23 February 2023
EMA/130457/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vafseo

International non-proprietary name: vadadustat

Procedure No. EMEA/H/C/005131/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-time curve
AUC_{tau}	area under the plasma drug concentration-time curve from time 0 until the last measurable concentration after dosing
BA	bioavailability
BCRP	breast cancer resistance protein
BCS	Biopharmaceutic Classification System
BEC	Blinded Expert Committee
BMI	body mass index
CDP	clinical development program
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
CL/F	mean apparent clearance
C_{max}	maximum observed plasma concentration
CPP	Critical process parameter
CRP	C-reactive protein
CSR	Clinical Study Report
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
DBP	diastolic blood pressure
DD	dialysis-dependent
DD-CKD	dialysis-dependent chronic kidney disease
DDI	drug-drug interaction
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapor Sorption
EAIR	exposure adjusted incidence rate
EC	European Commission
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EP	European Pharmacopoeia
EPO	erythropoietin
ERA-EDTA	European Renal Association–European Dialysis and Transplant Association
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EU	European Union
FAS	Full Analysis Set
FCS	fully conditional specification
FDA	Food and Drug Administration
GBD	Global Burden of Disease
GC	Gas Chromatography
GDP	Gross domestic product
GFR	glomerular filtration rate
GMP	Good Manufacturing Practice
Hb	haemoglobin
HD	hemodialysis
HDPE	High Density Polyethylene
HF	heart failure
HIF	hypoxia-inducible factor
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HR	hazard ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control

IR	Infrared
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	intravenous(ly)
JP	Japanese Pharmacopoeia
KA	absorption rate constant
KDIGO	Kidney Disease: Improving Global Clinical Outcomes
KF	Karl Fischer titration
LAGT	absorption lag time
LDPE	Low Density Polyethylene
LS	Least squares (mean)
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed model for repeated measures
MS	Mass Spectrometry
NAS	New Active Substance
NDD	non-dialysis-dependent
NDD-CKD	non-dialysis-dependent chronic kidney disease
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NSAE	non-significant adverse event
NYHA	New York Heart Association
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
PD	peritoneal dialysis
PDE	Permitted Daily Exposure
PEP	primary efficacy period
P-gp	P-glycoprotein
PH	prolyl-hydroxylase
Ph. Eur.	European Pharmacopoeia
PHD	prolyl hydroxylase domain
PK	pharmacokinetic
pmp	per million population
PP	Per protocol
PT	Preferred Term
PVA	polyvinyl alcohol
PVC	Polyvinyl chloride
QD	once daily
RBC	red blood cell (count)
RH	Relative Humidity
ROW	Rest of World
RRT	renal replacement therapy
SAE	serious adverse event
SAP	Statistical analysis plan
SBP	systolic blood pressure
SC	Subcutaneous(ly)
SD	standard deviation
SEP	secondary efficacy endpoint
SmPC	Summary of Product Characteristic
SMQ	Standardized MedDRA Query
SOC	System organ class
TEAE	treatment-emergent adverse event
TGA	Thermo-Gravimetric Analysis
TIBC	total iron-binding capacity
T_{max}	time to peak plasma concentrations
tRBC	life span of red blood cells
TSAT	transferrin saturation
TSE	Transmissible Spongiform Encephalopathy
UGT	glucuronosyltransferase
ULN	upper limit of normal
US	United States
USP/NF	United States Pharmacopoeia/National Formulary

USPI	US prescribing information
UV/Vis	Ultraviolet/visible Spectroscopy
V_d/F	volume of distribution
WNESA	Weight-Normalized prior Erythropoiesis-Stimulating Agent
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AKEBIA EUROPE Limited submitted on 25 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Vafseo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 July 2018.

The applicant applied for the following indication: Vafseo is indicated for the treatment of anaemia associated with chronic kidney disease (CKD) in adults.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0401/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001944-PIP01-16-M02 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance vadadustat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

Date	Reference	SAWP co-ordinators
25/06/2015	EMEA/H/SA/3103/2/2015/SME/II	Kolbeinn Gudmundsson and Sheila Killalea
25/06/2015	EMEA/H/SA/3103/1/2015/SME/III	Kolbeinn Gudmundsson and Minne Casteels
28/01/2016	EMEA/H/SA/3103/3/2015/SME/II	Ferran Torres and Kolbeinn Gudmundsson
22/02/2018	EMEA/H/SA/3103/4/2018/SME/I	Andrea Laslop and Rune Kjeken
12/12/2019	EMEA/H/SA/3103/1/FU/1/2019/II	Peter Mol and Hrefna Gudmundsdottir

The applicant received Scientific Advice on three occasions, as mentioned in the table above for the development of Vafseo for treatment of anaemia in adults with chronic kidney disease. The Scientific Advice pertained to the following Quality, Pre-Clinical and Clinical aspects:

- Drug substance starting materials
- Need for release testing for mutagenic impurities
- Need for microbial testing on drug substance level
- Genotoxic impurity assessment and control strategy
- Qualification of a potential drug substance impurity
- Drug substance comparability testing
- Drug substance release and stability testing
- Drug product release and stability testing
- Release and stability testing methodology
- Drug substance particle size control
- Bioequivalence between tablet strengths
- General non-clinical strategy
- Phase 3 study plans in dialysis- and non-dialysis-dependent CKD patients: number of pivotal studies, general study design, study populations, primary efficacy endpoints, secondary efficacy endpoints, primary analyses periods, safety endpoints, statistical analysis plan, non-inferiority margins for efficacy endpoints, non-inferiority margin for cardiovascular safety endpoints, adverse events of special interest, safety database

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Margareta Bego

The application was received by the EMA on	25 October 2021
The procedure started on	25 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 February 2022

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 February 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 July 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 August 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 September 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 November 2022
The CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation to be sent to the applicant on	15 December 2022
Working Party experts were convened to address questions raised by the CHMP on 24 October 2022, The CHMP considered the views of the Working Party as presented in the minutes of this meeting.	15 December 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	11 January 2023
The outstanding issues were addressed by the applicant in writing and during an oral explanation before the CHMP during the meeting on	26 January 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vafseo on	23 February 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	23 February 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Proposed indication is "treatment of anaemia associated with chronic kidney disease (CKD) in adults".

Chronic kidney disease (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. Renal anaemia is a common and serious complication which often develops during the progression of CKD and is present in almost all patients with end-stage renal disease (ESRD) (Kovesdy 2006; Locatelli 2004; Astor 2002).

2.1.2. Epidemiology and risk factors

Chronic kidney disease, defined as the presence of kidney damage or a decreased level of kidney function, is a major public health problem worldwide estimated to affect approximately 9.1% (697.5 million cases) of the population globally (Global Burden of Disease [GBD] CKD Collaboration 2020; KDIGO 2013). CKD represents a major worldwide burden on public health, particularly in aging populations (Levey 2007). In Europe, the average prevalence of CKD regardless of age lies between 5% and 11% [Zoccali et al., 2010].

Renal anaemia is a common and serious complication which often develops during the progression of CKD and is present in almost all patients with end-stage renal disease (ESRD) (Kovesdy 2006; Locatelli 2004; Astor 2002). Anaemia is twice as prevalent in people with CKD (15.4%) as compared to the general population (7.6%) (Stauffer 2014).

2.1.3. Biologic features Aetiology and pathogenesis

Although many factors contribute to anaemia in CKD, it occurs primarily due to an inadequate synthesis of endogenous erythropoietin (EPO) by the kidneys, leading to a deficiency in the production of red blood cell (RBC) progenitor cells by the bone marrow.

2.1.4. Clinical presentation, diagnosis

Anaemia in CKD patients significantly impairs quality of life and is associated with hospitalizations (Stauffer 2014; Xia 1999). Further, anaemia in CKD patients is associated with mortality and cardiovascular (CV) events, even after accounting for stage of CKD, albuminuria, and other cardiovascular risk factors such as diabetes mellitus, smoking, and hypercholesterolemia (Kovesdy 2006).

2.1.5. Management

Treatment for anaemia associated with NDD or dialysis-dependent (DD) patients with CKD includes iron supplementation, RBC transfusions and/or treatment with erythropoiesis-stimulating agents (ESA) [Kidney Disease: Improving Global Outcomes (KDIGO), 2012]. The European Renal association recommends maintaining Hb levels between 10.0 and 12.0 g/dL. A more recent analysis of 9220 CKD patients receiving ESA showed that the rate of Hb rise greater than 0.125 g/dL/month increases CV

incidence rates (Fusco 2017). All ESAs are administered either intravenously or subcutaneously and have complex dosing schedules.

Exogenous replacement of EPO by erythropoiesis-stimulating agents (ESAs) is an established method of treatment of anaemia in CKD. ESAs administered either intravenously (IV) or subcutaneously (SC), along with oral or IV iron therapy, are currently the cornerstones for treating anaemia in patients with CKD (Aranesp 2019; Epogen 2018; Mircera 2018). Treatment with exogenous recombinant ESAs can raise haemoglobin (Hb) levels, relieve symptoms of anaemia, and reduce the complications of anaemia, including those associated with RBC transfusions, which carry the risk of infection, iron overload, and impact candidacy for kidney transplantation, as multiple transfusions can increase the risk of alloimmunization and hence organ rejection. The shortcomings of ESA use include the need for IV and/or SC administration and the potential for unpredictable uncontrolled rise in Hb. Higher ESA doses and targeting near normal Hb levels with ESAs have been associated with excessive cardiovascular morbidity and mortality (McCullough 2013). Therefore, the unmet medical need for the treatment of anaemia in dialysis-dependent CKD (DD-CKD) and nondialysis-dependent CKD (NDD-CKD) remains high.

Inhibitors of HIF prolyl-hydroxylases have been explored as a novel mechanism for the treatment of anaemia associated with CKD. Inhibition of the prolyl 4-hydroxylase domain enzymes leads to HIF stabilization and increased cellular levels of HIF that in turn, effectively stimulate EPO expression and heighten the oxygen-carrying capacity of the blood via improved production of Hb and RBC. Roxadustat, an inhibitor of HIF-PH, is approved in EU for the treatment of anaemia associated with CKD. The vadadustat clinical program is focused on developing an orally active agent in the same class with roxadustat, inducing a lower and more consistent blood EPO level than results from exogenous ESA treatments.

2.2. About the product

Vadadustat is a hypoxia-inducible factor prolyl-hydroxylase inhibitor which leads to increased cellular levels of hypoxia-inducible factor thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization, Hb and red blood cell production.

Pharmacotherapeutic group: Other anti-anaemic preparations, ATC code: B03XA08

Proposed indication is "treatment of anaemia associated with chronic kidney disease (CKD) in adults".

Proposed dosing schedule is starting with 300 mg once daily (QD) and making dose adjustment in increments/reductions of 150 mg within the range of 150 mg to 600 mg to achieve or maintain haemoglobin levels within 10-12 g/dL (Do not increase the dose more frequently than once every 4 weeks).

2.3. Type of application and aspects on development

The vadadustat clinical program includes 2 pivotal global randomized, open-label, active-controlled studies in DD-CKD subjects (AKB-6548-CI-0016 and AKB-6548-CI-0017 which are known as the INNO2VATE studies) and 2 pivotal global randomized, open-label, active-controlled studies in NDD-CKD subjects (AKB-6548-CI-0014 and AKB-6548-CI-0015 which are known as the PRO2TECT studies).

Scientific Advice was obtained from the Medicines and Healthcare Regulatory Agency (MHRA, United Kingdom) on 08 January 2015 and the Medical Product Agency (MPA, Sweden) on 09 January 2015 regarding the design of the initially planned Phase 3 NDD-CKD clinical studies proposed (Studies CI-

0014 and CI-0015) and the potential registration pathway(s) for vadadustat in the European Community.

Scientific Advice was sought from the European Medicines Agency (EMA) regarding the overall quality, pre-clinical and clinical development program on 5 separate occasions between 2015 and 2019.

Key clinical program and study design features discussed with the EMA between 2015 and 2019 include the following:

- The conduct of 2 adequate and randomized, open-label, sponsor-blinded pivotal studies each to support the DD and NDD indication.
- Use of an active comparator in the pivotal studies.
- Target range of Hb for the US sites 10.0 to 11.0 g/dL and ex-US sites 10.0 to 12.0 g/dL, with enrolment of at least 30-40% of the total subjects in the pivotal studies population according to the "European" haemoglobin target.
- Starting dose of 300 mg QD and the proposed dose adjustments (150 to 600 mg QD),
- Primary efficacy endpoint of mean change in Hb between Baseline and primary evaluation period (Weeks 24 to 36).
- Key secondary efficacy endpoint of mean change in Hb between Baseline and secondary evaluation period (Weeks 40 to 52).
- Non-inferiority margin of -0.75 g/dL (lower bound of 2 sided 95% CI) for the treatment comparison for the primary and secondary efficacy endpoints.
- Primary safety endpoint of time to first major adverse cardiovascular event (MACE), defined as death, non-fatal myocardial infarction (MI), and non-fatal stroke.
- Non-inferiority margin of 1.3 (upper bound of 2 sided 95% CI for the hazard ratio [HR]) for the primary safety endpoint.
- Stratification factors: 1) geographic region (US versus Europe versus ROW); 2) NYHA HF Class 0 (no HF) or I versus II or III; and 3) Baseline Hb <9.5 versus ≥9.5 g/dL for studies CI-0014 and CI-0016 and <10.0 versus ≥10.0 g/dL for studies CI-0015 and CI-0017.

The Applicant summarized above the points included in regulatory interactions, however, CHMP expressed concerns and disagreement on some of these points e.g. open label design, rationale for stratifying patients based on heart failure class rather than GFR or CKD class, change of non-inferiority margin of -0.75 g/dL from -0.5 g/dL, regional differences in Haemoglobin target goals between the US and Europe, cardiovascular safety and additional safety issues.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 150, 300 and 450 mg of vadadustat as active substance.

Other ingredients are: microcrystalline cellulose (E460), sodium starch glycolate, hypromellose (E464), silica colloidal anhydrous (E551) and magnesium stearate (for the tablet core); polyvinyl alcohol

(E1203), macrogol (E1521), talc (E553b), titanium dioxide (E171), yellow iron oxide (E172, for the 300 mg strength), iron oxide red (E172, for the 450 mg strength) and ferrosoferric oxide (E172, for the 450 mg strength) (for the tablet coating).

The product is available in PVC/aluminium foil blisters, in multiple pack sizes.

2.4.2. Active substance

General information

The chemical name of vadadustat is 2-[[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino]acetic acid corresponding to the molecular formula $C_{14}H_{11}ClN_2O_4$. It has a relative molecular mass of 306.7 g/mol and the following structure:

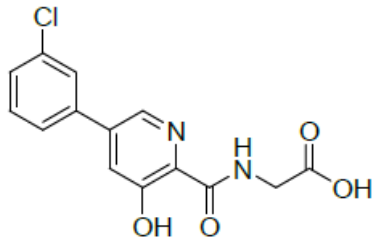


Figure 1: Active substance structure

The chemical structure of vadadustat was elucidated by a combination of MS (mass spectrometry), IR (infrared spectroscopy), UV/VIS (ultraviolet/visible spectroscopy), 1H-NMR and 13C-NMR (nuclear magnetic resonance) techniques. In addition, elementary, DSC (differential scanning calorimetry), TGA (thermogravimetric analysis) and DVS (dynamic vapor sorption) analyses were performed. The solid state properties of the active substance were measured by X-Ray powder diffraction (XRPD). Vadadustat has a non-chiral molecular structure.

Vadadustat is a white to off-white non-hygroscopic anhydrous powder, with a low aqueous solubility (0.041 mg/ml, pH-dependent with lower solubility at acidic pH and higher solubility at neutral pH) and high transmembrane permeability (Biopharmaceutics Classification System – BCS Class 2 compound).

Polymorphism has been observed for vadadustat. Polymorph screening had led to the identification of Form 1, Form 6, Form 7 and Form 8. Polymorphic Form 1 is the thermodynamically stable form which has been used in all clinical trials and is being manufactured as vadadustat active substance to be used in commercial finished product.

The Applicant requested vadadustat to be considered as a new active substance (NAS). During the assessment, a Major Objection was raised concerning the Applicant's justification of vadadustat NAS claim, requesting additional information about database searches performed by the Applicant for structurally related substances in relation to the therapeutic moiety of the claimed NAS. The Applicant has adequately addressed this issue and, therefore, vadadustat is to be qualified as a new active substance in itself as it was concluded that it is not a constituent of a medicinal product previously authorised within the European Union.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the dossier and it was considered satisfactory. There are 2 manufacturers involved in manufacture of the active

substance, using the same commercial process. Vadadustat is synthesized in several chemical main steps using well defined starting materials with acceptable specifications.

A detailed description of every stage of the manufacturing process has been provided, including raw material quantities and process conditions. The synthesis of the active substance is adequately described. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Process parameters and controls are defined and supported by batch data of the isolated intermediates in the vadadustat manufacturing process and of the active substance. Critical process parameters have been specified to control reaction completion and impurities formed.

The current vadadustat active substance manufacturing process involves no aseptic or sterilisation processes. Therefore, no process validation information is provided. No design space is claimed. No reprocessing or recovery is used in the manufacturing process of the active substance. The proposed commercial batch size for vadadustat has been included in the dossier. The current manufacturing process was used to produce the active substance batches that were used in all clinical studies and registration stability studies.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Observed and potential impurities (including potentially genotoxic impurities) in the starting materials and intermediates have been evaluated in carry over analyses. Spiking experiments with estimated purge factors have been performed to support the impurity profile of vadadustat. Impurities are controlled in starting materials and intermediates specifications where relevant and supported by batch data. Only one specified impurity has been included in the active substance release specification. A toxicological evaluation has been performed in the toxicological section where it is concluded that this impurity is not of toxicological concern. By demonstrating understanding of fate, purge and associated process controls that ensure that the level of potential genotoxic impurities is below acceptable limits in the active substance, no additional testing in the active substance is required. Residual solvents (including potential contaminants) are controlled according to ICH Q3C and elemental impurities according to ICH Q3D.

The active substance is packaged inside a low-density polyethylene (LDPE) bag which is compliant with the EC directive 2002/72/EC and EC 10/2011 as amended. The choice of the container closure system is considered justified.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), physical form (XRPD), residual solvents (GC), water content (KF), elemental impurities (ICP-MS), residue on ignition (Ph. Eur.), particle size distribution (laser diffraction), microbial count (Ph. Eur.).

The proposed active substance specification includes relevant testing parameters. The specification was established taking into account applicable ICH and EU guidelines and compendial considerations, as well as manufacturing capability, batch analysis data and stability results. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Control for impurities at intermediate stages with omission of tests at active substance level is acceptable based on carry over and purge analyses. During the assessment, the tightening of acceptance criteria for total impurities was requested and has been implemented by the Applicant. The control strategy for residual solvents and for the elemental impurities has been detailed in the characterisation of the active substance section and the applied limits are in line with ICH Q3C and ICH Q3D, respectively.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data are provided from both active substance manufacturers. The results comply with the proposed specification and similar results are obtained from both manufacturers, confirming consistency and uniformity of the active substance batches.

Stability

Stability data from 13 batches of active substance from the proposed manufacturers stored in representative container closure system for up to 36 months under long term conditions (25ºC/60% RH), for up to 36 months under intermediate conditions (30ºC/75% RH) and for up to 6 months under accelerated conditions (40ºC/75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, impurities, assay, water content, physical form, particle size distribution and microbial count. The analytical methods and limits used were the same as for release.

All results comply with specifications at all conditions and no changes/degradation is observed during storage.

Photostability testing following the ICH guideline Q1B was performed on 2 batches. Results on forced degradation studies under thermal, acidic, basic and oxidative stress were also provided for 1 batch. The photostability testing results show that no degradation was observed under the study conditions. The forced studies results demonstrate that assay and purity HLPC method is stability indicating, with minor degradation observed for the base and peroxide treatment.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container with no special storage condition.

2.4.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is an immediate release film-coated tablet containing 150 mg, 300 mg or 450 mg vadadustat, described as follows:

- 150 mg: Round white tablet debossed with "VDT" on one side and "150" on the other side, 8 mm (diameter)
- 300 mg: Oval yellow tablet debossed with "VDT" on one side and "300" on the other side, 8 mm (width) x 13 mm (length)
- 450 mg: Oval pink tablet debossed with "VDT" on one side and "450" on the other side, 9 mm (width) x 15 mm (length)

The choice of pharmaceutical form/strengths adequately addresses the proposed dosing regime, i.e. starting dose of 300 mg once daily and dose adjustment in increments/reductions of 150 mg within the range of 150-600 mg.

No novel excipients and no excipients of human or animal origin are used in the manufacture of vadadustat tablets. The chosen excipients are commonly used in immediate release film-coated tablets

and are described in Ph. Eur., except the Opadry White, Opadry Yellow and Opadry Pink coating mixtures, which consists of pharmacopoeial ingredients. The selection of each excipient in the proposed level have been adequately discussed and justified. The compatibility between the active substance and excipients has been demonstrated based on the stability results.

The formulation development including the steps taken from the initial clinical trial formulations to the proposed commercial formulation are described in sufficient details. For the first clinical trials a capsule formulation in various strengths in the range 40 mg to 315 mg was developed, followed by uncoated tablets in the strengths 315 mg and 150 mg. Film-coated tablets were initially developed in the 150 mg strength and further development studies were carried out to develop the dose-proportional 300 mg and 450 mg strengths. Adequate dissolution and bioequivalence studies were conducted to bridge early formulations to formulations used later in development and planned commercial formulations.

The proposed manufacturing process is a standard wet granulation process, selected based on the physicochemical properties of the active substance and the high drug load requirements of the dosage form. The choice of manufacturing process has been justified and the critical process parameters have been identified. Process parameter ranges have been satisfactorily investigated. The differences in the manufacturing process of the commercial product and the clinical trial batches have been adequately explained and discussed.

No overages are used in the manufacturing process. All drug product strengths can be manufactured from the same common blend.

The development of the dissolution method has been described in details and the proposed method is found acceptable. The dissolution method can discriminate changes to formulation and material properties and manufacturing process parameters.

The proposed packaging configuration for the bulk vadadustat tablets is double-LDPE bags inside an HDPE pail without desiccant, a commonly used packaging for solid oral dosage form pharmaceutical products and considered suitable for the transportation and storage of vadadustat tablets.

The finished product will be packaged in polyvinyl chloride (PVC)/aluminium foil blisters. The proposed packaging is considered suitable for packaging of the finished product based on the stability studies and complies with Ph. Eur. and EC requirements.

Manufacture of the product and process controls

The vadadustat finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP.

The manufacturing process is a standard wet granulation process and consists of the following 10 steps: blend pre-granulation, wet granulation, wet milling, drying, dry milling, blending, lubrication, compression, film-coating, packaging and labelling.

A flow diagram and a narrative description of the manufacturing process and in-process controls are provided in the dossier. The batch formula is given for the proposed commercial batch size.

All finished product strengths can be manufactured from the same common blend. Therefore, equipment, processes and proven acceptance ranges are applicable for Steps 1 – 7 for all tablet strengths.

An evaluation of the critical process parameters was performed during the manufacturing process development.

In-process controls during the finished product manufacture have been established based on the manufacturing process development studies and are considered adequate.

For the finished product in bulk container (double LDPE bag in HDPE pail), the proposed bulk holding time has been justified based on stability studies presented.

Process validation has not been provided, which is acceptable for a standard manufacturing process for an immediate release formulation. An appropriate process validation protocol to be followed for the first three commercial batches of each strength is presented.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), identification (HPLC, HPLC-UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (HPLC/Ph. Eur.), dissolution (HPLC/Ph. Eur.), water content (Karl Fischer/Ph. Eur) and microbial limits (Ph. Eur.).

The proposed specification tests are in line with ICHQ6A and Ph. Eur. requirements. The parameters included in the finished product specification are found adequate to control the quality of the finished product at release and shelf-life. During the assessment, the tightening of acceptance criteria for total impurities and for the shelf-life assay limit was requested and has been implemented by the Applicant.

All known impurities are considered process impurities originating from the active substance. No additional degradation products have been identified in the finished product. Therefore, the finished product specification only includes control of unspecified and total impurities. The proposed limit for impurities in the specification are justified based on the level seen in the batch analysis and stability studies.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk assessment and testing results of ICP-MS analysis revealed that the impurity levels for the elements considered in the finished product are below the control threshold of 30% of the permitted daily exposure (PDE) and, therefore, routine elemental impurities release testing is not conducted. This conclusion is endorsed.

No solvent is used during the manufacturing process of the finished product. Therefore, no residual solvent testing is required for vadadustat finished product.

In response to a Major Objection raised during the assessment, a risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is concluded that there is a potential risk of formation of nitrosamine impurities in the drug product, thus confirmatory testing has been carried out using appropriately validated analytical methods. No nitrosamine impurities were detected in 25 commercial batches tested. Hence, it is considered justified not to include a control test for nitrosamines in the finished product specification.

Descriptions of the analytical methods used to control the finished product are presented and appropriate validation of the methods in accordance with EU/ICH validation guidelines have been performed. The reference standard used for finished product testing is the same as the standard used to test the active substance and is considered acceptable.

Batch analysis (n=24) results are presented for pilot scale batches of each strength manufactured at the proposed manufacturing sites as well as commercial scale batches of the 150 mg and 300 mg strengths. In addition, batch analysis of the early development finished product batches, including clinical batches, is presented. The results showed that the finished product meet the specifications proposed and confirmed batch-to-batch consistency. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability studies have been carried out on finished product batches of each strength, manufactured at proposed manufacturing sites, according to ICH stability conditions and packaged in the proposed commercial packaging. Data at long-term storage conditions (25ºC/60% RH) and accelerated storage conditions (40ºC/75% RH) were provided.

The following parameters were tested: appearance, impurities, assay, dissolution, water content and microbial count (performed initially and then annually). The analytical methods and limits used were the same as for release (except for water content, for which the shelf-life limit is slightly higher).

In addition to the primary stability studies, supportive stability is presented for the finished product packed in HDPE bottles (not intended for marketing), tablets in bulk packaging and clinical trial batches.

No significant changes or trends were observed in any of the parameters tested. All results were well within the proposed specifications across all sample times and conditions.

A photostability study has been carried out in accordance with the ICH Q1B guideline and it was concluded that the vadadustat tablets are not sensitive to light.

Forced degradation studies have been performed in relation to the validation of the analytical methods for assay and related substances and it was confirmed that the methods are stability indicating.

Based on the submitted stability data, the proposed shelf-life of 36 months with no special storage conditions (as stated in the SmPC section 6.3) is acceptable.

Adventitious agents

No excipients of human or animal origin are being used in the finished product manufacturing process. Declarations that there are no TSE risks of any raw materials (active substance or excipients) used in the finished product are presented.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure, two Major Objections were raised, concerning (1) incomplete justification of the vadadustat New Active Substance claim and (2) incomplete risk evaluation for the presence of nitrosamine impurities in the product. The Major Objections, as well as all the other concerns, have been satisfactorily resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

Vadadustat is a novel, synthetic, orally bioavailable, small molecule inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIF-PHs). HIF-PHs initiate the degradation of the α-subunit of hypoxia-inducible factor under physiological conditions. Inhibition of HIF-PHs leads to HIF stabilization and increased cellular levels of HIF that in turn effectively stimulates erythropoietin expression and production of haemoglobin and red blood cells. Vadadustat is being developed as a treatment for anaemia associated with chronic kidney disease in adult patients on dialysis and not on dialysis. This type of (renal) anaemia develops when the kidney is impaired, leading to decreased erythropoietin (EPO) production. The kidney is an important oxygen-sensing organ, responding to systemic hypoxia with a rapid increase in EPO production by renal interstitial fibroblast-like cells (Hasse 2006), resulting in increased erythropoiesis.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Four in vitro pharmacology studies were conducted to demonstrate the activity of vadadustat and its metabolites on the biological target, stabilization of the two major forms of HIF-α in cells and production of EPO in cell culture. Time-resolved fluorescence energy transfer assays were conducted to assess the IC50 of PHD1, PHD2, and PHD3 enzymes by vadadustat (study No AKB-6548-NC-1026); the IC50 of PHD2 by the major human metabolite and a primary metabolite in dogs, vadadustat-O-glucuronide (study No AKB-6548-NC-1027); and the IC50 of PHD2 by B-504, a primary metabolite in rats and dogs (study No AKB-6548-NC-1028). Vadadustat was a potent inhibitor of PHD1, PHD2, and PHD3 that did not exhibit isotype selectivity, with IC50 values of 15.41, 11.91, and 7.63 nM, respectively (study No AKB-6548-NC-1026). Vadadustat-O-glucuronide (study No AKB-6548-NC-1027) and B-504 (study No AKB-6548-NC-1028) inhibited PHD2 at IC50 of 2.32 and 1.22 µM, respectively. The PHD2 inhibitory activity of these two metabolites were 100- to 200-fold less than vadadustat and, therefore, considered to be pharmacologically inactive. The activity of vadadustat-O-glucuronide and B-504 against the PHD1 and PHD3 isoforms was not determined. However, due to the high primary sequence homologies of the three human PHD isoforms it is anticipated that the IC50 values for both metabolites against the PHD1 and PHD3 isoforms would be similar in magnitude to that observed against the PHD2 isoform, as is the case with the parent compound vadadustat.

The stabilization of the two major human isoforms of the transcription factor HIFα and downstream EPO and VEGF secretion by vadadustat were assessed in Hep3B and HUVEC cell lines. Vadadustat

inhibition of PHD led to the stabilization of HIF-1α in a dose- and time-dependent manner in both of these cell lines. HIF-2α stabilization was only seen in the HUVEC cell line at 24 hours, demonstrating cell type dependence. Vadadustat stimulated EPO secretion (the HIF gene product) but not VEGF secretion in Hep3B cells under normoxic conditions, suggesting that unlike tissue hypoxia, chemical inhibition of the PHD enzymes in certain cells does not lead to measurable increases in soluble VEGF (study No EVT04989).

The in vivo pharmacological activity of vadadustat was evaluated in several mouse and rat studies. In vivo, the vadadustat-induced erythropoietic response was evaluated following a single intravenous dose of 60 mg/kg and 4-day repeat oral doses of 0, 30, 90, and 270 mg/kg. While 4-day dosing up to 90 mg/kg/day had no significant effects, EPO blood levels peaked 2 hours post dose at 270 mg/kg/day and returned to baseline levels by 24 hours. For i.v., vadadustat at a single dose of 60 mg/kg was effective at raising EPO plasma levels (study No SW07-0302).

The pharmacokinetic and pharmacodynamic effects of vadadustat were also evaluated in rats. Dose-dependent increases of systemic vadadustat exposure and serum EPO levels were noted following single oral doses of 50 and 150 mg/kg. Vadadustat was rapidly absorbed, with a Tmax of 0.5 to 1 hour, which preceded the increases in serum EPO levels (study No 6901490). Vadadustat administered at 30 mg/kg/day by once daily oral gavage for 14 days resulted in end of study AUC exposure levels that increased EPO levels up to 3.6-fold and haemoglobin parameter compared to control levels. Administration of 90 mg/kg/day by once daily oral gavage for 14 days resulted in end of study AUC exposure levels that increased EPO levels up to 42-fold, red blood cell parameters and total iron binding capacity and unsaturated iron binding capacity parameters compared to control levels (study No 6901491). No increase in VEGF levels was observed following vadadustat administration to rats at doses which resulted in changes in pharmacodynamic parameters (study Nos 6901490 and 6901491).

Single and repeat dosing in mice (study Nos SW07-0446, SW08-0102) and rats (study Nos SW08-0146 and 6901491) resulted in dose-dependent increases in erythrocyte mass (red blood cells, haemoglobin, and haematocrit) and associated haematological parameters (red cell distribution width, mean corpuscular volume, mean corpuscular haemoglobin) and a concomitant decrease in platelet counts. The increase in reticulocyte counts was sustained up to 8 days following a single dose of 150 mg/kg vadadustat rats (12.6, 16.8 and 17.9% on Days 1, 4, and 8, respectively) (study No SW08-0146), as well as following repeat doses of 270 mg/kg for 4 days in mice (study No SW07-0446) and 90 mg/kg for 14 days in rats (study Nos SW08-0146 and 6901491). Time-dependent moderate increases in red blood cells, haemoglobin, haematocrit, and red cell distribution width were noted 4 and 8 days after a single dose of 150 mg/kg in rats (study No SW08-0146). Similar effects were observed following repeated doses of vadadustat in mice (200 mg/kg for 7 days (study No SW08-0102) and in rats (90 mg/kg for 14 days; 6901491).

