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EU RISK MANAGEMENT PLAN (RMP) for

VAFSEO (VADADUSTAT)

Version: 2.0

Data Lock Point for this RMP: 18 Aug 2021

Date of Final Sign Off: 21 Feb 2023

EU Risk Management Plan for VAFSEO **(**Vadadustat)

RMP Version number: 2.0

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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List of Abbreviations, Acronyms, and Definition of Terms

Abbreviation/Acronym	Definition
ACR	Albumin to Creatinine Ratio
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under the Curve
BCC	Basal cell carcinoma
BCRP	Breast Cancer Resistance Protein
BEC	Blinded Hepatic Expert Committee
BP	Blood Pressure
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CHD	Coronary Heart Disease
CHO	Chinese Hamster Ovary
CV	Cardiovascular
Cmax	Maximum plasma concentration
CNS	Central Nervous System
COVID-19	Coronavirus disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DD	Dialysis Dependent
DRESS	Drug reaction with Eosinophilia and Systemic Symptoms
DVT	Deep Vein Thrombosis
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESA	Erythropoiesis-stimulating Agent
EMA	European Medicines Agency
EPO	Erythropoietin
EPAR	European Public Assessment Report
ESRD	End-stage Renal Disease
EU	European Union
GBD	Global Burden of Disease
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HD	Haemodialysis
HF	Heart Failure
HIF	Hypoxia-inducible Factor
HIF-PHI	Hypoxia-inducible Factor Prolyl-hydroxylase Inhibitor
HIV	Human Immunodeficiency Virus

Abbreviation/Acronym	Definition
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
IBD	International Birth Date
INN	International Non-proprietary Name
IR	Incidence Rate
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	The Kidney Disease Outcomes Quality Initiative
KRT	Kidney Replacement Therapy
MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MTPC	Mitsubishi Tanabe Pharma Corporation
N/A	Not Applicable
NAFLD	Non-alcoholic fatty liver disease
NDD	Non-dialysis Dependent
NHANES	National Health and Nutrition Examination Survey
NSAE	Non-serious Adverse Event
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
OAT	Organic Anion Transporter
PAD	Peripheral Arterial Disease
PASS	Post-authorisation Safety Study
PE	Pulmonary Embolism
p.m.p	Per million Population
PHD	Prolyl-hydroxylase
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PY	Patient Year
PYT	Patient year Time
QoL	Quality of Life
RBC	Red Blood Cell (count)
RCC	Renal Cell Carcinoma
RMP	Risk Management Plan
ROW	Rest of World
RR	Relative Risk
SAE	Serious Adverse Event
SCC	Squamous cell carcinoma
SD	Sprague Dawley/ Standard Deviation
SMQ	Standardised MedDRA query
SmPC	Summary of Product Characteristics
TE	Thromboembolic Event
TEAE	Treatment Emergent Adverse Event
TSAT	Transferrin Saturation
ULN	Upper Limit of Normal
US	United States
USRDS	Data from the US Renal Data System

Abbreviation/Acronym	Definition
VEGF	Vascular Endothelial Growth Factor
WADA	World Anti-Doping Agency
WHO	World Health Organisation

1 PART I: PRODUCT(S) OVERVIEW

Table 1-1 Active Substance Information	
Active substance(s) (INN or common name)	Vadadustat
Pharmacotherapeutic group(s) (ATC code):	B03XA08
Name of marketing authorisation applicant	Akebia Europe Limited
Medicinal products to which this RMP refers:	Total number of products to which the RMP refers: 1
Invented name of the product in the European Economic Area (EEA)	VAFSEO
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: n-acyl-alpha amino acid
	Summary of mode of action: Vadadustat inhibits the 2 isoforms of the prolyl-hydroxylase domain (PHD) enzymes leading to hypoxia-inducible factor (HIF) stabilisation and increased cellular levels of HIF that in turn, stimulates endogenous erythropoietin (EPO) expression and improves the oxygen-carrying capacity of the blood by stimulating haemoglobin (Hb) and red blood cell (RBC) production.
	Important information about its composition: Vadadustat is a novel synthetic small molecule having the following composition: (2-[[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl] amino] acetic acid)
eCTD link to the proposed product information, as appropriate	Module 1.3.1
Indication in the EEA:	Current: Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.
Dosage in the EEA	Current: The recommended starting dose is 300 mg once daily. Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Dose adjustment should be done in increments of 150 mg within the range of 150 mg to a maximum recommended daily dose of 600 mg to achieve or maintain haemoglobin levels within 10-12 g/dL.
	Proposed: Not applicable
Pharmaceutical Form(s)	Current: Film coated tablets
Pharmaceutical Strength(s)	Current:150, 300, and 450 mg
Is/will the product subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Module SI: Epidemiology of the Indication and Target Population(s)

Indication: Vadadustat is indicated for the treatment of symptomatic anaemia associated with CKD in adults on chronic maintenance dialysis.

Brand names of concerned product: VAFSEO™

Incidence and Prevalence:

Global Prevalence of CKD

CKD, defined as the presence of kidney damage or a decreased level of kidney function for 3 or more months, is a major public health problem worldwide.[1] It is estimated to affect around 8% to 16% of the general population globally.[2] The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines have classified CKD into five stages as per disease severity (as indicated in Table 2.1-1).

Prevalence of Kidney Failure in CKD

Table 2.1-1 Glomerular Filtration Rate (GFR) Category and Prevalence of Anaemia in CKD Patients*

GFR Category	GFR (mL/min/1.73 m^2)	Terms	Prevalence (%)
G1	≥90	Normal or High	4.0%
G2	60-89	Mildly decreased ‡	4.7%
G3a	45-59	Mildly to moderately decreased	12.3%
G3b	30-44	Moderately to severely decreased	22.7%
G4	15-29	Severely decreased	51.5%
G5	<15	Kidney failure	

GFR = Glomerular Filtration Rate
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfil the criteria for CKD
‡Relative to young adult level (normal value in young adult men and women of approximately 125 ml/min/1.73 m^2.)
*Data from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group

Prevalence and Incidence of CKD in Europe

The prevalence of CKD in Europe based on the report from Global Burden of Disease (GBD) CKD Collaboration[3] is presented in Table 2.1-2.

Table 2.1-2 Prevalence of CKD in Europe

Region	Prevalence in 2017 (95% CI)		
	Patient Count	Age-standardised rate per 100,000	Prevalence (%)
Eastern Europe	38,150,170	12,408	12.4%

Table 2.1-2	Prevalence of CKD in Europe		
Region	**Prevalence in 2017 (95% CI)**		
	(35,346,449 to 41,409,966)	(11,509 to 13,389)	
Central Europe	13,951,402 (12,930,450 to 15,136,020)	7659 (7115 to 8282)	7.6%
Western Europe	41,976,625 (38,902,049 to 45,587,058)	5446 (5069 to 5894)	5.4%

CI = Confidence Interval, CKD= Chronic Kidney Disease

Incidence of CKD Patients receiving Kidney Replacement Therapy (KRT)

KRT is either haemodialysis (HD), peritoneal dialysis or kidney transplantation. The incidence of kidney failure patients having KRT as per European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry's 2018 Annual Report was 129 per million population (p.m.p). Of this number, 62% were identified as male, 51% were ≥65 years of age, and 20% had diabetes mellitus as the cause of kidney failure. The prevalence of kidney failure (patients eligible for KRT) was 897 p.m.p, ranging from 229 p.m.p in the Ukraine to 2011 p.m.p in Portugal. The treatment modality at the onset of KRT was HD (84%), peritoneal dialysis (11%) and pre-emptive kidney transplantation (5%).[4]

Global or European level data for the incidence rate (IR) of CKD was not available.

Prevalence of Anaemia in CKD

Anaemia is an important complication of CKD which contributes significantly to the heavy symptom burden of CKD especially poorer quality of life (QoL) and an increased risk of adverse clinical outcomes. It has a major impact on the lives of people with CKD but it is potentially reversible with appropriate treatment.[1] Hb thresholds used to define anaemia are presented below in Table 2.1-3 .

Table 2.1-3	Haemoglobin (Hb) Threshold Used to Define Anaemia by the World Health Organisation (WHO)
Age or gender group	**Hb (g/dL)**
Men > 15 year	13
Non-pregnant females > 15 year	12
Pregnant females > 15 year	11

Hb = Haemoglobin, WHO = World Health organisation
Ref: KDIGO; Kidney International Supplements (2013) 3, 73-90

Anaemia is relatively common in CKD patients especially in those with increasing disease severity, with rates of up to 90% in Stage 5 CKD patients.[2]

Globally, the prevalence of anaemia is 24.8% in the general population. CKD emerges as an important contributor to overall anaemia burden in high-income countries (7.4%), Tropical Latin America (17.4%), Central Europe (9.8%), and Eastern Europe (10.8%).[5]

Risk Factors associated with the prevalence of anaemia in CKD

The risk factors mostly associated with the prevalence of anaemia in CKD are:

- CKD Stage: Prevalence of anaemia increases with CKD severity and there is a negative association between the prevalence of anaemia and GFR, indicating that the percentage of patients with anaemia increases as kidney function decreases. For example, the percentage of patients with Hb ≤12 g/dL increased from 26.7% to 75.5% as GFR decreased from ≥60 mL/min/1.73 m^2 to < 15 mL/min/1.73 m^2.[6]
- Patients receiving HD have decreased RBC survival due to the HD procedure.[60]
- Etiology of CKD: The prevalence of anaemia (Hb ≤ 12 g/dL) was highest among patients with CKD caused by diabetes (53.8%), followed by vascular disease (43.6%), hypertension (42.2%), multiple myeloma/ dysproteinemia (42.1%), and glomerulonephritis (38.9%).[6]
- Iron Stores in CKD: Transferrin saturation (TSAT) and ferritin levels were significant predictors of anaemia. Substantial number of anaemic patients with CKD were found to have insufficient iron stores to support erythropoiesis. Patients with TSAT of <20% were associated with 2 times higher risk of developing anaemia.[7]
- Older Age: Older age is associated with greater inflammation and age-related comorbidities. The presence of pro-inflammatory cytokines (e.g., IL-6) increases hepcidin expression, likely placing older patients at higher risk of developing anaemia. Furthermore, sex hormone regulation is also impacted with older age, and both testosterone and oestrogen have been shown to reduce circulating hepcidin.[2]
- Female Gender: Despite lower Hb thresholds for anaemia diagnosis in females (<12 g/dL vs. <13 g/dL for males), female patients with CKD tend to be at higher risk (~two times) of developing anaemia than their male counterparts.[2]
- Race and ethnicity: Prevalence of anaemia also varies among races and ethnic groups. Studies reported the prevalence of anaemia in the US population is almost 2 times higher in African Americans with CKD stages 3-4 (34.5%) than whites with CKD stages 3-4 (18.2%; P < 0.001).[8]

Prevalence of Anaemia in CKD patients in European countries

Prevalence of anaemia (Hb concentration below the <11 g/dL) in CKD patients on HD was 49%.[9]

Prevalence of anaemia in non dialysis dependent chronic kidney disease (NDD CKD) patients for select few European countries, is presented in below Table 2.1-4.

Table 2.1-4	Prevalence (%) of Anaemia in NDD CKD Patients in European Countries
France[a]	**CKD Stage 3-5:** 3% (Hb <10 g/dL); 25% (Hb10-12 g/dL)
Germany[a]	**CKD Stage 3-5:** 7% (Hb <10 g/dL); 32% (Hb10-12 g/dL)
Italy[b]	**CKD Stage 4:** 28% **CKD Stage 5:** 73%.
Netherlands[c]	**CKD Stage 4-5:** 48% (Hb <11 g/dL)
Ireland[d]	**CKD Stage 1-2**: 21% (Hb <12 g/dl) **CKD Stage 3:** 31.6% (Hb <12 g/dl) **CKD Stages 4-5**: 63% (Hb <12 g/dl)

CKD = Chronic Kidney Disease, Hb = Haemoglobin, NDD = Non Dialysis Dependent

References:

a: Wong MM, Tu C, Li Y, Perlman RL, Pecoits-Filho R, Lopes AA, Narita I, Reichel H, Port FK, Sukul N, Stengel B. Anemia and iron deficiency among chronic kidney disease Stages 3-5ND patients in the Chronic Kidney Disease Outcomes and Practice Patterns Study: often unmeasured, variably treated. Clinical kidney journal. 2020 Aug;13(4):613-24

b: Cozzolino M et al. Clinical Management of Chronic Kidney Disease Patients in Italy: Results from the IRIDE Study. Nephron.2018; 1-9

c: Voormolen N, Grootendorst DC, Urlings TA, Boeschoten EW, Sijpkens YW, Huisman RM, Krediet RT, Dekker FW. Prevalence of anemia and its impact on mortality and hospitalization rate in predialysis patients. Nephron Clinical Practice. 2010;115(2):c133-41

d: Stack AG. Quality of care and practice patterns in anaemia management at specialist kidney clinics in Ireland: a national study; Clinical Kidney Journal, 2018; 11 (1) 99-107

Natural history of anaemia in CKD in the untreated population, including mortality and morbidity:

People with CKD are prone to develop a variety of complications, which reflect loss of endocrine and excretory function of the kidneys and decline of metabolic functions. The incidence and prevalence of these complications increase with severity of CKD as defined predominantly by GFR categories.

The anaemia associated with CKD is usually normocytic and normochromic and without iron deficiency.[7] Data consistently indicated that more severe CKD was associated with greater prevalence of anaemia. The development of anaemia in patients with CKD is driven by at least two factors. First, compared to patients without CKD, the kidneys of patients with CKD produce less EPO and second, hepcidin a hormone that (at high levels) impairs dietary iron absorption, is elevated in patients with CKD.[2] Several other mechanisms of CKD related anaemia have been implicated including decreased RBC life span, chronic inflammation, metabolic abnormalities and effects of medications such as renin angiotensin system inhibitors.[10]

a) Mortality due to Anaemia in CKD

Population-based studies have demonstrated an increased risk of death and cardiovascular (CV) mortality as GFR falls below 60 mL/min/1.73 m^2 or when albumin is detected on

urinalysis.[11] Studies have shown that, the absolute risk for death increased exponentially with decreasing renal function.[12]

Anaemia in CKD is associated with higher risks of all-cause mortality and CV mortality. These effects tend to increase with anaemia severity, such that a Hb < 10 g/dL was linked to comparable or higher risk of each outcome (all-cause mortality and CV mortality) than when compared to a Hb of 10-12 g/dL.

Table 2.1-5 shows the Hazard Ratio (HR) of all-cause mortality and CV mortality in CKD patients with anaemia.

Table 2.1-5 Mortality due to Anaemia in CKD Patients Mean Hazard Ratio (95% CI)

		Hb <10 g/dL	Hb10-12 g/dL	Hb >12 g/dL
All-cause Mortality	**DD**	1.56 (1.43-1.71)	1.17 (1.09-1.26)	0.91 (0.87-0.96)
	NDD	1.70 (1.42-2.01)	0.97 (0.92-1.01)	-
CV Mortality	**DD**	1.50 (1.32-1.70)	1.24 (1.09-1.40)	1.00 (0.95-1.06)

CI = Confidence Interval, CKD = Chronic Kidney Disease, CV = Cardiovascular, DD=Dialysis Dependent; Hb = Haemoglobin, HR = Hazard Ratio, NDD=Non Dialysis Dependent
(-): Information not available

b) Morbidity due to Anaemia in CKD

A substantial body of evidence incriminates anaemia as a risk multiplier in CKD patients for major medical conditions, including coronary heart disease (CHD) and stroke.[13]

Inadequate treatment of anaemia may negatively affect cardiac function, cognitive function, physical capacity, and QoL in patients with CKD.

Table 2.1-6 shows the HR of risk of hospitalisation, major adverse cardiovascular events (MACE) and CKD progression in CKD patients with anaemia.

