
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTc

Actual Treatment	N	Time (hours)	ΔΔQTCF (msec)	90% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	45/46	3	13.3	(11.5, 15.1)	(10.8, 15.7)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

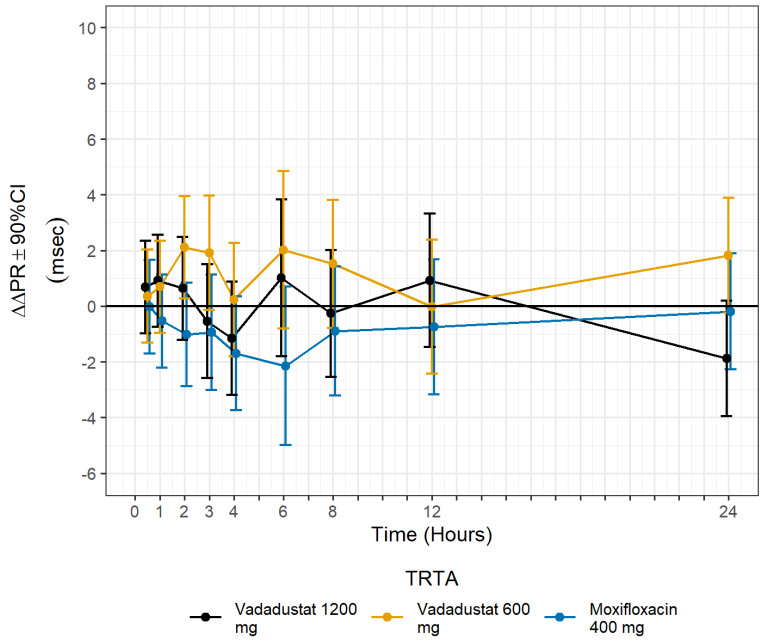
Figure 2: Mean and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

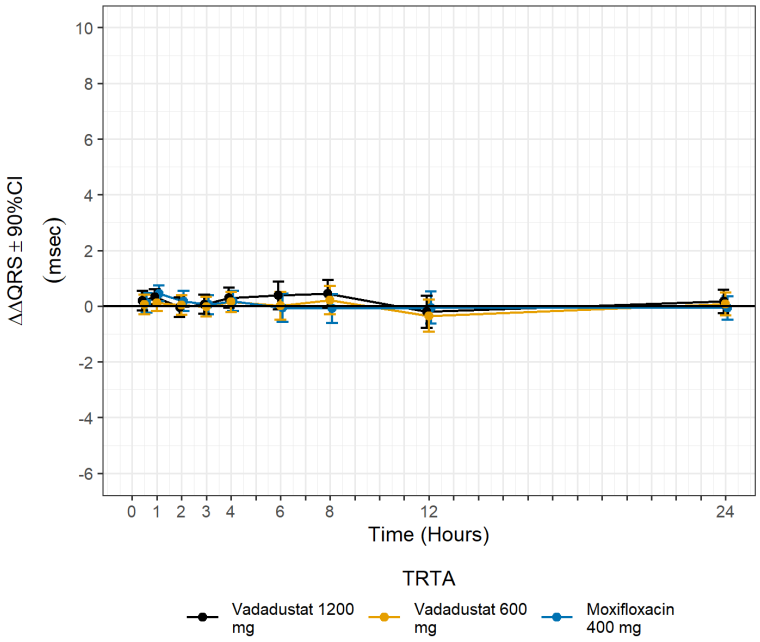
Figure 3: Mean and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

There were no observed QTcF values greater than 480 msec. There were no observed ΔQTc greater than 60 msec.

4.4.2 HR

There were no observed HR values above 100 beats/min.

4.4.3 PR

There were no observed PR values above 220 msec.

4.4.4 QRS

There were no observed QRS values above 120 msec with 25% increase over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

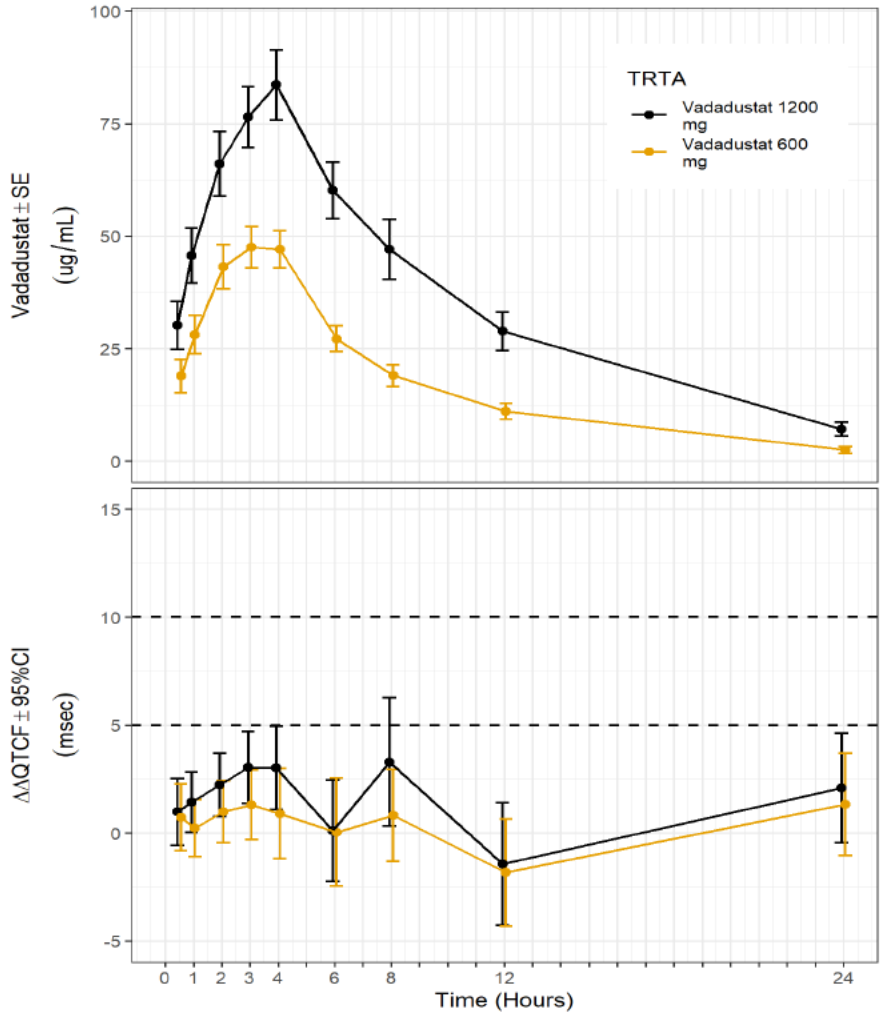
The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of vadadustat and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between vadadustat concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory

analysis: absence of - 1) significant changes in heart rate (more than 10 bpm increase or decrease in mean HR); 2) delay between vadadustat concentration and ΔQTc and 3) a non-linear relationship.

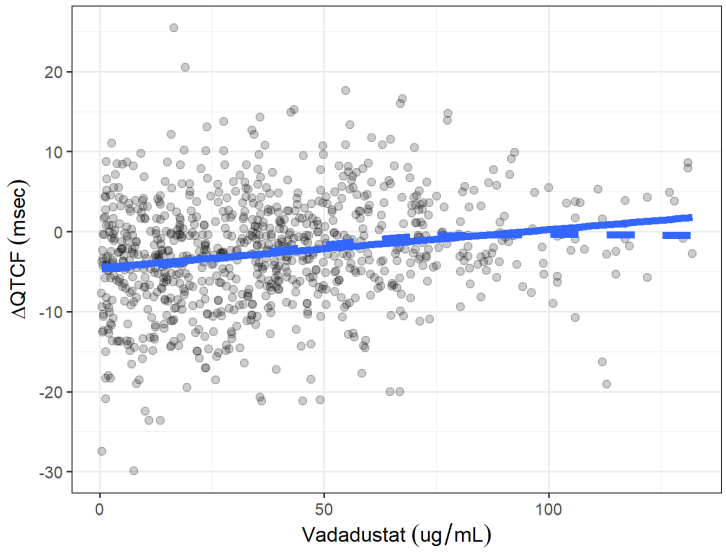
An evaluation of the time-course of vadadustat concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of vadadustat indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 6 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of vadadustat concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between vadadustat concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between vadadustat concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of vadadustat concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 4.

Figure 7: Goodness-of-fit plot for QTc

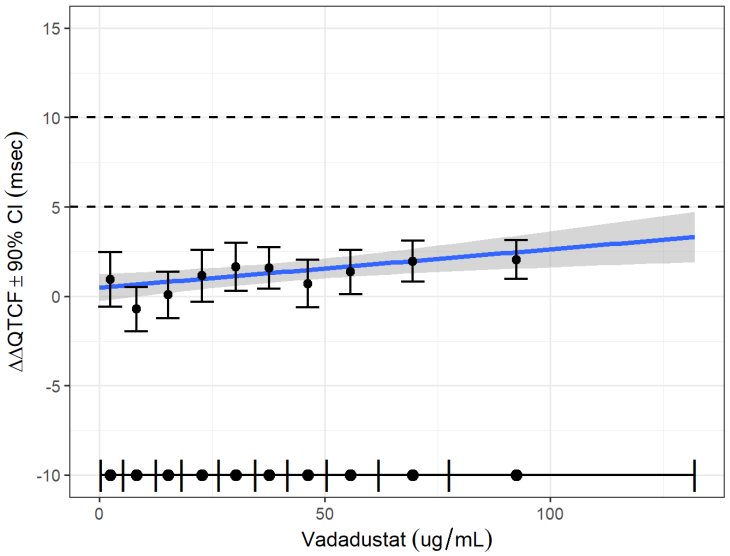


Table 4: Predictions from concentration-QTc model

Actual Treatment	Analysis Nominal Period Day (C)	Vadadustat (µg/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Vadadustat 600 mg	1	53.7	1.6	(1.1 to 2.2)
Vadadustat 1200 mg	1	89.1	2.4	(1.5 to 3.3)

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/s/

RAMAN K BAWEJA
08/09/2021 09:15:07 AM

GIRISH K BENDE
08/09/2021 09:18:08 AM

YU YI HSU
08/09/2021 09:58:53 AM

DALONG HUANG
08/09/2021 10:00:23 AM

DEVI KOZELI on behalf of MICHAEL Y LI
08/09/2021 11:58:23 AM
Signing on Mike's behalf as he is on leave

YANYAN JI
08/09/2021 11:59:33 AM

LARS JOHANNESEN
08/10/2021 07:41:33 AM

CHRISTINE E GARNETT
08/10/2021 09:35:33 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/4/2021

TO: Division of Non-Malignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Intergrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215192

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in October 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA 210874.

OSIS inspected the analytical site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4).

The final classification for both inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	PAREXEL Early Phase Clinical Unit	Medstar Harbor Hospital 3001 South Hanover Street, 7th Floor Baltimore, MD
Analytical	(b) (4)	

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/s/

JAMES J LUMALCURI
08/04/2021 12:10:38 PM