Well-defined exposure-response relationships were identified between long-term vadadustat treatment and haemoglobin or haematocrit levels in a pharmacokinetic-pharmacodynamic model-based exploratory analysis of mouse, rat and dog data during the repeat-dose toxicology studies. Across all the models, using the AUC may present a more physiologically relevant metric given that it seems to correlate with responses over a relevant physiological range. The animal exposures predicting an increase of 15% haemoglobin and haematocrit are in the range of 108292 to 241800 ng×h/mL, exposures in the range of those anticipated in humans when administering vadadustat at therapeutic doses up to 600 mg to obtain target haemoglobin values (study No AKEB-CSC-101).

2.5.2.2. Secondary pharmacodynamic studies

Vadadustat showed selectivity for the PHD isoforms based on 112 receptor binding assays and 42 enzyme assays (study No 14651) and subsequent follow up assessment of peripheral benzodiazepine and angiotensin converting enzyme activity. Vadadustat was shown to inhibit the rabbit aorta contractile response to angiotensin I in a concentration-dependent manner, in the same way the ACE antagonist captopril used as reference compound did, suggesting inhibition of the enzyme ACE and consequent production of angiotensin II, with an IC50 value of 72 µM (study No 100043777).

Based on the guidelines provided in study No 14651 on how to interpret the results, it is unclear which exceptions are considered acceptable when interpreting large negative results – in the example of the enzyme CaCMK2α, the Applicant singled out the result off -89 in the Pharmacology written summary, but deemed the evaluation of a potential effect of the drug on this enzyme unwarranted due to the drug's poor penetration to the brain (CAMK2α is a key protein kinase in the brain, involved in neural plasticity and memory) and lack of behavioural findings in functional observation battery and toxicological studies. For example, the result of -46% for the CDC2/CDK1 enzyme was not commented on. An OC was raised for the Applicant to comment on which exceptions are considered acceptable when interpreting large negative results. According to the Applicant, only results yielding <50% of binding were considered significant as an industry standard. Further, the result of -89% for CAMK2α is not expected to yield clinically relevant effects – at a maximum (peak) plasma concentration (Cmax) of 50 µg/mL in patients at a dose of 600 mg, the concentrations of vadadustat in the brain are 385 times lower than the concentration used in the in vitro assay; hence, no clinically relevant effects are to be expected. This is endorsed.

In the Pharmacology Written Summary, the Applicant did not elaborate on the potential impact of vadadustat on the receptors/enzymes which showed a weak to moderate effect in the presented study (according to the instructions for assessment, these are results showing an inhibition between 20 and 50%). These include the kainite, glycine, tumour necrosis factor-α and glucocorticoid receptors, the chemokine receptor CCR3, sodium channel (site 2) and the Lyn A kinase and metallo-matrix-protease 1 enzymes. These findings should be considered when assessing data from clinical studies in regard to potential for adverse reactions due to these off-target effects. For several enzymes, it was noted that the test compound interfered with the assay detection method; including two enzymes which were shown to have the highest interaction with vadadustat, the angiotensin converting enzyme (ACE) and the metallo-matrix-protease 1 enzyme (MMP-1).

2.5.2.3. Safety pharmacology programme

The potential effects of vadadustat on the CNS were evaluated in rats. In a Functional Observation Battery study a single dose oral administration of vadadustat to male Sprague-Dawley rats at 0, 120, 180 or 360 mg/kg did not result in any meaningful variations outside of historical control ranges on general behavior or on the various neurologically-related parameters evaluated, except for a dose-dependent reduction in defecation at doses of 120 to 360 mg/kg (study No 1008-2361). It was noted that the study lacked a description of the procedure of the conducted open field (manual or automated, number of observers etc.) as well as specification of the method used for grip strength measurement. However, this was not considered to influence the outcome of the study.

Vadadustat 120 to 360 mg/kg by oral gavage did not result in noteworthy effects on respiratory parameters measured by head-out plethysmography in male Sprague-Dawley rats (study No 1008-2371). Treatment-related increases in both tidal and minute volume were observed at a single oral dose of 360 mg/kg, but no adverse effects on respiratory function were observed. The effects on the

tidal and minute volume are consistent with the known ventilatory acclimation to hypoxia and is considered part of the expected pharmacology of a HIF stabilizing agent (Powell 2008).

In vitro, the effect of vadadustat at concentrations up to 284.4 µM was tested on the IKr current using HEK293 cells. There was a statistically significant inhibition of hERG observed at vadadustat concentrations ≥9.5 µM, but the effect was not concentration-dependent and plateaued at 23 ± 3% inhibition of the hERG tail current at a concentration of 28.9 µM (study No 701205-2). Although the hERG inhibition was statistically significant, the degree of inhibition is likely physiologically insignificant given that there was an absence of concentration-dependence and the inhibition plateaued at a 23%. This, coupled with the large difference between the lowest concentration used in the assay and the expected free drug concentration in vivo, make it unlikely that this inhibitory effect will translate into prolongation of the QT interval. In vitro evaluations of vadadustat on HEK293 Cells transfected with the hERG were also performed in non-GLP study No 701205-1. As this study was a non-GLP screening study in the discovery phase it was not evaluated in this assessment report.

In a non-GLP investigative study conducted to assess the haemodynamic effects of oral gavage dosing of vadadustat in naive telemetered rats an increase in pulmonary arterial pressure (PAP) was noted at 15- and 27-day repeated administrations at 90 mg/kg up to 8 hours after dosing, with an increase in systolic PAP, diastolic PAP, and mean PAP values of up to 82%, 167%, and 79%, respectively. While these changes were considered treatment-related effects secondary to polycythaemia, they were not considered deleterious (study No 021-1802). According to the applicant, although statistically significant, the observed increases in pulmonary artery pressure is physiologically irrelevant. It is a rather presumptuous statement, seeing that the need to conduct the study arose from two literature publications stating the relationship of PHD2 deficiency and severe pulmonary artery hypertension, implicating that inhibition of the PHD2/hypoxia-inducible factor-2α signalling may lead to the same effects, and that indeed statistically significant increases in pulmonary artery pressure were seen in telemetered rats. Further to this in the clinical assessment report the Applicant's argumentation on these findings are endorsed. They were not suggestive of an 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.

In conscious, telemetered rats, vadadustat following single oral administration at doses of 120 to 360 mg/kg induced in an initial transient, statistically significant, increase in systemic arterial pressures (systolic, diastolic and mean) at all doses. This was followed by a prolonged period of moderate, and occasionally statistically significant, decreases in arterial pressures at doses of 180 and 360 mg/kg, and moderately to severely increased heart rate that was similar in magnitude, and statistically significant, at all dose levels. Pulse pressure was not altered. Body temperature was significantly decreased over a similar time period as the fall in blood pressure at doses of 180 and 360 mg/kg (study No 1008-2391).

In conscious, telemetered dogs given a single dose of 60 to 360 mg/kg of vadadustat did not affect QTc and body temperature or activity. Mean heart rate was modestly elevated at all doses evaluated and the duration of effect was dose-dependent, associated with mild to moderate falls in blood pressures at ≥120 mg/kg and a sustained decrease in pulse arterial blood pressure at a dose of 360 mg/kg (study No 1008-2382).

In both the rat and the dog, vadadustat caused a transient decrease in blood pressure with a compensatory increase in HR. These changes are likely not attributed to the ACE inhibition observed in vitro since the circulating free fraction Cmax concentrations in the in vivo haemodynamic study are less than the in vitro ACE IC50 values. Moreover, the timing and direction of cardiovascular changes (decreases in blood pressure and increases in HR) are not consistent with clinical changes with ACE inhibitors (Pierdomenico 2002). Furthermore, the delayed onset following Cmax and extended duration

of the effect are consistent with a transcriptional event, such as HIF stabilization. Although the haemodynamic effects are consistent across species, the free fraction exposures and HR effects are larger in dogs than in rats. Consistent with the dedicated cardiovascular safety studies, there were no vadadustat-related effects on the morphology or intervals of the P-QRS-T complexes in rats and dogs in the repeat dose toxicology studies of up to 9 months in duration. No vadadustat-related effects on cardiovascular parameters were noted in a dedicated thorough QTc study in humans at oral doses of up to 1200 mg/day (study No CI-001).

With the exception of marginal increases in urea and urine protein excretion rates, the single oral dose of vadadustat at 120 or 180 mg/kg did not produce any significant effects on indices of renal excretory function, glomerular filtration rate, and water intake in male rats. The oral administration of vadadustat at 360 mg/kg produced similar increases in urea and urine protein excretion rates, compared to 120 and 180 mg/kg vadadustat, in addition to marginal increases in sodium and chloride excretion rates. Creatinine clearance was not affected by doses ≤360 mg/kg of vadadustat (study No 0209RA104.001).

The safety pharmacology assessment of vadadustat was carried out in accordance with the ICH guidelines S7A and ICH S7B. In vitro and in vivo safety pharmacology studies evaluating the effects of vadadustat on the central nervous, respiratory, cardiovascular and renal systems were conducted in compliance with GLP. Collectively, the in vitro and in vivo studies in rats and dogs suggest vadadustat is unlikely to adversely affect the central nervous cardiovascular, or respiratory systems in humans when given up to 600 mg daily. It was noted that in both rat and dog, vadadustat caused a transient decrease in blood pressure with a compensatory increase in HR.

2.5.2.4. Pharmacodynamic drug interactions

The Applicant provided a justification for omitting non-clinical pharmacodynamic drug interaction studies based on the availability of robust and relevant clinical data from clinical trials.

2.5.3. Pharmacokinetics

Pharmacokinetics of vadadustat was studied in mice, rats and dogs. The toxicokinetics of vadadustat in mice, rat and dog after repeated administration were assessed from pivotal toxicology studies carried out in accordance with GLP consistent with the ICH guideline S3A. The mouse, rat and dog, were selected as the relevant test species in the pivotal toxicology studies.

Methods of analysis

The bioanalytical program of vadadustat/Vafseo is comprehensive given the many studies conducted by different sponsors over the years of development. An assessment of selected pivotal studies reveals a program in good control and with both validation and study related bioanalysis in compliance with GLP. Incurred sample reproducibility was found to comply with guidelines in the assessed pivotal studies. Most studies were only analysing for parent compound, however the 2 years carcinogenicity study also included two major metabolites and the mouse carcinogenicity study one metabolite.

All bioanalytical method used LC/MS/MS for detection with appropriate internal standards as available, but different sample preparation methods were taken into use (solid phase extraction, protein precipitation or liquid/liquid extraction). Nevertheless, the methods appeared robust and adequate for the purpose of the studies. In two cases, long-term sample stability was found not to be evaluated (rabbit plasma for study 1817-009 and rat plasma for study 20057392). However, since long-term stability for >200 days was demonstrated in dog and rat plasma in other studies, this is not considered a concern at this stage of development.

The plasma concentration of the analytes vadadustat, O-Glucuronide and Acyl-Glucuronide were consistently reported as ng/mL.

Absorption

In in vitro absorption studies in Caco-2 cell monolayers, vadadustat has been shown to have high cell permeability, potentially via efflux transporters expressed in Caco-2 cells such as BCPR. The Applicant does not expect that intestinal efflux by BCRP will limit the oral absorption of vadadustat in humans. Upon PO administration as a suspension, vadadustat shows high oral bioavailability in rats (F > 90%) with rapid absorption (T_{max}: 1-2 h). In dogs, the single dose oral suspension PK study designed to calculate PK parameters such as CL, Vss, $T_{1/2}$, and $AUC_{0-\infty}$, a linear elimination phase was not observed upon IV administration in both sexes or upon PO administration in males. Therefore, the PK parameters could not be derived based on this study and a definitive bioavailability was not derived. The Applicant however suggests that the available data indicate a high oral bioavailability in the dog based on comparison of dose-normalized AUC_{0-t} following oral administration to AUC_{0-t} following IV administration, which is accepted. Moderate oral bioavailability was observed in dogs in a single study upon single PO administration of vadadustat formulated as a gelatin capsule (~30%). Other PK parameters were calculated from the oral capsule study in dogs.

The nonclinical single dose PK properties of vadadustat are characterized by low plasma CL in rats (males: 145 mL/hr/kg; females: 226 mL/hr/kg) and low-to-moderate plasma CL in dogs (males: 10.4 mL/min/kg; females: 8.27 mL/min/kg). The Vss was low in rats (males: 182 mL/kg; females: 258 mL/kg), lower than the volume of total body water. Estimates of the Vss in male and female dogs were moderate with values of 2.50 and 0.579 L/kg, respectively, which were similar to or slightly larger than the volume of total body water. Terminal $T_{1/2}$ values of vadadustat following oral administration are short in rats (0.5 to 2 hr in single-dose PK study, 1 to 6 hr in single and repeat-dose TK studies) and dogs (2 to 5 hr in single and repeat-dose TK studies and 4-9 hr in a single-dose oral capsule PK study). The PK properties of vadadustat were generally similar in male and female animals. There was no marked difference in vadadustat AUC_{0-last} values between the fed and fasted state in male Beagle dogs, as explored as part of the in vivo DDI studies conducted with phosphate binders.

In the 4 rat TK studies, there was no sex difference or significant accumulation upon repeated oral administration for up to 182 days. Oral vadadustat was rapidly absorbed (T_{max} of 1 to 2 hr) in all 4 studies. In the 3 rat TK studies with dosing durations of up to 3 months with doses ranging from 30 to 240 mg/kg/day, increases in C_{max} were less than dose proportional on Day 1 and day last regardless of the dose range examined; whereas, AUC_{0-last} on Day 1 and day last was dose proportional in the 28-day and 3-month studies, but greater than dose proportional on both sampling days in the 14-day study. In the 6-month TK study, both C_{max} and AUC_{0-last} on Day 1 were greater than dose proportional on Day 1 and essentially proportional up to 40 mg/kg and less than proportional at doses ≥40 mg/kg on Day 182. In the 3 dog TK studies, there was no sex difference or accumulation upon repeated oral administration for up to 274 days. Oral vadadustat was rapidly absorbed (T_{max} of 1 to 2 hr) in all 3 studies. In the 28-day TK study exploring doses of 30 to 120 mg/kg/day, increases in C_{max} on Days 1 and 28 were essentially dose proportional; however, increases in AUC_{0-last} on both sampling days were greater than dose proportional. In the 90-day TK study in which doses of 25 to 90 mg/kg were evaluated, increases in C_{max} and AUC_{0-last} on Days 1 and 90 were dose proportional. In the 9-month study exploring doses of 10 to 50 mg/kg/day, increases in C_{max} and AUC_{0-last} on Days 1 and 274 were greater than dose proportional. In the 2 rabbit developmental toxicity studies, orally administered vadadustat was rapidly absorbed (T_{max} of 1.0 hr) with short T1/2 (1.21 to 3.13 hr), which was not affected by dose or repeat administration. Based on mean C_{max} and AUC_{0-last} values, vadadustat exposure in pregnant rabbits increased greater than dose-proportionally with repeat administration. Vadadustat PK was nonlinear in pregnant rabbits, possibly due to saturation of tissue uptake and CL. In human subjects, increases in plasma exposure to vadadustat are dose-proportional.

In 3 mice TK studies, oral vadadustat was rapidly absorbed (T_{max} of 0.5 to 1 hr) in all 3 studies and no significant accumulation occurred upon repeated oral administration for up to 180 days. No sex differences were observed in the 2- and 3-months studies in mice, however, there appeared to be a sex-related difference (>2-fold) in systemic exposure in the 6-months carcinogenicity study in mice. In the 2-months TK study in which doses of 50 to 300 mg/kg were evaluated, increases in C_{max} was less than dose-proportional for males on Day 1 and for females on Days 1 and 56 and increases in $AUC_{0\text{-last}}$ were slightly greater than dose proportional for males on Day 1 and on both evaluation days for females. In the 3-months TK study, C_{max} increased in a less than dose-proportional manner in both sexes on Days 1 and 91. On Day 1, $AUC_{0\text{-t}}$ increased in a dose-proportional manner from 25 to 200 mg/kg/day for females but in a less than dose-proportional manner from 50 to 200 mg/kg/day for males. On Day 91, $AUC_{0\text{-t}}$ increased in a less than dose-proportional manner from 25 to 150 mg/kg/day for both sexes, but in a greater than dose-proportional manner from 150 to 200 mg/kg/day for females only. In the 6-months TK study exploring doses of 5 to 50 mg/kg/day, systemic exposure to vadadustat increased in a greater than dose-proportional manner from 5 to 50 mg/kg/day on Days 1 and 180 for males and in an approximately dose-proportional manner for females. Formation of two metabolites, vadadustat-O-glucuronide and vadadustat-acyl-glucuronide, were measured in the 3 months TK study in mice, where the metabolite-to-parent compound ratios ranged from 0.00914 and 0.168 for vadadustat-O-glucuronide and 0.00168 and 0.0173 for vadadustat-acyl-glucuronide, respectively. The exposure ($AUC_{0\text{-last}}$) to vadadustat-O-glucuronide on Day 91 when compared to Day 1 did not change at 100, 150, and 200 mg/kg/day, except for female animals at 200 mg/kg/day where the exposure was increased by approximately 2-fold. $AUC_{0\text{-last}}$ generally increased in a dose-proportional manner from 50 to 200 mg/kg/day. Apparent terminal $T_{1/2}$ for vadadustat-O-glucuronide ranged from 1.1 to 2.1 hr and was unaffected by dose or repeated administration. On Day 1, vadadustat-acyl-glucuronide $AUC_{0\text{-last}}$ increased in a greater than dose-proportional manner between 50 and 200 mg/kg/day. On Day 91, vadadustat-acyl-glucuronide $AUC_{0\text{-last}}$ increased in a greater than dose-proportional manner from 50 to 150 mg/kg/day in females and generally increased in a dose-proportional manner from 50 to 200 mg/kg/day in males. Accumulation was observed for vadadustat-acyl-glucuronide ranging from 0.377 to 3.88. Apparent terminal $T_{1/2}$ for vadadustat-acyl glucuronide ranged from approximately 1.1 to 3.3 hr and was unaffected by dose or repeated administration.

Distribution

In vitro, vadadustat exhibited high protein binding in plasma across all species tested (≥93.2% bound), with the highest extent of binding observed in human plasma (≥99.5% bound). Vadadustat-O-glucuronide exhibited moderate binding to human plasma (~88% bound) and to a lesser degree to rat plasma (84.9% to 85.6% bound) and mouse plasma (68.9% to 72.9% bound). The potential for vadadustat to partition into erythrocytes in whole blood in vitro has not been investigated. In the in vivo tissue distribution studies conducted in the rat and dog, levels of [^{14}C]-vadadustat-related radioactivity were consistently higher in plasma than in whole blood, suggesting that [^{14}C]-vadadustat-related radioactivity does not partition preferentially into erythrocytes.

Tissue distribution was investigated in Sprague-Dawley rats and Beagle dogs by assaying radioactively labelled vadadustat by Liquid scintillation counting (LSC). Following administration of [^{14}C]-vadadustat to rats and dogs, radioactivity was rapidly distributed to highly perfused organs such as the liver and kidneys with trace levels observed at 24 hr post-dose. In vivo distribution using [^{14}C]-vadadustat in rats and dogs indicated that radioequivalents distribute at low levels to the brain. In rats, the $T_{1/2}$ from different tissues were short and ranged from 2.3 to 6.7 hr. Aside from the liver, the highest amount of radioactivity remained in the stomach/GI tract and contents, however, only small amounts remained by the end of the study. Slightly longer $T_{1/2}$ were observed in dogs than in rats as tissue elimination half-life of radioactivity ranged from 3.8 to 8.3 hours with two exceptions. The longest $T_{1/2}$ was

observed for testes (19.5 hr) and adrenals (14.9 hr) for which large relative amounts remained after 24 hr compared to the initial time point at 2 hr (27% in adrenals and 34% in testes). Data does not suggest an accumulation of radioactivity in the adrenals and testes, however, increasing tissue-to-plasma ratios and longer elimination $T_{1/2}$ does suggest a slower elimination of radioactivity from these two tissues than from plasma. The total measured radioactive material in these tissues were less than 0.3% of the ^{14}C-dose by 2 hr which further declined to negligible amounts by 24 hr. In the repeat dose toxicity studies in dogs, adrenal histopathological changes were observed that were only partially reversible, which may correlate with the retention of drug substance in the adrenals. No effects have been observed on male fertility in rats in a reproductive study or in the repeat-dose toxicity studies in dogs for up to 9 months. Radioactivity passed the placental barrier in gravid rats and was present in fetal tissues at radioequivalents lower than in maternal tissue and were below the limit of quantitation by 24 hr post administration. Single p.o. administration of 50 mg/kg [14C]-vadadustat to lactating rats on postpartum day 11 showed that drug-related radioactivity was transferred into the milk. The ratio of milk concentration of radioactivity to the plasma concentration in rats was a maximum of 14.49 at 8 h after administration. The ratio of AUC0-last of the radioactivity concentration in the milk to AUC0-last of the radioactivity concentration in the plasma was calculated to be 6.13 (study No AE-8106-G).

The potential distribution to pigmented tissue is not considered sufficiently investigated as a pigmented rat species (e.g. Long Evans rats) was not used and as only "eyes" and "washed skin fur" was investigated in rats without considering specific distribution to the eye lens and uveal tract as well as differentiating between pigmented and non-pigmented skin. Further, skin was not included in the dog distribution study at all. However, available data in Sprague Dawley rats and Beagle dogs indicate that limited distribution occurs to the skin and eyes, thus the potential for distribution to pigmented tissues appear to be low as well as the risk for accumulation. Further, it was demonstrated in an in vivo study in Long-Evans (Crl:LE) pigmented rats that vadadustat is of limited phototoxic potential. Though distribution data in pigmented tissue is not available, this is considered acceptable as further information would not add to the current conclusion. Thus, no further information is warranted.

Metabolism

In three studies vadadustat was stable in in vitro incubations with mouse, rat, dog, monkey, or human liver microsomes at high protein concentrations (2 mg/mL), suggesting that metabolism via CYP P450 is unlikely (study Nos 1473, 9AKEBP2 and XT134105).

The microsomal stability of vadadustat in human kidney, intestine and liver microsomes was determined using high resolution mass spectrometry. Vadadustat was fairly stable in the in vitro microsomal incubations, though some formation of glucuronide metabolites was observed. One of the glucuronides was identified using an authentic standard of vadadustat-O-glucuronide, which was formed primarily in kidney microsomes (study No MC17M-0103).

The metabolism of vadadustat in rat, dog, and human hepatic microsomes, rat urine and human plasma and urine indicated that plasma contained predominantly parent vadadustat and a small amount of acyl-glucuronide that was the major metabolite excreted in urine. It was also determined that the major metabolic pathway in human, glucuronidation, was also present in rat and dog (study No AKB-001A). No human specific metabolites were identified.

Based on the results that vadadustat is not extensively metabolized by CYP P450 isozymes. Therefore, only human UGT phenotyping experiments were conducted, and CYP P450-based phenotyping assays were not conducted. UDP-glucuronosyltransferase reaction phenotyping of vadadustat showed that vadadustat-acyl-glucuronide was catalyzed by UGT1A1, UGT1A7, UGT1A8 and UGT1A9 and acyl-glucuronide was formed by UGT1A1 and UGT2B7 (study No XT134104).

In vivo rat and dog metabolism studies using [14C]-vadadustat demonstrated that vadadustat-O-glucuronide is the principal circulating metabolite in rats whereas, B-504 and vadadustat-O-glucuronide are the principal circulating metabolites in dogs. Vadadustat-O-glucuronide was primarily excreted via urine, while B-504 was the most abundant metabolite in the feces. Several other metabolites were observed but were not quantifiable due to the low levels of these metabolites (study Nos XS-1131 and XS-1133). The highest level of vadadustat-O-glucuronide observed after 3-month p.o. repeat-dose administration of vadadustat in mice was 17% of the parent AUC, and the vadadustat-acyl-glucuronide metabolite was found to be <2% of the parent AUC (study No 20035235). Metabolite B504 is also identified as an organic process-derived impurity of vadadustat, which is included in the drug substance specification. A toxicological evaluation has been performed in the toxicological section, where it is concluded that B504 is not of toxicological concern.

Excretion

Mass balance studies showed that the major elimination pathway for [14C]-vadadustat-derived radioactivity in the rat (study Nos 0830RA104.001 and XS-1129) and dog (study Nos 0831DA104.001 and XS-1132) was via hepatobiliary elimination into faeces, which was mainly in the form of parent drug. B-504 was the most abundant metabolite in faeces in rats accounting for approximately 10 to 14% of the dose. Urine elimination only accounted for up to 15% of the dose, which was mainly in the form of vadadustat-O-glucuronide in both species. Vadadustat showed high levels of biliary excretion (approximately 80% of dose) in rats. These data suggest that the fraction absorbed for vadadustat accounted for approximately 93% of the dose, which can be further corroborated with high oral bioavailability observed in a pharmacokinetic study. Approximately 23% of the radioactive dose underwent entero-hepatic recirculation in rats (study No XS-1129). The route of elimination of vadadustat in animals differs from that observed in humans. Urinary excretion is the primary route of elimination of vadadustat and metabolites in humans.

Single p.o. administration of 50 mg/kg [14C]-vadadustat to lactating rats on postpartum day 11 showed that drug-related radioactivity was transferred into the milk. The ratio of milk concentration of radioactivity to the plasma concentration in rats was a maximum of 14.49 at 8 h after administration. The ratio of AUC0-last of the radioactivity concentration in the milk to AUC0-last of the radioactivity concentration in the plasma was calculated to be 6.13 (study No AE-8106-G).

Pharmacokinetic drug interactions

A battery of in vitro assays evaluating the potential effect of vadadustat and vadadustat-O-glucuronide (the primary circulating metabolite in humans) on transporter test systems (substrate or inhibitor), UGT inhibition and CYP induction and inhibition was undertaken to determine the potential for drug interactions. The permeability of vadadustat and vadadustat-O-glucuronide was also assessed. Additionally, potential pharmacokinetic interactions between vadadustat and selected phosphate binders were investigated.

Based on CYP inhibition studies for vadadustat (study No 8275722) and vadadustat-O-glucuronide (study No XT175102), the potential to be a perpetrator of a CYP-mediated drug interaction via direct-, time-, or metabolism-dependent inhibition was unlikely at clinically relevant exposures in humans. In human hepatocyte incubations, vadadustat did not induce CYP1A2 or CYP3A4. Vadadustat is an in vitro inducer of CYP2B6 in human hepatocytes. Co-administration of vadadustat with sensitive substrates of CYP2B6 (e.g. efavirenz, bupropion) may alter the pharmacokinetics of these drugs (study No 8273558).

In vitro, vadadustat inhibited UGT1A1 with an IC50 value of 110 µg/mL. Based on application of a mechanism-based static pharmacokientic model, vadadustat is unlikely to cause a clinically relevant drug interaction via UGT1A1 inhibition in the intended patient population (study No XT11A028). In

vitro, vadadustat-O-glucuronide did not inhibit UGT1A1 or UGT1A9 (study No XT175102). In human hepatocyte incubations, vadadustat induced UGT1A1 mRNA expression at the highest concentration tested; however, changes in gene expression did not show a clear dose-dependence, and vadadustat did not increase UGT1A1-mediated enzyme activity. UGT1A1 induction is unlikely to result in a clinically relevant drug-drug interaction at clinically relevant exposures to vadadustat in humans (study No 8273558).

In vitro, vadadustat inhibited BCRP and OATP1B1 (study No XT138057), and both vadadustat and vadadustat-O-glucuronide inhibited OAT1 and OAT3 (study No XT138057). An accurate measurement of the IC50 value for P-gp inhibition by vadadustat could not be determined due to solubility limitations in that assay (study No XT178101). Calculation of R-values at relevant exposures to vadadustat and its major metabolite in patients revealed that inhibition of BCRP, OATP1B1, OAT1, and OAT3 may lead to a clinically relevant drug interaction with drugs that are sensitive substrates of these transporters. Clinical drug-drug interaction studies have been conducted to investigate whether in vitro inhibition of these transporters translates to alterations in PK parameters of sensitive substrates (see Summary of Clinical Pharmacology Studies).

In vitro, vadadustat was found to be a substrate of BCRP, OATP1B1, OAT1, and OAT3 (study Nos XT138057 and XT178101). Vadadustat-O-glucuronide was found to be a substrate of OATP1B3 (study No XT138057), MRP2 (study No XT138057) and OAT3 (study No XT138057). In a clinical drug-drug interaction study, co-administration of vadadustat with probenecid, an OAT1/OAT3 inhibitor led to an increase in AUC, indicating that co-administration of vadadustat with OAT inhibitors may lead to alterations in vadadustat PK properties. In contrast, in clinical drug-drug interaction studies, co-administration of vadadustat with cyclosporine (a BCRP, P-gp, and OATP1B1 inhibitor) did not impact the PK of vadadustat, suggesting the PK parameters of vadadustat are not expected to be affected by inhibitors of these transporters (see Summary of Clinical Pharmacology Studies).

In vivo drug-drug interaction studies with phosphate binders showed that there was a pharmacokinetic interaction of vadadustat with ferrous sulfate (study No 20190760) which was further investigated in a clinical drug-drug interaction study.

The Applicant has performed several investigative studies of the PK properties of vadadustat during the developmental stage. All studies support the current conclusions and the results are therefore not referenced in detail in the report.

2.5.4. Toxicology

The toxicology profile of vadadustat has been evaluated in single- and repeat-dose studies following oral administration across multiple species (mice, rats, and dogs) for up to 6 and 9 months in rats and dogs, respectively, and in reproductive and developmental toxicity studies in rats and rabbits. Genotoxic potential was assessed in vitro and in vivo in rats, and carcinogenicity was assessed in mice and rats. A dose-related erythropoietic response was observed in mice, rats, and dogs, showing that the appropriate pharmacological response occurs in the toxicological species used.

2.5.4.1. Single dose toxicity

No mortalities were observed in rats or dogs following single dose administration of 2000 mg/kg and 700/450 mg/kg, respectively. Dose limiting emesis were observed in dogs at doses ≥450 mg/kg, however, no other clinical pathology changes were observed. Liver effects in the form of vacuolation and inflammation as well as increased liver enzyme levels were observed in rats at ≥1000 mg/kg.

Furthermore, a weight loss of approximately 10% was noted in male rats at ≥1000 mg/kg. Other observed effects were pharmacologically related, occurring secondary to increased erythropoiesis.

2.5.4.2. Repeat dose toxicity

The main findings in rats after repeated oral dosing with vadadustat formulated in 0.25% (w/v) HPMC/0.1% Tween 80 were primarily pharmacologically mediated effects with increases in reticulocyte count and erythrocyte mass as a sign of increased erythropoiesis occurring at doses ≥ 40 mg/kg. Effects considered secondary to the pharmacological effects were also observed, i.e. increased blood viscosity presumably due to increased circulating erythrocyte mass (polycythemia), increased haematopoiesis resulting in cellular hypertrophy/hypercellularity, decreased tissue perfusion as well as congestion and haemorrhage in organ tissues leading to increased organ weights (i.a. spleen and lung). A prolongation of coagulation time (APTT) was also observed in one study, likely attributed to increases in erythrocyte mass. Further, alterations in parameters related to iron are observed, which are likely secondary to altered erythropoiesis and utilization of iron for heme (Hb) synthesis. Generally, the observed effects were not considered adverse as they were considered pharmacologically related, of low severity and were reversible. The Applicant has defined the level of adversity for increase in erythrocyte mass as the vadadustat dose that increases the circulating erythrocyte mass to levels that is associated with the fibrin thrombosis and necrosis leading to ischemia or infarctions in tissues such as heart, kidney, GI tract, lung and skeletal muscle, ultimately resulting in mortality. Fibrin thrombosis and necrosis in organs are considered to occur secondary to the pharmacologically induced hyperviscosity. The lowest dose level observed to result in mortalities following fibrin thrombosis and necrosis in rats were 60 mg/kg. At dose levels in animals where polycythemia, fibrin thrombosis and necrosis did not result in mortalities, the effects were reversible. Thus, the lowest NOAEL across the rat studies were derived at 40 mg/kg.