Table 2.1-6 Morbidity due to Anaemia in CKD Patients Mean HR (95% CI)

		Hb <10 g/dL	Hb10-12 g/dL	Hb >12 g/dL
Risk of Hospitalisation	**NDD CKD**	1.46 (1.02-2.09)	-	-
	DD CKD	-	1.09 (1.07-1.11)	0.91 (0.87-0.96)
MACE	**NDD CKD**	1.44 (1.17-1.76)	-	-
	DD CKD	2.31 (1.14-4.66)	1.19 (0.96-1.46)	0.88 (0.74-1.04)

Table 2.1-6	Morbidity due to Anaemia in CKD Patients Mean HR (95% CI)			
		Hb <10 g/dL	**Hb10-12 g/dL**	**Hb >12 g/dL**
CKD Progression	**NDD CKD**	1.65 (1.36-2.00)	1.41 (1.27-1.56)	-

CI = Confidence Interval, CKD = Chronic Kidney Disease; DD =Dialysis Dependent; Hb = Haemoglobin, MACE=Major Adverse Cardiac Events; NDD = Non-Dialysis Dependent
(-): Information not available
Source: Palaka E, Grandy S, Haale H v, McEwan P, Darlington O. The Impact of CKD Anaemia on Patients: Incidence, Risk Factors, and Clinical Outcomes- A Systematic Literature Review. International Journal of Nephrology; 2020: 1-21

Locatelli, F et al found that in five selected European countries (France, Germany, Italy, Spain, and UK) dialysis dependent chronic kidney disease (DD CKD) patients with a Hb <10 g/dl were 29% more likely to be hospitalized than patients with a Hb of 11-12 g/dl (P<0.001).[9]

i. Cardiovascular diseases

People with CKD are more likely to experience a CV event and a worse prognosis with higher mortality after an acute myocardial infarction (MI), and to have a higher risk of a recurrent MI, heart failure (HF) and sudden cardiac death.[1]

Anaemia has been linked to CV outcomes, both in individuals with kidney failure and in the general population. In chronic anaemia, hypoxia and decreased blood viscosity result in decreased peripheral resistance and increased venous return, both of which increase cardiac output. This, in turn, may lead to progressive left ventricular enlargement which is a risk factor for CHD events.[14]

Large cohort studies have demonstrated strong and independent associations between cardiovascular disease [CVD] (including acute coronary syndrome, stroke, HF and sudden cardiac death) and CKD by category of estimated GFR (eGFR), after adjusting for known CVD risk factors, a history of CVD events, and proteinuria. In those with an eGFR of 45-59 ml/min/1.73 m^2, risk is increased by 43% and in those with eGFR <15 ml/min/1.73 m^2, risk is increased by 343%.[15] Although people with GFR category G5 (GFR < 15 mL/min/1.73 m^2) are at the highest risk of a CVD event, there will be more events in people with GFR categories G3a-G3b (GFR 30-59 mL/min/1.73 m^2) because of the much higher prevalence at these categories (0.3%-0.5% for G5 vs 5%-10% for G3 stage of CKD).[16]

ii. Peripheral arterial diseases (PAD)

There is a strong link between CKD and PAD. Anaemia is common in CKD patients hospitalized for PAD. Anaemia is independently associated with overall adverse

outcomes for CKD as well as for the involved limbs in PAD. The risk of major amputation and death increases substantially at low levels of Hb.[17] Overall, prevalence of PAD in subjects with GFR <60 ml/min/1.73 m^2 is 16%. Prevalence of PAD increased from 4% in those with GFR > 60 to 22% in those with GFR <30 ml/min/1.73 m^2.

iii. Risk of Infections

CKD is associated with significant major infectious complications, which occur at rates 3 to 4 times than in the general population. Patients with CKD are at increased risk for infection (attributable to immune dysfunction), increased exposure to infectious agents, loss of cutaneous barriers, comorbid conditions, and treatment-related factors (e.g., HD and immunosuppressant therapy). Because iron plays a vital role in pathogen reproduction and host immunity, it is biologically plausible that iron deficiency influences infection risk in CKD.[18] Infection is an important cause of morbidity and mortality among patients with kidney failure and is the second leading cause of death following CVD. Data from the US Renal Data System (USRDS) suggest that higher rates (nearly 4 times) of hospital admission have occurred because of septicaemia in people with CKD compared with those without CKD.[19] Rates for pneumonia in CKD were nearly three times higher than those for non-CKD.

iv. Risk of Acute Kidney Injury (AKI)

CKD is considered the most consistent pre-existing condition associated with AKI. Because AKI frequently develops in the ischaemic conditions, anaemia (with reduced oxygen delivery) can be one of the reasons for the high incidence of AKI in hospital-admitted patients. It is helpful to monitor serum Hb or anaemia to prevent worse outcomes of AKI. Patients with both anaemia and AKI had a higher mortality risk because both anaemia and AKI aggravate organ dysfunction or delay of organ recovery.[20]

v. Major Neurological Problems

Patients with CKD are frequently afflicted with neurological complications. These complications can potentially affect both the central and peripheral nervous systems. Common neurological complications in CKD include stroke, cognitive dysfunction, encephalopathy, peripheral and autonomic neuropathies.[21] CKD has been linked to higher stroke risk. The combination of CKD and anaemia was associated with a substantial increase in stroke risk, independent of other known risk factors for stroke.[22]

c) Co-morbidities in Patients with CKD and Anaemia

i. Diabetes

Diabetes mellitus is the most common cause of CKD and kidney failure. Moderate to severe CKD is estimated to be found in 15-23% of patients with diabetes. For 45% of

patients who receive dialysis therapy, diabetes is the primary cause of their kidney failure.[23]

ii. Hypertension

Hypertension and CKD are closely associated with an intermingled cause and effect relationship. Blood pressure (BP) typically rises with declines in kidney function, and sustained elevations in BP hasten progression of kidney disease. In a large health screening registry, individuals with a baseline BP close to 180/100 mm Hg were approximately 15 times more likely to develop end-stage renal disease (ESRD) than individuals with a baseline BP close to 110/70 mm Hg.[24] Hypertension is present in 80-85% adult patients with CKD. While the prevalence of hypertension in people without renal dysfunction is 60%, it can be as high as 90% in patients with chronic renal failure.[25]

iii. Congestive Heart Failure (CHF)

CHF can cause or worsen both anaemia and CKD, and CKD can cause or worsen both anaemia and CHF. Thus, a vicious circle exists between these three conditions, with each causing or worsening the other. CHF is seen in up to 64% of patients referred to nephrologists with moderate to severe CKD.[26]

iv. Liver Disorders

According to National Health and Nutrition Examination Survey (NHANES) data of CKD patients in the United States (US) (1999 to 2016) the prevalence of liver disease was 3.44% in CKD patients of all stages. The prevalence of liver disease increases with severity of kidney dysfunction at least through Stage 4 (Table 2.1-7).[27]

Table 2.1-7 NHANES Data of CKD Patients in US from 1999 to 2016

Population	N	Prevalence of Liver disease (%)
All NHANES population	29,966	905 (3.03)
No CKD	16,470	437 (2.73)
CKD all Stages	13,496	468 (3.44)
CKD Stages 1-4	13,414	465 (3.44)
Stage 1	1428	61 (3.84)
Stage 2	9306	302 (3.23)
Stage 3	2471	87 (4.01)
Stage 4	209	15 (7.67)
Stage 5	82	3 (1.46)

CKD = Chronic Kidney Disease, N = Number of subjects, NHANES = National Health and Nutrition Examination Survey, US = United States

In general, there is evidence of an association between CKD or decreased eGFR with liver enzyme changes or liver dysfunction. This may be due, at least in part, to the shared pathogenic mechanism between kidney and liver dysfunction like insulin resistance, lipotoxicity, inflammation and oxidative stress.[28]

Chronic viral hepatitis [due to Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV)] can cause CKD and these infections can occur as a consequence of CKD management. CKD patients acquiring HBV or HCV infection have higher morbidity and mortality rates.[29] There is also evidence of an association with non-alcoholic fatty liver disease (NAFLD) with CKD.

v. Lung Disease

The lungs may be severely affected by advanced CKD. However, the prevalence of lung dysfunction is increased even in patients with CKD stage 1-4, to 10% for restrictive and 16% for obstructive lung function according to the NHANES 2007-2012. As GFR falls, pulmonary oedema and respiratory muscle dysfunction become more common due to fluid retention and metabolic, endocrine and CV alterations. Not only GFR but also urinary protein excretion may be linked to worsening lung function.[30]

vi. Malignancies

Acute kidney injury and CKD encompasses a complex set of diseases that can both lead to, and result from cancer. Kidney dysfunction creates an inflammatory microenvironment and oxidative stress, which can establish the ideal environment for cancer development. In support of this hypothesis, patients with end-stage renal disease have a higher risk of developing cancer than individuals with normal kidney function. Many of the current and newly developed cancer chemotherapeutic agents are nephrotoxic and can promote kidney dysfunction. Patients with cancer often have kidney problems, including CKD or acute kidney injury.[31]

After dialysis, cancer risk increases 10 to 80%, with relative risks (RR) significantly higher than the general population. There is also emerging evidence for an excess risk of cancer in patients at early CKD stages.[32]

Table 2.1-8 Relative risk or hazard ratio (95% CI) of all type cancer in patients with CKD

		NDD CKD	DD CKD
Per 10 ml/min/1.73 m^2 decrease in eGFR	Male	1.3 (1.1, 1.5)	1.8 (1.7,2.0)
	Female	1.0 (0.9,1.2)	1.1 (1.0,1.1)
HR of cancer per 1-SD increase of log ACR		1.2 ($p<0.001$)	1.2 (1.2,1.2)

ACR = Albumin creatinine ratio, CI = Confidence Interval, CKD = Chronic Kidney Disease, DD = Dialysis Dependent, eGFR = estimated Glomerular Filtration Rate, HR = Hazard Ratio, NDD = Non Dialysis Dependent, RR = Relative Risk
SD -Standard Deviation
Source: Stengel B. Chronic kidney disease and cancer: a troubling connection. J Nephrol. 2010; 23(3): 253-262.

Existing Treatment Options for Anaemia in CKD

In the last 30 years, there has been a major transition in approach to the treatment of anaemia in people with CKD beginning with the introduction of EPO therapy into clinical practice and the subsequent resurgence of interest in iron therapies.[1]

The current standard of care for anaemia secondary to CKD is the use of injectable erythropoiesis stimulating agents (ESAs) alone, or in combination with intravenous (IV) or oral iron supplementation.[1] While ESAs have been shown to be effective in treating anaemia for many patients with CKD, they have some well-recognized limitations.[33,34,35]

Treatment with exogenous recombinant ESAs is associated with shortcomings like the need for IV and/or subcutaneous administration and the potential for an unpredictable uncontrolled rise in Hb. Higher ESA doses and targeting near normal Hb levels with ESAs have been associated with excessive CV morbidity and mortality.[33,34,35,36,37,38,39] ESAs are associated with an increased risk of cancer progression or recurrence due to mechanisms that may be independent of the effect on Hb. The risk may be higher when Hb levels above 13 g/dL are achieved. In a few reported cases, EPO alfa induced antibodies have resulted in pure red cell aplasia, and dependence on blood transfusions to maintain acceptable Hb levels.[40,41,42] RBC transfusions are typically used for rescue therapy rather than first-line therapy due to the risks of transfusion reactions, blood-borne infection, iron overload and circulatory overload. In addition, use of transfused blood products can increase the risk of alloimmunisation and hence organ rejection, which can impact candidacy for kidney transplantation.

Roxadustat (brand name: Evrenzo), a HIF prolyl-hydroxylase inhibitor was approved in the Europe in August 2021 [Evrenzo | European Medicines Agency (EMA)] (europa.eu) as an alternative oral therapy option and is indicated for the treatment of adult patients with symptomatic anaemia associated with CKD. By inhibiting HIF prolyl-hydroxylase 2, roxadustat activates HIF2a and thereby increases endogenous production of EPO which stimulates production of Hb and RBC.

2.2 Module SII: Nonclinical Part of the Safety Specification

Vadadustat is a small molecule inhibitor of HIF-PHs, which are enzymes that degrade the HIF-α subunit, leading to dose-dependent increases in EPO and other HIF-regulated genes involved in erythropoiesis and iron homeostasis. Vadadustat inhibits PHD enzymes, thereby stabilizing the 2 major human isoforms of the transcription factor HIF-α (HIF-1α and HIF-2α) and contributing to increased EPO secretion. Repeat-dosing of vadadustat in mice and rats resulted in dose-dependent increases in several haematological markers, including EPO and Hb.

Table 2.2-1 below gives a summary of the key safety findings from non-clinical studies and relevance to human usage

Table 2.2-1 SII-1: Summary of Key Safety Findings from Non-clinical Studies and Relevance to Human Usage	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
Safety pharmacology: Safety pharmacology of vadadustat was assessed in vitro and in vivo in rats and dogs. There were no vadadustat-related adverse effects on the rat CNS renal and respiratory function, no behavioural changes. Vadadustat had no clinically relevant effect in the in vitro hERG assay and did not cause clinically relevant changes in the ECG (RR-interval, QRS-complex, ST-segment or T-wave) in rats or dogs.	No safety concern relevant to human use has arisen from these conventional safety pharmacology studies.
General Toxicology: The toxicology profile of vadadustat was evaluated in single- and repeat-dose studies in multiple species (mice, rats, dogs). In general, toxicities observed in toxicology studies were dose-responsive, reversing and consistent across species without appreciable progression of effects at increase in dosage duration. The majority of the toxicologic findings were due to exaggerated pharmacology of vadadustat (polycythemia/ hyperviscosity), which resulted in mortalities in all species at clinically relevant dose levels. A microscopic change unique to the dog was noted in the adrenal glands, and consisted of non-proliferative mononuclear cell infiltrates, hypertrophied multinucleated cells, and/or single cell necrosis in the adrenal gland cortex of males dosed at ≥ 10 mg/kg/day and females dosed at ≥ 25 mg/kg/day. These findings are likely sub-clinical given the few number of cells involved and were considered non-adverse.	The toxicities defining the NOAEL in the animal studies were secondary to polycythemia, an exaggerated pharmacological effect of vadadustat. Polycythaemia is clinically monitorable and will be managed in the clinical setting through dose titration to therapeutic Hb endpoints. In the pivotal clinical development studies in CKD patients adrenal disorders including adrenal insufficiency occurred in < 0.1% of patients; no difference in frequency of adrenal disorders as compared to comparator treatment darbepoetin alfa was observed. Overall, changes in adrenal gland are not considered relevant to humans.
Reproductive / developmental toxicity: Reproductive and developmental toxicity including fertility, pregnancy and breastfeeding of vadadustat was evaluated in rats and rabbits. Vadadustat was not teratogenic in the rat or the rabbit and had no effect on fertility or embryonic development in the rat. There was a decrease in rat fetal body weight at 160 mg/kg/day, a dose that caused maternal toxicity. The reduced body weight corresponded with an increased incidence of reduced skeletal ossification. A 10-week juvenile toxicity study in 7-Day old Sprague Dawley (SD) rats did not reveal any new safety findings.	Nonclinical studies did not identify a risk for fertility, pregnancy or breastfeeding. There was limited experience in patients who were pregnant or breastfeeding during the vadadustat clinical development program. According to the Summary of Product Characteristics, vadadustat should only be used during pregnancy and breast-feeding if the benefit justifies a potential risk for the foetus. More information will be collected during ongoing clinical studies and in the post-marketing setting via routine pharmacovigilance activities.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Non-clinical Studies and Relevance to Human Usage	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
Genotoxicity: Genotoxicity of vadadustat was assessed in vitro and in vivo in rats. Vadadustat was negative for mutagenicity, but positive results were obtained in the in vitro Chinese hamster ovary (CHO) cell assay for chromosomal aberrations and the GreenScreen assay. However, the in vivo chromosome aberration assay and COMET assays tested negative.	The in vitro chromosomal aberration assay in CHO cells and the GreenScreen assay have been reported to have irrelevant positive results or to be heavily influenced by cytotoxicity. Thus, a positive result is often not predictive of a positive carcinogenic outcome. The in vivo chromosome aberration assay and COMET assays tested negative, and the Ames assay was negative. Overall, the weight of evidence suggests that vadadustat is not genotoxic and does not represent a genotoxic risk to humans.
Carcinogenicity: Carcinogenicity of vadadustat was evaluated in mice and rats. Vadadustat was not carcinogenic in a 6-month study in Tg-rasH2 mice and in a 2-year study in SD rats.	In preclinical tests no risk of carcinogenicity was identified. More information will be collected during ongoing clinical studies and in the post-marketing setting via routine pharmacovigilance activities. Malignancies are included in this RMP as a potential risk (risks not considered important).