The initial toxicology studies in rats were performed with a solution of vadadustat in 1% methylcellulose (MC). However, unexpected mortality and moribundity was observed in a 14-days GLP study in rats, presumably due to the viscosity of the dosing suspension leading to issues with the dosing procedure, as 51 gavage-error deaths across all dose groups were observed. Subsequently, all toxicology studies were performed using a less viscous formulation with 0.25% (w/v) HPMC/0.1% Tween 80. Of further note, heart valvular findings (left atrioventricular (AV) valvular lesions, valvular endocardiosis (stromal thickening) and AV valve thrombus with fibrin) were observed in the 28 and 90 days GLP rat studies at ≥80 and ≥80/70 mg/kg, respectively (study KGI00028 and 20002194). The valvular changes were primarily associated with a thrombus (frequency of association: 67% in the 28-day study and 100% in the 90-day study). Heart valvular findings were only observed in the presence of polycythemia in rats and were not observed in dogs. The rat valvular histopathologic findings differ from those observed in serotonin receptor 5-HT2B-mediated drug-induced valvulopathy associated with anorectic drugs (fenfluramine/phentermine), as vadadustat did not show selectivity for the 5-HT2B receptor. It appears that rat heart valve pathology associates with polycythaemia, irrespective of whether it be through pharmacologic activation of the HIF pathway via prolyl hydroxylase (PHD) inhibition or through the nonpharmacological mechanism of hypoxia, resulting in the species-specific finding for rat heart physiology, a mechanism that is not unique to vadadustat.

Furthermore, focal C-cell hyperplasia was observed in two females at 20 and 60 mg/kg, respectively, and a single case of focal C-cell adenoma was observed in one female at 40 mg/kg in the 6 months GLP study (20008611). The Applicant states that the C-cell changes are thought to be unrelated to vadadustat administration given the absence of a clear dose-response or effect on thyroid weight. Further, no similar findings have been observed in the other rat studies or in repeat dose studies in dogs.

Effects observed in dogs appear to be similar to those observed in rats, with main findings related to the pharmacology of the active substance in repeat-dose studies up to 9 months. Pharmacologically-mediated effects with increases in reticulocyte count and erythrocyte mass as a sign of increased erythropoiesis occurred at doses ≥45 mg/kg. Secondary effects to increased erythropoiesis, i.e. hyperviscosity, were similar as those observed in rats, however, observed at a lesser degree in dogs. Based on an unscheduled death at 50 mg/kg in the 9 months dog study (20008612), which were related to polycythemia/hyperviscosity, the overall lowest NOAEL identified in dogs were 25 mg/kg. Emesis were observed in the 7-, 14- and 28 days dog study at doses ≥120 mg/kg, resulting in transient decreased body weight and food consumption, but was not observed in the subsequent studies in dogs, in which lower dose levels were investigated. Increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were noted in some studies in both rats (7 days non GLP, study SW08-0264) and dogs (28 days GLP, study KGI00029). Elevated liver enzymes have also been observed in patients (included in SmPC section 4.8 and as an identified risk in the RMP section 2.7) with increases in i.e. AST, ALT and bilirubin. Elevated liver enzyme levels are however reversible in both animals and patients following drug discontinuation and the clinical risk of developing hepatotoxicity is considered low. Thymic atrophy of minimal to moderate severity was observed across the 7-, 14- and 28-days studies (SW08-0193, KGI00007, KGI00029) in dogs (observed at 60 mg/kg in the 14 days study as the lowest dose). A single finding of small thymus was found in one male dog at 120 mg/kg after 28 days dosing, which corresponded microscopically with thymic atrophy. The thymic changes correlated with decreased mean thymic weights, though the weight change was non-linear and not statistically significant in 28 days dog study. The findings were characterized by decreased thymic tissue and loss of distinction between cortex and medulla. The microscopic findings and organ weight changes were reversible and immunostaining in the 28 days study showed no treatment related effects on cell proliferation. No direct cause for the thymic findings could however be identified, and the Applicant states that the relationship of vadadustat treatment to the thymic atrophy is equivocal, as it may also have been associated with a physiologic process (involution) or a secondary response to general stress or illness. The finding was not observed in dog studies of longer duration or in rats.

Adrenal gland histopathology changes were observed in studies in dogs of 14 days to 9 months duration at all dose levels. The adrenal gland changes in the cortex consisted of non-proliferative mononuclear infiltrates, hypertrophied multinucleated cells and single cell necrosis, which were minimal to mild in severity and at least partially reversible. No associated changes in clinical signs or adrenal weights were observed, nor any clinical chemistry parameters (i.e. decreases in sodium or chloride, nor correlation to increases in haemoglobin or haematocrit levels) to indicate adrenal gland insufficiency or dysfunction. Further, the histological findings were not considered associated with increased potassium levels. Results of cytologic evaluation of impression smears from adrenal glands did not provide evidence that the mononuclear cell infiltrates observed histologically were related to extramedullary haematopoiesis. The findings correlated with slow vadadustat elimination from the adrenal gland tissue in the distribution study in dogs, however, no accumulation was observed. In rats, increased adrenal weights correlating microscopically with minimal adrenal cortical hypertrophy were observed in some animals in the 90 days and 6 months GLP rat studies (90 days: ♀ at ≥80/70 mg/kg, ♂ 120/90 mg/kg; 6 months: surviving ♀ at ≥ 40 mg/kg) (study 20002194 and 20008611). The adrenal changes observed in rats are morphologically different from those observed in dogs. The Applicant discussed the relevance of the rat findings as a possible nonspecific stress response which was furthermore fully reversible. According to the Applicant, increased adrenal weights may also be an effect of increased RBC mass in blood vessels.

Effects in mice appear to be similar as those observed in rats and dogs. A mouse-specific (dose-independent) finding was observed in both Tg-rasH2 (CByB6F1) and CD-1 strains and consisted of necrosis and acinar atrophy of the lacrimal gland. The Applicant stated that the effects are most likely observed due to altered circulation related to increased Hct levels. As the effect has only been

observed in mice and as it was of low severity, it is accepted that the effect is considered of low clinical relevance. The NOAEL in mice was established at levels where the pharmacologically mediated effects did not result in mortalities in the main group, and thus the lowest overall NOAEL in (Tg-rasH2) mice was 100 mg/kg/day. Several mortalities were however also observed in the satellite TK and haematology groups in the 3 months study in CD-1 mice (study 20035235) starting from 50 mg/kg and above. The Applicant states that mortalities in the satellite group were also related to excessive pharmacology as observed in the main group and that the number of mortalities relative to the number of animals in the two high dose groups are comparable. Exposure margins for the satellite groups were between 0.41-1.24-fold and were comparable to other species.

2.5.4.3. Genotoxicity

Vadadustat was negative for mutagenicity (Ames assay) but positive results were obtained in the in vitro CHO assay for chromosomal aberrations and the GreenScreen assay. The positive in vitro chromosome aberration assay with CHO cells and equivocal GreenScreen assay suggested that vadadustat may be clastogenic and/or aneugenic. However, according to the Applicant both assays have previously been reported to have irrelevant positive results or to be influenced by cytotoxicity. Thus, a positive result, particularly when noted in the presence of either cytotoxicity or high levels of precipitation, is often not predictive of a positive carcinogenic outcome. Of note, vadadustat was not clastogenic in vivo in male SD rats nor did vadadustat cause DNA damage to liver cells in a COMET assay. Overall, the in vivo chromosome aberration assay and COMET assays tested negative and, in conjunction with the negative Ames assay result, the weight of evidence suggests that vadadustat is not genotoxic, which is agreed.

2.5.4.4. Carcinogenicity

A 6-month study was conducted to investigate the carcinogenic properties of vadadustat in transgenic mice. The main findings in the study were similar to the pharmacologically mediated effects observed in the dose-range findings studies and haematology PK study in mice and were generally related to increased erythropoiesis. Some tumour findings were observed in male and female mice, e.g. bronchioalveolar adenomas, splenic haemangiosarcoma, and/or harderian gland adenoma were statistically significant or fell outside of the historical control range for the laboratory. However, the findings are not considered treatment related as no statistically significant evidence of increased incidence of tumors in either sex that is outside the historical or published incidences in control animals with this strain of mouse is present.

The carcinogenic properties of vadadustat was furthermore investigated in SD rats. Due to the study protocol, the treatment groups were euthanized early when only 20 animals/sex remained in each the treatment group or the related control group. The carcinogenicity study in rats was scheduled for 104 weeks of daily treatment, however it was terminated at week 85/86 for females and week 94 for males as no signs of pre-neoplastic changes was observed or any other sign of toxicity increasing over time. The primary effects in rats dosed up to 20 mg/kg were the same as observed during the shorter term studies, i.e. pharmacologically related effects occurring in response to increased erythropoiesis. A statistically significant increasing trend in the incidence of benign granular cell tumor in the cervix, adrenal gland malignant pheochromocytoma and hepatocellular adenoma were noted in females. However, due to lack of dose-response relationship in the case of benign granular cell tumor in the cervix and the lack of vadadustat-related preneoplastic or other neoplastic changes in the adrenal gland or liver, the observed tumours were not considered treatment-related. As the incidence of pheochromocytoma was not statistically significant, this tumor was not considered to be related to treatment with vadadustat by both the study pathologist and peer review pathologist. The statistically

significant increase in adrenal gland malignant pheochromocytoma in female rats may raise some concern, when viewed together with the adrenal gland findings observed in repeat-dose studies in rats and dogs as well as the mode of action of vadadustat involving the HIF-signaling pathway. In dogs, the adrenal gland changes in the cortex consisted of non-proliferative mononuclear infiltrates, hypertrophied multinucleated cells and single cell necrosis, while in rats, increased adrenal weights correlating microscopically with minimal adrenal cortical hypertrophy were observed. Further, in the distribution study in dogs, it was observed that the elimination from the adrenal glands were slower than from plasma indicating retention, but not accumulation, in the tissue. The Applicant states that malignant pheochromocytomas are commonly observed in this strain of rat, and the incidence at the vadadustat high dose (4.29%) is within the historical control limits of the testing facility (1.67% - 6.00%). Though non-neoplastic adrenal findings were observed in both dogs and rats in the shorter duration repeat-dose studies up to 6 months, the adrenal findings were isolated to minimal hypertrophy of the adrenal cortex, whereas pheochromocytomas originate from chromaffin cells in the adrenal medulla. Thus, it is unlikely that there is any correlation between the findings in the short-term rat and dog studies with the pheochromocytomas findings in the 2-year rat study. Further, the Applicant states that no vadadustat-induced preneoplastic changes or benign tumours were observed in the adrenal medulla in the 2-year rat study.

2.5.4.5. Reproductive and developmental toxicity

In a dedicated fertility study in rats, no treatment-related effects were observed on male or female fertility parameters. Five unscheduled mortalities (one male at 80 mg/kg and 4 males at 120 mg/kg) were observed in correlation with treatment-related clinical signs including limb function impairment, scabbed area, black and watery feces, posture hunched, thin, unkempt appearance, decreased and rapid breathing, bilateral limb function impaired, decreased activity. Further, red discoloration of several organs was observed as well as enlarged spleen. These findings are similar to those observed in the general toxicity studies in rats related to exaggerated pharmacological effects. The general NOAEL of the study is 40 mg/kg whereas the NOAEL for fertility is 120 mg/kg.

Embryo-fetal developmental (EFD) toxicity was investigated in rats and rabbits. In rats, maternal toxicity was observed including reduced body weight gain and food consumption at ≥80 mg/kg/day while developmental toxicity was observed at 160 mg/kg/day including a reduction of mean fetal body weight corresponding to an increased incidence of reduced skeletal ossification. The NOAEL in rats is therefore established at 40 mg/kg/day for maternal toxicity while a NOAEL of 80 mg/kg/day is established for developmental toxicity. The developmental effects are considered to occur secondary to maternal toxicity. TK investigations confirmed that there is no difference in PK profile in gravid and nongravid rats. As pharmacological effects are observed at ≥40 mg/kg/day in the general toxicology studies, it is considered that sufficient exposure is achieved in the EFD study in rats. In rabbits, four deaths occurred at 50 mg/kg of which two could not be ruled out as treatment related. In one case, the animal was euthanised due to difficult and audible breathing. In the other cases, the cause of death could not be determined. No dose-response related developmental effects were observed in the study. For rabbits, a maternal NOAEL of 25 mg/kg/day is established, while the developmental NOAEL is 50 mg/kg/day. No teratogenic effects were observed in rats or rabbits at dose levels up to 160 and 50 mg/kg/day, corresponding to exposure multiples of 1.7 and 0.16 (to NDD-CDK patients), respectively. In the dose-range finding study in rats, up to 240 mg/kg/day was administered. No fetal teratogenicity was observed at any dose level, however, an increase in post-implantation loss was observed at ≥ 120 mg/kg/day and decreased fetal body weight at 240 mg/kg/day, which is consistent with previously published data in mice, which suggest that HIF-1α dependent pathways are important for maintenance of pregnancy. The effects were furthermore observed at doses that led to substantial

maternal toxicity. Based on the available data, it is accepted that vadadustat does not appear to have teratogenic potential at clinically relevant dose levels.

In a pre- and postnatal developmental study in rats, no effects of vadadustat were observed in the pregnant/lactating female rat and on the development of the conceptus and the offspring following exposure of the female from implantation through weaning. A slight reduction in body weight was observed in F1 females at 80 mg/kg/day during the study, however, body weights returned to control levels during the F1 growth phase and is thus not considered adverse. The maternal and developmental NOAEL is 80 mg/kg/day.

Vadadustat-related effects were investigated in juvenile rats in a 10-week study including a 6-week recovery period. The study used dose escalation as a lower dose was given from PND7-27 (5, 15 and 30 mg/kg), which was increased from PND28-76 (10, 30 and 80 mg/kg). The effects observed in juvenile rats were generally similar to effects observed in the general toxicological studies in adult rats (7 weeks to 6 months repeat dose studies), which have been discussed above. Mortalities were observed at the high dose level due to lung lesions, cardiac thrombosis with septicemia, lung lesions with septicemia, renal thrombosis with infarct, systemic thrombosis and cardiac thrombosis. The effects are considered a result of polycythemia/hyperviscosity due to the pharmacological action of vadadustat. Microscopic findings were present in several organs at 40/80 mg/kg, e.g. stromal proliferation of the valve and epicardial inflammation in the heart as well as nephropathy, tubular mineralization and focal vascular/perivascular inflammation in the kidneys. Some of the histological findings in organs were only partly reversible, however, they were considered of low severity and were also observed in adult animals. Reduced body weight and food consumption was observed at 40/80 mg/kg, which persisted in males at the end of the recovery period. The NOAEL for the effects were established at 15/30 mg/kg based on haemorrhage/necrosis of organs and thrombosis resulting in mortality observed at 40/80 mg/kg. Overall, the findings in juvenile rats are in line with the observations in adult rats at similar dose levels. Vadadustat had no effect on the day of sexual maturation in either males or females.

2.5.4.6. Toxicokinetic data

Effects in the repeat-dose toxicology studies in rats, dogs, mice and rabbits generally occurred at very low exposure ratios and consequently fractional safety margins were identified at the NOAELs in the different species, e.g. 0.43 (NDD-CKD patients) and 0.64 (DD-CKD patients) in rats after 6 months; 0.07 (NDD-CKD) and 0.11 (DD-CKD) in dogs after 9 months; 0.50 (NDD-CKD) and 0.75 (DD-CKD) in mice after 3 months; 0.04 (NDD-CKD) and 0.06 (DD-CKD) in rabbits in the EFD study. The fractional safety margins, which indicate that the effects occur at clinically relevant dose levels, are of concern as the observed effects also occur close to the pharmacologically active dose level of 40 and 45-60 mg/kg in rats and dogs, respectively. Mortalities occurred in several of the studies in mice, rats and dogs, and NOAELs were derived at dose levels for which hyperviscosity did not result in mortalities. Mortalities occurred at 200 mg/kg in mice (female), corresponding to exposure multiples of 1.19 (NDD-CKD) and 1.79 (DD-CKD); 60 mg/kg in rats, corresponding to exposure multiples of 0.52 (NDD-CKD) and 0.79 (DD-CKD) and at 50 mg/kg in dogs (female), corresponding to exposure multiples of 0.19 (NDD-CKD) and 0.29 (DD-CKD). The lowest safety margin to observed mortalities occurred in rabbits in the EFD study, where mortalities occurred at exposure multiples of 0.16 (NDD-CKD) and 0.24 (DD-CKD) to the maximum therapeutic dose of 600 mg. In the studies, the main cause of mortality was thrombosis accompanied by haemorrhage and infarction in different organs. The cause of mortality is therefore relevant in patients as it is based on exaggerated pharmacology, i.a. polycythaemia and hyperviscosity, and thromboembolic events have been reported in patients (RMP Module SII, section 2.7). As mentioned above, the Applicant however states that haemoglobin levels will be monitored in

the clinic to avoid the occurrence of hyperviscosity. In the clinic, the incidence level of thromboembolic events for vadadustat is also not considered considerably worse compared to incidence levels reported for the already approved substance darbepoetin alfa (incidence level of 10.5% for vadadustat in the pooled CKD population for the Phase 3 studies compared to 9.5% for darbepoetin alfa). It should also be taken into account that animals used for the toxicological studies were not anaemic at study start, thus findings may be exaggerated in test animals compared to the anaemic state of the patients to be treated. When considering all the information provided by the Applicant, it is agreed that the risk of hyperviscosity-related mortality in patients appears to be low when suitable monitoring and regulation of haemoglobin levels to target values are employed in patients.

2.5.4.7. Local Tolerance

No dedicated local tolerance studies have been submitted, which is acceptable due to the oral dosing route.

2.5.4.8. Other toxicity studies

No specific studies have been conducted to investigate antigenicity or allergic reactions. Since vadadustat is targeting the erythropoietin production directly and not any mammalian target, and as no indication of antigenicity has been observed in the repeat-dose toxicity studies, this is acceptable.

It is considered acceptable that no information has been submitted on immunotoxicity as no relevant findings have been observed in the repeat-dose toxicity studies in rats and dogs to indicate an immunotoxic potential.

As there appear to be only limited transfer across the blood-brain barrier and as the mode of action is not CNS-related, it is acceptable that the potential for developing dependence is not further investigated.

Two metabolites of vadadustat were identified in mice, rats and dogs; O-glucuronide and acyl-glucuronide. Acyl-glucuronide is only found in low amounts in humans (< 1%) whereas O-glucuronide is found in large amounts in humans (54% to 74%). It is however accepted that O-glucuronide metabolites are generally unreactive and is thus of low toxicological concern. No further information is therefore warranted for the identified metabolites. B-504 was also identified as a metabolite in mice, rats and dogs and were primarily found in faeces. As B-504 is also identified as a process-derived impurity, a toxicological evaluation has been included in the impurities section below. No specific human metabolites have been identified.

One organic impurity has been included in the drug substance specification at a limit of 0.11%, corresponding to a qualification threshold of 0.66 mg/day considering a maximum daily intake of 600 mg. It is identified as a metabolite, which is formed in humans, dogs and rats. B504 is not considered of mutagenic potential based on in silico modelling using DEREK Nexus and Leadscope. Several other impurities are identified as mutagenic impurities in the manufacture of vadadustat. However, the Applicant has stated that the impurities are purged in the manufacturing process of the drug substance to levels below the threshold of toxicological concern (TTC) according to ICH M7, which is accepted.

Vadadustat is UV absorbent at 315 nm and is thus of phototoxic potential. In a Neutral Red Uptake in vitro assay using BalbC/3T3 cells, vadadustat was confirmed to have potential phototoxic properties by evaluation of both Photo-Irritation Factor (PIF) and Mean Photo Effect (MPE) endpoints. Vadadustat was investigated for phototoxic potential in vivo in Long-Evans pigmented rats, which were

administered 60, 180, and 400 mg/kg/day vadadustat once daily by oral gavage for 3 consecutive days. Following dosing of vadadustat, animals were exposed to ultraviolet B (UVB), UVA, and visible light from a xenon lamp. There was no evidence of ocular or cutaneous phototoxicity elicited by exposure to UVR in vadadustat-treated animals up to 400 mg/kg/day, based on ophthalmology and dermal scoring. A positive control (8-Methoxypsoralen) was included in the investigation, which behaved as anticipated. Distribution to pigmented tissue was not investigated in the distribution studies in Sprague-Dawley rats and Beagle dogs. However, the studies indicated that the distribution to skin and eyes in general were low and taken together with the results of the in vivo phototoxicity study, the potential for phototoxicity appears to be low.

In an investigative in vitro study, it was shown that vadadustat did not cause an increase in haemolysis at concentrations up to 1000 µM in the rat, mouse, or dog whole blood. However, a slight decrease in blood pH was noted in blood treated with vadadustat at 1000 µM.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1 Summary of main study results

Substance (INN/Invented Name): vadadustat			
CAS-number (if available): 1000025-07-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD107	pH 4: 2.8 pH 7: 0.35 pH 9: 0.14	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Default: Refined:	3.00µg/L 4.2µg/L	> 0.01 threshold Y
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Kd^{ads} sewage sludge: 900 - 2918 $L \cdot kg^{-1}$ Koc^{ads} sewage sludge: 2424 - 7334 $L \cdot kg^{-1}$ Kd^{ads} soil: 75.6 - 238 $L \cdot kg^{-1}$ Koc^{ads} soil: 7199 - 13262 $L \cdot kg^{-1}$	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Significant shift to sediment observed (> 10% AR in sediment at or after Day 14) 20ºC: Total System DT_{50}: 18.5 – 34.5 days Water DT_{50}: 2.21 – 7.28 Sediment DT_{50}: 37.4 – 118 12º C (normalised): Sediment DT_{50}: 254 days (Taunton river) One significant transformation product	Vadadustat is very persistent in sediment, based on normalised 12ºC DT_{50} value.

		observed and identified. Reaches stable concentrations in sediment up to 57.4%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	NOEC (0-72 h; population growth and yield)	1.8	mg/ L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC (21 day; reproduction, growth)	2.6	mg/ L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC (post-hatch larval survival)	2.1	mg/ L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEL (3 h; respiration)*	10	mg/ L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC (development rate)	860	mg/ kg	*Chironomus riparius*

The n-octanol/water distribution coefficient (log Dow) of vadadustat was determined according to the OECD guideline number 107 "Shake-flask method". The mean log D_{ow} values determined at pH 4, 7 and 9 were 2.8, 0.35 and 0.14 respectively. It appears that vadadustat is not lipophilic and is below the trigger value for a fish bioconcentration study (i.e. log Dow of 3), therefore no further investigation into bioaccumulation is required as part of Phase II B testing.

In the initial screening for PEC in surface water, the estimated PECsurfacewater for vadadustat using both the default and refined Fpen, based on prevalence data, resulted in a PEC above the trigger value of 0.01 µg/l. Therefore, a Phase IIA assessment according to EMEA/CHMP/SWP/4447/00 corr. 2 (EMA, 2006) is required.

To investigate the environmental fate of vadadustat, the Applicant performed studies OECD 301B (Ready Biodegradable), OECD 308 (Transformation in Sediment/Water Systems) and OECD 106 (Batch Equilibrium Method). The studies showed that vadadustat will likely not be rapidly degraded and is unlikely to significantly bind to sewage solids, thus rendering it available to be released into surface waters. When released to surface water, vadadustat is likely to rapidly partition to sediment (surface water DT50 value = 2.21 – 7.28 days). During the sediment/water transformation study *ca* 50 - 84 % of the applied radioactivity was detected in the sediment phase at Day 14. Thus, a toxicity study for sediment dwelling organisms are required in a Phase IIB assessment. Once present in the sediment system, vadadustat degrades at a moderate rate to form the major transformation product, (up to 57.4%), multiple minor degradation products and non-extractable residues. Based on the determined log D_{ow} value, it appears that vadadustat is not lipophilic and is unlikely to bioaccumulate. The normalized DT_{50} value for vadadustat in sediment to 12ºC was calculated according to the ECHA guidance on persistence, bioaccumulation, and toxicity (PBT) assessment (ECHA, 2017) based on the Taunton River system. The normalized DT_{50} value of 254 days shows that vadadustat is very persistent in sediment.

To investigate the potential aquatic toxicity of vadadustat, the Applicant performed toxicity studies in sewage microorganisms (OECD 209), Early Life Stage Toxicity Test in fish (OECD 210, *Pimephales promelas,* Growth Inhibition Test in algae (OECD 201, *Raphidocelis subcapitata*) and Reproduction Test in *Daphnia* sp (OECD 211). Significant effects on the reproduction of *Daphnia magna*, respiration of sewage sludge microorganisms and on the growth of green freshwater algae were observed in the respective studies. No significant effects were observed in the fish early lifestage study. The most sensitive aquatic species to vadadustat was green algae where the 72 h NOEC for growth rate was determined to be 1.8 $mg \cdot L^{-1}$. PEC values were derived for vadadustat according to EMEA/CHMP/SWP/4447/00 corr. 2 (EMA, 2006):

Compartment	Model	PEC
Sewage	CHMP/SWP/4447/00 corr. 2 (EMA, 2006)	42 $\mu g \cdot L^{-1}$
Surface water	CHMP/SWP/4447/00 corr. 2 (EMA, 2006)	4.2 $\mu g \cdot L^{-1}$
Groundwater	CHMP/SWP/4447/00 corr. 2 (EMA, 2006)	1.05 $\mu g \cdot L^{-1}$

PNEC values were derived using the outcome of the presented ecotoxicity data with appropriate chronic assessment factors (AF):

Group	PNEC
Sewage Microorganisms	1 $mg \cdot L^{-1}$
Fish	0.21 $mg \cdot L^{-1}$
Aquatic Invertebrates	0.26 $mg \cdot L^{-1}$
Algae	0.18 $mg \cdot L^{-1}$
Groundwater Organisms	0.26 $mg \cdot L^{-1}$

When comparing the PEC:PNEC ratio for the different endpoints, all risk quotient values were below 1, thus indicating that vadadustat does not pose a risk for the investigated environmental compartments. Further, it is not likely that vadadustat will bioaccumulate or be persistent. As the aquatic degradation data available for vadadustat indicate that its residues will partition rapidly to sediment (>10% AR at or after Day 14), further assessment for effects on sediment dwellers is required in Phase II Tier B.

The effects of vadadustat on the preemergent aquatic early life stages of the insect *Chironomus riparius* were investigated in OECD Guideline 218. A NOEC for the development rate was established at 860 mg/kg dry sediment, which was the highest concentration tested. The PEC value in sediment was estimated at 5.58 mg/kg dry sediment according to ECHA guidance document R.16 (ECHA, 2012). Further, a PNEC for sediment dwellers were derived according to the recommendations of EMA/CHMP/SWP/44609/2010 Rev 1. (EMA, 2016), resulting in a PNEC sediment value of 43 mg/kg dry weight. The PEC:PNEC ratio was below 1, thus indicating a low risk of vadadustat for sediment dwelling organisms.

No specific environmental precautionary and safety measures are required. The following statement is however still considered appropriate and proposed for the Summary of Product Characteristics (SmPC) and Package (Patient) Leaflet of the medicinal product:

SmPC Section 6.6: *'Any unused product or waste material should be disposed of in accordance with local requirements.'*

Package Leaflet: *'Do not throw any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.'*

2.5.6. Discussion on non-clinical aspects

Pharmacology

Overall, the in vitro and in vivo primary pharmacodynamic studies provided adequate evidence that vadadustat is a potent inhibitor of HIF-PHDs that leads to stabilization of HIF transcriptional factors resulting in EPO production and activation of the erythropoietic response. The general pharmacology studies showed vadadustat inhibited PHD enzymes, thereby stabilizing the two major human isoforms of the transcription factor HIF-α (HIF-1α and HIF-2α) and contributing to increased EPO but not VEGF secretion. Repeat-dosing of vadadustat in mice and rats resulted in dose-dependent increases in several haematological markers including EPO and haemoglobin. Thus, proof of concept, mechanism of action and mode of action were demonstrated. Vadadustat is a selective molecule as assessed against a broad panel of receptors, ion channels, and enzymes. There were no vadadustat-related adverse effects on the rat CNS nor on rat renal and respiratory function. In both rat and dog, vadadustat caused a transient decrease in blood pressure with a compensatory increase in HR. Vadadustat had no meaningful effect in the in vitro hERG assay and did not cause changes of P-QRS-T complexes in rats or dogs. Thus, no safety pharmacological concern was identified at clinically relevant doses. Studies on pharmacodynamic drug interactions were omitted.

Pharmacokinetics

Overall, the pharmacokinetics of vadadustat were well-described in pharmacological and toxicological animal species and no concerns were raised for the investigations of pharmacokinetic properties of vadadustat.

Toxicology

Toxicology was investigated sufficiently in toxicologically relevant animal models, including rats, rabbits and dogs for up to 6 and 9 months, respectively. In brief, several signals were detected that were considered relevant for translation to human administration, i.e. pharmacologically exaggerated toxicities such as polycythemia/hyperviscosity which resulted in fibrin thrombosis and mortalities at clinically relevant dose levels as well as heart valvular findings. It is considered that the clinical risk of hyperviscosity and mortalities are low as haemoglobin levels will be closely monitored and regulated to target values in patients. Furthermore, the Applicant provided data demonstrating a lack of evidence of polycythemia as an increased risk of cardiac valve disorders in patients. In conclusion, it has been accepted that cardiac valve disorder is not an important potential risk for vadadustat, and further, that cardiac valve disorder will be monitored by routine pharmacovigilance practice. Appropriate information has been included in the SmPC and RMP.

Low safety margins were reported to clinical dose levels in the Embryo-Fetal Developmental studies in rats and mice, i.e. 1.7 and 0.16 (in NDD-CDK patients), respectively, at the highest doses tested. No evidence of teratogenic potential was observed at the dose levels included in the studies, up to 240 mg/kg/day in the dose range finding study in rats, however, an increase in post-implantation loss was observed at $\geq$ 120 mg/kg/day and decreased fetal body weight at 240 mg/kg/day, which is consistent with previously published data in mice, which suggest that HIF-1α dependent pathways are important for maintenance of pregnancy. The effects were observed at doses that led to maternal toxicity. It is accepted that the current data does not indicate any potential for teratogenic effects even at higher doses.

Adrenal gland histopathology changes were observed in studies in dogs of 14 days to 9 months duration at all dose levels and in the 90 days and 6 months GLP rat studies. In clinical trials in dialysis dependent (DD) and non-dialysis dependent (NDD) CKD patients, adrenal disorders including adrenal insufficiency occurred in ≤ 0.1% of patients treated with vadadustat, however, these incidences were not considered related to treatment.The Applicant has included a discussion of human relevance of the findings in the RMP section 2.2 and 2.7, where it is stated that the changes are overall not considered relevant to humans.

Based on the carcinogenicity studies the Applicant concluded that vadadustat is of low carcinogenic potential in mice and rats. However, it is noted that there is an increased trend in the occurrence of malignant adrenal pheochromocytoma in female rats. Due to the adrenal histological findings in rats and dogs in the general toxicology studies, the mode of action of vadadustat via alterations of the HIF pathway which has been associated with functional abnormalities of the adrenal gland including pheochromocytoma(EMA scientific advice EMA/CHMP/SAWP/818714/2015), and as a retention of vadadustat is observed in the adrenal gland tissue in dogs, a concern was raised for the potential of vadadustat to induce the development of malignant adrenal pheochromocytoma in humans. The Applicant however provided historical control data, documenting that the finding was within the historical control range. Further, the non-neoplastic adrenal findings in both dogs and rats in the shorter duration repeat-dose studies up to 6 months were isolated to minimal hypertrophy of the adrenal cortex, whereas pheochromocytomas originate from chromaffin cells in the adrenal medulla, rendering it unlikely that there is any correlation between the findings in the short-term rat and dog studies with the pheochromocytomas findings in the 2-year rat study. It is therefore considered sufficiently demonstrated that the malignant pheochromocytomas findings in the 2-year rat study appears to be of limited clinical relevance. Based on the global Phase 3 clinical studies, the incidence rate of malignancy-related events was reported as 3.3% (2.1 events per 100 PY) in the RMP.

Appropriate information is included in section 5.3 of the SmPC.

Vadadustat is not a PBT substance. Considering the above data, vadadustat is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall the nonclinical part of the dossier is considered approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2 Phase 1 and Phase 2 Clinical Pharmacology Assessment for Vadadustat.

Study Number/ CTD Location	Description	Vadadustat Dose	Formulation	No. Subjects Enrolled (Treated/Placebo)
Phase 1				
AKB-6548-CI-0001/5.3.3.1	Single ascending dose in healthy male subjects	Fasted: 80,160, 300, 600, 900, 1200 mg oral single dose vadadustat or placebo Fed: 300 mg oral single dose vadadustat	Capsule	48 enrolled (36 vadadustat; 12 placebo)
AKB-6548-CI-0002/5.3.3.1	Multiple ascending doses in healthy male subjects	500, 700, or 900 mg/day vadadustat or placebo	Capsule	34 enrolled (25 vadadustat; 9 placebo)
AKB-6548-CI-0008/5.3.3.1	Radiolabeled ADME in healthy male subjects	650 mg single dose of ^{14}C-labeled vadadustat (100 µCi)	Capsule	6 enrolled (6 ^{14}C-labeled vadadustat)
AKB-6548-CI-0009/5.3.3.2	Single dose in subjects on HD	Treatment A: 450 mg vadadustat administered, 4 hours prior to initiation of the HD Treatment B: 450 mg vadadustat administered 2 hours after completion of the HD	Tablet	12 enrolled (12 vadadustat – both treatments)
AKB-6548-CI-0010/5.3.4.1	Thorough QTc	600/1200 mg vadadustat/ placebo/ Positive Control: moxifloxacin	Tablet	50 enrolled (50 subjects received all 4 treatments in different sequences)
AKB-6548-CI-0012/5.3.3.4	DDI of ferrous sulfate in healthy subjects	450 mg vadadustat 450 mg vadadustat plus 325 mg ferrous sulfate	Tablet	10 enrolled (10 vadadustat and iron)
AKB-6548-CI-0019/5.3.3.4	DDI of celecoxib in healthy subjects	Day 1: 200 mg single dose of celecoxib alone (Reference) Days 3-9: 600 mg vadadustat QD Day 8: 200 mg single dose of celecoxib administered with 600 mg vadadustat (Test)	Tablet	12 enrolled (12 vadadustat and celecoxib)
AKB-6548-CI-0020/5.3.3.3	Multiple ascending doses in Japanese and white subjects	150 mg, 300 mg, 600 mg vadadustat or placebo	Tablet	48 enrolled (36 vadadustat; 12 placebo)
AKB-6548-CI-0024/5.3.3.3	Moderate hepatic impairment	450 mg vadadustat	Tablet	16 enrolled (16 treated)

Study Number/ CTD Location	Description	Vadadustat Dose	Formulation	No. Subjects Enrolled (Treated/Placebo)
AKB-6548-CI-0029/5.3.3.4	DDI of cyclosporine and probenecid	300 mg vadadustat	Tablet	40 enrolled (40 treated)
AKB-6548-CI-0030/5.3.3.4	DDI of rosuvastatin, pravastatin, atorvastatin, simvastatin, and sulfasalazine	600 mg vadadustat QD	Tablet	134 enrolled (134 treated)
AKB-6548-CI-0031/5.3.3.4	DDI of adefovir, furosemide, and digoxin	600 mg vadadustat QD	Tablet	62 enrolled (62 treated)
AKB-6548-CI-0033/5.3.3.4	DDI of rabeprazole	300 mg vadadustat	Tablet	19 enrolled (19 treated)
AKB-6548-CI-0034/5.3.3.2	Multiple higher doses in Subjects on HD	600, 750, 900 mg vadadustat QD or ESA (darbepoetin alfa or epoetin alfa)	Tablet	46 enrolled (39 vadadustat; 7 ESA)
AKB-6548-CI-0037/5.3.3.4	Single dose in presence of phosphate binders	300 mg vadadustat	Tablet	54 enrolled (54 treated)
MT-6548-J05/5.3.3.4	DDI of ferrous citrate, sucroferric oxyhydroxide, ferrous sulfate (sustained release tablet)	150 mg vadadustat	Tablet	61 enrolled (61 treated)
Phase 2				
AKB-6548-CI-0003/5.3.3.2	Single dose in subjects with Stage 3 and 4 CKD	500 mg oral single dose of vadadustat	Capsule	22 enrolled (22 treated)
AKB-6548-CI-0004/5.3.4.2	Repeat oral dose in subjects with Stage 3 and 4 CKD	Stage 3 CKD: 200, 300, 400, 500, 600, and 700 mg/day vadadustat Stage 4 CKD: 200, 300, 400, 500, and 600 mg/day vadadustat.	Capsule	10 enrolled (10 treated)
AKB-6548-CI-0005/5.3.4.2	Repeat oral dose in subjects with Stage 3 and 4 CKD	240, 370, 500, or 630 mg vadadustat or placebo	Capsule	93 enrolled (72 vadadustat; 19 placebo)
AKB-6548-CI-0007/5.3.5.1	Repeat oral dose in subjects with Stage 3, 4 and 5 CKD	150 to 600 mg vadadustat based on Hb response	Tablet	210 enrolled (138 vadadustat; 72 placebo)
AKB-6548-CI-0011/5.3.5.2	Repeat oral dose in subjects with DD-CKD	300 or 450 mg vadadustat	Capsule	94 enrolled (94 treated)

Study Number/ CTD Location	Description	Vadadustat Dose	Formulation	No. Subjects Enrolled (Treated/Placebo)
AKB-6548-CI-0021/5.3.5.1	Efficacy and safety in Japanese NDD-CKD subjects not being treated with ESA	150, 300, 600 mg vadadustat QD or placebo	Tablet	51 enrolled (37 vadadustat; 14 placebo)
AKB-6548-CI-0022/5.3.5.1	Efficacy and safety in Japanese DD-CKD subjects not being treated with ESA	150, 300, 600 mg vadadustat QD or placebo	Tablet	60 enrolled (45 vadadustat; 15 placebo)
AKB-6548-CI-0025/5.3.5.1	Efficacy and safety in DD-CKD Subjects converting from epoetin alfa	150, 300, 450, 600, 750, or 900 mg vadadustat dose range or epoetin alfa	Tablet	175 enrolled (134 vadadustat; 41 epoetin alfa)

ADME: adsorption, distribution, metabolism, and excretion; CKD: chronic kidney disease; DD: dialysis-dependent; DDI: drug-drug interaction; ESA: erythropoiesis-stimulating agent; HD: hemodialysis; Hb: hemoglobin; NDD: non-dialysis-dependent; QD: once daily.
Phase 3 efficacy studies are discussed in Module 2.7.3 and a complete list of vadadustat studies is provided in Module 5.2.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Vadadustat (AKB-6548) is a synthetic, orally bioavailable, small molecule (molecular weight 306.7 g/mol) being developed as an inhibitor of prolyl-hydroxylases (PHDs) for the treatment of anaemia associated with chronic kidney disease (CKD) in adults on dialysis (DD-CKD) and not on dialysis (NDD). Vadadustat is a potent pan inhibitor of the 3 isoforms which are present in humans: PHD1, PHD2, and PHD3. The proposed dose regimen is a starting dose of 300 mg once daily with up-titration every 4 weeks until the target haemoglobin level is reached (10-12 g/dL). The maximum dose of vadadustat is 600 mg/day.

The clinical pharmacology of vadadustat was evaluated in 24 clinical studies in healthy subjects and in patients with CKD. An overview of the clinical studies supporting the clinical pharmacology summary is presented in **Table above**.

Dose rationale

A 1-compartment linear population PK model with first order absorption adequately characterized the vadadustat concentration time profiles. The PK/pharmacodynamics model developed was a mechanistic RBC life span model based on the mechanism of action of vadadustat, which adequately described the time courses of EPO, reticulocyte count, and Hb.

Using the model and the proposed dosing algorithm, simulations were performed to evaluate the effects of different starting doses and the resulting Hb responses to support the Phase 3 dosing. The model was used for both the NDD and DD populations. Results of the simulations indicated that a starting dose of 300 mg QD along with the proposed dosing algorithm were optimal to maintain Hb levels of 10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL ex-US while minimizing excessive rises.

Analytical methods

Quantification of vadadustat, major metabolite vadadustat-O-glucuronide (vada-OG, 15%) and minor metabolite vadadustat-acyl-glucuronide (vada-AG, <1%) were determined in human plasma and urine by validated LC-MS/MS methods. In general, samples were analysed within the established long-term storage stability and ISR acceptance criteria were met, except for vada-AG. ISR was not conducted for vada-AG measurements in all studies.

Pop PK analysis

The final pop PK model for vadadustat was a one-compartment model with lag time, first-order absorption and first-order elimination. Intra-individual variability included on CL/F and Ka was high (CV 47%, 88.6%, respectively). Shrinkage was large on CL/F (31.6%). Residual variability ranged from CV% 47-107 and was described by a log-additive error model split into three parts. A total of 14021 observations from 4188 subjects were included in the Pop PK population representing a body weight span of 30.1-204 kg. Effect of food was included on lag time and Ka, effects of body weight was allometrically scaled with estimated exponents of 0.624 and 0.811 for CL and V. CL/F were split into one for healthy subjects and one for CKD patients. CL/F was lower in patients than in healthy subjects. Other covariates retained in the model were renal function, bilirubin, Japanese race on CL/F while concomitant medication NICP or iron/ICP were included on bioavailability. The final model was evaluated with bootstrap (n=100), GoF plots and pc-VPCs.

Parameter estimates of the final model and selected diagnostic are shown in Table and figures below.

Table 3 **Final Population Pharmacokinetic Model Parameter Estimates**

Parameter	Estimate	RSE (%)	2.5th to 97.5th Percentile(Bootstrap)	Shrinkage (%)
CL/F healthy, L/h	2.01	5.4	1.86; 2.18	--
CL/F CKD, L/h	0.722	1.7	0.691; 0.746	--
V2/F, L	11.6	2.0	10.7; 12.8	--
KA fasted, 1/h	2.11	11.5	1.66; 2.5	--
KA fed, 1/h	0.504	14.9	0.262; 1.14	--
KA food not controlled, 1/h	0.320	3.6	0.274; 0.367	--
LAGT fasted, h	0.348	4.1	0.309; 0.386	--
LAGT fed, h	0.475	0.6	0.452; 0.49	--
Bodyweight effect on CL/F	0.624	7.4	0.526; 0.706	--
Bodyweight effect on V2/F	0.811	6.9	0.644; 0.962	--
CL/F-NDD eGFR power	0.255	11.3	0.197; 0.314	--
CL/F-bilirubin power	-0.223	10.1	-0.27; -0.185	--
CL/F-Japanese descent	-0.187	16.0	-0.234; -0.143	--
F_{rel} – Non-iron containing phosphate binders (NICP)	-0.327	4.2	-0.372; -0.282	--
F_{rel} – Oral iron and iron containing phosphate binders (IRON OR)	-0.200	9.6	-0.238; -0.161	--
Inter-individual Variability (IIV)				
CL/F IIV as %CV	47.0	1.9	43.3; 50.3	31.6
KA IIV as %CV[a]	88.6	8.3	72.4; 107	13.2
Residual Variability				
Log-additive CV% intensive samples	47.1	1.8	42.1; 52.9	7.6
Log-additive CV% sparse samples 1	63.2	2.2	56.5; 68.1	7.6
Log-additive CV% sparse samples 2	107	0.8	105; 109	7.6

Bili: bilirubin (µmol/L); CKD: chronic kidney disease;; CV: coefficient of variation (calculated as 100 × square root of variance / mean); eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); F: absolute bioavailability; F_{rel}: relative bioavailability; IIV: inter-individual variability; KA: first-order absorption rate constant; LAGT: lag time; NDD: non-dialysis-dependent; SD: standard deviation; WT: body weight (kg); Pharmacokinetic abbreviations are defined in the table on page 13

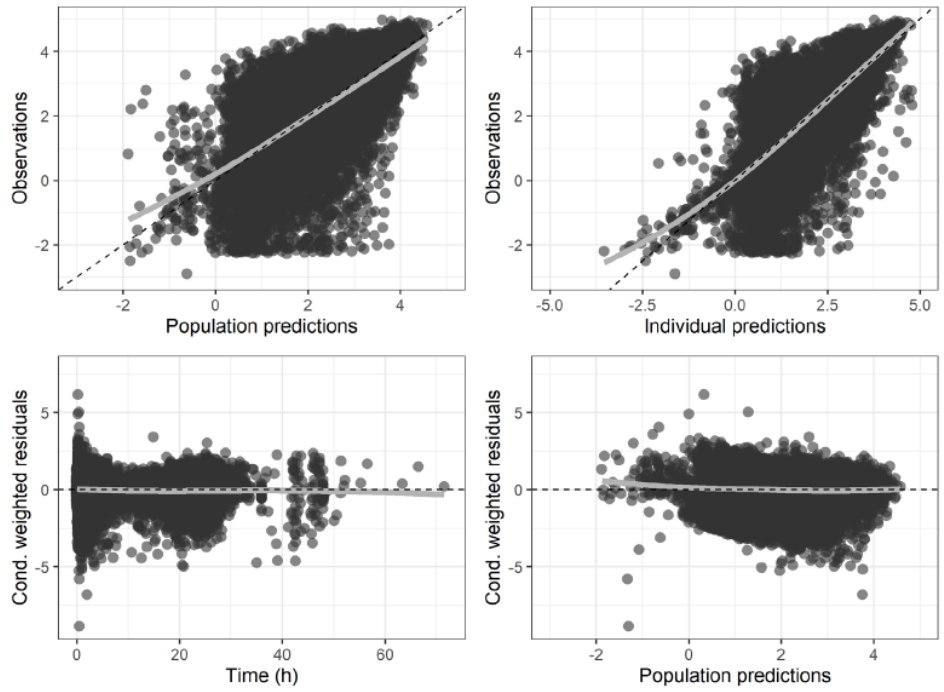
Log-additive CV% sparse samples 1: residual error for sparse data except CI-0016 and CI-0017; Log-additive CV% sparse samples 2: residual error for sparse data from CI-0016 and CI-0017; RSE: relative standard error (100 × standard error/estimate; RSE on standard deviation terms is RSE of variance / 2)

CL/F for healthy subjects=$2.01\times(WT/75)^{0.624}\times(Bili/0.3)^{-0.223}\times(1-0.187(\text{if Japanese}))\times\exp(\eta_{CL/F})$

CL/F for NDD-CKD subjects=$0.722\times(WT/75)^{0.624}\times(eGFR/20)^{0.255}\times(Bili/0.3)^{-0.223}\times(1-0.187(\text{if Japanese}))\times\exp(\eta_{CL/F})$

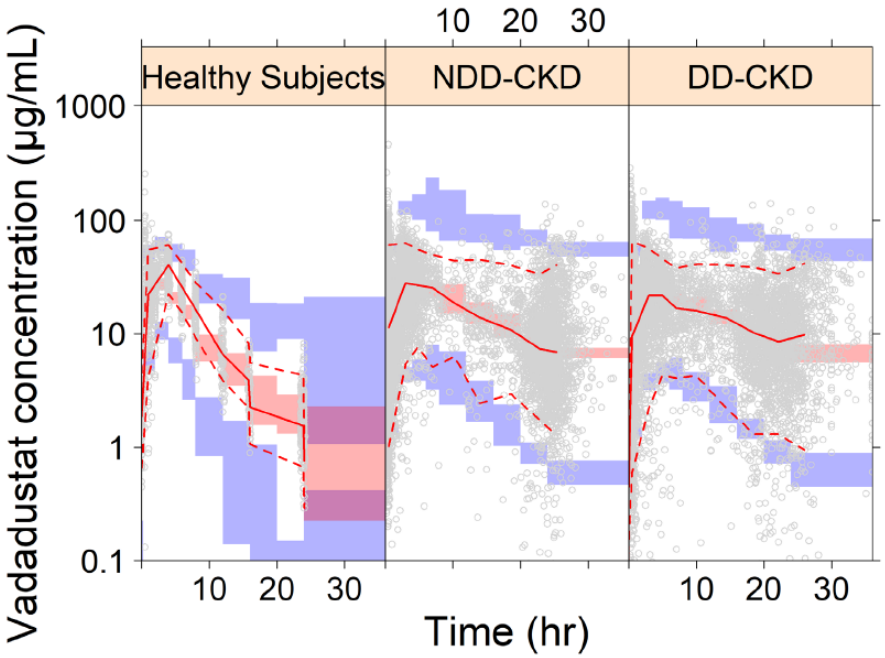
CL/F for DD-CKD subjects=$0.722\times(WT/75)^{0.624}\times(Bili/0.3)^{-0.223}\times(1-0.187(\text{if Japanese}))\times\exp(\eta_{CL/F})$

Figure 2 3. Goodness-of-fit Plots for the Final Population PK Model



Cond.: conditional; PK: pharmacokinetic.

Figure 3 . Prediction-corrected VPCs for Final Model Stratified by Population



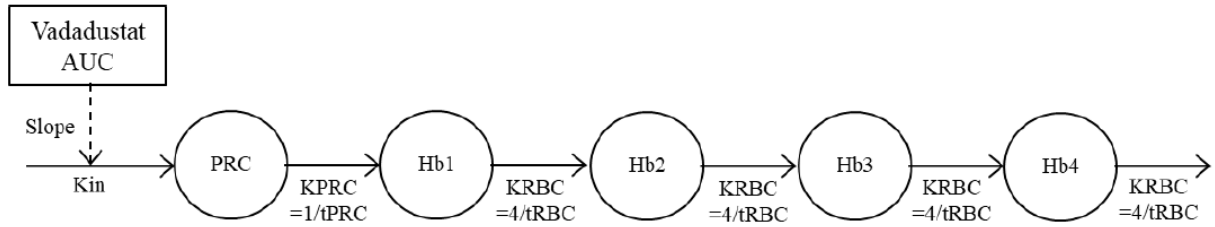
CKD: chronic kidney disease; DD: dialysis-dependent; NDD: non-dialysis-dependent; VPC: visual predictive check.
Note: The blue and pink shaded areas represent the 95% confidence interval for the 5th, 50th, and 95th percentiles for 100 simulations, and the red dashed and solid lines represent corresponding statistics for the prediction-corrected observed data.
Panels show all data up to 36 hours post last dose included in the analysis and are plotted against time after last dose.
Source: popPK-Report-content.r

Due to the large data package, a formal covariate analysis was not performed and data was added in several stages during model development.

PK/PD analysis

A PK/PD model using haemoglobin (Hb) response as PD endpoint based on a large data set (47988 Hb observations from 3952 CKD patients) pooled across eight Phase 2 and 3 studies was developed to quantify the effect of vadadustat. The Hb dynamics was described by a semi-mechanistic model incorporating an input precursor cell compartment using AUCtau to determine the input rate, followed by a series of transit compartments to reflect the Hb/RBC life span.

Figure 4 **Hb PK/PD Model Structure**



Abbreviations: AUC = area under the concentration-time curve; Hb = hemoglobin; Kin = precursor production rate; Kprc = Transition rate constant from precursor cell to red blood cell; Nrbc = number of red blood cell life span compartments; PK/PD = pharmacokinetic/pharmacodynamic; Trbc = red blood cell life span.

Prior ESA dose (WNESA), disease and Japanese descent were evaluated as covariates on endogenous Hb, tRBC, and RSA parameters. Covariate selection was guided by explorative evaluation and scientific considerations since the model had very long run times. The final model was evaluated using model diagnostics such as GoF plots, pcVPCs and non-parametric bootstrap analysis (n=100).

Table 4 Parameter Estimates of the Final Hb PK/PD Model

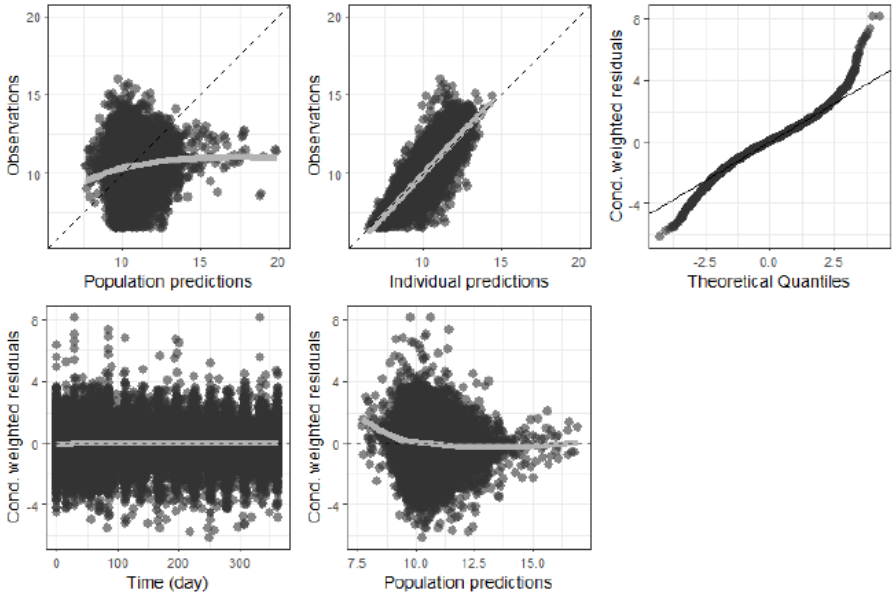
Parameter	Estimate	RSE (%)[a]	2.5th-97.5th Percentile (Bootstrap)	Shrinkage (%)
Endogenous Hb DD-CKD (Studies CI-0011, CI-0016, and CI-0017; g/dL)	9.40	1.7	[9.3 to 9.49]	-
Endogenous Hb NDD-CKD (Studies CI-0007, CI-0014, and CI-0015; g/dL)	9.60	0.0	[9.54 to 9.65]	-
Endogenous Hb NDD-CKD, Japanese (Study J-01; g/dL)	9.98	0.8	[9.8 to 10.1]	-
Endogenous Hb DD-CKD, Japanese (Study J-03; g/dL)	9.68	0.7	[9.54 to 9.8]	-
RSA (-)	0.0976	0.2	[0.0904 to 0.105]	-
tRBC (days)	61.5	0.1	[58.8 to 69.7]	-
tPRC (days)	19.2 FIX			-
Slope in non-Japanese (1/(mg·h/mL))	0.346	0.4	[0.328 to 0.38]	-
WNESA ~ endogenous Hb	-0.231	23.3	[-0.298 to -0.174]	-
WNESA on RSA	0.934	2.5	[0.489 to 1.35]	-
Japanese descent ~ slope	-0.369	11.1	[-0.452 to -0.298]	-
IIV				
IIV endogenous Hb (SD)	0.799	21.6	[0.773 to 0.827]	7.1
IIV tRBC (%CV)	127	13.2	[118 to 139]	39.1
IIV slope (SD)	0.336	2.3	[0.32 to 0.364]	10.1
Residual variability				
Residual error	0.0604	0.1	[0.0591 to 0.0614]	

Source: Rscript 4.pk-prm-table-base-intermediate-final-model

[a] The RSEs for omega and sigma are reported on the approximate standard deviation scale (SE/variance estimate)/2.

Abbreviations: AUC = area under the concentration-time curve; CI = confidence interval; CV = coefficient of variation; Hb = hemoglobin; IIV = inter-individual variability; RSA = residual prior erythropoiesis-stimulating agent effect; RSE = relative standard error; SD = standard deviation; SE = standard error; Slope = slope parameter translating vadadustat exposure to fractional increase in precursor production rate; tPRC = precursor cell residence time; tRBC = red blood cell life span; WNESA = weekly weight-normalized prior erythropoiesis-stimulating agent.

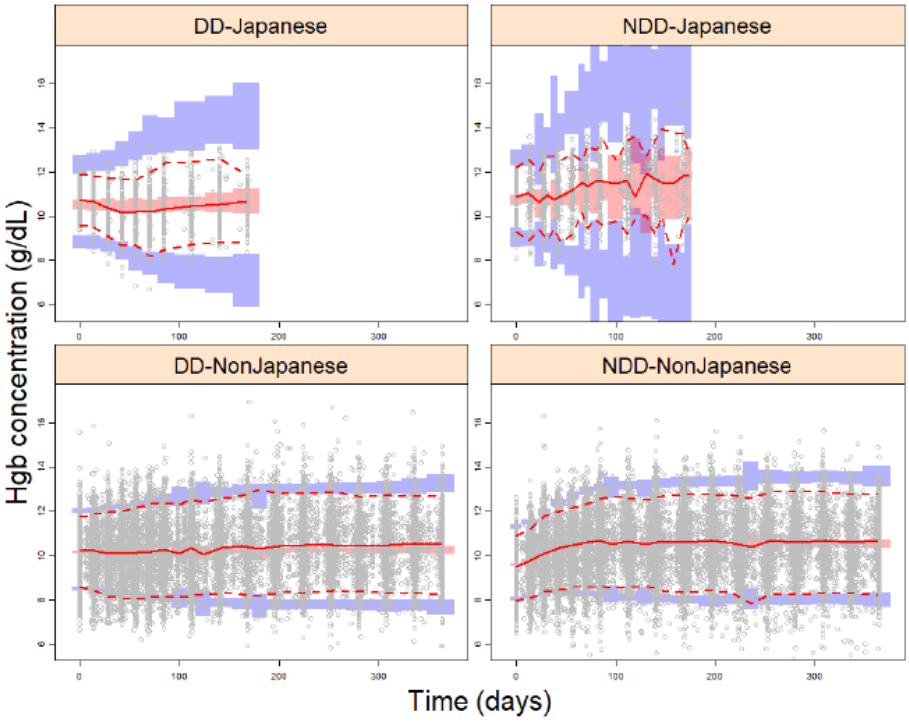
Figure 5 **Goodness-of-fit Plots of the Final Model**



Source: Rscript 5.2.diagnostics-final-model
Note: The gray circles represent individual observations; the gray solid line a LOESS line of the presented data, and the black dotted lines represent the identity line for observations/PRED-IPRED plots and the zero line for CWRES plots.
Abbreviations: CWRES = conditional weighted residuals; GOF = goodness-of-fit; IPRED = individual-predicted hemoglobin concentrations; LOESS = locally estimated scatterplot smoothing; PRED = population-predicted hemoglobin concentrations.

The pc-VPCs stratified per disease (DD/NDD) and Japanese descent showed the model in general could capture the observed haemoglobin concentrations during the treatment period. In Japanese, the variability seemed overpredicted.

Figure 6 Prediction-corrected VPC of Final Model Stratified by Disease Status and Japanese Descent



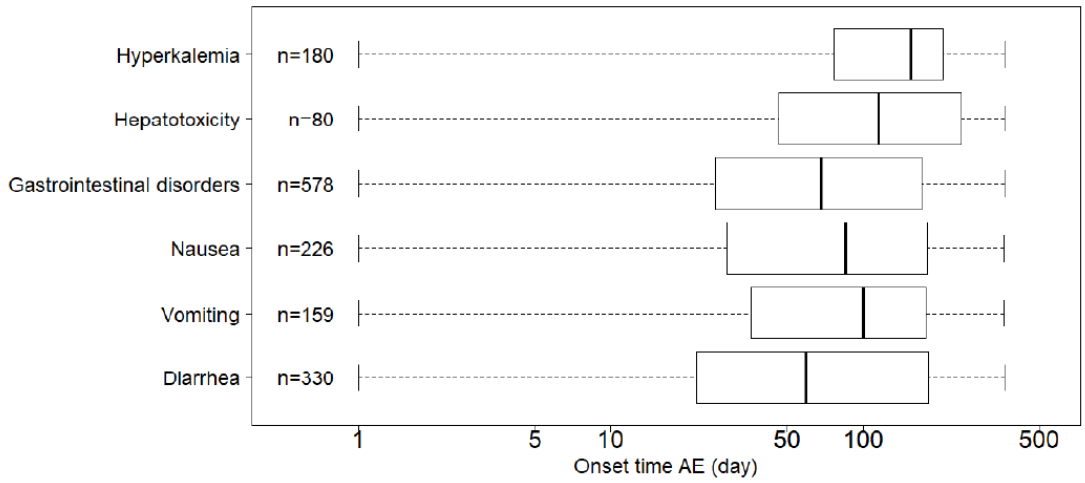
Source: 5.2.diagnostics-final-model
Note: The gray circles represent the observed data. The red solid and dashed lines represent median and 5th to 95th percentiles of the observed data. The blue and pink areas represent median and 5th to 95th percentiles of the simulated data with their 90% CI.
Abbreviations: CI = confidence interval; DD = dialysis dependent; Hb = hemoglobin; NDD = non-dialysis dependent; pcVPC = prediction-corrected visual predictive check.

The model indicated a lower vadadustat effect (increase in endogeneous Hb per unit AUC) for Japanese compared to non-Japanese CKD patients. The effect of vadadustat 300 mg on Hb seemed stable over the treatment period. Body weight accounts for most variability in PK exposure. The Pop PK population represented a body weight span of 30.1-204 kg.

Exposure-safety analyses

Exposure-safety relations were explored using logistic regression modelling. The safety data set came from 3473 subjects with CKD.

Figure 7 **Time to Onset for each SSE, with horizontal boxplots showing onset distributions**



Source: Safety-ER.r
Abbreviation: n = number; SSE = selected safety endpoint.

Post-hoc exposure estimates were derived using the final population PK model. The exposure metrics used were time-averaged AUC up to the event and the time-averaged AUC during 4 weeks preceding the event. Logistic regression analysis showed absence of exposure (AUC up to the event) effects on the incidence of any of the safety endpoints, ($p>0.001$). Based on the AUC 4 weeks preceding the event, a significant E-R relationship was found for nausea, GI disorders, and hyperkalaemia where higher exposure lead to higher incidences (See Tables below).

Table 5 **p-Values Based on Logistic Regression, Exposure Metric Average AUC until the Event**

Selected Safety Endpoint	p-Value
Diarrhea	0.0443
Vomiting	0.489
Nausea	0.00422
GI disorders	0.00912
Hepatotoxicity	0.998
Hyperkalemia	0.0531

Source: Safety-ER.r
Note: Bold: significant effects $p<0.001$.
Abbreviations: AUC = area under the concentration-time curve; GI = gastrointestinal.

Table 6 *p-Values Based on Logistic Regression, Exposure Metric Average AUC 4 Weeks Preceding the Event*

Adverse Event	p-Value
Diarrhea	0.00432
Vomiting	0.197
Nausea	**0.000124**
GI disorders	**0.000364**
Hepatotoxicity	0.120
Hyperkalemia	**0.000179**

Source: Safety-ER.r
Note: Bold: significant effects p<0.001.
Abbreviation: AUC = area under the concentration-time curve; GI = gastrointestinal.

Kaplan-Meier plots were also generated and stratified by vadadustat exposure quartiles. Cox PH regression was attempted but biased due to violation of the PH assumption for several end-points.

Table 7 *Test Proportional Hazard Assumption for Time Independency*

	p-Value for Independence of Schönfeld Residuals with Time	
Adverse Event	AUC up to Event	AUC 4 Weeks Preceding Event
Diarrhea	0.00293	8.45e-08
Vomiting	0.191	0.000579
Nausea	0.0808	7.94e-07
GI disorders	2.22e-05	6.48e-13
Hepatotoxicity	0.155	0.0368
Hyperkalemia	0.368	0.0462

Source: Safety-ER.r
Note: Assumption is violated when p<0.05.
Abbreviations: AUC = area under the concentration-time curve; GI = gastrointestinal.