CNS = Central nervous system, CHO = Chinese hamster ovary, CKD = Chronic Kidney Disease, ECG = Electrocardiogram, hERG = human Ether-a-go-go Related Gene; NOAEL = No Observed Adverse Effect Level, RMP = Risk Management Plan, SD = Sprague Dawley

Overall, non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, reproductive toxicity/ lactation, genotoxicity or carcinogenicity.

2.3 Module SIII: Clinical Trial Exposure

Clinical Trial Exposure by Duration of Exposure[a]

Table 2.3-1 below shows the clinical trial exposure to vadadustat by duration of exposure.

Table 2.3-1 SIII.1: Clinical Trial Exposure to Vadadustat by Duration of Exposure		
Duration of Exposure	**Persons**	**Person Time (Years)**
Cumulative for all patient groups		
<1 month	955	17.73
≥1 month to < 3 months	460	72.62
≥3 months to < 6 months	754	277.29
≥6 months to < 12 months	960	720.87
≥12 months to < 24 months	1507	2070.12
≥24 months to < 36 months	601	1430.54
≥36 months	116	380.88

[a] Exposure data were generated on 08 Oct 2021. In the completed clinical trials no additional subjects were exposed to vadadustat between 12 Apr 2021 and 18 Aug 2021 (the data cut-off date of this RMP). Ongoing clinical trials are not included.

Table 2.3-1 SIII.1: Clinical Trial Exposure to Vadadustat by Duration of Exposure		
Duration of Exposure	**Persons**	**Person Time (Years)**
Total	**5353**	**4970.03**
DD CKD Subjects		
<1 month	175	6.32
≥1 month to < 3 months	232	38.59
≥3 months to < 6 months	447	163.96
≥6 months to < 12 months	488	371.08
≥12 months to < 24 months	873	1199.59
≥24 months to < 36 months	284	666.17
≥36 months	4	12.19
Total	**2503**	**2457.91**
Source Trials: AKB-6548-CI-0009, AKB-6548-CI-0011, AKB-6548-CI-0016, AKB-6548-CI-0017, AKB-6548-CI-0022, AKB-6548-CI-0025, AKB-6548-CI-0034, MT-6548-J02, MT-6548-J03, MT-6548-J04		
NDD CKD Subjects*#		
<1 month	111	3.97
≥1 month to < 3 months	228	34.03
≥3 months to < 6 months	307	113.33
≥6 months to < 12 months	472	349.79
≥12 months to < 24 months	634	870.53
≥24 months to < 36 months	317	764.36
≥36 months	112	368.69
Total	**2181**	**2504.69**
Source Trials: AKB-6548-CI-0003, AKB-6548-CI-0004, AKB-6548-CI-0005*, AKB-6548-CI-0007, AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0021, MT-6548-J01. *Two subjects from trial AKB-6548-CI-0005 were excluded because of missing dose # Clinical trials were also conducted in the NDD-CKD population and contribute to the overall safety profile of AESIs for vadadustat. These studies are discussed in Section 2.4 Module SIV: Populations Not Studied in Clinical Trials and Section 2.7 Module SVII: Identified and Potential Risks of the RMP.		
Healthy Subjects*		
<1 month	661	7.41
Total	**661**	**7.41**
Source Trials: AKB-6548-CI-0001, AKB-6548-CI-0002, AKB-6548-CI-0006, AKB-6548-CI-0008, AKB-6548-CI-0010, AKB-6548-CI-0012, AKB-6548-CI-0013, AKB-6548-CI-0019, AKB-6548-CI-0020, AKB-6548-CI-0024, AKB-6548-CI-0027, AKB-6548-CI-0028, AKB-6548-CI-0029, AKB-6548-CI-0030, AKB-6548-CI-0031, AKB-6548-CI-0033, AKB-6548-CI-0037, MT-6548-J05 * 19 Subjects enrolled and dosed in two different trials were only counted once		
Hepatic-impaired Subjects (without CKD)		
1 day	8	0.02
Total	**8**	**0.02**

AESI = Adverse Event of Special Interest, CKD = Chronic Kidney Disease, DD = Dialysis Dependent
Source Trial: AKB-6548-CI-0024

Table 2.3-2 below shows the clinical trial exposure to vadadustat by age group and gender.

Clinical Trial Exposure by Age Group and Gender

Table 2.3-2 SIII.2: Clinical Trial Exposure to Vadadustat by Age Group and Gender				
Age Group	**Persons**		**Person Time (Years)**	
	M	**F**	**M**	**F**
Cumulative for all patient groups				
Adults (18 to 64 years)	**1745**	**1360**	**1297.73**	**1287.77**
Elderly people	**1156**	**1092**	**1189.44**	**1195.09**
65-74 years	640	651	651.61	694.10
75-84 years	427	356	446.57	391.13
85 + years	89	85	91.27	109.86
Total	**2901**	**2452**	**2487.17**	**2482.86**
DD CKD Subjects				
Adults (18 to 64 years)	**907**	**682**	**889.72**	**689.55**
Elderly people	**531**	**383**	**510.16**	**368.48**
65-74 years	354	263	338.67	259.75
75-84 years	165	108	158.36	98.87
85 + years	12	12	13.13	9.86
Total	**1438**	**1065**	**1399.88**	**1058.03**
Trial Source: AKB-6548-CI-0009, AKB-6548-CI-0011, AKB-6548-CI-0016, AKB-6548-CI-0017, AKB-6548-CI-0022, AKB-6548-CI-0025, AKB-6548-CI-0034, MT-6548-J02, MT-6548-J03, MT-6548-J04				
NDD CKD Subjects[#]				
Adults (18 to 64 years)	**382**	**467**	**402.68**	**596.12**
Elderly people	**625**	**707**	**679.29**	**826.60**
65-74 years	286	386	312.94	434.34
75-84 years	262	248	288.21	292.27
85 + years	77	73	78.14	100.00
Total	**1007**	**1174**	**1081.97**	**1422.72**
Trials: AKB-6548-CI-0003, AKB-6548-CI-0004, AKB-6548-CI-0005, AKB-6548-CI-0007, AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0021, MT-6548-J01 [#] Clinical trials were also conducted in the NDD-CKD population and contribute to the overall safety profile of AESIs for vadadustat. These studies are discussed in Section 2.4 Module SIV: Populations Not Studied in Clinical Trials and Section 2.7 Module SVII: Identified and Potential Risks of the RMP.				
Healthy subjects				
Adults (18 to 64 years)	**453**	**207**	**5.32**	**2.09**
Elderly people	**0**	**1**		**0**
65-74 years	0	1		0
Total	**453**	**208**	**5.32**	**2.10**
Trials: AKB-6548-CI-0001, AKB-6548-CI-0002, AKB-6548-CI-0006, AKB-6548-CI-0008, AKB-6548-CI-0010, AKB-6548-CI-0012, AKB-6548-CI-0013, AKB-6548-CI-0019, AKB-6548-CI-0020, AKB-6548-CI-0024, AKB-6548-CI-0027, AKB-6548-CI-0028, AKB-6548-CI-0029, AKB-6548-CI-0030,AKB-6548-CI-0031, AKB-6548-CI-0033, AKB-6548-CI-0037, MT-6548-J05				
Hepatic-impaired Subjects (without CKD)				
Adults (18 to 64 years)	**3**	**4**	**0.01**	**0.01**
Elderly people	**0**	**1**		**0**
65-74 years	0	1		**0**
Total	**3**	**5**	**0.01**	**0.01**

AESI = Adverse Event of Special Interest, CKD = Chronic Kidney Disease, DD = Dialysis Dependent, F = Female, M = Male, NDD = Non-Dialysis Dependent
Source Trial: AKB-6548-CI-0024

Table 2.3-3 below shows the clinical trial exposure to vadadustat by dose

Clinical Trial Exposure by Dose

Table 2.3-3 SIII.3: Clinical Trial Exposure to Vadadustat by Dose		
Dose of Exposure	**Persons**	**Person Time (Years)**
Cumulative for all indications (Person time)		
80 mg	6	0.02
150 mg	176	9.69
150-600 mg	2407	2450.88
150-750 mg	1890	2435.62
150-900 mg	134	40.45
160 mg	6	0.02
200-700 mg	10	0.77
240 mg	18	1.93
300 mg	160	9.60
315 mg	8	0.04
370 mg	16	1.86
450 mg	92	0.60
500 mg	47	2.25
600 mg	314	12.90
630 mg	19	2.13
650 mg	6	0.02
700 mg	9	0.22
750 mg	12	0.33
900 mg	27	0.56
1200 mg	55	0.15
Total	**5353**	**4970.03**
DD CKD Subjects		
150 mg	18	3.99
150-600 mg	2269	2403.81
150-900 mg	134	40.45
300 mg	16	4.29
450 mg	12	0.07
600 mg	29	4.62
750 mg	12	0.33
900 mg	13	0.35
Total	**2503**	**2457.91**
Source Trials: AKB-6548-CI-0009, AKB-6548-CI-0011, AKB-6548-CI-0016, AKB-6548-CI-0017, AKB-6548-CI-0022, AKB-6548-CI-0025, AKB-6548-CI-0034, MT-6548-J02, MT-6548-J03, MT-6548-J04		
NDD CKD Subjects[#]		
150 mg	17	4.57
150-600 mg	138	47.07
150-750 mg	1890	2435.62
200-700 mg	10	0.77
240 mg	18	1.93
300 mg	16	4.04
370 mg	16	1.86
500 mg	39	2.03
600 mg	18	4.68

Table 2.3-3 SIII.3: Clinical Trial Exposure to Vadadustat by Dose		
Dose of Exposure	**Persons**	**Person Time (Years)**
630 mg	19	2.13
Total	**2181**	**2504.69**
Trials: AKB-6548-CI-0003, AKB-6548-CI-0004, AKB-6548-CI-0005, AKB-6548-CI-0007, AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0021, MT-6548-J01 # Clinical trials were also conducted in the NDD-CKD population and contribute to the overall safety profile of AESIs for vadadustat. These studies are discussed in Section 2.4 Module SIV: Populations Not Studied in Clinical Trials and Section 2.7 Module SVII: Identified and Potential Risks of the RMP.		
Healthy Subjects		
80 mg	6	0.02
150 mg	141	1.14
160 mg	6	0.02
300 mg	128	1.27
315 mg	8	0.04
450 mg	72	0.51
500 mg	8	0.22
600 mg	267	3.59
650 mg	6	0.02
700 mg	9	0.22
900 mg	14	0.21
1200 mg	55	0.15
Total	**661**	**7.41**
Trials: AKB-6548-CI-0001, AKB-6548-CI-0002, AKB-6548-CI-0006, AKB-6548-CI-0008, AKB-6548-CI-0010, AKB-6548-CI-0012, AKB-6548-CI-0013, AKB-6548-CI-0019, AKB-6548-CI-0020, AKB-6548-CI-0024, AKB-6548-CI-0027, AKB-6548-CI-0028, AKB-6548-CI-0029, AKB-6548-CI-0030, AKB-6548-CI-0031, AKB-6548-CI-0033, AKB-6548-CI-0037, MT-6548-J05		
Hepatic-impaired Subjects (without CKD)		
450 mg	8	0.02
Total	**8**	**0.02**

AESI = Adverse Event of Special Interest, CKD = Chronic Kidney Disease, DD = Dialysis Dependent, NDD = Non-Dialysis Dependent

Trials: AKB-6548-CI-0024

* strengths of 40 mg, 200 mg gelatin capsules, 315 mg capsule or a 315 mg tablet, 325 mg capsules used as part assessments in Phase I program

Table 2.3-4 below shows the clinical trial exposure to vadadustat by ethnic origin

Clinical Trial Exposure by Ethnic Origin

Table 2.3-4 SIII.4: Clinical Trial Exposure to Vadadustat by Ethnic Origin		
Race	**Persons**	**Person Time**
White	3108	3068.57
Black	1118	1046.07
Asian	781	540.79
Other	346	314.60
Total	**5353**	**4970.03**
DD CKD Subjects		
White	1367	1455.56
Black	606	605.97
Asian	377	259.91

Table 2.3-4 SIII.4: Clinical Trial Exposure to Vadadustat by Ethnic Origin		
Race	**Persons**	**Person Time**
Other	153	136.46
Total	**2503**	**2457.91**
Trials: AKB-6548-CI-0009, AKB-6548-CI-0011, AKB-6548-CI-0016, AKB-6548-CI-0017, AKB-6548-CI-0022, AKB-6548-CI-0025, AKB-6548-CI-0034, MT-6548-J02, MT-6548-J03, MT-6548-J04		
NDD CKD Subjects[#]		
White	1328	1608.19
Black	355	438.56
Asian	315	279.89
Other	183	178.05
Total	**2181**	**2504.69**
Trials: AKB-6548-CI-0003, AKB-6548-CI-0004, AKB-6548-CI-0005, AKB-6548-CI-0007, AKB-6548-CI-0014, AKB-6548-CI-0015, AKB-6548-CI-0021, MT-6548-J01 [#] Clinical trials were also conducted in the NDD-CKD population and contribute to the overall safety profile of AESIs for vadadustat. These studies are discussed in Section 2.4 Module SIV: Populations Not Studied in Clinical Trials and Section 2.7 Module SVII: Identified and Potential Risks of the RMP.		
Healthy Subjects		
White	405	4.79
Black	157	1.54
Asian	89	0.99
Other	10	0.09
Total	**661**	**7.41**
Trials: AKB-6548-CI-0001, AKB-6548-CI-0002, AKB-6548-CI-0006, AKB-6548-CI-0008, AKB-6548-CI-0010, AKB-6548-CI-0012, AKB-6548-CI-0013, AKB-6548-CI-0019, AKB-6548-CI-0020, AKB-6548-CI-0024, AKB-6548-CI-0027, AKB-6548-CI-0028, AKB-6548-CI-0029, AKB-6548-CI-0030, AKB-6548-CI-0031, AKB-6548-CI-0033, AKB-6548-CI-0037, MT-6548-J05		
Hepatic-impaired Subjects (without CKD)		
White	8	0.02
Total	**8**	**0.02**
Trials: AKB-6548-CI-0024		

AESI = Adverse Event of Special Interest, CKD = Chronic Kidney Disease, DD = Dialysis Dependent, NDD = Non-Dialysis Dependent

2.4 Module SIV: Populations Not Studied in Clinical Trials

Two of the global Phase 3 studies (INNO$_2$VATE: Study CI-0016 and Study CI-0017) were conducted in adult DD CKD subjects with baseline Hb values between 8 to 11 g/dL in Study CI-0016 and between 8 to 11 g/dL in the US and 9 to 12 g/dL outside of the US in Study CI-0017.

Study CI-0016 included subjects with incident DD CKD who initiated dialysis within 16 weeks of beginning their study participation. Study CI-0017 included subjects on chronic maintenance dialysis for more than 12 weeks and were being treated with an ESA for anaemia.

Two of the global Phase 3 studies (PRO$_2$TECT: Study CI-0014 and Study CI-0015) were conducted in adult NDD CKD subjects with baseline Hb values less than 10 g/dL and who were not being treated with an ESA.

Study CI-0015 included subjects diagnosed with CKD with baseline Hb values between 8 and 11 g/dL in the US and between 9 and 12 g/dL outside of the US who were being treated with an ESA for anaemia.

2.4.1 SIV.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 2.4.1-1 below shows the exclusion criteria in pivotal clinical studies

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies

Exclusion Criterion	Reason for Exclusion	Is it considered to be included as missing information?	Rationale *If not included as Missing Information*
Anaemia due to cause other than CKD (e.g. haematologic malignancy).	Anaemia from causes other than CKD would confound vadadustat results in the target population of patients with anaemia due to CKD	No	Anaemia associated with CKD is the target indication, and treatment of anaemia caused by other diseases is not an indication for vadadustat
Red blood cell transfusion within the last 8 weeks.	Recent red blood cell transfusions prior to start of study medication influences baseline conditions	No	This exclusion criterion was introduced to avoid confounding effects on efficacy evaluation during early treatment phase. During the study rescue therapy with red blood cell transfusions was allowed.
Active malignancy or history of active malignancy within 2 years.	Serious complications of end stage renal disease include an increased frequency of cancer, making evaluation of vadadustat difficult. Furthermore, active malignancies frequently cause anaemia (see above).	No	Malignancies is considered as a potential risk and will be monitored through routine pharmacovigilance. (Note: there was no difference in the frequency of malignancies between vadadustat and the comparator in the Phase 3 clinical trials)
Recent cardiovascular or thromboembolic event, or severe concomitant cardiac disease (CHF NYHA class IV, acute coronary syndrome).	Serious complications of ESRD include an increased frequency of cardiovascular disease and mortality, making evaluation of vadadustat difficult	No	CKD itself is a risk factor for cardiovascular and thromboembolic events. Increased mortality, myocardial infarction, stroke and thromboembolism are included in Section 4.4 (Special Warnings and precautions for use) in the SmPC. Furthermore, these safety concerns will continue to be monitored as Important identified risk.
ALT, AST, or total bilirubin >2x upper limit of normal.	Because liver function affects EPO production, including patients with abnormal liver function would make evaluation of vadadustat difficult	No	Liver disorders are known comorbidities in CKD patients. Elevated liver enzymes (includes transaminases increased, ALT increased, AST increased, hepatic enzyme increased), including,

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason for Exclusion**	**Is it considered to be included as missing information?**	**Rationale** ***If not included as Missing Information***
			occasionally elevated bilirubin is considered as an Identified risk and mentioned in Sections 4.2 (Posology and method of administration (Monitoring); Section 4.4 (Special warnings and precautions for use); and Section 4.8 (Undesirable effects) of the SmPC
Uncontrolled hypertension	Uncontrolled hypertension is considered a complication of CKD/ESRD. Serious complications of ESRD include an increased frequency of cardiovascular disease and mortality, making evaluation of vadadustat difficult	No	Worsening of hypertension is an identified risk, also specified under Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) of the SmPC.
History of prior organ transplantation or scheduled organ transplant.	Organ transplant and subsequent immunosuppression after transplantation confounds evaluation of safety and efficacy of investigational product.	No	Through routine pharmacovigilance activities will collect and assess safety profile of vadadustat in this subset of population.
History of haemosiderosis or haemochromatosis.	Iron overload independent from effect of vadadustat treatment	No	Treatment of anaemia in patients after haemosiderosis/ haemochromatosis is not an indication of vadadustat
Females who are pregnant breast feeding; females of childbearing potential w/o contraception.	Unknown benefit-risk in pregnant or breast-feeding women	No	Through routine pharmacovigilance activities will collect and assess safety profile of vadadustat in this subset of population. See section 4.6 (Fertility, Pregnancy and Lactation) of the SmPC
INNO$_2$VATE only: Incident Dialysis: patients with ESA resistance <8 weeks of screening.	ESA resistance <8 weeks of screening would make evaluation of the effect of vadadustat on Hb and RBC production difficult (note: rescue therapy with ESAs was allowed according to protocol)	No	Through routine pharmacovigilance activities will collect and assess safety profile of vadadustat in this subset of population.
Hypersensitivity	Avoid hypersensitivity reaction to any excipients of vadadustat preparation.	No	Contraindication in the SmPC Section 4.3: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC (List of excipients) Also specified under SmPC section 4.8 (Undesirable effects).

ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, CHF = Congestive Heart Failure, CKD = Chronic Kidney Disease, EPO = Erythropoietin, ESRD = End Stage Renal Disease, NYHA = New York Heart Association, SmPC = Summary of Product Characteristics, RBD = Red Blood Cell

2.4.2 SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 SIV.3: Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

All subjects in the global Phase 3 studies by definition, had various degrees of renal insufficiency. Adequate and well-controlled studies have not been conducted with vadadustat in pregnant women. There is no data in humans regarding the effect of vadadustat in human milk, on the breastfed infant, or on milk production. The development and health benefits for the infant should be considered along with the mother's clinical need for vadadustat and any potential adverse effects on the breastfed infant. Vadadustat has not been studied in the paediatric population.

Table 2.4.3-1 below shows the exposure of special populations included or not in the clinical trial development programme

Table 2.4.3-1 Exposure of Special Populations Included or not in the Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities	
Patients with hepatic impairment	The development programme included 8 subjects with moderate hepatic impairment (Child-Pugh Class B) in a Phase 2 clinical pharmacology study.
Patients with renal impairment	Inclusion criterion in the development program. Therefore, all subjects in the global Phase 3 studies by definition had various degrees of renal insufficiency
Patients with cardiac failure	In the pooled CKD Population for Global Phase 3 Studies, a total of 993 (13.4%) subjects with a NYHA HF class II or III were enrolled in the studies.
Immunocompromised patients	Immunocompromised subjects were not evaluated in the clinical development programme
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with a disease severity different from inclusion criteria in clinical trials were not included in the clinical development programme. Of note, only milder forms of CKD were not studied.

Table 2.4.3-1 Exposure of Special Populations Included or not in the Clinical Trial Development Programmes	
Type of Special Population	**Exposure**
Patients with relevant different ethnic origin/relevant genetic polymorphisms	
Population with relevant different ethnic origin	Population with specific ethnic origin was not a criterion for exclusion in the clinical development programme. In the pooled CKD Population for Global Phase 3 Studies the exposure to vadadustat in different races and ethnicities was as follows: <u>Ethnicities:</u> - DD CKD: Hispanic or Latino 38.5%, not Hispanic or Latino 58.6%, not reported 2.1%, unknown 0.9%. - NDD CKD: Hispanic or Latino 32.2%, not Hispanic or Latino 66.1%, not reported 0.6%, unknown 1.1%. <u>Races:</u> - DD CKD: American Indian or Alaska Native 0.9%, Asian 15.9%, Black or African American 21.5%, Native Hawaiian or Other Pacific Islander 0.6%, White 56.8%, other 1.8%, Multiple 0.4% and not reported 2.2% - NDD CKD: American Indian or Alaska Native 2.7%, Asian 14.4%, Black or African American 16.3%, Native Hawaiian or Other Pacific Islander 0.5%, White 60.9%, other 4.0%, Multiple 0.3% and not reported 0.9%
Subpopulations carrying relevant genetic polymorphisms	Population with any specific genetic polymorphisms was not a criterion for exclusion in the clinical development programme.
Other	Not applicable

CKD = Chronic Kidney Disease, DD = Dialysis Dependent, HF = Heart Failure, NDD = Non-Dialysis Dependent, NYHA = New York Heart Association

2.5 Module SV: Post-authorisation Experience

A marketing authorisation for vadadustat for the indication of renal anaemia was received in Japan by Mitsubishi Tanabe Pharma Corporation (MTPC) on 29 Jun 2020 (IBD). Vadadustat, under the trade name VAFSEO™, was launched in Japan on 26 Aug 2020.

2.5.1 SV.1: Post-authorisation Exposure

2.5.1.1 SV.1.1: Method Used to Calculate Exposure

Vadadustat is approved in Japan as a film-coated, immediate-release tablet in the following strengths: 150 mg, 300 mg, and 450 mg. The starting dose of vadadustat in adult patients is 300 mg orally once daily. Thereafter, the dose may be adjusted according to the patient's condition. The starting dose 300 mg once daily could be titrated up every 4 weeks or down titrated at any time in increments of 150 mg with a maximum dose of

600 mg once daily to achieve and maintain target Hb levels. There is no standard dosage or duration of treatment. Therefore, estimated patient-year (PY) exposure is calculated for each individual formulation of vadadustat and assumes that treated patients have taken one full tablet of vadadustat per day, which means the number of tablets sold for each formulation is equal to the patient-day exposure for that particular formulation. Since PY exposure is equal to patient-day exposure divided by 365 days, the PY exposure for each individual formulation of vadadustat is equal to the number of tablets sold divided by 365. It is noted that not all of the vadadustat tablets have as yet been delivered to patients as an inestimable amount could still be in the supply chain.

It is important to note that the estimated patient years of treatment (PYT) are not equivalent to the absolute number of patients treated. It should also be noted that the overall PYT estimates are likely to underestimate the true number of patients exposed to vadadustat since PYT estimates reflect the number of patients who could have been treated for one year based on the tablets distributed. However, since many patients do not stay on therapy for a whole year, even for chronic conditions, the real number of patients is likely to be higher. Also to be noted, that at times PYT estimate can be overestimates, as there might be patients who end up taking 2 tablets per day to achieve desired recommended dosage.

2.5.1.2 SV.1.2: Exposure

Due to the building of the supply chain and other factors that were associated with the launch of vadadustat, it is difficult to estimate patient exposure for vadadustat accurately. The shipment volumes of vadadustat tablets as of 28 June 2021 were 724,400 × 150 mg tablets and 1,020,100 × 300 mg tablets. The calculation of exposure is as follows:

- Total number of Tablets sold = 724,400 + 1,020,100 = 1,744,500
- Total patient days exposure = 1,744,500
- Estimated PYT = 1,744,500 ÷ 365 = 4779 PYT

2.6 Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

HIF stabilizers as a class, based on their erythropoietic properties, can be the subject of misuse in amateur and elite sports to increase athletic performance. Hence, vadadustat was listed by World Anti-Doping Agency (WADA) as a prohibited substance for athletes in- and out-of-competition.[43]

There were 15 events of suspected abuse or misuse of vadadustat reported in 7 subjects, and these were recorded as Special Situations in the global Phase 3 studies (Module 2.7.4 Section 5.6). Most of these special situation cases were reported as missed doses or taking more than prescribed doses and none of the special situations of suspected abuse/misuse led to treatment emergent adverse events (TEAEs) and none of them were considered misuse for illegal purposes

Post-marketing Data (Japan Only):

As of the data cut-off date of 18 Aug 2021, no case reports of drug misuse or drug abuse have been received.

More information will be collected in the post-marketing setting via routine pharmacovigilance (PV) activities to monitor the misuse or abuse potential of vadadustat.

2.7 Module SVII: Identified and Potential Risks

2.7.1 SVII.1: Identification of Safety Concerns in the Initial RMP Submission

The initial identification of safety concerns with the first submission of this RMP is presented in the following sections.

2.7.1.1 SVII.1.1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The risks not taken forward as safety concerns are presented below.

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP:

(a) Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

- **Drug-drug interaction with iron supplements and phosphate binders (both iron and non-iron containing) (Identified Risk)**

Based on structural attributes, absorption of vadadustat may be affected due to complex formation with phosphate binders or iron. This could lead to reduced absorption of vadadustat in the presence of high doses of concomitantly administered oral iron alone or iron/non-iron containing phosphate binders.

Study CI-0037 showed that there was moderate interaction when 300 mg vadadustat was administered with a non-iron-containing phosphate binder (1600 mg sevelamer carbonate and 1334 mg calcium acetate), reducing exposure up to 55%, and iron-containing phosphate binder (2 g ferric citrate), reducing exposure up to 90% (Module 2.7.2

Section 1.3.1.6). The interaction with non-iron containing phosphate binders can be reduced by administering vadadustat 1 hour prior to or 2 hours after binder administration.[44]

Study CI-0012 and Study MT-6548-J05, showed that maximum plasma concentration (C_{max}) and area under the concentration curve (AUC) values for vadadustat were reduced by 50% up to 90% (Module 2.7.2 Sections 2.2.4.7 and Section 2.2.4.1), when dosed concomitantly with ferrous sulfate immediate release tablet or with the co-administration of oral iron or iron-containing phosphate binders (sodium ferrous citrate, ferric citrate hydrate, sucroferric oxyhydroxide). It is recommended that vadadustat be administered at least 1 hour prior to oral iron supplements, products containing iron or iron-containing phosphate binders.[45,46]

- **Drug-drug interaction with OAT 3, OAT1/3 and BCRP substrates (Identified Risk)**

In vitro data suggests vadadustat is a substrate of organic anion transporter (OAT)1/3 and an inhibitor of the organic anion transporter OAT3 and also clinically relevant inhibitor of the drug transporter breast cancer resistance protein (BCRP). (Module 2.7.2 Sections 2.2.4.4).[47]

Exposure of sulfasalazine (a BCRP substrate) increased 4.5-fold[48] and furosemide (an OAT1/OAT3 substrate) increased 2-fold[49] when co-administered with vadadustat in healthy subjects (Module 2.7.2 Section 2.2.4.4 and Section 2.2.4.5). However, no effect was observed on the exposure of adefovir (an OAT1 substrate) (Module 2.7.2 Section 2.2.4.5) indicating, that clinically, vadadustat is an OAT3 inhibitor.[49] Exposure of vadadustat increased approximately 2-fold when co-administered with probenecid (a general UGT and OAT1/3 inhibitor).(Module 2.7.2 Section 2.2.4.3).[50]

In the above drug-drug interaction studies none of the observed TEAEs were serious or led to discontinuation from study drug or led to death.

Available information regarding the risk of interaction with vadadustat and the drugs acting on OAT3 or BCRP substrate has not impacted the overall positive benefit-risk balance for vadadustat.

It is recommended to monitor for signs of excessive effects of the co-administered OAT3 and BCRP substrates. If co-administrated with strong or moderate OAT1 or OAT3 inhibitors, patients should be managed cautiously and evaluated for excessive effects of vadadustat. See Section 4.5 of the Summary of Product Characteristics (SmPC) (Interaction with other medicinal products and other forms of interaction).

- **Elevated Liver Enzymes (Identified Risk)**

Elevated liver enzymes were captured in the development programme in two separate ways, (i) as adverse events reported by investigators or (ii) as specific elevations of liver enzymes above the upper limit of normal (ULN).

In the pooled DD-CKD Population, Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for elevated liver enzymes[b] were reported in 3.2% of subjects receiving vadadustat and 3.7% of subjects receiving darbepoetin alfa treatment.

Based on laboratory data, in the pooled DD-CKD population the elevated serum alanine aminotransferase (ALT) (3x ULN), aspartate aminotransferase (AST) (3x ULN), and bilirubin (2x ULN) were seen in 1.8%, 1. 4% and 0.3% of patients treated with vadadustat, respectively and in pooled CKD population

In the pooled CKD Population for Global Phase 3 Studies, MedDRA PTs for elevated liver enzymes were reported in 3% of subjects receiving vadadustat and 3.2% of subjects receiving darbepoetin alfa treatment.Based on laboratory data, elevated serum ALT (3x ULN), AST (3x ULN), and bilirubin (2x ULN) were seen in 1.8%, 1.8% and 0.1% of patients treated with vadadustat, respectively in the pooled CKD population.

All of the liver enzyme abnormalities resolved or were resolving, and no instances of acute liver failure, death attributed to vadadustat or the development of chronic liver disease were observed. Although incidence of elevated liver enzymes was similar between the two treatment groups, per investigator assessment, more events were considered related to vadadustat than darbepoetin alfa.

Based on the data from clinical development and post-marketing reports, elevated liver enzymes (includes transaminases increased, ALT increased, AST increased, hepatic enzyme increased), including, occasionally elevated bilirubin is considered an identified risk for vadadustat. Elevated liver enzymes and increased blood bilirubin are listed in Section 4.8 and are mentioned in Section 4.2, Section 4.4 of the SmPC. Routine risk communication and minimisation measures will ensure the overall public health impact of this risk is low.