Table 8 p-Values Exposure Estimate Based on Cox Regression

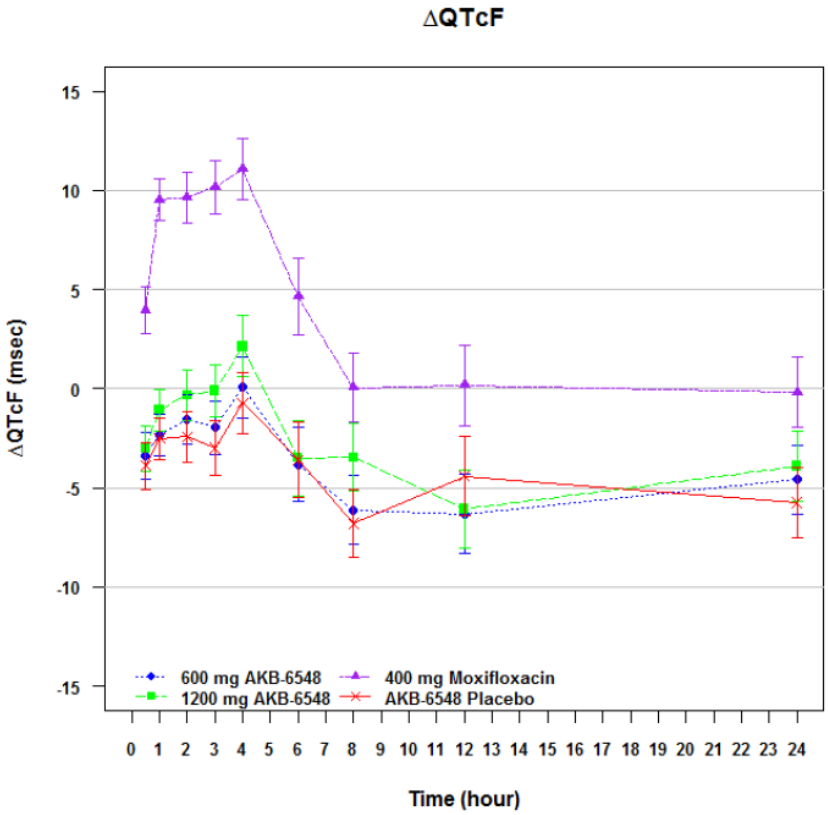
Selected Safety Endpoint	p-Value
Diarrhea	0.0374
Vomiting	0.841
Nausea	0.0186
GI disorders	0.0176
Hepatotoxicity	0.988
Hyperkalemia	0.00438

Source: Safety-ER.r
Abbreviation: GI = gastrointestinal.

TQT analysis

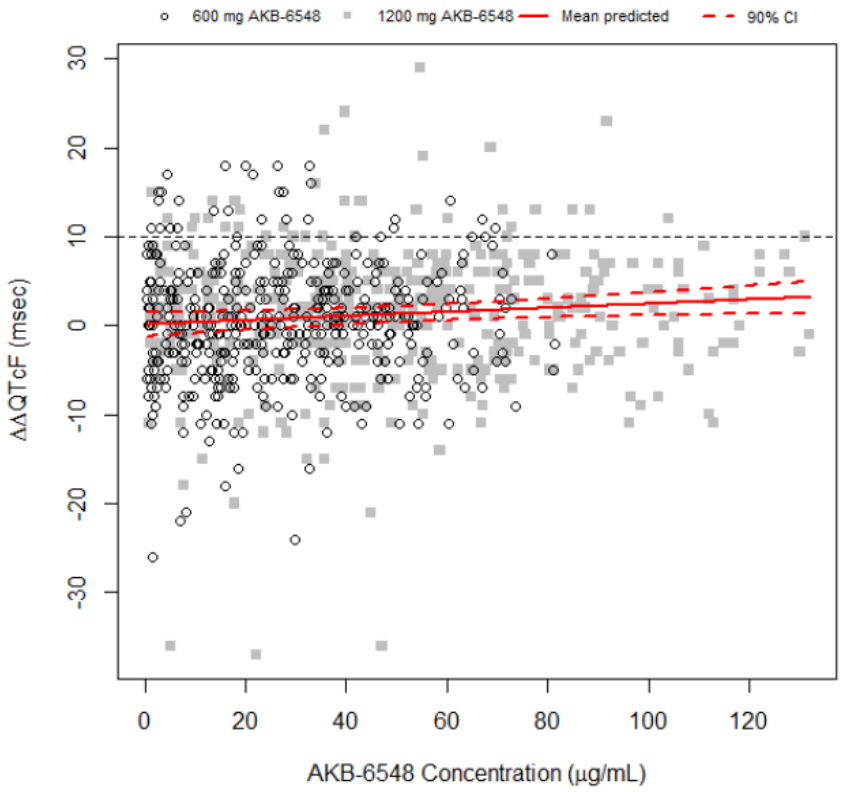
A clinical placebo-controlled TQT study was conducted using 50 subjects, of which 47 completed the study. The subjects received single doses of 600 mg and 1200 mg vadadustat and 400 mg moxifloxacin (positive control) and placebo sequentially with a 7-day washout in-between.

Figure 8 Change-from-Baseline across Treatment Groups and Timepoints for QTcF (ΔQTcF)*



The concentration-QTc relation was evaluated using a linear mixed-effects model with an intercept. The plot of the observed median-decile drug concentrations and associated mean ΔΔQTc (90% CI) together with the mean (90% CI) predicted ΔΔQTcF was used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration response relationship.

Figure 9 **Relationship between Vadadustat Plasma Concentrations and ΔΔQTcF with 90% CI (PK/QTc Population)**



Source: Figure 1, Analysis of the Relation between QTcF Changes and Plasma Concentrations of vadadustat (Section 14.2.2)
Abbreviation: CI = confidence interval Note:

A statistically significant relation (p= 0.0529) of vadadustat and placebo-corrected ΔQTcF was detected but the upper bound of the 90% CI was <10 ms.

Table 9 **Exposure-Response Analysis of Vadadustat-Associated ΔΔQTcF Prolongation (PK/QTc Population)**

Model	AIC	Parameter	Estimate (90% CI)	P-Value	Between-Subject Variation
1	5444	Intercept (msec)	0.12 (-1.24;1.49)	0.8809	5.05
		Slope(msec per µg/mL)	0.0233 (0.0036;0.0430)	0.0529	0.0592
		Residual Variability (msec)	5.88		
2	5442	Intercept (msec)	Fixed to 0 with variability		5.05
		Slope(msec per µg/mL)	0.0247 (0.0112;0.0381)	0.0036	0.0592
		Residual Variability (msec)	5.88		
3	5551	Slope(msec per µg/mL)	0.0259 (0.0084;0.0434)	0.0170	0.0622
		Residual Variability (msec)	6.53		

Source: Table 1, Analysis of the Relation between QTcF Changes and Plasma Concentrations of vadadustat(Section 14.2.2)
AIC = Akaike's Information Criterion; CI = confidence interval.

For HR, PR interval, and QRS interval, similar analyses were presented. The effects on HR, PR interval, and QRS interval were small and considered not clinically relevant.

Absorption

Vadadustat has pH dependent solubility (above pH 7.5) and in vitro results from Caco-2 cells indicate its high permeability. Therefore, vadadustat can be considered a BCS II compound. I*n vitro*, vadadustat was not a substrate of P-gp, but was a substrate of BCRP.

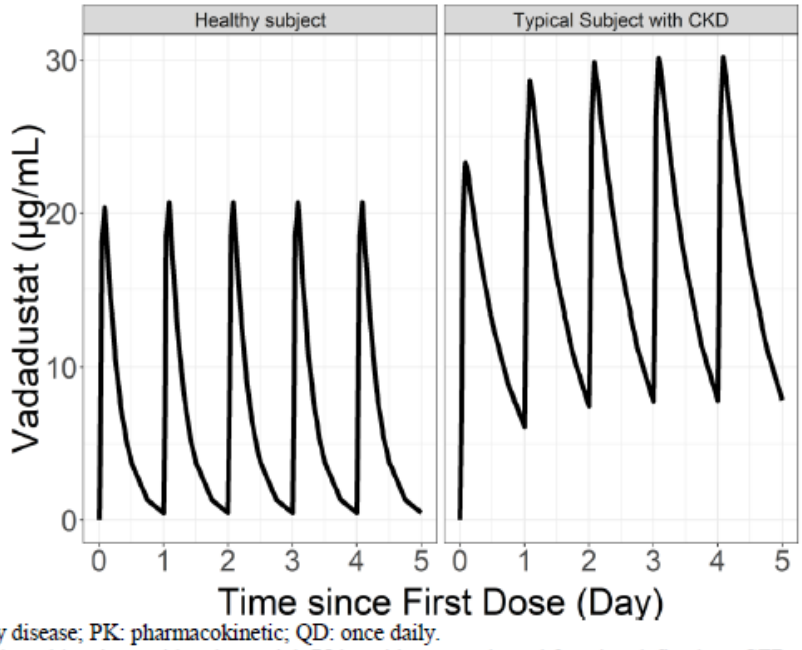
Co-administration with rabeprazole (a PPI) did not affect exposure to vadadustat and vadadustat-O-glucuronide. These results indicate that vadadustat can be co-administered with proton pump inhibitors.

Absorption of vadadustat may be significantly reduced due to complex formation with iron or phosphate binders. Therefore, it is recommended to take vadadustat at least 1 hour before or 2 hours after administration of non-iron containing phosphate binders and at least 1 hour before oral iron products or iron-containing phosphate binders. Vadadustat could form complexes (via chelation) with other products containing calcium, iron, magnesium, or aluminum which affects the solubility and hence absorption of vadadustat. Therefore, vadadustat should be administered 1 hour before or 2 hours after the administration of these products.

The median absorption time of vadadustat to reach Cmax was 2 to 3 hours. Vadadustat is minimally accumulated in healthy subjects with an accumulation ratio for AUC of 1.03 in steady state. In patients with CKD, the accumulation is predicted to be 1.32 in steady state and steady state is typically achieved within three days after treatment initiation.

The Figure below shows simulated vadadustat PK profiles in typical subjects to illustrate the level of accumulation and attainment of steady state in a typical healthy subject and subjects with CKD.

Figure 10 **Vadadustat PK Profile in a Typical Healthy Subject and Subject with CKD with 300 mg QD Dosing under Fasted Condition**



CKD: chronic kidney disease; PK: pharmacokinetic; QD: once daily.
Note: A typical healthy subject is considered to weigh 75 kg with a normal renal function defined as eGFR of 100 mL/min/1.73 m^2 and bilirubin level of 0.3 µmol/L A typical subject with CKD is defined as having bodyweight 75 kg and renal function defined as eGFR of 20 mL/min/1.73 m^2 and bilirubin level of 0.3 µmol/L.
Source: popPK-Report-content-suppl.r

Bioavailability

The absolute bioavailability of vadadustat has not been evaluated.

In an ADME study, 6 healthy male subjects were administered a single, 650 mg dose of [14C]-vadadustat (100 μCi). Serial blood, urine and faecal samples were collected until subjects were discharged. The mean (SD) cumulative percent of the radioactive dose recovered in the urine and faeces is shown in **Table below**. A mean total of 85.9% of the [14C] vadadustat dose was recovered in urine and faeces by 72 hours after dosing with 58.9% of the dose recovered in urine and 26.9% of the dose recovered in faeces.

Table 10 Mean (CV%) [SD] Cumulative Excretion of Total Radioactivity in Urine and Feces of Vadadustat After a Single Oral Dose of 650 mg [^{14}C] Vadadustat in a Capsule in Healthy Male Subjects (AKB-6548-CI-0008)

Analyte	% Cumulative Urine Excretion	% Cumulative Feces Excretion
Total Radioactivity	58.9 (15.6) [9.19]	26.9 (55.1) [14.8]
Vadadustat	0.397 (36.7) [0.146]	--

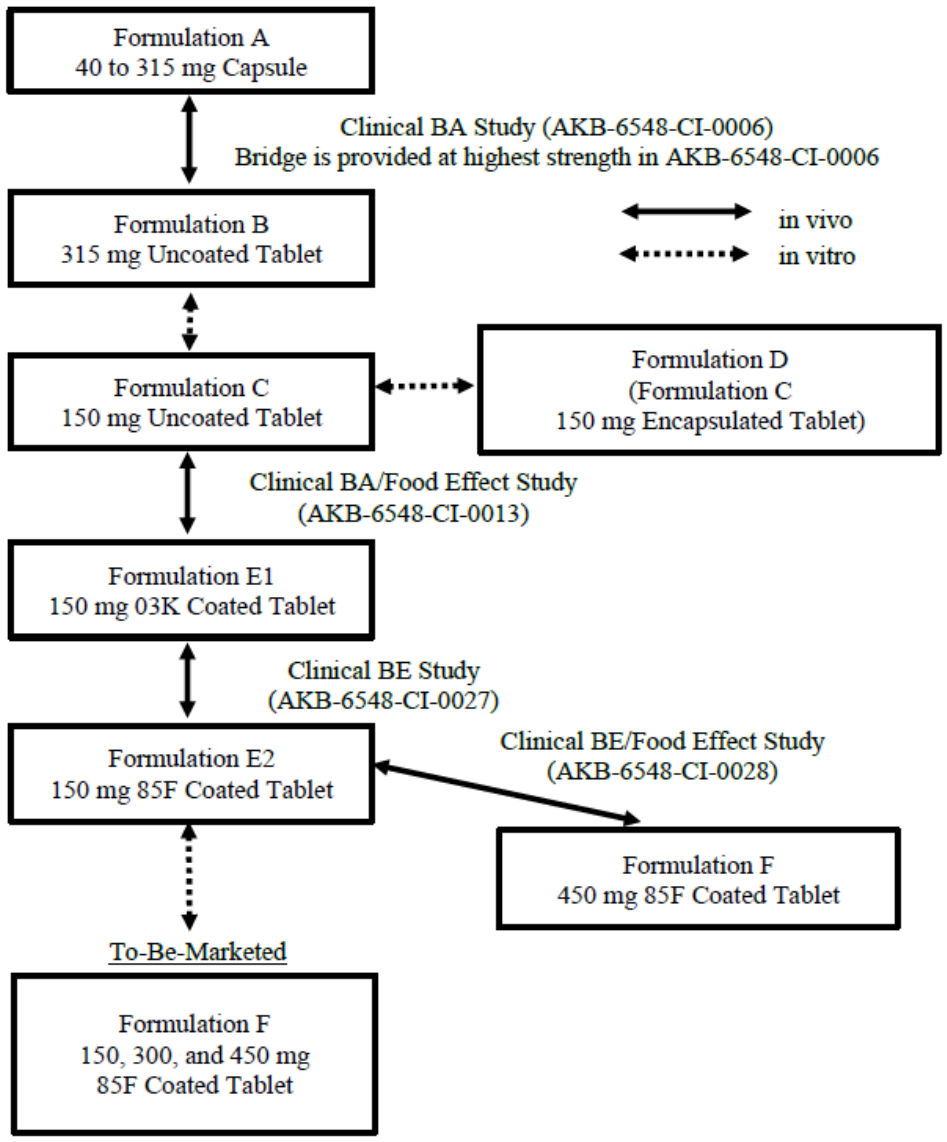
SD: standard deviation; --: not available
Source: AKB-6548-CI-0008 Table 14.2.2.10, Table 14.2.2.12, Table 14.2.3.4, Table 14.2.3.5.

Based on the ADME study and the recovery in urine, it may be concluded that the extent of absorption was at least 58.9%.

In healthy subjects, the AUCinf and Cmax of vadadustat decreases up to 21% and 29%, respectively, when administered with food compared with fasting. Time to maximum concentration (Tmax) increased from to 2 hrs to 3.5 hrs with food intake. The same relative changes with and without concomitant food intake are expected in the patient population. Based on these results, it is acceptable to state that the product can be taken with or without food.

Several different formulations of vadadustat have been used in the development program and the PK bridge was adequately established between early formulations to formulations used later in development and formulation intended for the market (**Figure below**). To-be-marketed tablets (formulation F) are film-coated tablets developed in 150, 300 and 450 mg strengths.

FiFigure 11 inical Trial Formulation Bridging



BA: bioavailability; BE; bioequivalence.
Coating 03K refers to hydroxypropyl methylcellulose (HPMC)-based film-coating and Coating 85F refers to polyvinyl alcohol (PVA)-based film-coating.

Source: Module 2.7.1. Summary of Biopharmaceutics and Associated Analytical Methods

Distribution

Vadadustat has a high protein binding (>99%). The protein binding was independent of disease state i.e. it was similar in plasma derived from healthy subjects or subjects with CKD. The mean blood to plasma ratio was less than 1 (0.50 to 0.55), suggesting minimal distribution to the RBCs. Based on popPK analysis, the volume of distribution is 11.6 L in subjects with CKD.

Elimination

Vadadustat is extensively metabolised by multiple UGTs with the vadadustat-O-glucuronide a major metabolite in plasma. Vadadustat-O-glucuronide is primarily formed by UGT1A9 and is considered

pharmacologically inactive. In the ADME study, 20 metabolites were detected in plasma, 19 in urine, and six in feces. Approximately 59% of a dose is recovered in urine and 27% in faeces. Renal excretion of unchanged vadadustat amounts to less than 1% of a dose.

In popPK analyses, subjects with CKD had a mean clearance of 0.8 L/h with a half-life of 14 hours.

Dose proportionality and time dependencies

Dose proportionality was demonstrated for Cmax and AUC in the proposed dose range of 150 to 600 mg vadadustat in both single and multiple dosing. Time dependency was not thoroughly addressed; the Applicant has provided accumulation ratios, and in patients with CKD, the estimated accumulation is 32% following multiple dosing.

Intra- and interindividual variability

Based on the final popPK model, population parameter estimates, including interindividual variability, are shown in **Table 4** above.

In the typical subject with CKD (non-Japanese, bodyweight 75 kg, eGFR 20 mL/min/1.73m2, bilirubin 0.3 µmol/L), the interindividual variability of CL/F, expressed as CV, was 47.0%. For the absorption rate constant (ka), the interindividual variability, expressed as CV, was 89%.

Following single dose in subjects with NDD-CKD (study CI-0003) and DD-CKD (study CI-0009), inter-individual variability, expressed as CV, was 32.3% and 38.3-47.5% for Cmax, and 34.5% and 51.7-55.9% for AUClast, respectively. Thus, although moderate, a higher inter-individual variability is observed in DD-CKD patients.

PK in target population

Expected steady state exposure and elimination values in the target population, based on popPK results, for a total of 96 healthy subjects and 2000 subjects with NDD-CKD and 2090 subjects with DD-CKD are provided in **Table below**. PK values are similar between NDD- and DD-CKD. The PK differences (longer half-life and approximately 2-fold higher exposure (AUC)) between patients and healthy subjects are moderate, which is considered reassuring.

Table 11 **Descriptive Statistics of Posthoc PK Parameter Values at Steady State on a Dosing Regimen of 300 mg QD**

Statistic	AUCss (µg·hr/mL)			Cmax (µg/mL)			Half-life (hr)			CL/F (L/hr)		
	HV	NDD	DD	HV	NDD	DD	HV	NDD	DD	HV	NDD	DD
n	96	2000	2090	96	2000	2090	96	2000	2090	96	2000	2090
Mean	188	394	333	21.3	22.3	18.9	5.15	14.3	13.9	1.68	0.796	0.785
Standard deviation	49.2	264	180	4.42	11.7	8.31	1.03	21.4	7.08	0.388	0.331	0.328
CV%	26.2	66.9	54	20.7	52.4	44	20	150	51.1	23.1	41.6	41.8
Minimum	117	67.6	65	14.2	5.03	5.94	3.62	3.89	3.53	0.823	0.019	0.066
10^{th} percentile	134	209	176	16.8	13.1	11	3.97	8.36	8.57	1.14	0.458	0.454
Median	177	346	301	20.9	20.3	17.4	5.06	12.7	13	1.68	0.745	0.728
90^{th} percentile	261	593	506	27	32.1	27.7	6.44	19	19	2.22	1.17	1.17
Maximum	363	4130	2500	35.8	179	110	7.99	880	149	2.53	3.17	3.12
Geometric mean	182	351	301	20.9	20.5	17.5	5.05	12.8	12.9	1.63	0.732	0.725
Geometric CV%	25	47.7	45.9	20.1	40	38.4	19.5	39.7	36.8	24.8	44.6	42.0

AUCss: steady-state area under the concentration-time curve; CKD: chronic kidney disease; CL/F: apparent clearance; Cmax: maximum drug plasma concentration; CV: coefficient of variation; DD: dialysis-dependent subjects with CKD; HV: healthy subjects; n: number of observations; NDD: non-dialysis-dependent subjects with CKD; PK: pharmacokinetic; QD: once daily.
Note: Geometric mean calculated as exp(mean(log(PK parameter))); geometric CV% calculated as 100 × sqrt(exp(sd(log(AUCss))^2)-1).
Source: popPK-Report-content-suppl.r

Effect of dialysis on vadadustat PK

Dialysis was not found to affect clearance of vadadustat in a clinically relevant way. The exposure (AUC) when vadadustat was administered 4 hours prior to hemodialysis was 23% higher compared with administration 2 hours after hemodialysis (**Table below**). Exploration of dialysate concentrations indicated that, in accordance with the very high protein binding, only approximately 1.9% is removed during dialysis.

Table 12 **Effect of Dialysis on Pharmacokinetics Following a Single Dose of 450 mg Vadadustat in Subjects with DD-CKD (AKB-6548-CI-0009)**

	Geometric Mean			
Parameter	450 mg Vadadustat Dosed 4 hours Prior to Dialysis[a] (Treatment A)	450 mg Vadadustat Dosed 2 hours After Dialysis[b] (Treatment B)	Ratio (Treatment A/B) (%)	90% CI
AUC_{last}[c], µg·h/mL	370	300	123	97.9, 155
AUC_{inf}[c], µg·h/mL	384	312	123	97.6, 155
C_{max}[c], µg/mL	34.3	32.8	105	78.9, 139

CKD: chronic kidney disease; CI: confidence interval; DD: dialysis-dependent; Pharmacokinetic abbreviations are defined in the table on page 13
a Treatment A: vadadustat dosing 4 hours prior to start of hemodialysis session
b Treatment B: vadadustat dosing 2 hours after hemodialysis
c N=12
Source: AKB-6548-CI-0009 Table 14.2.13.

Special populations

Impaired renal function

A popPK comparison of vadadustat exposures in different stages of renal impairment is provided. For visualization of exposure effects across CKD stages, subjects with NDD-CKD and DD-CKD were grouped according to CKD stages, and subjects with DD-CKD were treated as a separate class (**Table below**). CKD stage 4, which includes the average eGFR value of the NDD-CKD population, was considered the reference population. Compared to the reference population, AUCss was 15% lower, 4% lower, 15% higher, and 12% lower for CKD stage 3a, 3b, 5, and subjects with DD-CKD, respectively. Trends for Cmax were similar but somewhat less pronounced. A slight increase in exposure of vadadustat with increasing renal impairment has thus been demonstrated. The differences are small but the trend is clear.

Table 13 **Summary of AUCss and Steady-state Cmax in the NDD-CKD and DD-CKD Populations with 300 mg QD Dosing, Stratified by CKD Stages**

CKD Stage	Stage 3a	Stage 3b	Stage 4	Stage 5	DD
NDD-CKD and DD-CKD - AUCss					
N	90	380	907	610	2087
GM	292	328	343	393	301
GCV	46.4	44.8	45.4	49.8	45.9
Median (90% PI)	286 (147 - 590)	327 (170 - 621)	340 (174 - 682)	394 (189 - 851)	302 (148 - 598)
GMR (90% CI)	0.85 (0.79 - 0.92)	0.96 (0.92 - 1)	1	1.15 (1.1 - 1.19)	0.88 (0.85 - 0.9)
NDD-CKD and DD-CKD - Steady-state Cmax					
N	90	380	907	610	2087
GM	18	20	20	22	18
GCV	36.9	36.2	38.3	43.7	38.4
Median (90% PI)	17.7 (11 - 32.9)	19.7 (11.3 - 34.5)	20.1 (11.3 - 36.6)	22.1 (11.2 - 43.1)	17.4 (9.78 - 32.1)
GMR (90% CI)	0.90 (0.85 - 0.97)	0.99 (0.96 - 1.03)	1	1.10 (1.06 - 1.13)	0.87 (0.85 - 0.89)

AUCss: steady-state area under the concentration-time curve; CI: confidence interval; CKD: chronic kidney disease; Cmax: maximum drug plasma concentration; DD: dialysis-dependent; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; GCV: geometric coefficient of variation; GM: geometric mean; GMR: geometric mean ratio; N: sample size; NDD: non-dialysis-dependent; PI: prediction interval; QD: once daily.
Note : Stage 1 (n=1) and stage 2 (n=15) not shown.
Source: popPK-Report-content-suppl.r

Impaired hepatic function

In a hepatic impairment study, the PK profile of vadadustat following a single oral 450 mg dose in subjects with hepatic impairment was compared to the profile in subjects with normal hepatic function. Point estimates of the geometric mean ratios of the primary parameters AUC and Cmax unbound and

plasma total are presented in **Table below**. The study results indicated that the effect of moderately decreased liver function on vadadustat PK was minimal.

PopPK analyses found that increased bilirubin is associated with decreased CL/F in both the NDD-CKD and DD-CKD population; the effect, however, is small and not considered clinically relevant. Deviations in ALT, AST, or albumin levels did not affect vadadustat exposure (10% or less for all).

Table 14 Plasma Vadadustat C_{max} and AUC Values Following 450 mg Vadadustat Dose in Subjects with Moderate Hepatic Function Compared to Subjects with Normal Hepatic Function (AKB-6548-CI-0024)

	Geometric LS Mean			
Parameter	Moderate	Normal	Ratio (Moderate/Normal)	90% CI
C_{max}, µg/mL	51.6	50.3	1.02	(0.79, 1.32)
AUC_{last}, µg·h/mL	410	389	1.05	(0.82, 1.35)
AUC_{inf}, µg·h/mL	414	391	1.06	(0.82, 1.36)
$C_{max\ unbound}$, µg/mL	0.433	0.360	1.20	(0.90, 1.61)
$AUC_{last\ unbound}$, µg·h/mL	3.44	2.78	1.24	(0.89, 1.72)
$AUC_{inf\ unbound}$, µg·h/mL	3.47	2.79	1.24	(0.89, 1.73)

CI: confidence interval; LS mean: least squares mean; PK: pharmacokinetic; Pharmacokinetic abbreviations are defined in the table on page 13
Source: AKB-6548-CI-0024 Table 14.2.3.1 and Table 14.2.3.2.

Gender

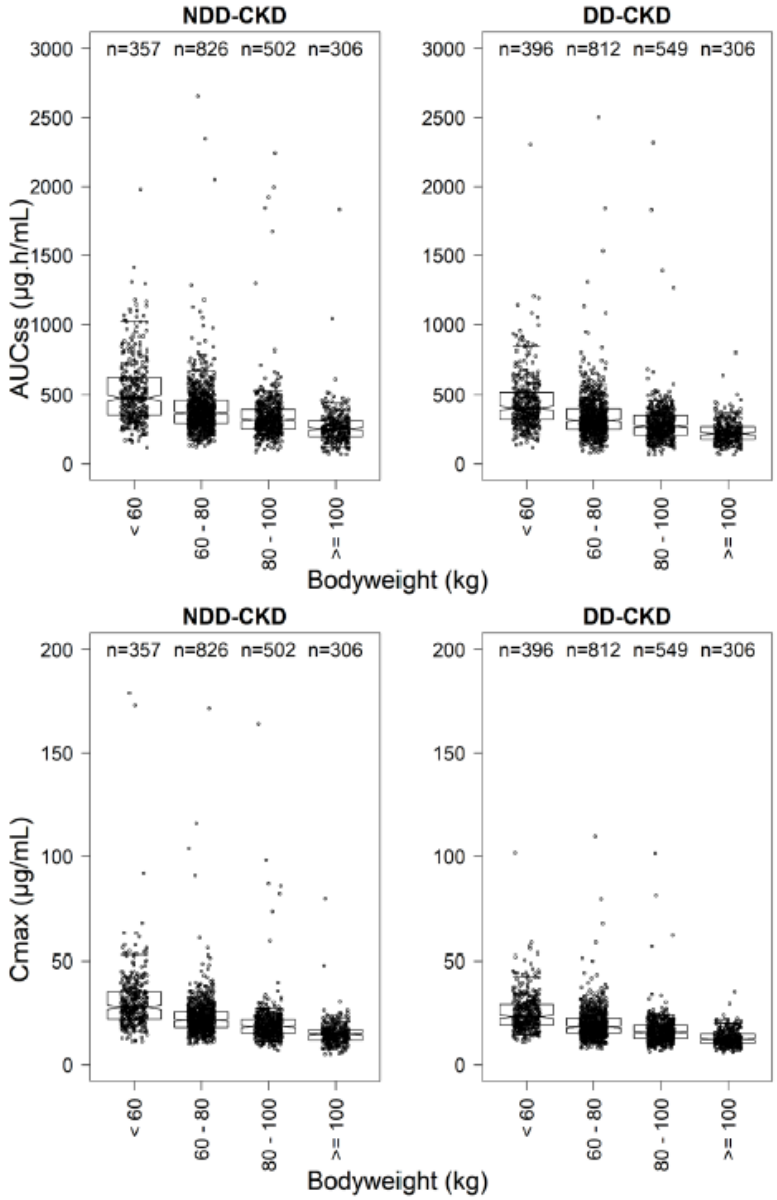
The effect of sex on the PK of vadadustat was evaluated by population PK analysis. Sex was not found to be a statistically significant covariate.

Weight

The body weights of subjects with DD-CKD included in the population PK analysis ranged from 46.9 to 118 kg (at 5th and 95th percentile), and the estimated AUC_{ss} ranged from +34.2% to -24.8% of the AUC of subjects with the median body weight (75 kg) of subjects with DD. The body weights of subjects with NDD-CKD included in the population PK analysis ranged from 49 to 118 kg (at 5th and 95th percentile), and the estimated AUC_{ss} ranged from +30.5% to -24.7% of the AUC of subjects with the median body weight (75 kg) of subjects with NDD.

Stratified by four weight intervals, the impact of bodyweight on vadadustat exposure is displayed in **Figure below**, in which the 60-80 kg group serves as the reference group.

Figure 12 **AUCss and Steady-state Cmax in the NDD-CKD and DD-CKD Populations with 300 mg QD Dosing, Stratified by Bodyweight**



AUCss: steady-state area under the concentration-time curve; CI: confidence interval; CKD: chronic kidney disease; Cmax: maximum drug plasma concentration; DD: dialysis-dependent; n: number of observations; NDD: non-dialysis-dependent; PK: pharmacokinetic; QD: once daily.
Note: PK parameters were calculated using posthoc predicted model parameters and grouped by covariate classes. The box denotes the median and 25th and 75th percentiles, and whiskers denote the 5th and 95th percentiles of the subjects in the group. Notches represent the 95% CI of the median, calculated as median ± 1.57 × interquartile range/sqrt(n).
Source: popPK-Report-content-suppl.r

Race

Japanese descent is a covariate on CL/F in the population PK model. Apart from confounding bodyweight effects, which were addressed separately in the population PK model, subjects with CKD from Japanese descent have an 18.7% lower CL/F (**Table 4 page 46**).

Age

According to popPK analysis, age was not found to be a significant covariate for vadadustat PK. The baseline age in the PK studies ranged from 18 to 104 years, which is a substantial age range. Vadadustat has not yet been studied in children. A waiver was granted for the paediatric population from birth to less than 4 months of age and deferral was granted for paediatric population from 4 months to less than 18 years of age in the treatment of anaemia secondary to chronic kidney disease.