- **Worsening of Hypertension (Identified Risk)**

In the pooled DD-CKD Population, a total of 333 (14.3%) subjects experienced an event of hypertension [Standardised MedDRA query (SMQ) Hypertension, broad] in the

[b] Alanine aminotransferase increased, Aspartate aminotransferase increased, Transaminases increased, Hepatic enzyme increased, Liver function test abnormal

vadadustat treatment group compared with 389 (18.4%) subjects in the darbepoetin alfa treatment group (ISS Table 14.3.1.12a).

In the pooled CKD Population for Global Phase 3 Studies, a total of 663 (18.0%) subjects experienced an event of hypertension [Standardised MedDRA query (SMQ) Hypertension, broad] in the vadadustat treatment group compared with 776 (21.0%) subjects in the darbepoetin alfa treatment group. The RR (95% CI) of vadadustat/darbepoetin alfa was 0.86 (0.78, 0.94). The most frequently reported PTs for hypertension adverse events of special interest (AESI) were hypertension, hypertensive urgency, hypertensive crisis, and increased blood pressure. (ISS Table 14.3.1.13c).

Most events in both treatment groups (77.8%) had an outcome recovered/resolved. Ninety-six percent of events in the vadadustat treatment group were reported as unrelated compared to 95.4% of events reported as unrelated in the darbepoetin alfa treatment group.

Most patients had several confounding factors and co-morbidities associated with the worsening BP control, including smoking, underlying CKD, diabetes mellitus, peripheral arterial occlusive disease, coronary artery disease (CAD), CHF, and inadequately controlled hypertension at baseline.

Post-marketing data (Japan only): As of 18 Aug 2021, 22 spontaneous case reports with 22 MedDRA PTs under the SMQ Hypertension (broad) were reported. With an estimate of 4779 PYT of exposure this calculates to a reporting rate of 0.460 adverse events / 100 PYT. The reported terms were hypertension (10 case reports), BP increased (11) and BP systolic increased (1). Two case reports were serious (one report each of hypertension and BP increased) and no case with fatal outcome was reported. In 12 cases in which information about the patients' medical history was available, the patients had underlying hypertension.

This safety concern is considered as an identified risk with low public health impact because of possible early detection and management. According to the SmPC Section 4.4, administration of vadadustat in patients with CKD may be associated with worsening of hypertension. Hypertension is also listed in Section 4.8 of the SmPC. Routine risk communication and minimisation measures will ensure the overall public health impact of this risk is low.

- **Malignancies (Potential Risk)**

CKD and cancer are interconnected in many ways: cancer can cause CKD directly or indirectly, through cancer therapy (chemotherapy nephrotoxicity) whereas CKD may conversely be a risk factor for cancer. Based on US Renal Data System (1998 to 2002)

cancer prevalence data, 31% of subjects with ESRD had a diagnosis of cancer at least 2 years before start of ESRD treatment. Cancers most strongly associated with dialysis include Kaposi sarcoma, tumours of the oral cavity, kidney, bladder, stomach, liver, lung, cervix, and thyroid.[32]

In the global Phase 3 clinical studies in DD CKD and NDD CKD, 132 malignancies related events were reported in 121 subjects out of 3686 subjects (PY=6335.3) exposed to vadadustat treatment. The IR of malignancies related events in the global Phase 3 clinical studies was 3.3% (2.1 events per 100 PY) (ISS Table 14.3.1.13c). In the Phase 3 clinical trials the most frequently reported malignancies were non-melanoma skin cancers [basal cell carcinoma (0.4%) and squamous cell carcinoma (0.4%)].

Pooled DD CKD Population for the Phase 3 Studies:

A total of 47 (2.4%) subjects experienced an event of malignant or unspecified tumours in the vadadustat treatment group compared with 66 (3.4%) subjects in the darbepoetin alfa treatment group. The RR (95% CI) of vadadustat/darbepoetin alfa was 0.72 [0.49, 1.03]). Cases of renal cell carcinoma (RCC) were reported for 0.1% of subjects in the vadadustat treatment group and 0.2% of subjects in the darbepoetin alfa treatment group. (ISS Table 14.3.1.13a).

Pooled NDD CKD Population for the Phase 3 Studies:

A total of 74 (4.3%) subjects experienced an event of malignant or unspecified tumours in the vadadustat treatment group compared with 83 (4.8%) subjects in the darbepoetin alfa treatment group. The RR (95% CI) of vadadustat/darbepoetin alfa was 0.89 [0.65, 1.21). The most frequent PTs were non-melanoma skin cancer [basal cell carcinoma (BCC): 0.8% and 0.7% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively and squamous cell carcinoma (SCC) of the skin: 0.8% and 0.6% of subjects, respectively]. Cases of RCC were reported for 0.0% of subjects in the vadadustat treatment group and 0.1% of subjects in the darbepoetin alfa treatment group. (ISS Table 14.3.1.13b).

Pooled CKD Population for the Phase 3 Studies:

A total of 121 (3.3%) subjects experienced an event of malignant or unspecified tumours in the vadadustat treatment group compared with 149 (4.0%) subjects in the darbepoetin alfa treatment group. The RR (95% CI) of vadadustat/darbepoetin alfa was 0.81 [0.64, 1.03). Cases of RCC were reported for 0.1% of subjects in the vadadustat and darbepoetin alfa treatment groups. (ISS Table 14.3.1.13c).

Post-marketing data (Japan only): As of 18 Aug 2021, four cases of malignancies (SMQ Malignant or Unspecified Tumors, broad) have been reported (0.0837 AE / 100 PYT; 4 were serious and 2 had a fatal outcome). The adverse events (AEs) reported were acute myeloid leukaemia, renal cancer (recurrence), hepatic cancer (recurrence), hepatic neoplasm. All reported malignancies were reported with a short latency (few months) to start of vadadustat treatment and/or were reoccurrences of pre-existing malignancies. As such a causal relationship between vadadustat and the reported malignancies is implausible.

At this time, there is little evidence suggesting that the transient stabilization of HIF-α via the pharmacological inhibition of PHD enzymes correlates with tumorigenesis. While the existing clinical and nonclinical data for vadadustat do not suggest that the transient and temporal pharmacologic activation of HIF through the inhibition of PHDs causes tumorigenesis, a link cannot be ruled out.

In consideration of this and high background incidence of malignancies in the target population the public health impact is considered to be low. This safety concern is considered as a potential risk and will be monitored through routine pharmacovigilance. All cases of malignancy will be evaluated and included in Periodic Safety Update Reports (PSUR).

- **Myopathy and Rhabdomyolysis with concomitant use of specific statins (rosuvastatin and simvastatin) (Potential Risk):**

In vitro data indicates that vadadustat is an inhibitor of BCRP and OATP1B1, which are liver uptake transporters. Rosuvastatin is a substrate for BCRP and OATP1B1/1B3. Simvastatin is a substrate for BCRP and OATP1B1. However, vadadustat had no interaction with the OATP1B1/3 substrate pravastatin. Interactions with vadadustat via BRCP may result in increased blood levels of the simvastatin and rosuvastatin (Module 2.7.2 Section 2.2.4.4).[47]

In the global Phase 3 clinical studies for subjects taking vadadustat concomitantly with any statins (1998 subjects; PY=3590.2), there were a total of 14 subjects (IR: 0.7%; 0.4 event per 100 PY**)** who experienced rhabdomyolysis (13 subjects) or myopathy (1 subject) (ISS Table 14.3.1.2.6c). Seven of the subjects received atorvastatin concomitantly, 4 simvastatin, 2 pravastatin and 1 rosuvastatin. However, cases of rhabdomyolysis (as identified with the SMQ rhabdomyolysis/myopathy, narrow) were also observed in patients who did not receive concomitant statins and/or in patients randomized to darbepoetin alfa. An overview of the incidence of rhabdomyolysis/myopathy in Global Phase 3 studies is provided in Table 2.7.1.1-1.

Table 2.7.1.1-1	Incidence of Rhabdomyolysis/ Myopathy in Global Phase 3 Clinical Studies		
	All Subjects	**Subjects With Statins**	**Subjects Without Statins**
Number of patients on vadadustat	n = 3686	n = 1998	n = 1688
Number of patients with rhabdomyolysis (%)	18 (0.49%)	14 (0.7%)	4 (0.24%)

Pooled DD CKD Population for the Phase 3 Studies:

In the pooled DD CKD population for the Phase 3 studies, 943 subjects (PY=1644.8), were exposed to vadadustat concomitantly with any statins. Of these, 850 subjects (90.1%) experienced any TEAE. For darbepoetin alfa 969 subjects (PY=1667.5) were exposed to any statin concomitantly. Of these 894, subjects (92.3%) experienced any TEAE (ISS Table 14.3.1.2.6a). The distribution of these TEAEs were qualitatively similar in both the treatment arms.

In the DD CKD population in the Phase 3 studies of vadadustat cases of rhabdomyolysis (SMQ rhabdomyolysis/myopathy, narrow) were observed in both (darbepoetin and vadadustat) study arms as well as in subjects with and without concomitant statin. An overview of the incidence of rhabdomyolysis/myopathy in the pooled DD-CKD population is outlined in Table 2.7.1.1-2.

Table 2.7.1.1-2	Incidence of Rhabdomyolysis/ Myopathy in the Pooled DD CKD Population		
	All Subjects	**Subjects With Statins**	**Subjects Without Statins**
Number of patients on vadadustat	n = 1947	n = 943	n = 1004
Number of patients with rhabdomyolysis (%)	6 (0.31%)	5 (0.53%)	1 (0.1%)

CKD = Chronic Kidney Disease, DD = Dialysis Dependent

A search for TEAEs belonging to the SMQ rhabdomyolysis/myopathy (narrow) revealed a total of 5 TEAEs of rhabdomyolysis in 5 unique subjects (no case report of myopathy). There was 1 TEAE reported by the investigator as SAE (severe; outcome was recovered). The remaining 4 TEAEs were reported as non-serious adverse events (NSAEs) (3 were moderate and 1 was mild in severity). Action taken with vadadustat was no change in 4 subjects and was not applicable for remaining 1 subject. Causality for the reported events rhabdomyolysis was assessed as not related with vadadustat treatment by the study investigator.

Table 2.7.1.1-3 below shows the rhabdomyolysis/myopathy cases reported in the pooled DD-CKD population

Table 2.7.1.1-3 Rhabdomyolysis/ Myopathy[#] cases reported in Pooled DD CKD Population

No	Serious-ness	Baseline CPK values	Concomitant Statin	CPK values at the time of event	Action taken with Vadadustat	Action taken with Statins	Comments
1	Serious	34 IU/L	Simvastatin	3667 IU/L	Dose not changed	Dose not changed	Investigator attributed reported event to incident of fall.
2*	Non-serious	123 IU/L	Simvastatin	NA	Not applicable	Dose not changed	Investigator attributed to co-existing critical lower limb ischemia.
3	Non-serious	149 IU/L	Simvastatin	NA	Dose not changed	Withdrawn	Patient had medical history of intermittent chronic rhabdomyolysis
4*	Non-serious	201 IU/L	Atorvastatin	NA	Dose not changed	Dose not changed	Confounded by co-existing events like DVT, Septic shock.
5	Non-serious	2311 IU/L	Atorvastatin	NA	Dose not changed	Dose not changed	High CPK at baseline

CKD = Chronic Kidney Disease, NA: Not available, DD = Dialysis Dependent, DVT = Deep Vein Thrombosis

[#] All cases were of rhabdomyolysis (none of myopathy)

Investigator determined causality for all cases was `not-related' to vadadustat

All events were resolved except those marked with * where outcome was not recovered.

Pooled NDD CKD Population for the Phase 3 Studies:

In the pooled NDD CKD population for the Phase 3 studies, 1055 subjects (PY=1945.4) were exposed to vadadustat concomitantly with any statins. Of these 976 subjects (92.5%) experienced any TEAE. For darbepoetin alfa 1042 subjects (PY=1949.4) were exposed to any statin concomitantly. Of these 966 subjects (92.7%) experienced any TEAE (ISS Table 14.3.1.2.6b). The distribution of these TEAE were qualitatively similar in both the treatment arms.

In the NDD CKD population in the phase 3 Studies of vadadustat cases of rhabdomyolysis (SMQ rhabdomyolysis/myopathy, narrow) were observed in both (darbepoetin alfa and vadadustat) study arms as well as in subject with and without concomitant statin. An overview of the incidence of rhabdomyolysis/myopathy in the pooled NDD CKD population is outlined in Table 2.7.1.1-4.

Table 2.7.1.1-4	Incidence of Rhabdomyolysis/ Myopathy in the Pooled NDD CKD Population		
	All Subjects	**Subjects With Statins**	**Subjects Without Statins**
Number of patients on vadadustat	n = 1739	n = 1055	n = 684
Number of patients with rhabdomyolysis/ myopathy (%)	12 (0.69%)	9 (0.85%)	3 (0.43%)

CKD = Chronic Kidney Disease, NDD = Non Dialysis Dependent

Of the 976 TEAEs in the vadadustat treatment arm, a search for TEAEs belonging to SMQ rhabdomyolysis/ myopathy (narrow), revealed a total of 9 TEAEs in 9 unique subjects. There were 8 TEAEs of rhabdomyolysis, out of which 5 were reported as serious adverse events (SAEs) by investigator (2 were severe and 3 were of moderate severity) and 3 were reported as NSAEs(1 was moderate and 2 were mild in severity). One TEAE was non-serious myopathy (moderate in severity). All these 9 events of rhabdomyolysis or myopathy recovered and were assessed as unrelated to vadadustat. Study drug vadadustat was withdrawn in 2 subjects, was interrupted in 1 subject, while in 5 subjects no change was made to vadadustat dosage regimen. In the remaining 1 subject, action taken with study drug was not applicable.

Table 2.7.1.1-5 below shows the rhabdomyolysis/myopathy cases reported in the pooled NDD-CKD population.

Table 2.7.1.1-5	Rhabdomyolysis/ Myopathy cases reported in Pooled NDD CKD Population						
No	**Serious-ness**	**Baseline CPK values**	**Concomitant Statin**	**CPK values at the time of event**	**Action taken with Vadadustat**	**Action taken with Statins**	**Comments**
1	Serious	187 IU/L	Simvastatin (40 mg)	NA	Not applicable	Interrupted	The investigator attributed to statin medication
2	Non-serious	24 IU/L	Rosuvastatin (NA)	NA	Withdrawn	Withdrawn	-
3	Serious	66 IU/L	Atorvastatin (10 mg)	19260 IU/L	Dose not changed	Withdrawn	Both statin and losartan (concomitant medication) were discontinued
4	Serious	73 IU/L	Pravastatin (20 mg)	3243 IU/L	Dose not changed	Withdrawn	Confounded with other events including acute kidney injury, sepsis, and pneumonia.
5*	Non serious	258 IU/L	Atorvastatin (NA)	NA	Dose not changed	Withdrawn	-

Table 2.7.1.1-5 Rhabdomyolysis/ Myopathy cases reported in Pooled NDD CKD Population							
No	**Serious-ness**	**Baseline CPK values**	**Concomitant Statin**	**CPK values at the time of event**	**Action taken with Vadadustat**	**Action taken with Statins**	**Comments**
6	Non-serious	75 IU/L	Atorvastatin (20 mg)	NA	Dose not changed	Dose not changed	-
7	Serious	21 IU/L	Atorvastatin (40 mg)	18934 IU/L	Withdrawn	Withdrawn	Confounded by the concomitant use of azithromycin.
8	Serious	2284 IU/L	Atorvastatin (20 mg)	14247 IU/L	Interrupted	Interrupted	Confounded by co-existing hepatic insufficiency (elevated liver enzymes) and high baseline CPK.
9	Non-serious	160 IU/L	Pravastatin (40 mg)	418 IU/L	Dose not changed	Withdrawn	Confounded by presence of renal insufficiency (AKI and acute renal failure)

AKI = Acute Kidney Injury, CKD = Chronic Kidney Disease, NA: Not available, NDD = Non Dialysis Dependent
* Only case of Myopathy, remaining 8 cases were for rhabdomyolysis
Investigator determined causality for all cases were `not-related' with the use of vadadustat; all events were resolved
Outcome in all the cases of rhabdomyolysis and myopathy was `recovered'

Pooled CKD Population for the Phase 3 Studies:

In the pooled CKD population for the Phase 3 studies, in vadadustat treatment arm, a search for TEAEs belonging to SMQ rhabdomyolysis/myopathy (narrow) revealed a total of 14 TEAEs in 14 unique subjects (IR: 0.7%; 0.4 event per 100 PY). There were 13 TEAEs of rhabdomyolysis and 1 TEAE of myopathy. All these 14 events of rhabdomyolysis or myopathy were assessed by the study investigator as unrelated to vadadustat and had confounding factors such as co-existing illnesses and concomitant medications.

Post-marketing data (Japan only): In the post-marketing setting no case of rhabdomyolysis (SMQ rhabdomyolysis/ myopathy, narrow) in patients with concomitant statin use was reported.

Considering low observed frequency in clinical program and appropriate routine risk minimisation measures and communication, the overall impact on the public health is considered to be low. This safety concern is considered as a potential risk and will be monitored through routine pharmacovigilance. All cases of myopathy and

rhabdomyolysis with concomitant use of specific statins (rosuvastatin and simvastatin) will be evaluated and included in PSUR.

Thromboembolic Events (Including Myocardial Infarction and Stroke) (Identified Risk)

Vascular thrombosis is a theoretical risk from stabilisation of HIF-α and the resulting increase in erythropoiesis. In nonclinical toxicology studies, vascular thrombosis was attributed to the exaggerated pharmacological response resulting in polycythemia, blood hyperviscosity, and the formation of fibrin thrombi in multiple organs. Adverse consequences associated with the exaggerated pharmacology in rodents included increased mortality, accompanied by haemorrhage, thrombosis, and organ infarction due to increased blood viscosity. In mice, associated fibrin thrombosis or necrosis in the kidney and heart were seen.

Pooled DD CKD Population for the Phase 3 Studies:

In the pooled DD CKD population for the Phase 3 studies, 267 thromboembolic events were reported for 1947 subjects (IR: 13.7%; 11.5 events per 100 PY) in vadadustat treatment arm compared to 234 thromboembolic events for 1955 subjects (IR: 12%; 11.3 events per 100 PY) in darbepoetin alfa treatment group. Acute myocardial infarction (4.5%), cerebrovascular accident (0.8%), and transient ischaemic attack (0.8%) were reported in the vadadustat treatment group, along with other thromboembolic events.

(ISS Table 14.3.1.3a).

Pooled NDD CKD Population for the Phase 3 Studies:

In the pooled NDD CKD population for the Phase 3 studies, 120 thromboembolic events were reported for 1739 subjects (IR: 6.9%; 4.5 events per 100 PY) in vadadustat treatment arm compared to 118 thromboembolic events for 1732 subjects (IR: 6.8%; 4.5 events per 100 PY) in darbepoetin alfa. The most frequently reported PTs for vadadustat treatment group were acute myocardial infarction (4%), cerebrovascular accident (0.9%) and transient ischaemic attack (0.8%).
(ISS Table 14.3.1.3.1.2b)

Pooled CKD Population for the Phase 3 Studies:

In the pooled CKD population for the Phase 3 studies, 387 thromboembolic events were reported for 3686 subjects (IR:10.5%; 8.1 events per 100 PY) in vadadustat treatment arm compared to 352 thromboembolic events for 3687 subjects (IR: 9.5%; 7.9 events per 100 PY) in darbepoetin alfa. The most frequently reported PTs for vadadustat treatment

group were acute myocardial infarction (4.2%), cerebrovascular accident (0.9%) and transient ischaemic attack (0.8%). (ISS Table 14.3.1.3.1.2c)

Major Adverse Cardiac Events:

In the global Phase 3 clinical studies, composite MACE including CV and thrombotic events were analysed as a primary safety endpoint. The MACE analysis was conducted in the safety data from the global Phase 3 CKD patient population who received at least 1 dose of study drug.

An independent Endpoint Adjudication Committee (EAC) was implemented to ensure that all potential endpoints were judged on a blinded basis and uniformly using the same criteria. The EAC adjudicated all potential AEs that met the criteria of a MACE (death, stroke, myocardial infarction) or other events requiring adjudication (hospitalisation for heart failure, thromboembolic event), in the adjudication database. A programmatic review of the reported AE terms was utilised to determine whether there were any AEs that may be potential events for adjudication that were not reported.

The MACE analyses focused on statistical evaluation of major cardiac events including death, non-fatal MI, and non-fatal stroke (primary MACE endpoint), as well as other CV related events, and sensitivity analyses were performed using the intent-to-treat population. (Combined MACE report)

The adjudication database differs from the clinical database regarding investigator-reported terms and included potential endpoints that were manually entered as identified by the EAC or SMQ reconciliation process, that may or may not have been acknowledged by the site.

Overall, thromboembolic events were reported at low frequency in the pivotal Phase 3 clinical development programme. The frequency of thromboembolic events was lower in NDD CKD patients (2%) than in DD CKD patients (8.1%) in the respective pooled global Phase 3 trials.

- **MACE Analysis of Pooled NDD CKD Phase 3 Population**

In the NDD CKD population, thromboembolic events [including PTs: vascular access thrombosis, arterial thrombosis, deep vein thrombosis (DVT), pulmonary embolism (PE)] were reported for 1.9% of subjects in the vadadustat treatment group and 2.2% of subjects in the darbepoetin alfa treatment group. In addition, non-fatal MI was reported in 3.9% and nonfatal stroke was reported in 2% subjects in vadadustat treatment arm compared with 2.8% non-fatal MI and 1.6% non-fatal stroke in darbepoetin alfa treatment arm.

The number of subjects with any MACE, and MACE per 100 PY for the individual components of MACE (death, non-fatal MI, and non-fatal stroke) were higher in the vadadustat treatment group (382 subjects out of 1739 subjects, IR 22%; 13.9 events per 100 PY) than the darbepoetin alfa treatment group (344 subjects out of 1732 subjects, IR 19.9%; 12.4 events per 100 PY).

In the NDD CKD studies, non-inferiority was not met for the primary safety outcome of time to first MACE, as the upper limit of the 95% CI was 1.355. For all key secondary MACE end points the upper bound of the 95% CI was below the non-inferiority limit of <1.30 except for the composite endpoint of time to CV MACE, i.e., CV death, non-fatal MI, and non-fatal stroke (HR 1.16; 95% CI: 0.947, 1.420). (Module 2.5 Table 16)

For composite CV MACE, the incidence of 'CV death' was lower in vadadustat treatment arm (7.3%) compared with the darbepoetin alfa treatment group (7.6%). However, subjects with non-fatal MI (3.9% vs 2.8%) and non-fatal stroke (2%vs 1.6%) were higher for the vadadustat treatment group compared with the darbepoetin alfa treatment group.[57]

Regional differences in treatment care were observed between the US and ex-US populations impacting the overall HR. The NDD CKD population in the US region is more homogenous, with a consistent standard of care, and had consistent MACE results between studies CI-0014 (correction) and CI-0015 (conversion). Marked inconsistencies were observed in the regions of Europe and ROW between studies CI-0014 and CI-0015. These data are confounded by a heterogeneous population at baseline, differences in regional treatment care, and a pre-selection of subjects stable on darbepoetin alfa at baseline in Europe.

The observed MACE rate with darbepoetin alfa showed wide variability, MACE rate in darbepoetin alfa treated patients was 22.7% in the US and 18.4% in ROW. However, in Europe, the most notable observation was that MACE rate for darbepoetin alfa treated subjects was lower (14.2%) which impacted the overall HR for vadadustat compared to darbepoetin alfa. This lower rate increased the overall HR for the NDD CKD population and was influenced by the fact that 61% of subjects in Europe had previously received darbepoetin alfa prior to being enrolled into the conversion trial under the NDD CKD program. Subjects that converted from a low dose of ESA to a same or equivalent dose of darbepoetin alfa may have been more clinically stable. These differences may have contributed to the unexpectedly low rate of MACE (11.4%) in the darbepoetin alfa group, given that ESAs are standard of care for patients with anaemia of CKD, physicians are familiar with managing ESA changes and there are well-established conversion algorithms.

Table 2.7.1.1-6 MACE incidence in NDD CKD patient population by region								
Study Primary Mace	**Overall (N = 3471)**		**US (N = 1723)**		**EU (N = 583)**		**ROW (N = 1165)**	
	Vadadustat	**Darbepoetin**	**Vadadustat**	**Darbepoetin**	**Vadadustat**	**Darbepoetin**	**Vadadustat**	**Darbepoetin**
CI-0014 + CI-0015 #events/N (%)	382/1739 (22.0%)	344/1732 (19.9%)	204/861 (23.7%)	196/862 (22.7%)	56/295 (19.0%)	41/288 (14.2%)	122/583 (20.9%)	107/582 (18.4%)
HR 95% CI	1.17 (1.012, 1.355)		1.06 (0.872, 1.292)		1.56 (1.039, 2.350)		1.25 (0.960, 1.618)	
CI-0014 #events/N (%)	214/878 (24.4%)	192/870 (22.1%)	121/531 (22.8%)	119/527 (22.6%)	15/71 (21.1%)	16/68 (23.5%)	78/276 (28.3%)	57/275 (20.7%)
HR 95% CI	1.16 (0.955, 1.412)		1.05 (0.812, 1.348)		0.84 (0.406, 1.746)		1.57 (1.112, 2.210)	
CI-0015 #events/N (%)	168/861 (19.5%)	152/862 (17.6%)	83/330 (25.2%)	77/335 (23.0%)	41/224 (18.3%)	25/220 (11.4%)	44/307 (14.3%)	50/307 (16.3%)
HR 95% CI	1.16 (0.930, 1.446)		1.07 (0.782, 1.461)		2.05 (1.237, 3.392)		0.91 (0.607, 1.374)	

CI = Confidence Interval, CKD = Chronic Kidney Disease, EU = European Union, HR = Hazard Ratio, MACE = Major Adverse Cardiac Event, NDD = Non-Dialysis Dependent, ROW = Rest of World, US = United States

Source: PRO_2TECT MACE In-text Table 11 and Table 12, Post-text Tables 12.2.1 and 12.3

- **MACE analysis of Pooled DD CKD Phase 3 Population**

In DD CKD patient population, thromboembolic events were reported for 8.7% of subjects in the vadadustat treatment group and 7.6% of subjects in the darbepoetin alfa treatment group. In addition, non-fatal MI was reported in 4.2% and non-fatal stroke was reported in 1.6% subjects in vadadustat treatment arm compared with 4.5% non-fatal MI and 2.2% non-fatal stroke in darbepoetin alfa treatment arm.

The number of subjects with any MACE, and MACE per 100 PY for the individual components of MACE (death, non-fatal MI, and non-fatal stroke) were similar in the vadadustat (355 subjects out of 1947 subjects, IR 18.2%; 13.2 events per 100 PY) and darbepoetin alfa (377 subjects out of 1955 subjects, IR 19.3%; 14.2 events per 100 PY) treatment groups.

The HR 95% [CI]) for the time to first MACE for vadadustat compared to darbepoetin alfa was 0.96 (0.833, 1.113). The upper bound of the 95% CI of the HR was below the prespecified noninferiority margin of 1.30 for the EMA, thereby establishing non-inferiority of vadadustat to darbepoetin alfa. The analyses of key secondary endpoints using expanded MACE (MACE plus hospitalisation for heart failure or thromboembolic events excluding vascular access thrombosis), CV MACE, CV deaths, and all-cause mortality also demonstrated non-inferiority of vadadustat to darbepoetin alfa (HR [95% CI]: 0.96 [0.840, 1.096], 0.95 [0.795, 1.144], 0.96 [0.766, 1.195], and 0.95 [0.812, 1.118], respectively.[58]

The safety profile of vadadustat was comparable to that of darbepoetin alfa in the DD CKD population and demonstrated non-inferiority to darbepoetin alfa in time to first MACE, regardless of geographic region.

Post-marketing data (Japan only): As of 18 Aug 2021, thirteen post-marketing cases were reported with 13 thromboembolic adverse events (SMQ Embolic and Thrombotic Events). Twelve of these cases reported serious adverse events, and 2 had a fatal outcome (2 myocardial infarctions; see Table 2.7.1.1-78). With an estimate of 4779 PYT this calculates to an estimate of 0.272 adverse events / 100 PYT.

The reported serious events were myocardial infarction/acute myocardial infarction (4), cerebral infarction (6), pulmonary embolism (1), pulmonary infarction (1) Two cases with serious and fatal thromboembolic events are discussed below.

Table 2.7.1.1-78	Serious and Fatal Thromboembolic Events reported in the Post-marketing setting; Japan Only (SMQ Embolic and Thrombotic Events)
Adverse event	**Comment**
Myocardial infarction	An [redacted] patient experienced [redacted], 51 days after starting of vadadustat therapy with a fatal outcome. No additional clinically relevant details are available for assessment.
Acute myocardial infarction	A [redacted] patient experienced [redacted] 7 days after start of vadadustat. Patient had comorbidities of [redacted] No additional clinically relevant details are available for assessment.

Thromboembolic events including MI and stroke are common in the targeted CKD population and the presence of renal anaemia has been linked to adverse CV outcomes. With routine risk minimisation measures and appropriate communication, the overall impact on the public health is considered to be low.

(b) Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

- **Hypersensitivity (Identified Risk)**

In the pooled DD-CKD Population, a total 8.0% of subjects in the vadadustat treatment group and 8.7% of subjects in the darbepoetin alfa treatment group experienced an event of hypersensitivity (SMQ Hypersensitivity, broad) (ISS Table 14.3.1.12a).

In the pooled CKD Population for Global Phase 3 Studies a total 7.7% of subjects in the vadadustat treatment group and 7.9% of subjects in the darbepoetin alfa treatment group experienced an event of hypersensitivity (SMQ Hypersensitivity, broad). The RR (95% CI) of vadadustat/darbepoetin alfa was 0.97 (0.83, 1.13) (ISS Table 14.3.1.13c). Most of these events (93%) were NSAEs and were assessed as unrelated (94.6%) to study drug. Reports of anaphylactic reaction were rare in both the vadadustat treatment group (3 subjects) and darbepoetin alfa treatment group (2 subjects). All reported anaphylactic reactions were assessed as unrelated, except one case with vadadustat where possibility of reasonable causal relationship could not be ruled out. However, in this case there were possible confounders including the subject's medical history of allergy and underlying systemic lupus erythematosus, which predisposes patients to higher level of hypersensitivity to exogenous antigens.

Post-marketing data (Japan only): As of 18 Aug 2021, 39 spontaneous case reports with 42 adverse events (MedDRA PTs) under the SMQ Hypersensitivity (broad) were

reported. With an estimate of 4779 PYT of exposure this calculates to a reporting rate of 0.879 adverse events / 100 PYT.

Two cases reported 3 serious adverse events (MedDRA PTs of shock, drug reaction with eosinophilia and systemic symptoms (DRESS) and drug eruption); one of these cases had a fatal outcome:

- A [redacted] patient was reported with [redacted]) and approximately 3 months after start of treatment with vadadustat; the reporting physician considered the AE not related to vadadustat and the event is suggestive of an accident.
- A patient with a medical history of [redacted] was reported with a serious adverse events of [redacted] and [redacted] approximately 2 months after start of treatment with vadadustat. The events were considered causally related to vadadustat by the reporter as well by the Marketing Authorisation Holder.

Based on above data from clinical development and post-marketing setting, hypersensitivity will continue to be monitored as an identified risk of vadadustat. Vadadustat is contraindicated in patients with hypersensitivity to the active substance or any of the excipients of the product (SmPC Section 4.3). Routine risk communication and minimisation measures will ensure the overall public health impact of this risk is low.