Table 15 Elderly Subjects in the Population PK Dataset by Trial

Trial	Age 65-74 Number subjects in this age range/total number	Age 75-84 Number subjects in this age range/total number	Age 85+ Number subjects in this age range/total number
CI-0003	7	5	0
CI-0007	52	24	3
CI-0009	3	0	0
CI-0011	19	4	0
CI-0014	216	181	63
CI-0015	265	208	62
CI-0016	35	18	3
CI-0017	376	155	21
CI-0021	16	10	2
CI-0022	15	5	0
J01	47	57	11
J03	60	37	0
Total	1111	704	165

Pharmacokinetic interaction studies

In silico

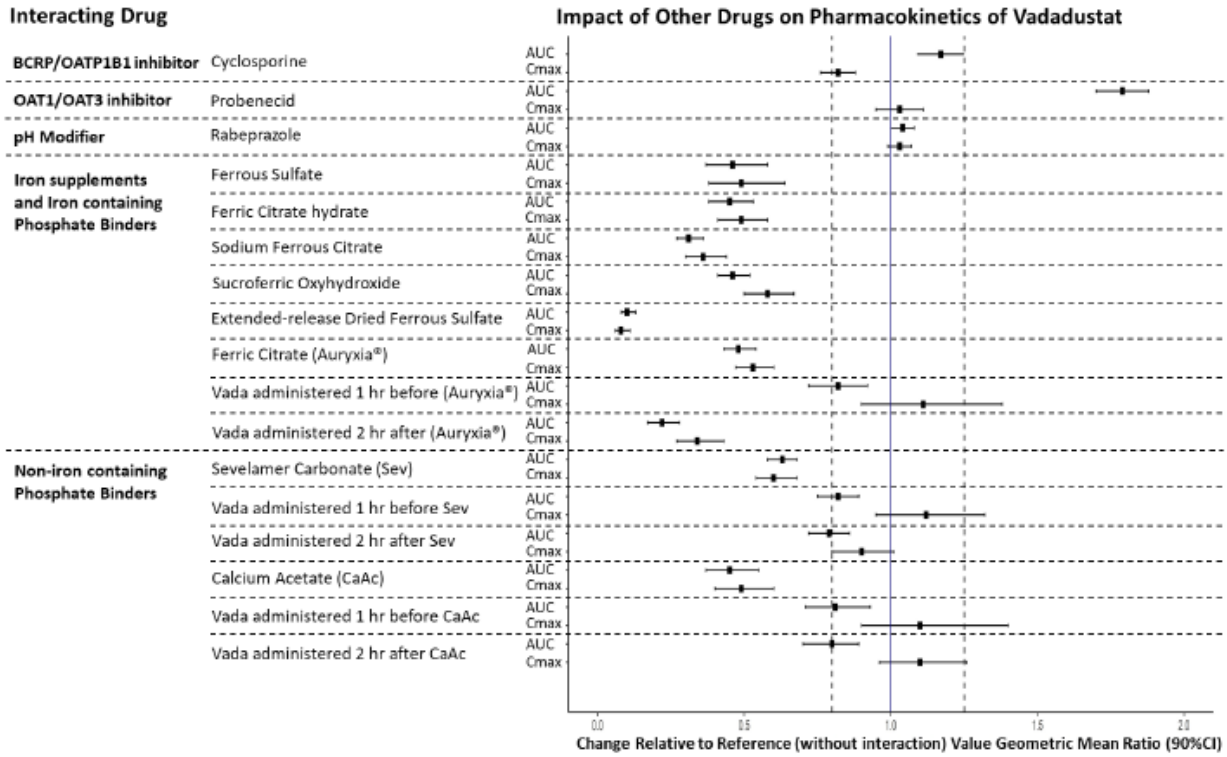
A mechanism-based static PK model was applied to the data for direct CYP inhibition, which showed that the computed area under the plasma concentration time curve ratio (AUCR) values for all the CYP isoforms evaluated were <1.25. Therefore, in vivo clinical DDI studies to evaluate vadadustat as an inhibitor of CYPs was deemed not necessary. Further, vadadustat was not an inhibitor of UGT1A1.

Clinical studies

Effect of other medicinal products on the PK of vadadustat

Clinical studies suggest that OAT1/3 inhibitors possibly cause a weak to moderate increase in vadadustat exposure and that iron or phosphate binders decrease the absorption of vadadustat (due to complex formation), thus decreasing the vadadustat exposure by approximately 50%. This is reflected in the SmPC. It is unlikely that BCRP or OATP1B1 inhibitors affect the vadadustat PK, and vadadustat exposure is not affected by proton pump inhibitors (**Figure below**).

Figure 13 **Impact of Co-administered Drugs on Vadadustat Exposure**



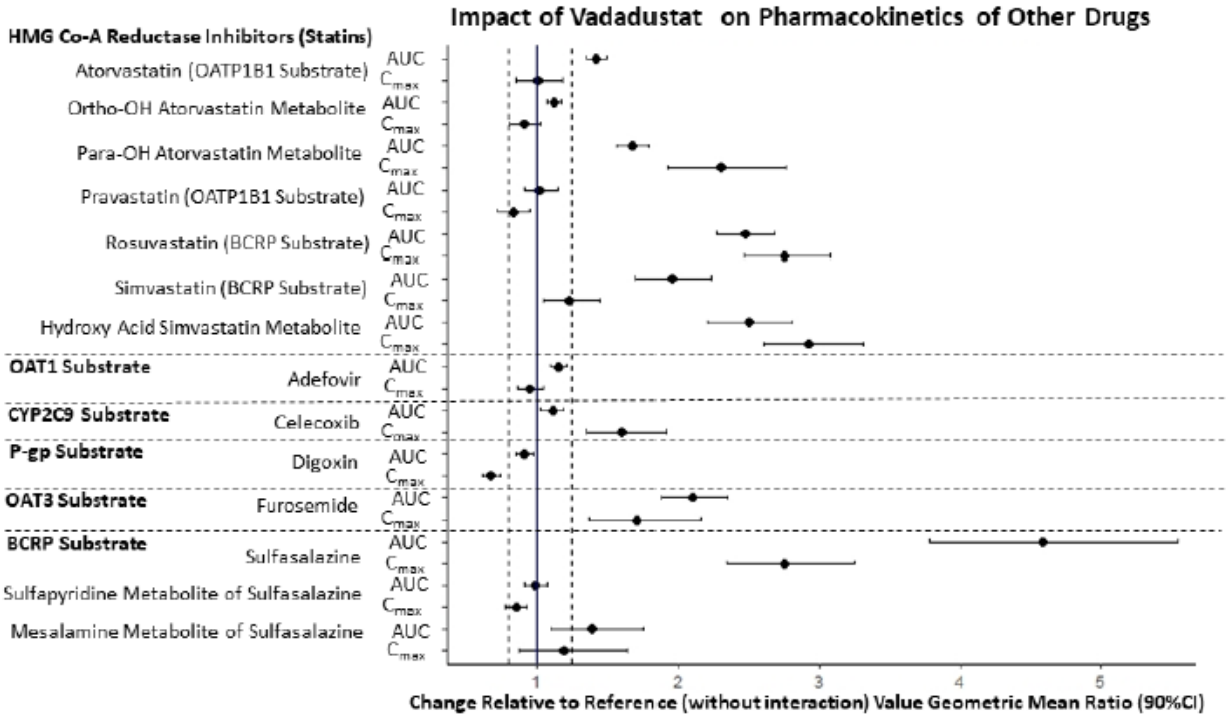
BCRP: breast cancer resistance protein; CI: confidence interval; FDA: Food and Drug administration; OAT: organic anion transporter; OATP: organic anion-transporting polypeptide; Pharmacokinetic abbreviations are defined in the table on page 13
Note: Based on FDA guidance, an increase in exposure of ≥1.25- to <2-fold is classified as a weak interaction and decrease in exposure ≥20% to <50%, ≥50% to <80%, or ≥80% is classified as a weak, moderate, or strong interaction, respectively (FDA 2020). The solid vertical line represents geometric mean ratio of 1 and dotted vertical lines represent bioequivalence bounds of 0.80 to 1.25.

Effect of vadadustat on the PK of other medicinal products

Based on clinical DDI studies, vadadustat is unlikely to cause DDI with substrates of P-gp, OATP1B1, and OAT1 (**Figure below**). On the other hand, vadadustat is a moderate inhibitor of BCRP and OAT1/3 and has the potential to inhibit both OAT1 and OAT3.

Vadadustat was not an *in vitro* inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Figure 14 **Impact of Vadadustat (600 mg) on the Exposure of Other Drugs**



BCRP: breast cancer resistance protein; CI: confidence interval; CYP: cytochrome; FDA: Food and Drug Administration; OAT: organic anion transporter; OATP: organic anion-transporting polypeptide; P-gp: P-glycoprotein; Pharmacokinetic abbreviations are defined in the table on page 13.

Note: Based on FDA guidance, an increase in exposure of ≥1.25- to <2-fold, ≥2- to <5-fold, or ≥5-fold is classified as a weak, moderate, or strong interaction, respectively, and decrease in exposure ≥20% to <50%, ≥50% to <80%, or ≥80% is classified as a weak, moderate, or strong interaction, respectively (FDA 2020). The solid vertical line represents geometric mean ratio of 1 and dotted vertical lines represent bioequivalence bounds of 0.80 to 1.25.

Pharmacokinetics using human biomaterials

Vadadustat transporters

Vadadustat was shown to be a substrate of OAT1, OAT3, BCRP, and the hepatic transporter OATP1B1. Vadadustat-O-glucuronide was shown to be a substrate of OAT3 and MRP2, and possibly OATP1B3.

Effect of vadadustat on metabolising enzymes

In vitro, vadadustat was a substrate of multiple UGTs. It was not an inhibitor of selected metabolising enzymes (CYPs or UGTs) but a mild inductor of CYP2B6 and UGT1A1.

Effect of vadadustat on transporters

Vadadustat has the potential to inhibit BCRP, OAT1, OAT3, and OATP1B1, and it may be a possible inhibitor of P-gp. In the P-gp study, however, there was solubility limits, making the interpretation of the study results difficult (**Table below**).

Table 16 Summary of In Vitro Transporter Inhibition Potential of Vadadustat

Transporter	Substrate	IC_{50} (µg/mL)	R-value
P-gp	Digoxin	>80	--
BCRP	Prazosin	10.4	231 (>10)
OATP1B1	[^{3}H]-Estradiol-17β-glucuronide	4.02	1.2 (>1.1)
OATP1B3	[^{3}H]-Estradiol-17β-glucuronide	>30	--
OCT2	[^{14}C]-Metformin	>30	--
OAT1	[^{3}H]-Aminohippurate	3.76	0.12 (>0.1)
OAT3	[^{3}H]-Estrone-3-sulfate	0.336	1.3 (>0.1)
MATE1	[^{14}C]-Metformin	>30	--
MATE2-K	[^{14}C]-Metformin	>30	--
BSEP	[^{3}H]-taurocholic acid	>500	--

BCRP: breast cancer resistance protein; BSEP: bile salt export pump; CKD: chronic kidney disease; CTD: Common Technical Document; CYP: cytochrome P450 isozyme; IC50: concentration at which 50% inhibition is observed; MATE1 and 2-K: multidrug and toxin extrusion 1 and 2-K; MATE: multidrug and toxin extrusion protein; NC: not calculated; ND: not determined; OAT: organic anion transporter; OAT1 and 3: organic anion transporter 1 and 3; OATP: organic anion-transporting polypeptide; OATP1B1 and 1B3: organic anion-transporting polypeptide 1B1 and 1B3; OCT: organic cation transporter; OCT2: organic cation transporter 2; P-gp: P-glycoprotein; PK: pharmacokinetic; UGT: uridine diphosphate glucuronosyltransferase; Pharmacokinetic abbreviations are defined in the table on page 13
For P-gp and BCRP inhibition, R-value = I_{gut}/IC_{50}, where I_{gut} is dose/250 mL (600 mg/250 mL = 2400 µg/mL). It should be noted that the I_{gut} concentration calculated as per guideline recommendations far exceeds the measured aqueous solubility at 37°C at pH 4.3 of 0.053 mg/mL (53 µg/mL) (Module 3.2.S.1.3 General Properties).

2.6.2.2. Pharmacodynamics

Mechanism of action

Vadadustat is a novel, synthetic, orally bioavailable, small molecule inhibitor of hypoxia inducible factor (HIF) prolyl-hydroxylase (PH) enzymes. HIF-PH enzymes are also referred to as prolyl hydroxylase (PHD) enzymes. Vadadustat inhibits the 3 isoforms of the PHD enzymes leading to HIF stabilization and increased cellular levels of HIF that in turn, stimulates endogenous EPO expression and improves the oxygen-carrying capacity of the blood by stimulating Hb and RBC production.

Primary and Secondary pharmacology

EPO

EPO increase caused by vadadustat was observed in the phase 1 studies CI-0001, CI-0002, and CI-0020 in healthy subjects, in the phase 1 patient study CI-0034 (**Table 24**), and in the phase 2 study CI-0025 (**Table 18**). There were no significant differences in EPO peak concentration and AUC among Japanese and White subjects in the vadadustat 150 mg or 300 mg groups, including the placebo group. However, in the 600 mg group, the EPO AUC exposure of Japanese subjects was 40% higher than that of White subjects and was 21% to 27% higher even after excluding 1 subject with outlier of EPO concentrations. However, the mean, median and distribution of AUC of EPO in Japanese and White subjects was not significantly different (**Figure *15***). The increase of EPO caused by vadadustat returned to approximately the baseline value 24 hours after administration, and the increase did not reach supraphysiologic levels observed with ESAs.

Table 17 **Mean (SD) Pharmacodynamics Parameters for Baseline-unadjusted Serum EPO Concentration by Vadadustat Dose and Dosing Day in Subjects with DD-CKD (AKB-6548-CI-0034)**

Parameter (Unit)	Vadadustat 600 mg N=12		Vadadustat 750 mg N=10		Vadadustat 900 mg N=13	
Statistic	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
C_{max} (mU/mL)						
Mean (SD)	53.3 (25.0)	58.9 (36.9)	115 (123)	103 (91.9)	72.3 (52.6)	122 (200)
AUC_{0-11} (h·mU/mL)[a]						
Mean (SD)	319 (150)	410 (286)	569 (623)	677 (533)	455 (438)	981 (1854)
T_{max} (h)						
Median (min, max)	10.09 (3.08, 23.73)	4.50 (0.00, 10.27)	10.94 (5.00, 23.77)	5.01 (0.00, 11.00)	10.00 (4.00, 23.92)	10.00 (0.00, 11.08)

DD-CKD: dialysis-dependent chronic kidney disease; EPO: erythropoietin; SD: standard deviation; Pharmacokinetic abbreviations are defined in the table on page 13

a AUC_{0-11} for Day 1, AUC_{last} for Day 8 (AUC_{last} corresponds to AUC_{0-11} on Day 8).

Source: AKB-6548-CI-0034 Table 14.2.4.2.

Table 18 **Summary of Pharmacodynamics Parameters for Baseline-Unadjusted Serum EPO Concentration for Vadadustat Treatment Groups by Epoetin Alfa Stratification at Weeks 1 and Week 1+1 in Subjects with DD-CKD in the Main Study (AKB-6548-CI-0025)**

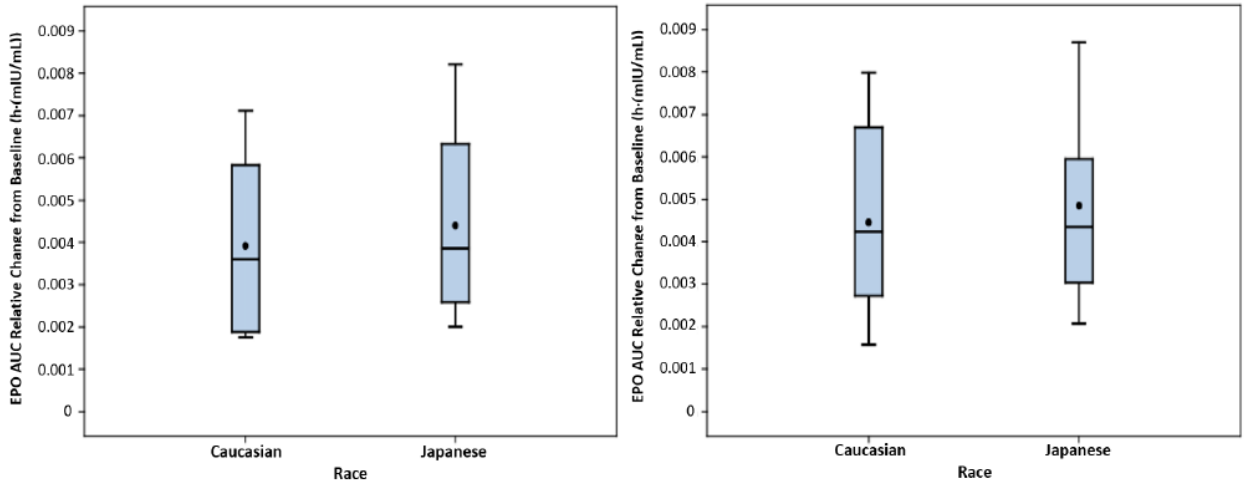
Parameter	Vadadustat 300 mg		Vadadustat 450 mg		Vadadustat 600 mg	
Statistics	Week 1	Week 1+1	Week 1	Week 1+1	Week 1	Week 1+1
Low Epoetin Alfa Stratum ≤90 U/kg/week						
AUC_{0-5} (h·µg/mL)						
n	33	30	27	27	0	0
Geometric Mean (SD)	58.5 (193)	65.7 (57.8)	76.4 (412)	80.2 (123)	--	--
C_{max} (µg/mL)						
n	33	30	27	28	0	0
Geometric Mean (SD)	17.6 (47.8)	19.3 (14.7)	25.5 (180)	23.9 (37.6)	--	--
T_{max} (h)						
n	33	30	27	28	0	0
Median (min, max)	4.50 (0.00, 9.50)	2.75 (0.00, 6.92)	4.50 (0.00, 10.5)	4.51 (0.00, 7.43)	--	--
High Epoetin Alfa Stratum >90 to <300 U/kg/week						
AUC_{0-5} (h·µg/mL)						
n	15	13	20	21	15	12
Geometric Mean (SD)	56.0 (44.7)	74.9 (41.8)	79.9 (320)	61.6 (43.1)	102 (104)	89.9 (103)
C_{max} (µg/mL)						
n	15	13	20	21	15	12
Geometric Mean (SD)	17.5 (15.6)	20.5 (12.8)	23.4 (99.2)	18.1 (10.9)	33.2 (108)	27.2 (34.3)
T_{max} (h)						
n	15	13	20	21	15	12
Median (min, max)	2.00 (0.00, 12.0)	2.02 (0.00, 6.80)	4.53 (0.00, 9.62)	0.00 (0.00, 6.95)	0.00 (0.00, 9.03)	2.47 (0.00, 7.00)

DD-CKD: dialysis-dependent chronic kidney disease; Max: maximum; Min: minimum; SD: standard deviation; --: not determined; Pharmacokinetic abbreviations are defined in the table on page 13

Geometric Mean = exp(mean of log[value]); Geometric CV% = sqrt(exp(variance for log transformed value)-1)*100.

Source: AKB-6548-CI-0025 Table 14.2.12.3.1.1.

Figure 15 **Box Plots of Dose Normalized AUC Erythropoietin Relative Change from Baseline – Single Dose (Left Panel) and Multiple Dose (Right Panel) in Healthy Japanese and White Subjects (AKB-6548-CI-0020)**



EPO: erythropoietin, IQR: interquartile range; Pharmacokinetic parameters are defined in the table on page 13
Baseline: Day -1 EPO AUC
Relative change from baseline was derived as the exponentiated difference on the log scale: EXP[Ln(AUC EPO Day X) – Ln(AUC EPO Day-1)], where Day X is 1 or 10.
The center line is the median and the dot is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the interquartile range.
Source: AKB-6548-CI-0020 Section 14.2, Table 14.2.6.4.3.

A tabulated comparison between EPO response in NDD- and DD-CKD patients is shown in Table below. The change from baseline is comparable for both ESA naïve and prior ESA users.

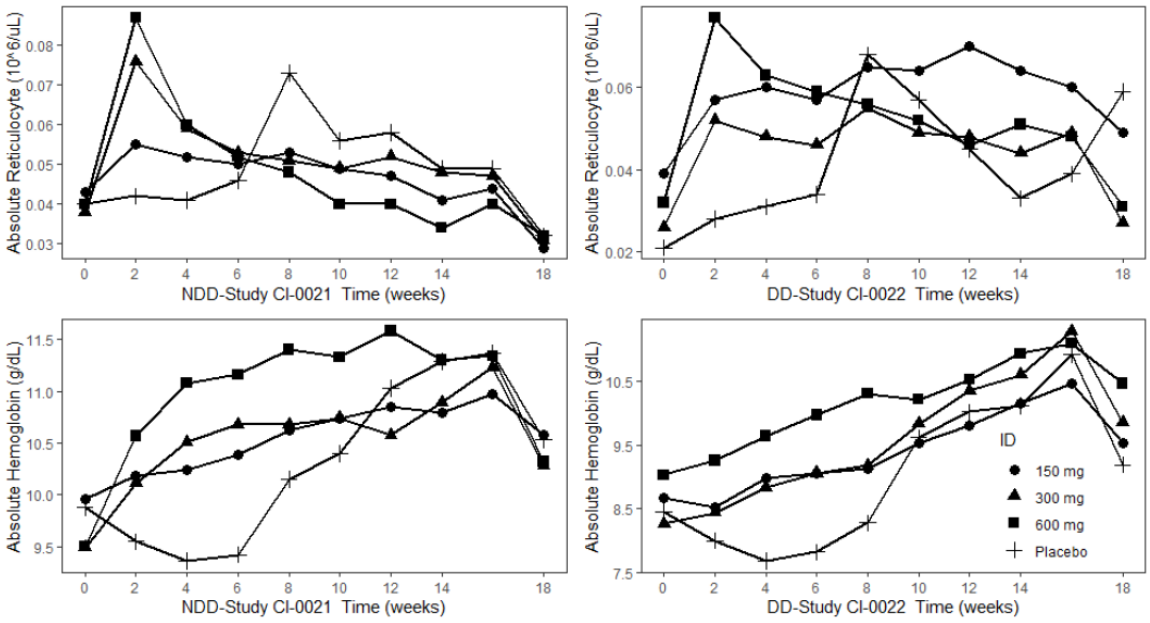
Table 19		Comparison of EPO Responses in Vadadustat-treated Subjects in NDD-CKD and DD-CKD Populations in Pivotal Trials			
Population		NDD-CKD Population EPO level (mIU/ml)		DD-CKD Population EPO level (mIU/ml)	
Trial		CI-0014	CI-0015	CI-0016	CI-0017
		Correction (ESA Naïve)	Conversion (prior ESA)	Correction (ESA naïve/ limited use)	Conversion (prior ESA)
Baseline	n	851	841	178	1752
	Mean (SD)	15.199 (14.042)	15.423 (14.9337)	17.752 (29.2976)	26.296 (75.9830)
	Median	10.95	11.05	10.87	11.315
	Min, Max	2.50, 181.15	2.50, 40.69	2.50, 331.13	2.50, 1516
Week 4	n	795	791	169	1661
	Mean (SD)	16.163 (15.1761)	14.684 (14.55320)	20.332 (41.5648)	20.409 (39.2618)
	Median	12.44	10.94	11.98	11.93
	Min, Max	2.50, 188.59	2.50, 173.23	2.50, 446.56	2.50, 774.94
Week 12	n	763	777	162	1611
	Mean (SD)	17.349 (23.2873)	16.725 (46.7393)	22.370 (49.6504)	27.002 (84.31540)
	Median	11.28	11.16	12.29	13.04
	Min, Max	2.50, 313.82	2.50, 1240.47	2.68, 454.17	2.50, 1564.22
Week 28	n	681	727	151	1487
	Mean (SD)	19.649 (47.2026)	17.442 (38.7142)	19.892 (42.7964)	22.749 (51.5250)
	Median	11.28	11.15	11.58	12.61

Table 20		Comparison of EPO Responses in Vadadustat-treated Subjects in NDD-CKD and DD-CKD Populations in Pivotal Trials			
	Min, Max	2.50, 990.98	2.50, 613.12	3.24, 503.81	2.50, 981.00
Week 52	n	503	517	90	1174
	Mean (SD)	20.137 (37.2416)	21.056 (45.9829)	17.592 (19.8879)	32 (101.3792)
	Median	12.05	11.58	12.23	13.74
	Min, Max	2.50, 470.04	2.50, 613.12	2.66, 164.70	2.50, 2107.47

Source: CI-0014 Table 14.3.5.7.1, CI-0015 Table 14.3.5.7.1, CI-0016 Table 14.3.5.7.1, CI-0017, Table 14.3.5.7.1.

The rise in **reticulocytes** are relatively dose dependent and associated with Hb increase with vadadustat treatment (**Figure and Table below**).

Figure 16 Reticulocyte Change from Baseline Over Time in Phase 2 in Subjects with DD-CKD



DD-CKD: dialysis-dependent chronic kidney disease; EOT: end of treatment; NDD: non-dialysis-dependent
Note: EOT 16 weeks with 2 weeks follow up on Week 18
Source: AKB-6548-CI-0021 Table 14.2.2.5.1, AKB-6548-CI-0022 Table 14.2.2.5.1.

Table 21 Summary of Mean (SD) Change from Baseline at End of Treatment for Selected Hematology Parameters in Phase 2 DD-CKD and NDD-CKD Studies

	DD-CKD				NDD-CKD					
	AKB-6548-CI-0022		AKB-6548-CI-0025 (Main Study)		AKB-6548-CI-0005		AKB-6548-CI-0007		AKB-6548-CI-0021	
	Vada	Pbo to Vada	Vada	EPO	Vada	Pbo	Vada	Pbo	Vada	Pbo to Vada
N	35	5	74	33	63	18	105	63	33	13
MCV, fL	2.71 (2.560)	2.62 (2.295)	0.1 (3.34)	-0.2 (4.33)	1.2 (2.98)	-0.5 (1.95)	0.8 (3.32)	0.4 (2.97)	0.90 (3.563)	2.45 (4.047)
MCH, pg	0.86 (1.060)	0.20 (0.539)	0.3 (1.13)	-0.4 (1.20)	0.6 (0.90)	-0.3 (1.13)	0.0 (1.30)	-0.3 (0.91)	0.20 (0.976)	0.60 (1.171)
MCHC, g/dL	-0.03 (0.712)	-0.72 (0.402)	0.23 (1.225)	-0.32 (1.372)	0.2 (1.32)	-0.1 (1.11)	-0.4 (1.32)	-0.3 (1.46)	-0.09 (0.980)	-0.18 (1.133)
HCT, %	6.71 (4.606)	7.34 (5.740)	-0.6 (4.38)	1.5 (4.45)	3.0 (2.76)	-0.4 (2.40)	3.0 (3.80)	0.1 (3.13)	4.62 (3.450)	4.54 (2.463)
RDW, %	-0.03 (0.794)	-0.02 (0.370)	-0.08 (1.239)	0.58 (1.593)	0.02 (0.756)	-0.01 (0.667)	-0.06 (1.069)	-0.10 (1.153)	-0.01 (0.714)	-0.41 (1.403)
Hb g/dL	0.06 (0.89)	-1.49 (0.82)	-0.14 (1.19)	0.44 (1.25)	1.06[b] (0.70)	-0.03 (0.65)	0.88 (1.16)	-0.08 (0.93)	1.07 (0.94)	-0.46 (0.56)

CKD: chronic kidney disease; DD: dialysis-dependent; EPO: epoetin alfa; HCT: hematocrit; ITT: intent to treat; Pbo: placebo; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; N: number; NDD: non-dialysis-dependent; RDW: red cell distribution width; SD: standard deviation; Vada: vadadustat

a MCHC converted from % to g/dL (1:1)

b Vadadustat groups included 66 subjects for hemoglobin analysis

Source: AKB-6548-CI-0005 (ITT) 14.3.2.1a, AKB-6548-CI-0007 (ITT) 14.3.3.1, (MITT) 14.2.10.1.1, AKB-6548-CI-0021 (Safety Population) 14.3.4.3, (MITT) 14.2.2.5.1, AKB-6548-CI-0022 (Safety Population) 14.3.4.3, (MITT) 14.2.2.5.1, AKB-6548-CI-0025 Main Study (Safety Population) 14.3.5.1a.1.

In **Table below**, the effect of vadadustat on selected iron-related parameters is shown.

Table 22 Summary of Mean (SD) Change from Baseline at End of Treatment for Selected Iron-related Parameters in Phase 2 DD-CKD and NDD-CKD Studies

	DD-CKD					NDD-CKD					
	AKB-6548-CI-0011	AKB-6548-CI-0022		AKB-6548-CI-0025 (Main Study)		AKB-6548-CI-0005		AKB-6548-CI-0007		AKB-6548-CI-0021	
	Vada	Vada	Pbo to Vada	Vada	Epo	Vada	Pbo	Vada	Pbo	Vada	Pbo to Vada
N	69	35	5	77	33	64	18	109	63	33	13
Ferritin (ng/mL)	-71.7 (361)	-113 (65.7)	-78.1 (63.7)	-111 (315)	-21.3 (448)	-75.5 (78.2)	-19.6 (41.7)	-79.9 (123)	-33 (79.6)	-67.1 (46.7)	-90 (51.2)
N	69	35	5	77	33	64	18	108	63	33	13
TIBC (µg/dL)	26.1 (29.1)	76.1 (38.3)	66.0 (45.0)	49.5 (37.5)	-8.0 (29.1)	35.2 (29.9)	-9.9 (25.7)	32.0 (32.7)	0.8 (24.5)	46.0 (39.2)	54.6 (34.6)
Serum Iron (µg/dL)	12.7 (33.4)	-8.2 (34.3)	0.8 (29.7)	-4.1 (38.8)	-13.6 (40.7)	2.6 (20.0)	-8.6 (25.8)	6.2 (24.3)	-1.1 (21.4)	9.2 (32.0)	2.9 (22.1)
TSAT (%)	2.2 (15.3)	-12.9 (12.55)	-10.3 (12.3)	-7.6 (16.3)	-4.1 (17.7)	-2.8 (7.5)	-2.1 (9.1)	-1.1 (10.1)	-0.8 (8.3)	-1.37 (10.8)	-5.06 (10.7)
N	67	35	5	74	27	63	18	118	66	33	13
Hepcidin (ng/mL)	-14.6 (47.0)	-94.6 (48.2)	-76.9 (70.7)	-66.8 (92.5)	-82.6 (105)	-89.2 (150)	-32.5 (104)	-68.7 (92)	-11.4 (85.4)	-17.7 (35.4)	-18.6 (21.9)

Vadadustat impact on QTc

The Phase 1 TQT study that evaluated a single oral therapeutic (600 mg) and supratherapeutic (1200 mg) dose of vadadustat demonstrated that vadadustat did not have a significant effect on the ΔΔQTcF as the upper end of the 90% CI interval was <10 msec. A small but statistically significant effect on the QTcF interval was demonstrated with a slope of the relationship between plasma concentrations for vadadustat and ΔΔQTcF of 0.0233 msec/µg/mL (90% CI: 0.0036 to 0.043). The predicted effect on ΔΔQTcF was low within the studied range of plasma concentrations of vadadustat with the upper bound of the 90% CI clearly below 10 msec. The concentration effect analysis supports the conclusion from the primary analysis that vadadustat does not have a clinically meaningful effect on cardiac repolarization.

Exposure-response analyses

Exposure-efficacy relationships

The Applicant has provided popPK/Hb equations for estimation of individual Hb levels. A typical exposure-efficacy evaluation based on e.g. exposure quartiles has not been provided. However, since dose titration (up or down as needed) is the proposed way of achieving the target Hb level, a typical exposure-response evaluation, like the one conducted for exposure-safety, is not needed.

Exposure-safety relationships

The following selected safety endpoints (SSE, all grades at the first occurrence) were included in the exposure-safety analysis:

- Diarrhea
- Nausea
- Vomiting
- Gastrointestinal (GI)-related adverse events (nausea, vomiting, abdominal pain, diarrhea)
- Hepatotoxicity
- Hyperkalemia

Among these safety endpoints, hepatotoxicity and hyperkalemia were adverse events of special interest (AESI).

The exposure-safety analysis was performed using the data in 3474 subjects from the global Phase 3 studies (CI-0014, CI-0015, CI-0016, and CI-0017), including 836, 840, 168, and 1630 subjects with CKD treated with vadadustat from these 4 studies, respectively. Among the 3473 subjects included in the exposure-safety analysis, a total of 1553 events at the first occurrence were counted across the 6 SSEs.

The final vadadustat population PK model was used to derive exposure metrics. There were 2 exposure metrics used for the exposure-safety analysis: the time-averaged AUC up to the event (primary exposure metric) and the time-averaged AUC during 4 weeks preceding the event (secondary exposure metric). In case of no event, the time-averaged AUC over the full treatment period was used for both the primary and secondary exposure metric.

Logistic regression analysis (Table 9.9.6, Methods) indicated a statistically significant exposure-response relationship between the time-averaged AUC during 4 weeks preceding the event and nausea, GI disorders, and hyperkalaemia. The model-predicted AE incidences at the 10th, 50th, and 90th percentile of the predicted exposure ranges in the phase 3 studies based on the logistic regression parameter estimates is provided in **Table below.** Predicted changes in incidence of event occurrence over the exposure range were small and not clinically meaningful and further illustrated the absence of meaningful exposure trends.

Table 23 **Model-Predicted Adverse Event Incidence at the 10th, 50th, and 90th Percentiles of Exposures as Predicted for Study CI-0014, CI-0015, CI-0016, and CI-0017, Based on Logistic Regression Parameter Estimates**

	Model-Predicted Incidence (95% CI)		
Selected Safety Endpoint	AUC - P10 (155 µg·h/mL)	AUC - P50 (336 µg·h/mL)	AUC - P90 (617 µg·h/mL)
Diarrhea	0.087 (0.076, 0.1)	0.093 (0.084, 0.104)	0.104 (0.091, 0.118)
Vomiting	0.044 (0.036, 0.053)	0.045 (0.039, 0.053)	0.048 (0.039, 0.059)
Nausea	0.057 (0.049, 0.067)	0.063 (0.056, 0.072)	0.074 (0.063, 0.085)
Gastrointestinal disorders	0.153 (0.139, 0.169)	0.164 (0.152, 0.177)	0.181 (0.164, 0.199)
Hepatotoxicity	0.023 (0.017, 0.031)	0.023 (0.018, 0.029)	0.023 (0.017, 0.032)
Hyperkalemia	0.047 (0.039, 0.056)	0.051 (0.044, 0.059)	0.058 (0.048, 0.069)

Note: Exposure percentiles are the average across all SSEs, based on the exposure distribution from each SSE
AE: adverse event; CI: confidence interval; SSE: selected safety endpoint. Pharmacokinetic abbreviations are defined in the table on page 13
AUC-P10, AUC-P50, AUC-P90: the average 10th, 50th, and 90th percentile across AEs for the 'time average area under the curve until the event'
Source: AKE-PKPD-VADADUSTAT-1954-PKPD-ER, Table 5-18.

2.6.3. Discussion on clinical pharmacology

Vadadustat (AKB-6548) is a synthetic, orally bioavailable, small molecule (molecular weight 306.7 g/mol) developed as an inhibitor of hypoxia-inducible factor (HIF) prolyl-hydroxylases (PHDs) for the treatment of anaemia associated with chronic kidney disease (CKD) in adults on dialysis (DD-CKD) and not on dialysis (NDD). The proposed dose regimen is a starting dose of 300 mg once daily with up-titration every 4 weeks until the target haemoglobin level is reached (10-12 g/dL). The maximum dose of vadadustat is 600 mg/day. The clinical pharmacology of vadadustat was evaluated in multiple (24) clinical studies in healthy subjects and in patients with CKD to characterize pharmacokinetic (PK) and provide an assessment of intrinsic and extrinsic factors affecting PK. Further, the pharmacodynamic (PD) markers EPO, reticulocytes, and Hb were evaluated in Phase 1 studies of healthy subjects and in Phase 2 studies of CKD patients.

Quantification of vadadustat, major metabolite vadadustat-O-glucuronide (vada-OG, 15%) and minor metabolite vadadustat-acyl-glucuronide (vada-AG, <1%) were determined in human plasma and urine by validated LC-MS/MS methods. Overall, the analytical methods and bioanalysis conducted in the vadadustat development programme are considered acceptable.

Exposure metrics were determined by non-compartmental methods using SAS statistical software. Population PK analysis and PKPD analysis were performed using NONMEM. The final pop PK model for vadadustat was a one-compartment model with lag time, first-order absorption and first-order elimination. A total of 14021 observations from 4188 subjects were included in the Pop PK population representing a body weight span of 30.1-204 kg. Formal covariate analysis was not performed and data was added in several stages during model development. Effect of food was included on lag time

and Ka, effects of body weight was allometrically scaled with estimated exponents of 0.624 and 0.811 for CL and V. CL/F were split into one for healthy subjects and one for CKD patients. CL/F was lower in patients than in healthy subjects. Other covariates retained in the model were renal function, bilirubin, Japanese race on CL/F while concomitant medication NICP or iron/ICP were included on bioavailability. The methods used for model development and model evaluation are generally acceptable.

ε-shrinkage was reported and was acceptably low (7.6%). ŋ-shrinkage for apparent clearance (CL/F) was above 30% (31.6%) and was largely driven by the Phase 3 data which contributed 3474 of the total 4188 subjects (83%) to the dataset. Distribution of post-hoc ETA CL/F values was narrower compared to model-estimated distribution, however with still some heterogeneity present which was deemed sufficient for evaluation of covariate effects. Individual exposure estimates in the E-R analysis were obtained from post hoc parameter estimates and due to shrinkage effect, it is likely that the predicted exposure range will be narrower and could reduce ability to detect E-R relationship. Therefore, results from E-R analyses should be interpreted with caution.

A semi-mechanistic PK/Hb model was developed to describe influence of vadadustat exposure (AUC) on life span of red blood cells and thus life span of Hb. The model was developed based on earlier models describing effect of EPO on Hb and is considered reasonable. A linear E-R relationship was best describing relationship between vadadustat exposure and Hb response. Based on the estimated slope, increase in Hb of 3.46% could be expected for increase in AUC of 100 µg*h/mL in non-Japanese subjects with CKD and 2.18% increase could be expected for the same increase in exposure in Japanese subjects with CKD. However, according to Pop PK model, exposure in Japanese subjects was substantially higher compared to non-Japanese subjects, so the overall response was considered comparable in both populations.

Dose proportionality was demonstrated for Cmax and AUC in the proposed dose range of 150 to 600 mg vadadustat in both single and multiple dosing. The absolute bioavailability of vadadustat has not been evaluated. Based on the ADME study and the recovery in urine, it may be concluded that the extent of absorption was at least 59%. The median absorption time of vadadustat to reach Cmax was 2 to 3 hours. Vadadustat is minimally accumulated in healthy subjects with an accumulation ratio for AUC of 1.03 in steady state. In patients with CKD, the steady state accumulation is predicted to be minor (32%). The estimated interindividual variability in apparent clearance and the absorption rate constant ranges from 47-89%. This variability is considered moderate.

In healthy subjects, the AUC_{inf} and C_{max} of vadadustat decreases up to 21% and 29%, respectively, when administered with food compared with fasting. Time to maximum concentration (Tmax) increased from to 2 hrs to 3.5 hrs with food intake. The same relative changes with and without concomitant food intake are expected in the patient population. Based on these results, it is acceptable to state that the product can be taken with or without food.

Vadadustat has a high protein binding (>99%) and does not distribute to the RBCs. Based on popPK analysis, subjects with CKD has a vadadustat volume of distribution, mean clearance, and half-life of 11.6 L, 0.8 L/h, and 14 hours, respectively.

Vadadustat plasma protein binding (PPB) was determined in vitro by rapid equilibrium dialysis method in healthy subjects and subjects with CKD (studies XS-1137 and AL-7053-G). The Applicant did not distinguish binding to different plasma proteins in conducted studies but assumes the vadadustat, as a negatively charged organic acid, binds predominantly to albumin. Although the measured fractions of unbound vadadustat were small (less than 1%) and number of subjects sampled low, which is associated with uncertainties in the estimation, still a trend was noted towards decreasing PPB with increasing concentration and increasing degree of renal impairment. Nevertheless, it is considered that with titration to the target Hb level, any differences in fraction unbound that may emerge between CKD patients would not translate into clinical safety concerns.

As regards to the elimination of vadadustat, approximately 59% of a dose is recovered in urine and 27% in faeces. Renal excretion of unchanged vadadustat amounts to less than 1% of a dose. Vadadustat is extensively metabolised with 20 metabolites detected in plasma. *In vitro*, vadadustat is a substrate of multiple UGTs with UGT1A9 being the most active. The apparent clearance in CKD patients is 0.80 L/h.

In the ADME study, vadadustat and vadadustat-O-glucuronide were the only major circulating drug-related components (i.e., representing more than 10% of the overall plasma radioactivity AUC) observed in human plasma. Vadadustat-O-glucuronide is considered pharmacologically inactive but is suggested to inhibit the OAT1 and OAT3 transporters. Vadadustat is primarily metabolised via direct glucuronidation by multiple UGTs. The applicant has provided a discussion on the possible influence of genetic polymorphisms of UGT1A9 or UGT1A1 on vadadustat PK. Since the parent molecule, vadadustat, which is responsible for efficacy, accounts for approximately 75% of the systemic exposure, while vadadustat-O-glucuronide and vadadustat-acyl-glucuronide accounted for 15% and <0.1% of systemic exposure, and that vadadustat dose will be titrated to the effect, any impact of genetic polymorphisms in UGT1A1/9 is considered to be minor.

No time dependency was observed with the dose-normalized Ctrough steady-state concentrations from pivotal Phase 3 trials.

Based on popPK estimates, the steady state exposure is expected to be similar between NDD- and DD-CKD. Compared to healthy subjects, the exposure over time (AUC) in patients is approximately 2-fold higher due to lower clearance. Overall, the PK differences between patients and healthy subjects are moderate, which is considered reassuring. Dialysis was not found to affect clearance of vadadustat in a clinically relevant way.

Based on popPK simulations, bodyweight, Japanese descent, and bilirubin were the predominant intrinsic factors impacting vadadustat exposure. A slight increase in exposure of vadadustat with increasing renal impairment has been demonstrated. In the clinical hepatic impairment study, the effect of moderately decreased liver function (Child Pugh B) on vadadustat PK was minimal. According to the dossier, being of Japanese descent accounted for an 18.7% reduction in CL/F. The baseline body weight in the PK studies ranged from 30 to 204 kg, which is a substantial weight range. For both DD- and NDD-CKD, the estimated vadadustat AUCss at the 5th and 95th weight percentiles was +30-34% and -25%, respectively, of the AUC of subjects with the median body weight (75 kg). Age and gender were not found to be significant covariates for vadadustat PK. Overall, no dose adjustments in special populations are proposed in the SmPC, which is considered acceptable.

Regarding the potential of vadadustat to be involved in drug-drug interactions, several scenarios have not been sufficiently investigated with respect to their clinical relevance.

Given in vitro results that cannot dismiss a potential for clinically relevant interaction, the applicant has agreed to put adequate warnings in the product information about the potential of vadadustat to interact with CYP2C8 and CYP3A4 substrates.

Taking into account the substantial steady-state exposure to vadadustat-O-glucuronide metabolite in CKD patients, the applicant has agreed to conduct an in vitro CYP inhibition study with the major metabolite vadadustat-O-glucuronide as a Post-Approval Measure (PAM Classified as REC).

The Applicant agreed to conduct in vivo study on CYP2B6 induction post-approval and SmPC section 4.5 has been updated with regards to potential CYP2B6 induction (PAM Classified as REC).

The pharmacodynamic endpoints were levels of EPO, Hb, and reticulocytes. The PD endpoints are all considered clinically relevant. In both healthy subjects and patients, a relationship between dose and

EPO response has been demonstrated. The EPO response is estimated to be 21% to 27% higher in Japanese subjects, a difference that is not considered of clinical relevance. EPO responses from vadadustat between DD- and NDD-CKD patients are comparable.

As for Hb, it is noted that Hb increased in vadadustat treatment groups whereas Hb decreased in placebo treated groups. However, in study CI-0025 vadadustat did not increase Hb whereas EPO did.

Secondary PD endpoints were hepcidin, ferritin, and transferrin. Compared to placebo or active comparator, the changes in the iron-related biochemical parameters observed following vadadustat treatment indicate a more active erythropoiesis in the vadadustat treatment arms.

The Applicant states that no consistent trends of change in VEGF were observed. Through the inhibition of HIF-PH, apart from stimulating EPO increase, it is expected that vadadustat will also have effect on levels of VEGF. Measurements from four pivotal trials indicate stable VEGF values within 5 to 10% of the baseline values during 52 weeks of treatment, with no suggestion of an increase. During long-term treatment (>1 year) VEGF levels tended to decrease.

A clinical TQT study was conducted using 50 subjects, of which 47 completed the study. The subjects received single doses of 3 active treatments (1200 mg, 600 mg vadadustat and 400 mg moxifloxacin) and placebo sequentially with a 7-day washout in-between. The concentration-QTc relation was evaluated using a linear mixed-effects model with an intercept. A statistically significant relation (p= 0.0529) of vadadustat and placebo-corrected ΔQTcF was detected but the upper bound of the 2-sided 90% CI was <10 ms.

No information was provided regarding potential PD interactions.

The Applicant has provided popPK/Hb equations for estimation of individual Hb levels. This is not considered as an exposure-efficacy analysis. However, since dose titration (up or down as needed) is the proposed way of achieving the target Hb level, a typical exposure-response evaluation, like the one conducted for exposure-safety, is not needed.

Exposure-safety relations were explored using logistic regression modelling. The safety data set came from 3473 subjects with CKD. Post-hoc exposure estimates were derived using the final population PK model. The regression analysis indicated a statistically significant exposure-response relationship between the time-averaged AUC during 4 weeks preceding the event and nausea, GI disorders, and hyperkalaemia. However, based on the exposure range obtained in the phase 3 studies and the observed safety incidences, the exposure-safety relationship is considered flat for all safety parameters. The Applicant has used the predicted 10th, 50th, and 90th exposure percentile as exposure metric. Frequently, such analyses are based on exposure quartiles but the present approach is acceptable.

Safety-exposure analysis investigated relationship of vadadustat exposure with selected AEs of GI disorders, diarrhea, vomiting, nausea, hepatotoxicity and hyperkalemia. Since results from the pivotal Phase 3 studies indicate increased risk of MACE in NDD-CKD patients with vadadustat treatment, the applicant additionally explored exposure-response relationship for MACE and non-fatal myocardial infarction in NDD-CKD patients. The relationship was evaluated using logistic regression and time-averaged daily AUC up to the event as exposure metric. 1657 subjects with NDD-CKD from trials CI-0014 and CI-0015 were included in this analysis. The results suggest that vadadustat exposure was not a meaningful predictor for MACE or non-fatal myocardial infarction in this population. However, due to issues with a pop PK model, results from E-R analyses should be interpreted with caution.

2.6.4. Conclusions on clinical pharmacology

Considering the nature of the product (small molecule), the pharmacology package is considered adequate and the proposed dosing of vadadustat seems appropriate, including in the special populations evaluated. No major objections were identified with respect to the clinical pharmacology. The Applicant has agreed to conduct an in vitro CYP inhibition study with the metabolite vadadustat-O-glucuronide and an in vivo study on CYP2B6 induction as a Post-Approval Measure (PAM - Classified as REC).

2.6.5. Clinical efficacy

In this submission, the clinical efficacy data supporting the use of vadadustat tablets taken orally once daily (QD) for the treatment of anaemia associated with CKD in adult patients on dialysis or not on dialysis is presented. The vadadustat clinical program includes 2 pivotal global randomized, open-label, active-controlled studies in DD-CKD subjects (AKB-6548-CI-0016 and AKB-6548-CI-0017 which are known as the INNO2VATE studies) and 2 pivotal global randomized, open-label, active-controlled studies in NDD-CKD subjects (AKB-6548-CI-0014 and AKB-6548-CI-0015 which are known as the PRO2TECT studies) (Table below).

There were 4 additional supportive regional Phase 3 studies that included subjects in Japan; 3 subjects with DD-CKD (MT-6548-J03, MT-6548-J04, and MT-6548-J02) and 1 in subjects with NDD-CKD (MT-6548-J01). These Phase 3 studies were conducted by the Mitsubishi Tanabe Pharma Corporation (MTPC) and are not discussed in full in this SCE due to the differences in subject characteristics and endpoints analyzed in comparison to the pivotal global studies.

Additional data from 6 Phase 2 studies in subjects with DD-CKD and NDD-CKD support the efficacy conclusions from the pivotal global Phase 3 studies.

Table 24 Description of Pivotal Clinical Efficacy Studies Conducted Globally (US, Europe, and ROW)

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age (SD)	Primary Endpoint
AKB-6548-CI-0016 (83 in US, Europe, and ROW)[a]	18 Jul 2016 – 31 Jan 2020	Phase 3, randomized, open-label, active-controlled study	DD-CKD	DD-CKD subjects who initiated chronic maintenance dialysis (either peritoneal or HD) for end-stage kidney disease within 16 weeks prior to Screening, with mean screening Hb 8.0 and 11.0 g/dL, serum ferritin ≥100 ng/mL, TSAT ≥20%, male or female subjects ≥18 years of age	Single oral doses of vada QD (starting dose: 300 mg vada [2 × 150 mg vada tablets] or IV or SC injections of darbepoetin alfa (dose and dose frequency determined by the PI in US sites and the SmPC in non-US sites, or current dose) over 3 treatment periods (correction period [Weeks 0 to 23], maintenance period [Weeks 24 to 52], and long-term treatment period [Week 53 to EOT]) with algorithm-guided dose adjustments due to changes in Hb levels (dose adjustments: 150 to 600 mg vada [1 to 4 × 150 mg vada tablets] or darbepoetin alfa determined by investigator)	≥36 weeks	Vada: 181 (59.1/40.9; 56.5 (14.80) Darbe: 188 (60.1/39.9); 55.6 (14.60)	Change in average Hb between Baseline and the PEP (Weeks 24 to 36)
AKB-6548-CI-0017 (275 in US, Europe, and ROW)[b]	17 Aug 2016 - 16 Jan 2020	Phase 3, randomized, open-label, active-controlled study	DD-CKD	DD-CKD subjects who are currently receiving ESA treatment for anemia, Mean screening Hb 8.0 and	Single oral doses of vada QD (starting dose: 300 mg vada [2 × 150 mg vada tablets] or IV or SC injections of darbepoetin alfa (dose and dose frequency determined by the PI in US sites and the SmPC in non-US sites, or current dose) over	≥36 weeks	Vada: 1777 (55.7/44.3); 57.9 (13.86) Darbe: 1777 (56.5/43.5); 58.4 (13.84)	Change in average Hb between Baseline and the PEP (Weeks 24 to 36)

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age (SD)	Primary Endpoint
				11.0 g/dL (US), 9.0 and 12.0 g/dL (outside of the US), Ferritin ≥100 ng/mL TSAT ≥20%, male or female subjects ≥18 years of age	3 treatment periods (correction and conversion period [Weeks 0 to 23], maintenance period [Weeks 24 to 52], and long-term period [Week 53 to EOT]) with algorithm-guided dose adjustments due to changes in Hb levels (dose adjustments: 150 to 600 mg vada [1 to 4 × 150 mg vada tablets] or darbepoetin alfa determined by PI or SmPC)			
AKB-6548-CI-0014 (274 in US, Europe, and ROW)[c]	17 Dec 2015 - 04 Jun 2020	Phase 3, randomized, open-label, active-controlled study	NDD-CKD	NDD-CKD Subjects who are not being treated with ESA, Mean Screening Hb <10.0 g/dL, Serum ferritin ≥100 ng/mL and TSAT ≥20%, male and female subjects ≥18 years of age	Single oral doses of vada QD (starting dose: 300 mg vada [2 × 150 mg vada tablets] or IV/SC injections of darbepoetin alfa (dose and dose frequency determined by the investigator in US sites and the SmPC in non-US sites) over 3 treatment periods (correction period [Weeks 0 to 23], maintenance period [Weeks 24 to 52], and long-term period [Week 53 to EOT]) with algorithm-guided dose adjustments due to changes in Hb levels (dose adjustments: 150 to 600 mg vada [1 to 4 × 150 mg vada tablets] or darbepoetin alfa determined by PI or SmPC)	≥36 weeks	Vada: 879 (46.0/54.0); 65.2 (14.27) Darbe: 872 (42.0/58.0) 64.9 (13.71)	Change in average Hb between Baseline and the PEP (Weeks 24 to 36)
AKB-6548-CI-0015 (328 in US, Europe, and ROW)[d]	09 Feb 2016 - 18 Jun 2020	Phase 3, randomized, open-label, active-controlled study	NDD-CKD	NDD-CKD - subjects who are currently receiving ESA treatment for anemia, mean screening Hb 8.0 to 11.0 g/dL (US) and 9.0 and 12.0 g/dL (outside US), male and female subjects >18 years of age	Single oral doses of vada QD (starting dose: 300 mg vada [2 × 150 mg vada tablets] or IV/SC injections of darbepoetin alfa (dose and dose frequency determined by the investigator in US sites and the SmPC in non-US sites, or current dose) over 3 treatment periods (correction and conversion period [Weeks 0 to 23], maintenance period [Weeks 24 to 52], and long-term period [Week 53 to EOT]) with algorithm-guided dose adjustments due to changes in Hb levels (dose adjustments: 150 to 600 mg vada [1 to 4 × 150 mg vada tablets] or darbepoetin alfa determined by PI or SmPC)	≥36 weeks	Vada: 862 (45.7/54.3): 67.3 (13.14) Darbe: 863 (43.5/56.5) 66.5 (13.52)	Change in average Hb between Baseline and the PEP (Weeks 24 to 36)

CKD: chronic kidney disease; darbe: darbepoetin alfa; DD: dialysis-dependent; EOT: end of treatment; ESA: erythropoiesis-stimulating agent; FPFV: first patient, first visit; Hb: hemoglobin; HD: hemodialysis; IV: intravenous; LPLV: last patient, last visit; NDD: non-dialysis-dependent; PEP: primary efficacy period; PI: prescribing information; QD: once daily; ROW: Rest of World; SC: subcutaneous; SD: standard deviation; SmPC: Summary of Manufactured Product Characteristics; TSAT: transferrin saturation; US: United States; vada: vadadustat

a In CI-0016, Europe included Germany, Italy, Poland, and Portugal and the ROW included Argentina, Brazil, Mexico, Republic of Korea, Russian Federation, and Ukraine

b In CI-0017, Europe includes Bulgaria, France, Germany, Italy, Poland, Portugal, Serbia, and United Kingdom. Rest of World included Argentina, Australia, Brazil, Canada, Israel, Mexico, Republic of Korea, Russian Federation, and Ukraine.

c In CI-0014, Europe included Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Romania, Serbia, Slovak Republic, Spain, Turkey, and United Kingdom and the Rest of World includes Argentina, Australia, Brazil, Canada, Chile, Colombia, Israel, Malaysia, Mexico, Republic of Korea, Russian Federation, South Africa, and Ukraine

d In CI-0015, Europe included Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Romania, Serbia, Slovak Republic, Spain, Turkey, and United Kingdom and the Rest of World includes Argentina, Australia, Brazil, Chile, Colombia, Israel, Malaysia, Mexico, Republic of Korea, Russian Federation, South Africa, and Ukraine

Table 25 **Pivotal and Supportive Vadadustat Clinical Efficacy Studies**

Design/ Study Number (Number of Study Sites)	Subjects with DD-CKD		Subjects with NDD-CKD	
	Pivotal	Supportive	Pivotal	Supportive
Phase 3, global, active-controlled studies				
AKB-6548-CI-0016 (83 in US, Europe, ROW)[a]	X			
AKB-6548-CI-0017 (275 in US, Europe, ROW)[b]	X			
AKB-6548-CI-0014 (274 in US, Europe, ROW)[c]			X	
AKB-6548-CI-0015 (328 in US, Europe, ROW)[d]			X	
Phase 3, regional, active-controlled studies				
MT-6548-J03 (115 in Japan)		X		
MT-6548-J01 (86 in Japan)				X
Phase 3 regional, uncontrolled studies				
MT-6548-J02 (25 in Japan)		X		
MT-6548-J04 (25 in Japan)		X		
Phase 2 regional, active-controlled studies				
AKB-6548-CI-0025 (39 in US)		X		
Phase 2 regional, placebo-controlled studies				
AKB-6548-CI-0022 (31 in Japan)		X		
AKB-6548-CI-0021 (30 in Japan)				X
AKB-6548-CI-0005 (29 in US)				X
AKB-6548-CI-0007 (61 in US)				X
Phase 2 regional, uncontrolled studies				
AKB-6548-CI-0011 (22 in US)		X		

CKD: chronic kidney disease; DD: dialysis-dependent; NDD: non-dialysis-dependent; ROW: Rest of World; US: United States.

a In CI-0016, Europe included Germany, Italy, Poland, and Portugal and the ROW included Argentina, Brazil, Mexico, Republic of Korea, Russian Federation, and Ukraine

b In CI-0017, Europe includes Bulgaria, France, Germany, Italy, Poland, Portugal, Serbia, and United Kingdom. Rest of World included Argentina, Australia, Brazil, Canada, Israel, Mexico, Republic of Korea, Russian Federation, and Ukraine.

c In CI-0014, Europe included Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Romania, Serbia, Slovak Republic, Spain, Turkey, and United Kingdom and the Rest of World includes Argentina, Australia, Brazil, Canada, Chile, Colombia, Israel, Malaysia, Mexico, Republic of Korea, Russian Federation, South Africa, and Ukraine

d In CI-0015, Europe included Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Romania, Serbia, Slovak Republic, Spain, Turkey, and United Kingdom and the Rest of World includes Argentina, Australia, Brazil, Chile, Colombia, Israel, Malaysia, Mexico, Republic of Korea, Russian Federation, South Africa, and Ukraine

However as the approved indication is restricted only to the DD-CKD patients due to safety issues only the relevant studies are reflected in the SmPC.

2.6.5.1. Dose response study(ies)

Prior to the start of the pivotal global Phase 3 studies, the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles of vadadustat had been characterized in completed Phase 1/2 studies that included 1 ethno-bridging study in White and Japanese subjects (AKB-6548-CI-0020), 1 completed Phase 1 study in subjects undergoing chronic hemodialysis (CI-0009), 3 completed Phase 2a studies in NDD-CKD subjects (AKB-6548-CI-0003, AKB-6548-CI-0004, and AKB-6548-CI-0005), 1 completed Phase 2b study in NDD-CKD subjects (AKB-6548-CI-0007), and 1 completed Phase 2 study in DD-CKD subjects (AKB-6548-CI-0011). This includes Phase 2a studies that evaluated Stage 3 and 4 NDD-CKD subjects in a single-dose PK study (CI-0003), a multi-dose, 28-day, open-label, dose escalation pilot study (CI-0004), a randomized, placebo-controlled study with 5 different dose groups dosed for 42 days (CI-0005), and a Phase 2b study that evaluated Stages 3, 4, and 5 NDD-CKD subjects dosed for 20 weeks (CI-0007) and a Phase 2 study that evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks (CI-0011).

Studies CI-0003 and CI-0004 are not mentioned in this report due to their short duration and few subjects enrolled; CI-0003 enrolled 22 subjects who were given a single-dose of 500 mg vadadustat while CI-0004 enrolled 10 subjects who were given doses of vadadustat between 200 and 700 mg QD for 28 days.

Vadadustat demonstrated dose proportional PK and dose-dependent changes in serum EPO and/or Hb in Phase 1 and Phase 2 studies over the dose range of 80 to 1200 mg after single administration and 500 to 900 mg after repeated daily administration. In these Phase 1 and 2 studies, vadadustat also showed an increase in reticulocyte counts as well as increases in TIBC and decreases in hepcidin and ferritin. The Phase 2 supportive studies in DD-CKD (CI-0025, CI-0022, CI-0011) and NDD-CKD (CI-0005, CI-0007, and CI-0021) evaluated Hb as the primary endpoint and generally demonstrated favourable changes from baseline in mean Hb at the end of the treatment period. The studies also evaluated other hematologic parameters including, mean corpuscular Hb, mean corpuscular Hb concentrations, mean corpuscular volume, and erythrocyte distribution width. Generally, the changes in these select hematologic parameters were not clinically meaningful and unremarkable. However, when considering the totality of the data, it is indicative of upregulated erythropoiesis that ultimately results in improved Hb in vadadustat-treated subjects.

The pivotal global INNO2VATE and PRO2TECT studies used a starting dose of 300 mg and maintenance doses of between 150 and 600 mg QD, with dose adjustments made every 4 weeks to maintain Hb levels. The starting dose and dosing algorithm were developed using a population PK/PD model with plasma PK and PD measurements from previously conducted clinical studies with vadadustat (CI-0003, CI-0004, CI-0005, and CI-0010). Using this model and the proposed dosing algorithm, simulations were carried out to evaluate the effects of different starting doses and the resulting Hb responses to support the dosing rationale. Results of the simulations indicated that a starting dose of 300 mg QD along with the proposed dosing algorithm were optimal to achieve Hb >10.0 g/dL in order to maintain Hb levels of 10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL outside US while minimizing excessive Hb rises.

2.6.5.2. Main studies

INNO2VATE Studies:

- AKB-6548-CI-0016: PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE CORRECTION OR MAINTENANCE TREATMENT OF ANAEMIA IN SUBJECTS WITH INCIDENTDIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (DD-CKD) (INNO2VATE – CORRECTION/CONVERSION)
- AKB-6548-CI-0017: PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE MAINTENANCE TREATMENT OF ANAEMIA IN SUBJECTS WITH DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (DD-CKD) (INNO2VATE – CONVERSION)

PRO2TECT Studies:

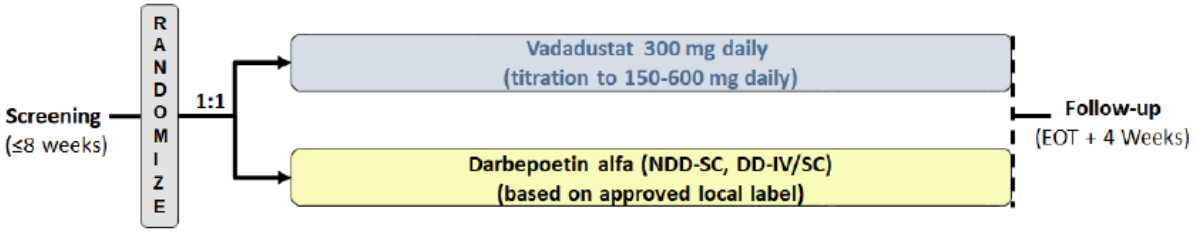
- AKB-6548-CI-0014: PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE CORRECTION OF ANAEMIA IN SUBJECTS WITH NON-DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD) (PRO2TECT - CORRECTION)
- AKB-6548-CI-0015: PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE MAINTENANCE

TREATMENT OF ANAEMIA IN SUBJECTS WITH NON-DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD) (PRO2TECT - CONVERSION)

Methods

All 4 studies are randomised, open-label (sponsor-blind), active-controlled (darbepoetin alfa), non-inferiority efficacy and safety cardiovascular outcomes studies as illustrated in Figure 2.

Figure 17 Summary of Study Designs for the PRO$_2$TECT (NDD-CKD) and INNO$_2$VATE (DD-CKD) Studies



DD-CKD: dialysis-dependent chronic kidney disease; EOT: end-of-treatment; IV: intravenous; NDD-CKD: non-dialysis-dependent chronic kidney disease; SC: subcutaneous

In these pivotal global studies, the starting dose of vadadustat was 300 mg once daily (QD), with up-and-down titration to 150 mg to 600 mg QD to achieve target Hb levels (10.0 to 11.0 g/dL in US and 10.0 to 12.0 g/dL ex-US).

As prespecified, subjects were stratified by geographic region (United States [US] versus Europe versus Rest of World [ROW]), New York Heart Association (NYHA) Heart Failure Class, and by baseline Hb level at study entry.

Key inclusion and/or exclusion criteria, treatment groups, Hb target range, and treatment guidelines are described in Table below.