(c) Other reasons for considering the risks not important

- **Adrenal disorders**

In the pooled DD-CKD Population, adrenal disorders, including events of adrenal insufficiency, were rare (0.1%) and occurred in the same proportion of subjects in both vadadustat and darbepoetin alfa treatment groups (ISS Table 14.3.1.12a).

Adrenal gland histologic findings (non-proliferative mononuclear infiltrates, hypertrophied multinucleated cells, and single cell necrosis) have been noted in vadadustat dog toxicology studies of ≥14 days duration, which were considered subclinical, reversible, non-adverse and unique to dog adrenal glands.

In the pooled CKD Population for Global Phase 3 Studies, adrenal disorders, including events of adrenal insufficiency, were rare (<0.1%) and occurred in the same proportion of subjects in both vadadustat and darbepoetin alfa treatment groups (ISS Table 14.3.1.13c). Within adrenal disorder medical topic [High Level Term (HLT)- Adrenal Gland Disorders] a total of 4 cases of adrenal mass were seen in the vadadustat treatment group, all were assessed as non-serious and mild. Events were assessed as not related and attributed to incidental findings or ESRD. In addition, a total of 2 serious events of

adrenal insufficiency (out of 5) were seen in the vadadustat treatment group. Both events were assessed as unrelated as they were attributed to either low cortisol at baseline or weaning of ongoing cortisol treatment. There were no reports of decreased sodium or chloride, or increased potassium.

Post-marketing data (Japan only): As of 18 Aug 2021, no case with events from the MedDRA HLT adrenal gland disorders has been reported.

In view of the above findings adrenal disorders do not impact the overall risk benefit profile of vadadustat.

- **Retinopathy**

In in vitro and animal studies, HIF stabilisation has been demonstrated to increase the serum levels of the pro-angiogenic protein vascular endothelial growth factor (VEGF).[52,53] Retinal-related TEAEs including deterioration of the pre-existing retinal disorders, may theoretically be associated with HIF stabilisation. In humans, higher intraocular levels of HIF and VEGF have been associated with retinopathy. However, minimal evidence is available, from clinical studies, to support the theory of retinal effects due to HIF stabilisation and subsequent increase in VEGF.

Fundoscopic examinations performed in the regional Phase 3 Japanese studies revealed retinal haemorrhage reported for 2 (4.8%) vadadustat-treated subjects, and macular degeneration, retinal vein occlusion, and macular fibrosis reported for 1 (2.4%) subject each in Study MT-6548-J02 (single-arm study of vadadustat) (MT-6548-J02 Appendix 16.2.7).

In the pooled DD-CKD Population, adverse events under the SMQ Retinal Disorders (narrow) were reported for 2.6 % of subjects in the vadadustat treatment group and 2.4% of subjects in the darbepoetin alfa treatment group (RR 1.107, CI 0.7652, 1.6014). A total of 77 events were reported for vadadustat under medical topic retinal effects due to VEGF expression from 61 unique subjects (ISS Table 14.3.1.12a).

In the pooled CKD Population for Global Phase 3 Studies, adverse events under the SMQ Retinal Disorders (narrow) were reported for 2.0% of subjects in the vadadustat treatment group and 2.1% of subjects in the darbepoetin alfa treatment group (RR 0.937, CI 0.6846, 1.2823; ISS Table 14.3.1.13c). A total of 91 events were reported for vadadustat under medical topic retinal effects due to VEGF expression from 74 unique subjects. Of these majority (~95%) of events were non-serious. No evidence was found to support an association between vadadustat and retinal-related TEAEs.

Post-marketing data (Japan only): As of 18 Aug 2021, four spontaneous case reports with 4 events under the SMQ Retinal Disorders (broad) were reported. With an estimate of 4779 PYT of exposure this calculates to a reporting rate of 0.084 adverse events reports / 100 PYT. Of the 4 case reports, there was 1 serious case, and no case had a fatal outcome.

The reported PTs were retinal vascular occlusion, retinal haemorrhage, visual acuity reduced and diabetic retinal oedema.

One case reported 1 serious adverse event of [redacted]) in a [redacted] patient, approximately two months after start of vadadustat therapy. No additional information was available for this case.

Overall, the frequency of the adverse event retinopathy reported in patients using vadadustat both in clinical trials and in post-marketing setting is low. Patients with CKD have a high risk of retinopathy due to a high incidence of concomitant diabetes mellitus and hypertension. Therefore, the risk of retinopathy is not considered to alter the overall benefit-risk profile of vadadustat.

- **Hyperkalemia**

In the nonclinical development of vadadustat, hyperkalemia was noted in the 14-, 28-, and 91-day dog toxicology studies. Hyperkalemia resolved following the non-dosing period in each study (Module 2.6).

In the pooled DD-CKD Population, hyperkalemia (MedDRA PTs: hyperkalemia, blood potassium abnormal, and blood potassium increased) was reported for 7.4% of subjects in the vadadustat treatment group and 9.9% of subjects in the darbepoetin alfa treatment group (ISS Table 14.3.1.12a).

In the pooled CKD Population for Global Phase 3 Studies, hyperkalemia (MedDRA PTs: hyperkalemia, blood potassium abnormal, and blood potassium increased) was reported for 9.9% of subjects in the vadadustat treatment group and 11.9% of subjects in the darbepoetin alfa treatment group. The relative risk (95% CI), vadadustat/darbepoetin alfa was 0.829 (0.7274, 0.9457) (ISS Table 14.3.1.13c). There were no clinically meaningful increases in potassium levels from baseline observed in vadadustat compared to darbepoetin alfa-treated subjects. The majority of hyperkalemia events in the vadadustat treatment arm (76%) were NSAEs.

Post-marketing data (Japan only):

As of 18 Aug 2021, two spontaneous case reports with 2 adverse events (one each with hyperkalaemia and blood potassium increased) were reported. With an estimate of 4779

PYT of exposure this calculates to a reporting rate of 0.042 adverse events / 100 PYT. There was one serious case report (hyperkalaemia), and no case had a fatal outcome.

The serious adverse event of hyperkalaemia started approximately 4 months after start of vadadustat therapy and resolved after 11 days with vadadustat ongoing. The underlying chronic kidney disease is a plausible alternative explanation of the adverse event.

Hyperkalemia is an electrolyte imbalance associated with the underlying medical condition of CKD, especially in the dialysis population. Therefore, hyperkalaemia as a safety concern does not impact the benefit-risk profile of vadadustat.

- **Cardiac valve disorders**

Heart valvular histopathology findings were noted in the 28- and 90-day rat studies only at doses/exposures which caused polycythemia. The valvular lesions were not considered clinically relevant because: 1) observations were rat-specific (no corollary in mouse or dog studies); 2) findings were identified only in the presence of polycythemia; 3) polycythemia, even if it develops, is reversible in patients treated with vadadustat; 4) heart valve lesions were also noted with EPO in nonclinical studies but has not been seen in patients despite being marketed globally for more than 30 years.

In the pooled DD-CKD Population, cardiac valve disorders [MedDRA High Level Group Term (HLGT) cardiac valve disorders] were reported in 2.1% of vadadustat and 2.8% of the darbepoetin alfa treatment groups (ISS Table 14.3.1.12a).

In the pooled CKD Population for Global Phase 3 Studies, cardiac valve disorders [MedDRA HLGT cardiac valve disorders] were reported in 2.3% of both vadadustat and darbepoetin alfa treatment groups (ISS Table 14.3.1.13c). Most events were NSAEs (87%); and mild to moderate in severity (82%). All the cardiac valve disorders events (NSAEs and SAEs) were assessed as not related to either drug (vadadustat and darbepoetin alfa) as most patients had a history of hypertension, advanced age, worsening of CKD, previous history of cardiac related issues-cardiomyopathy and pre-existing valvular disorders.

Post-marketing data (Japan only):

As of 18 Aug 2021, no case report with a PT from the MedDRA HLGT cardiac valve disorders has been reported.

Cardiac valve disorders are therefore not considered to alter the overall benefit-risk profile of vadadustat.

- **Congestive heart failure (CHF)**

In the pooled DD-CKD Population, CHF (SMQ Cardiac failure, narrow) was reported for 8.3% subjects in the vadadustat treatment group and 10.1% of in the darbepoetin alfa treatment group (ISS Table 14.3.1.12a).

In the pooled CKD Population for Global Phase 3 Studies, CHF (SMQ Cardiac failure, narrow) was reported for 10.3% subjects in the vadadustat treatment group and 11.5% of in the darbepoetin alfa treatment group. The relative risk (95% CI), vadadustat/darbepoetin alfa: 0.897 (0.7870, 1.0217) (ISS Table 14.3.1.13c). The most frequent PTs were cardiac failure congestive (3.9%), pulmonary oedema (2.4%), cardiac failure acute (1.6%), cardiac failure (1.4%), and acute pulmonary oedema (1.0%). Most of the cases reported underlying CKD as etiology. There was no case with investigator determined causality as related to the study drug. No evidence was found to support an association between vadadustat and CHF.

Post-marketing data (Japan only):

As of 18 Aug 2021, 20 spontaneous case reports with 21 adverse events under the SMQ Cardiac Failure (narrow) were reported. With an estimate of 4779 PYT of exposure this calculates to a reporting rate of 0.439 adverse events / 100 PYT. All 21 adverse events were serious and 12 had fatal outcome. The reported terms were:

- Cardiac failure 18 AEs
- Cardiac failure congestive 2 AEs
- Cardiac failure acute 1 AE

The 12 fatal cases of cardiac failure occurred mostly in old patients (all were 80 years or older, and 7 were above 90 years of age). In 50% of the patients a cardiac or vascular disease was reported as concomitant condition. Patients with CKD are more likely to experience a cardiovascular event and have a higher risk of heart failure and sudden cardiac death. As such underlying CKD especially in old patient provides for an alternative explanation for the above observations.

Overall, the case reports of cardiac failure during clinical development and in the post-marketing setting do not change the benefit-risk profile of vadadustat.

- **Pulmonary hypertension**

In the pooled DD-CKD Population, pulmonary hypertension (MedDRA SMQ Pulmonary hypertension, narrow) was reported for 2.1% of subjects in the vadadustat treatment group and 2.6% of subjects in the darbepoetin alfa treatment group. The relative risk (95% CI), vadadustat/darbepoetin alfa: 0.810 (0.5558, 1.1809) (ISS Table 14.3.1.12a).

In the pooled CKD Population for Global Phase 3 Studies, pulmonary hypertension (MedDRA SMQ Pulmonary hypertension, narrow) was reported for 2.4% of subjects in the vadadustat treatment group and 2.6% of subjects in the darbepoetin alfa treatment group. The relative risk (95% CI), vadadustat/darbepoetin alfa: 0.916 (0.6873, 1.2208) (ISS Table 14.3.1.13c).

Equal distribution of the events among the vadadustat and darbepoetin alfa treatment groups were suggestive of no association between vadadustat with pulmonary hypertension, but rather supported the association of the pulmonary hypertension with the underlying CKD and comorbidities that are common characteristics of the CKD population.

Post-marketing data (Japan only): As of 18 Aug 2021 one spontaneous case report with an adverse event under the SMQ Pulmonary hypertension (narrow) was reported. This was a case report of an [redacted] patient who experienced [redacted]. The patient had medical history [redacted] and received carvedilol `for heart protection. The event started approximately 4 months after start of vadadustat. Concomitant conditions of this patient provide for an alternative explanation for the reported adverse event.

Overall, the case reports of pulmonary hypertension during clinical development and in the post-marketing setting do not change the benefit-risk profile of vadadustat.

2.7.1.2 SVII.1.2: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified risk:

There are no important identified risks for Vadadustat.

Important Potential Risk: Hepatotoxicity

Risk-benefit impact:

In pooled DD-CKD population, hepatotoxicity was reported for 6.0% of subjects in the vadadustat treatment group and 6.9% of subjects in the darbepoetin alfa treatment group. Overall, 288 subjects (141 vadadustat, and 147 darbepoetin alfa) were identified having TEAEs (serious and non-serious), that were suggestive of hepatic dysfunction identified by Drug related hepatic disorders comprehensive search, broad SMQ and lab related findings (ISS Table 14.3.1.12a).

In pooled CKD population, hepatotoxicity was reported for 6.8% of subjects in the vadadustat treatment group and 6.5% of subjects in the darbepoetin alfa treatment group.

Overall, 338 subjects (164 vadadustat, 173 darbepoetin alfa, and 1 epoetin alfa-treated subjects) were identified having TEAEs (serious and non-serious), that were suggestive of hepatic dysfunction identified by Drug related hepatic disorders comprehensive search, broad SMQ and lab related findings (ISS Table 14.3.1.13c).

Taking into consideration the totality of data from the clinical program, the overall hepatic profiles of vadadustat and darbepoetin alfa appear to be similar.

No cases met the biochemical criteria for Hy's Law (Hepatic Expert Report).

Hepatotoxicity is considered as important potential risk. With routine risk minimisation measures and appropriate communication, the overall impact on the public health is considered to be low.

(Detailed discussion is provided in Module SVII.3)

2.7.2 SVII.2: New Safety Concerns and Reclassification with a Submission of an Updated RMP

This section is not applicable as this is the initial RMP.

2.7.3 SVII.3: Details of Important Identified Risks, Important Potential Risks, and Missing Information

2.7.3.1 SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks

Important Identified risk:

There are no important identified risks for Vadadustat.

Important Potential Risk: Hepatotoxicity

MedDRA terms: SMQ Drug related hepatic disorders comprehensive search (narrow)

Potential mechanisms:

No potential mechanism has been identified from the nonclinical studies regarding the risk of hepatotoxicity. Moreover, vadadustat is a hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) which leads to increased cellular levels of HIF. Most evidence points towards a tissue protective role of HIFs during acute liver injury, while in conditions of chronic liver disease, inhibition of HIFs may be desirable. Pharmacologic approaches to enhance hepatic stabilization of HIFs during liver disease can be achieved by pharmacologic inhibitors of PHDs.[59]

Evidence sources and strength of evidence:

The sources of evidence were from hepatic events data from clinical studies.

Hepatotoxicity was reported for 6.0% of subjects in the vadadustat treatment group and 6.9% of subjects in the darbepoetin alfa treatment group, in pooled DD-CKD population (ISS Table 14.3.1.12a).

Hepatotoxicity was reported for 6.8% of subjects in the vadadustat treatment group and 6.5% of subjects in the darbepoetin alfa treatment group, in pooled CKD population. (ISS Table 14.3.1.13c).

Characterization of the risk:

Frequency

AESI of hepatotoxicity (SMQ Drug related hepatic disorders comprehensive search, broad) was reported for 6.0% of subjects in the vadadustat treatment group and 6.9% of subjects in the darbepoetin alfa treatment group, in the pooled DD-CKD population. Overall, 288 subjects (141 vadadustat, and 147 darbepoetin alfa) were identified having TEAEs (serious and non-serious), that were suggestive of hepatic dysfunction identified by Drug related hepatic disorders comprehensive search, broad SMQ and lab related findings (ISS Table 14.3.1.12a).

AESI of hepatotoxicity (SMQ Drug related hepatic disorders comprehensive search, broad) was reported in 6.8% of subjects in the vadadustat treatment group and in 6.5% of subjects in the darbepoetin alfa treatment group, in the pooled CKD population. (ISS Table 14.3.1.13c). Overall, in the clinical development programme 338 subjects (164 vadadustat, 173 darbepoetin alfa, and 1 epoetin alfa-treated subjects) were identified to have TEAEs (serious and non-serious), that were suggestive of hepatic dysfunction identified by SMQ Drug related hepatic disorder comprehensive search (broad) and/or lab related findings.

These hepatic events were adjudicated in an unblinded manner while the clinical development progressed and then subsequently underwent blinded hepatic expert assessment after the clinical development was completed, to minimize bias.

During a Phase 2 development, one vadadustat-treated subject experienced a drug-related treatment-emergent SAE of abnormal hepatic parameters. Initially an external hepatic expert assessed this case to have met the biochemical criteria for Hy's law based on ALT >3 × ULN and total bilirubin >2 × ULN, *although the alkaline phosphatase (ALP) was also elevated >5 × ULN*. Later upon re-assessment by Hepatic Expert Committee (Unblinded), it was determined that this case was suggestive of mixed-type hepatobiliary injury with a cholestatic component and was assessed as non-classic case of Hy's Law. After the Global Phase 3 clinical development for vadadustat completed, Blinded Expert Committee (BEC) re-adjudicated this case (Sep 2020) and did not report this as a Hy's

Law case but rather determined it as a `severe hepatic injury event' probably related to vadadustat. No other cases met biochemical criteria for Hy's Law. (Hepatic Expert Report)[51]

All the liver enzyme abnormalities resolved or were resolving at the time of last follow-up, and no instances of acute liver failure, death attributed to vadadustat or the development of chronic liver disease were observed. Overall, the risk of serious hepatotoxicity from vadadustat is considered low and not different from that seen with darbepoetin alfa which is not known to cause hepatotoxicity.

Post-marketing data (Japan only): A search by use of the SMQ Drug related hepatic disorders comprehensive search (narrow) with a cut-off date of 18 Aug 2021 identified 10 spontaneous reports with potential liver injury (MedDRA PTs: hepatic function abnormal (6 reports), liver disorder, hepatitis, hepatic cancer recurrent, hepatic neoplasm (1 report each). Three reports were assessed as serious (1 report each of hepatitis, hepatic cancer recurrent and hepatic neoplasm.) and no case had a fatal outcome. Hepatic neoplasm and hepatic cancer recurrent were diagnosed approximately 1 month after start of vadadustat therapy, and were considered unrelated by the reporter. The 10 reports calculate to a reporting rate of 0.209 adverse events / 100 PYT.

Seriousness and Reversibility:

Hepatic parameter changes (includes transaminases increased, ALT increased, AST increased, hepatic enzyme increased, and liver function test abnormal) have been observed in global Phase 3 studies. The majority of the events were non serious, and all resolved or were resolving after drug discontinuation.

Post marketing Data (Japan only): As of 18 August 2021, there has been 10 case reports of potential liver injury, 3 were serious. No case had a fatal outcome.

Risk factors and risk groups:

In general, known risk factors for hepatotoxicity include age, gender, drug interactions, high alcohol intake, malnutrition, HCV, HBV, HIV infections, and genetic predisposition. Patients with hepatic steatosis, alcohol liver disease, and other acquired or inherited liver diseases may be at a higher risk for developing hepatotoxicity. Patients

pre- or concomitantly treated with other medications associated with hepatotoxicity may be at higher risk for hepatotoxicity.

Preventability:

As a cautionary measure, ALT, AST, and bilirubin must be evaluated prior to the initiation of vadadustat, monthly for 3 months after initiation and as clinically indicated thereafter.

Instructions for discontinuation: Vadadustat must be discontinued if ALT or AST elevations > 3x ULN are accompanied by a bilirubin increase > 2x ULN, or if there is persistent ALT or AST > 3x ULN.

The Section 4.2 and Section 4.4 of the SmPC states that *Vafseo is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C) as the safety and efficacy has not been evaluated in this population.*

Impact on the risk-benefit balance of the product:

Taking into consideration the totality of data from the clinical programme, the overall hepatic profiles of vadadustat and darbepoetin alfa appear to be similar. Darbepoetin alfa does not have a known hepatotoxicity profile or warning provided in the label.

Vadadustat doses are titrated from 300 mg according to the Hb response to be within the Hb target range. Therefore, no dose adjustment is recommended based on age, sex or race, renal impairment or mild or moderate hepatic impairment.

Hepatotoxicity may have a significant impact on the patient requiring hospitalization or be life-threatening in serious cases. However, as hepatotoxicity can be minimized in clinical practice through monitoring of liver enzymes, it is not expected to change the favourable benefit-risk of vadadustat that is used to treat a for the treatment of symptomatic anaemia associated with CKD in adults on chronic maintenance dialysis.

Available information regarding the risk of hepatotoxicity does not impact the overall positive benefit-risk ratio of vadadustat. More data will be collected regarding this risk through proposed routine PV activities (special clinical measures for hepatotoxicity, targeted follow up questionnaire for hepatotoxicity, hepatotoxicity specific Summary Safety Reports) beyond adverse reactions reporting and signal detection and any potential impact to the benefit-risk ratio will continue to be evaluated.

Public health impact:

No clear pattern of liver test abnormalities, nor time to onset of these biochemical events was apparent based on the entire hepatic AE and SAE dataset. All the liver enzyme

abnormalities resolved or were resolving where data were available, and no instances of acute liver failure, death attributed to vadadustat, or the development of chronic liver disease were observed. The overall clinical impression, based on the totality of the available data, that the risk of serious hepatic injury, appears to be very low and not different from darbepoetin alfa. With routine risk minimisation measures and appropriate communication, the overall impact on the public health is considered to be low.

2.7.3.2 SVII.3.2: Presentation of Missing Information

There is no missing information with vadadustat.

2.8 Module SVIII: Summary of the Safety Concerns

Table 2.8-1 SVIII-1: Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	• Hepatotoxicity
Missing Information	None

3 PART III: PHARMACOVIGILANCE PLAN (Including Post-Authorisation Safety Studies)

3.1 III.1: Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include:

3.1.1 Specific Clinical Measures for Hepatotoxicity:

Section 4.2 and Section 4.4 of the SmPC includes specific clinical measures for healthcare professionals.

Monitoring

An increase in ALT, AST (frequency common) and/or bilirubin (frequency uncommon) attributed to Vafseo was reported. ALT, AST, and bilirubin must be evaluated prior to the initiation of Vafseo, monthly for 3 months after initiation and as clinically indicated thereafter.

3.1.2 Specific Adverse Reaction Follow-up Questionnaire for Hepatotoxicity:

Targeted follow-up questionnaire will be implemented to obtain structured information on hepatotoxicity from the healthcare professionals.

Please see Annex 4 of the RMP for details.

3.2 III.2: Additional Pharmacovigilance Activities

No additional pharmacovigilance activities are planned for vadadustat.

3.3 III.3: Summary Table of Additional Pharmacovigilance Activities\

No planned additional pharmacovigilance activities to date.

4 PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

This section is not applicable for the current version of the RMP.

5 PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

5.1 V.1: Routine Risk Minimisation Measures

Table 5.1-1	**V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern**
Safety Concern	**Routine Risk Minimisation Activities**
Important Identified Risks	
None	
Important Potential Risks	
Hepatotoxicity	Routine risk communication: Inclusion in the Summary of Product Characteristics (SmPC): - Section 4.2: Posology and method of administration - Section 4.4: Special warnings and precautions for use. - Section 4.8: Undesirable effects. PL section: - Section 2: What you need to know before you take VAFSEO (subsection: Warnings and precautions) - Section 4: Possible side effects Other routine risk minimisation measures beyond the Product Information: Legal status: Product is subject to medical prescription
Important Missing Information	
None	

5.2 V.2: Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. Therefore, there is no need for additional risk minimisation activities.

5.3 V.3: Summary of Risk Minimisation Measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concerns are presented in Table 5.3-1.

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Important Identified Risks		
None		
Important Potential Risks		
Hepatotoxicity	**<u>Routine risk minimisation measures:</u>** Inclusion in SmPC: - Section 4.2: Posology and method of administration - Section 4.4: Special warnings and precautions for use. - Section 4.8: Undesirable effects. PL section: - Section 2: What you need to know before you take VAFSEO (subsection: Warnings and precautions) - Section 4: Possible side effects **<u>Additional risk minimisation measures:</u>** None	**Routine pharmacovigilance activities: beyond adverse reactions reporting and signal detection:** • Specific clinical measures for hepatotoxicity • Targeted follow-up questionnaire for hepatotoxicity
Important Missing Information		
None		

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 VI.1: Summary of the Risk Management Plan for VAFSEO (vadadustat).

This is a summary of the risk management plan (RMP) for VAFSEO. The RMP details important risks of VAFSEO, how these risks can be minimised, and how more information will be obtained about VAFSEO's risks and uncertainties (missing information).

VAFSEO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how vadadustat should be used.

This summary of the RMP for VAFSEO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of VAFSEO’s RMP.

6.1.1 I. The Medicine and What it is Used for

VAFSEO is authorised for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis (see SmPC for the full indication). It contains vadadustat as the active substance and it is given by oral route. Pharmaceutical forms and strengths are as follows.

VAFSEO (vadadustat) is approved as a film-coated, immediate-release tablet in 150 mg, 300 mg, and 450 mg dosage strengths.

Further information about the evaluation of VAFSEO’s benefits can be found in VAFSEO’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage. <link to the EPAR summary landing page>.

6.1.2 II. Risks Associated With the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of VAFSEO, together with measures to minimise such risks and the proposed studies for learning more about VAFSEO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals

- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of VAFSEO is not yet available, it is listed under `missing information' below.

6.1.2.1 II.A: List of Important Risks and Missing Information

Important risks of VAFSEO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VAFSEO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6.1.2.1-1 II.A-1: List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	• Hepatotoxicity
Missing Information	None

6.1.2.2 II.B: Summary of Important Risks

Table 6.1.2.2-12 II.B-1: Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	The sources of evidence were from non-clinical studies, and hepatic events data from clinical studies.
Risk factors and risk groups	In general, known risk factors for hepatotoxicity include age, gender, drug interactions, high alcohol intake, malnutrition, HCV, HBV, HIV infections, and genetic predisposition. Patients with hepatic steatosis, alcohol liver disease, and other acquired or inherited liver diseases may be at a higher risk for developing hepatotoxicity. Patients pre- or concomitantly treated with other medications associated with hepatotoxicity may be at higher risk for hepatotoxicity.
Risk minimisation measures	**Routine risk minimisation measures:** Inclusion in SmPC: - Section 4.2: Posology and method of administration - Section 4.4: Special warnings and precautions for use. - Section 4.8: Undesirable effects. PL section: - Section 2: What you need to know before you take VAFSEO (subsection: Warnings and precautions) - Section 4: Possible side effects **Additional risk minimisation measures:** None

6.1.2.3 II.C: Post-authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of vadadustat.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no studies required for vadadustat.

7 PART VII: ANNEXES TO THE RISK MANAGEMENT PLAN

7.4 Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Table of contents:

Follow-up Form

Specific Adverse Reaction Follow-up Form	Akebia THERAPEUTICS

Hepatotoxicity Events Questionnaire

Case Report Details

Patient Initials: _____	Age: _____
Sex: ☐ Male ☐ Female ☐ Not stated	Manufacturer's Control Number: _____
Vadadustat start date: ____ DD-Mmm-YYYY_____	AE onset date: __DD-Mmm-YYYY__

Specify the type healthcare professional

☐ Physician,

☐ Pharmacist

☐ Nurse

☐ Other (Specify)_____

Follow-up Questions

1. Please provide a summary of patient's medical history and laboratory investigations if any.

☐ Gallstones	☐ History of viral hepatitis
☐ Pre-existing liver disease	☐ Right heart failure
☐ Left heart failure	☐ Hepatic enzyme abnormal
☐ Spider angiomas	☐ Easily bruised skin
☐ Yellowing of the skin and eyes (jaundice)	☐ Reddened palms (palmar erythema)
☐ Pancreatitis	☐ Cholestasis
☐ Dark coloured urine	☐ Fluid retention in the abdomen and legs
☐ Alanine aminotransferase abnormal	☐ Aspartate aminotransferase abnormal
☐ Blood bilirubin abnormal	

Specify other if any: _____

_____

2. Please specify if the patient has any prior history of hepatic events, or any liver impairment. Provide details with dates.

☐ Hepatic failure ☐ Hepatotoxicity

☐ Jaundice ☐ Hepatitis

☐ Acute on chronic liver failure ☐ Cholestatic liver injury

☐ Hepatic cirrhosis ☐ Hepatic fibrosis

Details of previous treatment(s): _____

_____

Details of current treatment(s): _____

_____

Specify other if any: _____

_____

3. Please provide the information on liver imaging or liver biopsy.

☐ Liver Ultrasound

☐ Computer tomography (CT) Scan

☐ Magnetic resonance imaging (MRI)

☐ Histopathology

☐ Percutaneous Transhepatic Cholangiography

Specify baseline liver test abnormalities, need for close observation or other if any:

_____

_____

4. Please specify the type of the reported hepatic event(s) and provide description or specification.

☐ Direct

☐ Idiosyncratic

☐ Indirect

Description/ specification.: _____

☐ Hepatocellular

☐ Mixed

☐ Cholestatic hepatotoxicity

Description/ specification.: _____

5. Please specify if the patient has any risk factors, if any

☐ Gallstones

☐ History of viral hepatitis

☐ Right heart failure

☐ Left heart failure

☐ Inherited metabolic diseases

☐ Pre-existing liver disease

☐ Pancreatitis

☐ Cholestasis

☐ Recent Blood Product Transfusion

☐ Hepatic failure

☐ Hepatotoxicity

☐ Jaundice

☐ Hepatic cirrhosis

☐ Hepatic fibrosis

☐ Cholestatic liver injury

☐ Acute on chronic liver failure

☐ Other (Specify): _____

_____

6. Please provide all concomitant medications the patient has been/is receiving:

☐ Pain relief medications (paracetamol/acetaminophen, ibuprofen, diclofenac, etc.)

Specify: _____

☐ Anti-seizure medications (phenytoin, valproic acid, carbamazepine, etc.)

Specify: _____

☐ Antibiotics (tetracyclines, sulfonamides, isoniazid, etc.)

Specify: _____

☐ Statins (lovastatin, atorvastatin, simvastatin, etc.)

Specify: _____

☐ Cardiovascular drugs (amiodarone, hydralazine, quinidine, etc.)

Specify: _____

☐ Antidepressants

Specify: _____

☐ Other (Specify): _____

7. Please provide seriousness assessment of hepatotoxicity
   ☐ Fatal
   ☐ Life-threatening
   ☐ Hospitalization (initial or prolonged)
   ☐ Non-serious

   Specify: _____
   _____

8. Please provide the outcome of this event
   ☐ Death,
   ☐ Recovered
   ☐ Not recovered
   ☐ Recovering
   ☐ Worsened
   ☐ Unknown
   ☐ Recovered with sequelae

   Specify the sequelae: _____

9. Please provide clinical signs/symptoms of hepatotoxicity or indicate patient was asymptomatic:
   ☐ No clinical signs/symptoms

   ☐ Clinical signs/symptoms present: (Please specify) _____

Clinical Signs	Clinical Symptoms
☐ Scleral icterus	☐ Fatigue
☐ Abdominal swelling	☐ Orthopnea
☐ Ascites	☐ Shortness of breath with exertion
☐ Asterixis	
☐ Pedal oedema	

   Other (Specify) _____

   _____

10. Please specify amount, regularity and duration of the patient's alcohol consumption by checking appropriate box below:
    ☐ Alcohol consumption: Details of units consumed per week _____

    ☐ No alcohol consumption

    ☐ Unknown

11. Please specify any clinical action taken with vadadustat following the event(s).
    ☐ Specific clinical measures, Specify: _____
    ☐ Stop the drug administration, Specify: _____
    ☐ Other _____

12. Please specify if the patient started any new medications.
    _____
    _____

13. Please indicate your causality assessment for the individual hepatic events in relation to vadadustat, provided with supporting rationale or other details.
    ☐ Certainly related
    ☐ Probably related
    ☐ Possibly related
    ☐ The causality cannot be excluded
    ☐ Unrelated
    Specify: _____
    _____

14. Please provide any additional information that will assist in the assessment of this adverse event.
    _____
    _____

Thank you for completing this form.

_____

Reporter's name

_____

Reporter's signature

_____

Date

7.6 Annex 6: Details of Proposed Additional Risk Minimisation Activities (if applicable)

This section is not applicable for the current version of the RMP.