Table 26 Key Elements of INNO$_2$VATE and PRO$_2$TECT Program

	INNO$_2$VATE: DD-CKD		PRO$_2$TECT: NDD-CKD	
Study	**CI-0016**	**CI-0017**	**CI-0014**	**CI-0015**
		Key Entry Criteria		
CKD Type	Incident dialysis (≤16 weeks)	Chronic dialysis (≥12 weeks)	NDD-CKD eGFR ≤60 mL/min/1.73 m^2	
Hb (g/dL) Entry Criteria	8.0-11.0	US: 8.0-11.0 Ex-US: 9.0-12.0	<10.0	US: 8.0-11.0 Ex-US: 9.0-12.0
Allowed ESA Use at Entry	Maintained on ESA or no ESA use. Excluded very high ESA doses*	Maintained on ESA; dosed within 6 weeks prior to or during Screening	No ESA use within 8 weeks of randomization	Maintained on ESA; dosed within 6 weeks prior to or during Screening
Iron Parameters at Entry	Ferritin ≥100 ng/mL and TSAT ≥20%			
		Treatment Groups		
Vadadustat	Starting Dose: 300 mg QD, Dose Range: 150-600 mg QD			
Control	Darbepoetin alfa dosed according to the US PI (US) or the European SmPC (ROW)			
Hb Target Range	US: 10.0-11.0 g/dL; Ex-US: 10.0-12.0 g/dL			
Iron Supplementation	Iron supplementation to maintain ferritin ≥100 ng/mL or TSAT ≥20%			
RBC Transfusion Guidance	At the discretion of the investigator given as medically necessary			
ESA Rescue Guidance	Optional if following criteria are met: ≥6 weeks on study Worsening symptoms of anemia Hb <9.5 g/dL However, in the event the subject did not meet the above criteria for ESA rescue, ESA rescue was permitted when medically necessary at the discretion of the investigator ESA rescue therapy to be stopped when Hb ≥10.0 g/dL		Optional if following criteria are met: ≥6 weeks on study Worsening symptoms of anemia Hb <9.0 g/dL However, in the event the subject did not meet the above criteria for ESA rescue, ESA rescue was permitted when medically necessary at the discretion of the investigator ESA rescue therapy to be stopped when Hb ≥9.5 g/dL	
		Endpoints		
Efficacy Endpoints	*Primary:* Change in average Hb between Baseline and Weeks 24-36 *Key Secondary*: Change in average Hb value between Baseline and Weeks 40-52			
Safety Endpoints	*Primary:* Time to first occurrence of EAC-adjudicated MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke *Key Secondary:* Time to first MACE plus hospitalization for HF or thromboembolic event, excluding vascular access thrombosis (MACE+); Time to CV mortality, non-fatal MI, or non-fatal stroke; Time to CV mortality; Time to all-cause mortality			

DD-CKD: dialysis-dependent chronic kidney disease; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; NDD-CKD: non-dialysis-dependent chronic kidney disease; QD: once daily; PI: prescribing information; RBC: red blood cell; ROW: Rest of World; SmPC: Summary of Product Characteristics; TSAT: transferrin saturation; US: United States.

* Very high doses, suggestive of ESA resistance, within 8 weeks prior to or during Screening defined as follows: epoetin >7700 units/dose 3 times per week or >23000 U/week; darbepoetin alfa: >100 µg/week; methoxy polyethylene glycol-epoetin beta: >100 µg every other week or >200 µg/month.

Source: Module 2.7.3, Table 2 and Module 2.7.4, Table 1

The pivotal global Phase 3 studies consisted of the screening, treatment and follow up periods.

- Screening period of up to 8 weeks.
- Treatment periods onwards consisting of
    - Initial period on study drug from Weeks 0 to 23 for conversion to study drug for maintaining Hb (CI-0016, CI-0017, and CI-0015) or for correction of Hb (CI-0014)

- Primary Efficacy Period (PEP) from Week 24 to 36
- Secondary Efficacy Period (SEP) from Week 40 to 52
- Long-term treatment period (Week 53 to end of treatment [EOT]) where study drug was continued to assess long-term use

• Follow-up period (EOT + 4 weeks) for post-treatment visit for safety (either in person or via telephone)

Subjects who discontinued study drug were followed to the end of study (EOS) to assess MACE.

Subjects enrolled in the INNO2VATE and PRO2TECT studies were to be treated with vadadustat or darbepoetin alfa for at least 36 weeks and to have the opportunity to continue long-term treatment until global study completion. The duration of treatment in these studies was event-driven based on achieving an adequate number of independently adjudicated MACE endpoints to allow meaningful comparison between treatment groups for the pooled MACE analyses in the INNO2VATE and PRO2TECT studies. In order to accomplish this, 631 MACE were required to be achieved in each of the INNO2VATE and PRO2TECT studies, respectively.

- **Study Participants**

Adult subjects (≥18 years of age) enrolled in the pivotal global INNO2VATE and PRO2TECT studies. In the case of INNO2VATE, subjects were receiving maintenance dialysis (either peritoneal or hemodialysis) for anaemia associated with ESRD (DD-CKD), while PRO2TECT enrolled subjects with anaemia associated with NDD-CKD and an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m2 during screening.

While similar, there were important differences in the inclusion and exclusion criteria for the 2 INNO2VATE studies consistent with the incident dialysis nature of study CI-0016 and the prevalent dialysis nature of study CI-0017. As a result, subjects in CI-0016 were required to have initiated chronic maintenance dialysis (either peritoneal or hemodialysis) within 16 weeks of screening, while subjects in CI-0017 were required to be receiving chronic maintenance dialysis (either peritoneal or hemodialysis) for at least 12 weeks prior to screening. In CI-0016, subjects that met the criteria of ESA resistance within 8 weeks prior to or during screening were excluded from the study (epoetin >7700 units/dose 3 times per week or >23000 units per week; darbepoetin alfa >100 µg/week; methoxy polyethylene glycol-epoetin beta >100 µg every other week or >200 µg every month) while CI-0017 required subjects to be maintained on ESA therapy at screening, with a dose received within 6 weeks prior to or during screening.

There were also important differences in the inclusion and exclusion criteria for the 2 PRO2TECT studies. CI-0014 was a correction of Hb study in which ESA use was prohibited within 8 weeks prior to randomization while CI-0015 was a conversion study in which subjects were required to be currently maintained on ESA therapy, with a dose received within 6 weeks prior to or during screening.

Concomitant use of an ESA with study drug was strictly prohibited in all 4 pivotal studies although ESAs could be given as rescue. The impact of ESA rescue and the interpretability of the primary and key secondary outcomes was investigated in sensitivity analyses.

The mean Hb levels for eligibility were different in the 4 pivotal global studies, reflective of the different subject populations enrolled. In the conversion studies CI-0017 and CI-0015, the average screening Hb was between 8.0 and 11.0 g/dL (inclusive) for subjects in the US and 9.0 and 12.0 g/dL (inclusive) ex-US (Europe and ROW). In CI-0016, the average screening Hb levels was to be between 8.0 and 11.0 g/dL (inclusive). For CI-0014, the average screening Hb was less than 10.0 g/dL.

In all studies, the following laboratory inclusion criteria were required to avoid confounding effects of vitamin or iron deficiency on RBC production:

• Serum ferritin ≥100 ng/mL,

• Transferrin saturation (TSAT) ≥20%,

• Folate and vitamin B12 measurements ≥ lower limit of normal.

Subjects presenting with anaemia due to a cause other than CKD or with active bleeding or recent blood loss, RBC transfusion within 8 weeks prior to Randomization, as well as those with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anaemia, thalassemia, or pure red cell aplasia were excluded from the studies.

- **Treatments**

The pivotal global INNO2VATE and PRO2TECT studies used a starting dose of 300 mg QD and maintenance doses of between 150 and 600 mg QD, with dose adjustments made every 4 weeks to maintain Hb levels as specified by the Dose Adjustment Algorithm provided with the study protocol. The starting dose and the proposed dosing algorithm for these studies were designed to maintain Hb in a predictable and controlled manner while minimizing abrupt increases or excessive rises in Hb levels.

Initial feedback from the FDA and European Medicines Agency in 2015 encouraged the use of an active control design. The pivotal global Phase 3 studies therefore used the active comparator, darbepoetin alfa as it is marketed and available globally and has a well-characterized safety profile. For darbepoetin alfa, the initial dose was based on the current PI for investigational sites in the US and the SmPC for all other investigational sites (ex-US) for adult patients with DD-CKD and NDD-CKD.

Given the different dosing regimens and route of administration (vadadustat [oral] and darbepoetin alfa [IV/SC injection]), a double dummy design would have been required to preserve the double-blind. Practical considerations to execute a double blind, double dummy design in the study population included the potential for dosing errors and inappropriate dose adjustments, delays in dosing, discomfort and risks inherent in repeated injections of placebo, and would require extensive coordination to maintain the blind. Randomization using an interactive web response system enabled the sponsor and clinical research organization to be blinded. These considerations would have severely impacted the ability to conduct these global studies. Additionally, the endpoints both efficacy and safety were outcomes that required laboratory and/or diagnostic measurements. For these reasons, the Sponsor decided to use an open-label study design with measures to ensure study integrity and blinding of key study personnel (sponsor and external committee). The sponsor also implemented a dose adjustment algorithm to provide guidelines to investigators for dose adjustment.

Importantly, an independent, blinded adjudication committee evaluated all major adverse cardiovascular event (MACE) endpoints for the studies. Hb was selected as an objective measure of efficacy that was determined via a central laboratory and is a standard, objective laboratory assessment that is not subject to bias.

RBC transfusion as rescue therapy is defined as RBC transfusion therapy grouped temporally into episodes, which contained multiple administrations based on the gap in time between the end of 1 episode and the start of the next with a maximum gap for an episode of 7 days. Investigators used their local institution's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, a RBC transfusion was administered as clinically indicated. In less severe instances but where there may have been worsening of anaemia or moderate to severe symptoms of anaemia, RBC transfusions were permitted at the discretion of the

investigator given medical necessity. Reasons for RBC transfusion were captured in the appropriate eCRF. Study drug (vadadustat or darbepoetin alfa) could be continued during the transfusion period.

Rescue episodes are defined as exposure to the therapy grouped temporally, which contained multiple administrations based on the gap in time between the end of 1 and the start of the next. The maximum gap for ESA medication within a single episode was 30 days. Concomitant use of an ESA with study drug was strictly prohibited.

Starting at Week 6, subjects in both treatment groups were allowed (although not required) to have their Hb rescued with ESA therapy. When possible, a subject on vadadustat had to be on the maximum dose of vadadustat for 2 weeks prior to ESA rescue. A subject on darbepoetin alfa could be rescued with another ESA per the standard of care. To qualify for ESA rescue, a subject had to fulfill both of the following criteria:

• Experienced worsening of the symptoms of anaemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared to Baseline

• Hb of <9.5 g/dL

However, in the event the subject did not meet the above criteria for ESA rescue, ESA rescue was permitted when medically necessary at the discretion of the investigator. Following ESA rescue, the study drug was resumed at the same dose as previously used or 1 dose higher and adjusted according to the Dose Adjustment Algorithms.

- **Objectives**

The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa

- for the maintenance treatment of anaemia after the correction of Hb or conversion from current ESA therapy, in subjects who have recently initiated dialysis treatment for DD-CKD (CI-0016).

- for the maintenance treatment of anaemia in subjects with DD-CKD (CI-0017).

- for the correction and maintenance of Hb in subjects with anaemia secondary to NDD-CKD (CI-0014).

- for the maintenance treatment of anaemia in subjects with NDD-CKD after conversion from current ESA therapy (CI-0015).

- **Outcomes/endpoints**

The primary efficacy endpoint in the INNO2VATE and PRO2TECT studies was the change in average Hb between baseline and Weeks 24 to 36 (primary evaluation period, PEP) and the common key secondary efficacy endpoint was the change in average Hb value between baseline and Weeks 40 to 52 (secondary evaluation period, SEP).

Other key secondary efficacy endpoints include the following:

• Proportion of subjects with Hb values within the target range during the PEP (Weeks 24 to 36).

• Proportion of subjects with Hb values within the target range during the SEP (Weeks 40-52).

Other efficacy endpoints included the following (but not limited to):

• Proportion of time with Hb values within the target range during the PEP (Weeks 24-36).

• Proportion of time with Hb values within the target range during the SEP (Weeks 40-52).

• Proportion of subjects with Hb increase of >1.0 g/dL from Baseline.

• Time to achieve Hb increase of >1.0 g/dL from Baseline.

• Mean change in Hb between Baseline (mean pretreatment Hb) and the PEP (mean Hb from Weeks 24-36) stratified by pre-Baseline ESA exposure.

• Proportion of subjects receiving RBC transfusion(s) from Baseline to Week 52.

• Proportion of subjects receiving IV iron therapy from Baseline to Week 52.

• Mean monthly dose of IV elemental iron administered from Baseline to Week 52 in subjects who have received IV iron.

• ESA rescue.

• Dose adjustments from Baseline to Week 52.

• Progression of CKD (for NDD-CKD population).

• Having average Hb value in the geography-specific target range in Weeks 24 to 36 (yes/no variable)

• Having average Hb value in the geography-specific target range in Weeks 40 to 52 (yes/no variable)

The efficacy and safety endpoints utilized in the pivotal Phase 3 studies were widely used and generally recognized as reliable, accurate and relevant.

The pivotal global Phase 3 studies included Hb assessments as an objective measure of efficacy and these were determined via a central laboratory. As such, the efficacy assessments were not considered to be subject to bias in these pivotal studies. To minimize the potential for bias, the sponsor and contract research organization study teams remained blinded to 'by treatment' aggregated analyses, except for the unblinded statistician and Drug Safety and Pharmacovigilance personnel. In addition, the study involved blinded adjudication of the safety endpoint of MACE, which with the use of an independent data monitoring committee, and an identical schedule of visits, procedures, as well as blinded assessments further reduced the potential for bias. However, certain personnel directly involved in medical oversight of the study, regulatory reporting of safety information, and on-site monitoring activities may have become unblinded to the treatment assignments of individual subjects during the study. In addition, to reduce subjectivity, adjustments to doses for vadadustat and darbepoetin alfa were guided by Hb concentration and the Dose Adjustment Algorithms that were provided to the investigators in the study protocol.

In addition, there was a double-blind, placebo-controlled study conducted in subjects with DD-CKD in Japan (CSR J03) that was adequately powered for the primary efficacy analyses.

- **Sample size**

AKB-6548-CI-0016: It was anticipated that 300 subjects at approximately 140 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled.

AKB-6548-CI-0017: It was anticipated that 3300 subjects at approximately 300 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled.

AKB-6548-CI-0014: It was anticipated that 1850 subjects at approximately 390 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled.

AKB-6548-CI-0015: It was anticipated that 1850 subjects at approximately 480 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled.

- **Randomisation and Blinding (masking)**

Subjects enrolled in each pivotal global Phase 3 study were randomized to vadadustat and darbepoetin alfa in a 1 to 1 ratio. Groups were stratified by geographic region (US versus Europe versus ROW), by NYHA Heart Failure Classification (0 [no heart failure] or Class I versus Class II or III), and by study entry Hb level. In studies CI-0014 and CI-0016 a baseline Hb of <9.5 versus ≥9.5 g/dL was chosen while in CI-0015 and CI-0017 a baseline Hb level of <10.0 versus ≥10.0 g/dL was selected. These stratification factors were selected to ensure the treatment groups in the pivotal studies were balanced in terms of geographic distribution, degree of anaemia, and severity of an important cardiovascular risk factor, including NYHA heart failure classification.

The Sponsor used an open-label study design with measures to ensure study integrity and blinding of study personnel. The Endpoint Adjudication Committee remained blinded throughout the full course of the study (evaluated all major adverse cardiovascular event (MACE) endpoints for the studies).

- **Statistical methods**

The statistical methods used in the analyses of data in the pooled INNO2VATE studies, CI-0016, and CI-0017 and as well as in the pooled PRO2TECT studies, CI-0014, and CI-0015 were prespecified prior to database lock.

Analysis of Primary Efficacy Data

The primary efficacy endpoint was to assess the change in average Hb between Baseline and Weeks 24 to 36 (PEP). The primary analysis in the INNO2VATE studies, CI-0016, and CI-0017 and as well as in the PRO2TECT studies, CI-0014, and CI-0015 used the randomized population and analysis of covariance (ANCOVA) with multiple imputation as the primary statistical model. Randomized population is defined as all subjects randomized.

In addition, mixed model repeated measures (MMRM) was utilized as a supportive analysis for the primary endpoint.

In all studies, non-inferiority of vadadustat to darbepoetin alfa was to be concluded if the lower bound of the 95% confidence interval (CI) for the difference in estimated change in average Hb from baseline in the 2 treatment groups was greater than the prespecified non-inferiority margin of -0.75. This ensures a 1-sided alpha of 0.025 for the primary endpoint. If the lower limit of the 2-sided 95% CI for the difference between the mean in the vadadustat group and the mean in the darbepoetin alfa group was above zero, superiority was established, and the finding was to be interpreted as providing evidence of a greater change from baseline in average Hb for vadadustat comparative to darbepoetin alfa.

Analysis of Secondary and Other Efficacy Data

Evaluation of the key secondary efficacy endpoint, which was the change in average Hb value between Baseline and Weeks 40 to 52 (SEP), employed the same approach described for the primary endpoint for the INNO2VATE studies, CI-0016, and CI-0017 and as well as in the PRO2TECT studies, CI-0014, and CI-0015 studies.

Other secondary efficacy endpoints included iron-related parameters, iron supplementation, and additional analyses related to Hb, reticulocyte counts, RBC transfusion, and ESA rescue.

Sensitivity analyses were conducted for both the primary and key secondary endpoint using the following:

- Full Analysis Set (FAS; all randomized subjects who received at least 1 dose of study drug and had at least 1 postdose Hb assessment)
- Per Protocol (PP; all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least 1 Hb assessment during the primary efficacy period, and had no critical or major protocol deviations affecting the primary endpoint analyses, ie, prior to Week 36) populations. Considerations for sensitivity analyses included narrow and broad rescue for the Randomized population, and a mixed model for repeated measures (MMRM) model using observed data only.

Post-hoc Specifications and Analysis of Rescue Therapy

In the pivotal global INNO2VATE and PRO2TECT studies, the protocol-specified criteria for narrow ESA rescue for vadadustat-treated subjects were strictly defined as a decline in Hb to <9.5 g/dL (INNO2VATE) and <9.0 g/dL (PRO2TECT) and/or an associated worsening of symptoms of anaemia. For broad-on-treatment rescue, any ESA exposure, including inadvertent administration of ESA, was deemed ESA rescue therapy in vadadustat-treated subjects. For darbepoetin alfa-treated subjects, ESA rescue was defined in the protocol as the receipt of any ESA agent other than darbepoetin alfa, ie, increases in the darbepoetin alfa dose were not considered ESA rescue unless the investigator designated the administration as such. In other words, there were no protocol prespecified dose-related criteria to define ESA rescue with darbepoetin alfa in subjects randomized to the darbepoetin alfa treatment group.

As a result, the sponsor conducted post-hoc analyses of ESA rescue that in addition to the prespecified narrow and broad-on-treatment ESA rescue definitions, also included subjects who received ⩾50% or ⩾100% increase in the dose of darbepoetin alfa from the previous closest reported dose. The ⩾50% or ⩾100% dose increases were selected because they are substantially higher than what is recommended in the darbepoetin alfa US PI and SmPC, which is an increase of 25% from the previous dose and potentially represents a need for ESA 'rescue' treatment for subjects on darbepoetin alfa as relevant to real-life clinical practice.

Results

- **Participant flow**

From the Global Phase 3 program, there were 7399 adult CKD subjects randomized 1:1 to either vadadustat or darbepoetin alfa treatment in the studies, including 3923 subjects randomized into INNO2VATE (subjects with DD-CKD), and 3476 subjects randomized into PRO2TECT (subjects with NDD-CKD, Table below).

Table 27 Subjects in INNO2VATE and PRO2TECT Global Phase 3 Studies (Randomized Population)

INNO2VATE Studies	Vada n (%)	Darbe n (%)	Total n (%)	Study Population
CI-0016	181 (9.2)	188 (9.6)	369 (9.4)	≥18 years with DD-CKD and incident dialysis[a,b], and Hb ≥8.0 g/dL and ≤11.0 g/dL
CI-0017	1777 (90.8)	1777 (90.4)	3554 (90.6)	≥18 years with DD-CKD and chronic outpatient dialysis[b], current ESA treatment, and Hb ≥8.0 g/dL and ≤11.0 g/dL at US sites and ≥9.0 g/dL and ≤12.0 g/dL ex- US
Total Subjects (N)	1958	1965	3923	
PRO2TECT Studies	**Vada n (%)**	**Darbe n (%)**	**Total n (%)**	**Study Population**
CI-0014	879 (50.5)	872 (50.3)	1751 (50.4)	≥18 years with NDD-CKD, eGFR ≤60 mL/min/1.73 m^2, not currently treated with an ESA, and Hb <10.0 g/dL
CI-0015	862 (49.5)	863 (49.7)	1725 (49.6)	≥18 years with NDD-CKD, eGFR ≤60 mL/min/1.73 m^2, current ESA treatment, and Hb ≥8.0 g/dL and ≤11.0 g/dL at US sites and ≥9.0 g/dL and ≤12.0 g/dL ex-US
Total Subjects	1741	1735	3476	

CKD: chronic kidney disease; darbe: darbepoetin alfa; DD: dialysis-dependent; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; N: number of subjects; n: number of subjects within specific category; NDD: non-dialysis-dependent; US: United States; vada: vadadustat.
a initiation of chronic maintenance dialysis within 16 weeks prior to screening
b peritoneal or hemodialysis
Source: CSR AKB-6548-CI-0016 Table 14.1.1, CSR AKB-6548-CI-0017 Table 14.1.1, CSR AKB-6548-CI-0014 Table 14.1.1, CSR AKB-6548-CI-0015 Table 14.1.1

Table 28 Subject Disposition – End of Study Drug treatment for the DD-CKD Population in INNO2VATE and the NDD-CKD Population in the PRO2TECT Global Phase 3 Studies (Randomized Population)

	INNO2VATE						PRO2TECT					
	Pooled		AKB-6548-CI-0016		AKB-6548-CI-0017		Pooled		AKB-6548-CI-0014		AKB-6548-CI-0015	
Category	Vada N=1958 n (%)	Darbe N=1965 n (%)	Vada N=181 (%)	Darbe N=188 (%)	Vada N=1777 n (%)	Darbe N=1777 n (%)	Vada N=1741 n (%)	Darbe N=1735 n (%)	Vada N=879 (%)	Darbe N=872 (%)	Vada N=862 (%)	Darbe N=863 (%)
Subjects treated	1947 (99.4)	1955 (99.5)	179 (98.9)	186 (98.9)	1768 (99.5)	1769 (99.5)	1739 (99.9)	1732 (99.8)	878 (99.9)	870 (99.8)	861 (99.9)	862 (99.9)
Subjects not treated	11 (0.6)	10 (0.5)	2 (1.1)	2 (1.1)	9 (0.5)	8 (0.5)	2 (0.1)	3 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)
Subjects completed treatment	999 (51.0)	1263 (64.3)	121 (66.9)	139 (73.9)	878 (49.4)	1124 (63.3)	990 (56.9)	1100 (63.4)	466 (53.0)	516 (59.2)	524 (60.8)	584 (67.7)
Discontinued study drug treatment	959 (49.0)	702 (35.7)	60 (33.1)	49 (26.1)	899 (50.6)	653 (36.7)	749 (43.0)	634 (36.5)	411 (46.8)	355 (40.7)	338 (39.2)	279 (32.3)
Subjects with missing status of treatment compliance	0	0	0	0	0	0	2 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	0	0
Primary reason for discontinuation from study drug treatment												
Unacceptable toxicity, drug intolerability, or adverse event	114 (5.8)	61 (3.1)	15 (8.3)	6 (3.2)	99 (5.6)	55 (3.1)	214 (12.3)	170 (9.8)	115 (13.1)	105 (12.0)	99 (11.5)	65 (7.5)
Investigator's decision	105 (5.4)	44 (2.2)	11 (6.1)	2 (1.1)	94 (5.3)	42 (2.4)	73 (4.2)	56 (3.2)	31 (3.5)	26 (3.0)	42 (4.9)	30 (3.5)
Subject became pregnant	2 (0.1)	2 (0.1)	1 (0.6)	0	1 (0.1)	2 (0.1)	1 (0.1)	0	0	0	1 (0.1)	0
Kidney transplant	120 (6.1)	105 (5.3)	7 (3.9)	11 (5.9)	113 (6.4)	94 (5.3)	34 (2.0)	23 (1.3)	13 (1.5)	8 (0.9)	21 (2.4)	15 (1.7)
Lack of efficacy	64 (3.3)	5 (0.3)	1 (0.6)	0	63 (3.5)	5 (0.3)	26 (1.5)	6 (0.3)	15 (1.7)	6 (0.7)	11 (1.3)	0
Subject no longer wanted to receive study drug	233 (11.9)	113 (5.8)	20 (11.0)	10 (5.3)	213 (12.0)	103 (5.8)	173 (9.9)	130 (7.5)	99 (11.3)	64 (7.3)	74 (8.6)	66 (7.6)
Death[a]	148 (7.6)	193 (9.8)	1 (0.6)	11 (5.9)	147 (8.3)	182 (10.2)	68 (3.9)	82 (4.7)	38 (4.3)	43 (4.9)	30 (3.5)	39 (4.5)
Other[a]	173 (8.8)	179 (9.1)	4 (2.2)	9 (4.8)	169 (9.5)	170 (9.6)	160 (9.2)	167 (9.6)	100 (11.4)	103 (11.8)	60 (7.0)	64 (7.4)

Darbe: darbepoetin alfa; DD-CKD: dialysis-dependent chronic kidney disease; N: number of subjects; n: number of subjects within specific category; NDD-CKD: non-dialysis-dependent chronic kidney disease; vada: vadadustat
Completed treatment for an individual subject was defined as a subject that was on study drug treatment at the time of study closure.
a. "Death" was identified from the free text of "Other" collected on the case report forms and summarized separately.
Source: ISE Table 14.1.2.1a, CSR AKB-6548-CI-0016 Table 14.1.1, CSR AKB-6548-CI-0017 Table 14.1.1 ISE Table 14.1.2.1b, CSR AKB-6548-CI-0014 Table 14.1.1, CSR AKB-6548-CI-0015 Table 14.1.1

Exposure to study drug in the pooled DD-CKD and NDD-CKD populations in INNO2VATE and PRO2TECT studies, respectively, is presented by treatment group in Table below.

Table 29 Summary of Study Drug Exposure in the DD-CKD Population for INNO$_2$VATE and the NDD-CKD Population for the PRO$_2$TECT Studies (Safety Population)

Parameter	INNO$_2$VATE Pooled		PRO$_2$TECT Pooled	
Statistics	Vada N=1947	Darbe N=1955	Vada N=1739	Darbe N=1732
Total duration of exposure, weeks[a]				
Mean (SD)	59.45 (37.568)	71.25 (36.729)	69.24 (47.739)	75.46 (48.518)
Median	55.86	71.71	59.43	67.00
Q1, Q3	28.86, 85.00	43.86, 96.14	33.29, 101.86	36.14, 112.14
Min, Max	0.1, 163.1	0.1, 169.1	0.1, 204.1	0.1, 208.1
Total duration category, n (%)				
<4 weeks	73 (3.7)	29 (1.5)	56 (3.2)	39 (2.3)
≥4 and <13 weeks	182 (9.3)	89 (4.6)	135 (7.8)	104 (6.0)
≥13 and <26 weeks	178 (9.1)	122 (6.2)	139 (8.0)	95 (5.5)
≥26 and <39 weeks	196 (10.1)	158 (8.1)	238 (13.7)	252 (14.5)
≥39 and <52 weeks	271 (13.9)	240 (12.3)	207 (11.9)	191 (11.0)
≥52 and <78 weeks	461 (23.7)	519 (26.5)	315 (18.1)	315 (18.2)
≥78 and <104 weeks	311 (16.0)	395 (20.2)	229 (13.2)	252 (14.5)
≥104 weeks	275 (14.1)	403 (20.6)	420 (24.2)	484 (27.9)

Darbe: darbepoetin alfa; DD-CKD: dialysis-dependent chronic kidney disease; N: number of subjects; n: number of subjects within specific category; NDD-CKD: non-dialysis-dependent chronic kidney disease; Q1: first quartile; Q3: third quartile; SD: standard deviation; vada: vadadustat.
a Duration (weeks) = (last treatment date – first treatment date + 1)/7
Source: ISS Table 14.1.4.2a and ISS Table 14.1.4.2b

- **Recruitment**

AKB-6548-CI-0016: 18 Jul 2016 (first subject signed informed consent) to 31 Jan 2020 (last subject last visit). It was anticipated that 300 subjects at approximately 140 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled. The actual number of subjects enrolled was 369 at 83 centers in 10 countries.

AKB-6548-CI-0017: 17 Aug 2016 (first subject signed informed consent) to 16 Jan 2020 (last subject last visit). It was anticipated that 3300 subjects at approximately 300 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled. The actual number of subjects enrolled was 3554 at 275 centers in 18 countries.

AKB-6548-CI-0014: 17 Dec 2015 (first subject signed informed consent) to 04 Jun 2020 (last subject last visit). It was anticipated that 1850 subjects at approximately 390 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled. The actual number of subjects enrolled was 1751 at 274 centers in 15 countries.

AKB-6548-CI-0015: 09 Feb 2016 (first subject signed informed consent) to 18 Jun 2020 (last subject last visit). It was anticipated that 1850 subjects at approximately 480 investigative sites in North America, Latin America, Europe, and Asia Pacific would be enrolled. The actual number of subjects enrolled was 1725 at 328 investigative sites in 26 countries.

- **Conduct of the studies**

For darbepoetin alfa-treated subjects, ESA rescue was defined in the protocol as the receipt of any ESA agent other than darbepoetin alfa, i.e., increases in the darbepoetin alfa dose were not considered ESA rescue unless the investigator designated the administration as such. In other words, there were no protocol prespecified dose-related criteria to define ESA rescue with darbepoetin alfa in subjects randomized to the darbepoetin alfa treatment group. The sponsor conducted post-hoc analyses of ESA rescue that in addition to the prespecified narrow and broad-on-treatment ESA rescue definitions, also included subjects who received ≥50% or ≥100% increase in the dose of darbepoetin alfa from the previous closest reported dose.

AKB-6548-CI-0016: The original protocol dated 22 Mar 2016 was amended 6 times, lastly on 26 Feb 2019.

AKB-6548-CI-0017: The original protocol dated 06 May 2016 was amended 5 times, lastly on 26 Feb 2019.

AKB-6548-CI-0014: The original protocol dated 15 Oct 2015 was amended 7 times, lastly on 26 Feb 2019.

AKB-6548-CI-0015: The original protocol dated 10 Nov 2015 was amended 7 times, lastly on 26 Feb 2019.

- **Baseline data**

Demographics and other baseline characteristics in the pooled and individual INNO2VATE and PRO2TECT studies are presented in Table 39 and Table 40.

Although all subjects included in the trials had an eGFR ≤ 60 mL/min/1.73 m2 at screening, slightly less than 1% (20 subjects in Trial CI-0014 and 13 subjects in Trial CI-0015) turned out to have an eGFR slightly above 60 mL/min/1.73m2 at the start of the trial. These subjects remained in the trial and are highlighted in red in Tables below

Table 30 Number of Subjects by KDIGO Cohort in Trial AKB-6548-CI-0014

Treatment	N	GFR (ml/min/1.73m^2)	CKD Class	N (%)
AKB300	879	<15	G5	301 (34.2)
AKB300	879	>=15 - <30	G4	384 (43.7)
AKB300	879	>=30 - <45	G3b	158 (18.0)
AKB300	879	>=45 - <60	G3a	29 (3.3)
AKB300	879	>=60 - <90	G2	7 (0.8)
DALFA	872	<15	G5	292 (33.5)
DALFA	872	>=15 - <30	G4	381 (43.7)
DALFA	872	>=30 - <45	G3b	141 (16.2)
DALFA	872	>=45 - <60	G3a	45 (5.2)
DALFA	872	>=60 - <90	G2	13 (1.5)

AKB300: vadadustat; CKD: chronic kidney disease; DALFA: darbepoetin alfa; KDIGO: Kidney Disease Improving Global Outcomes; N: number.
Source: Appendix 21, Section 3.21.

Table 31	Number of Subjects by KDIGO Cohort in Trial AKB-6548-CI-0015			
Treatment	**N**	**GFR (ml/min/1.73m²)**	**CKD Class**	**N (%)**
AKB300	862	<15	G5	244 (28.3)
AKB300	862	>=15 - <30	G4	406 (47.1)
AKB300	862	>=30 - <45	G3b	169 (19.6)
AKB300	862	>=45 - <60	G3a	38 (4.4)
AKB300	862	>=60 - <90	G2	5 (0.6)
DALFA	863	<15	G5	242 (28.0)
DALFA	863	>=15 - <30	G4	413 (47.9)
DALFA	863	>=30 - <45	G3b	152 (17.6)
DALFA	863	>=45 - <60	G3a	48 (5.6)
DALFA	863	>=60 - <90	G2	8 (0.9)

AKB300: vadadustat; CKD: chronic kidney disease; DALFA: darbepoetin alfa; KDIGO: Kidney Disease Improving Global Outcomes; N: number.
Source: Appendix 21, Section 3.21.

In the DD-CKD trials, the percentage of subjects with a preferred term "Nephrectomy" was 1.9% in Trial CI-0016 and 3.1% in Trial CI-0017. A maximum of 1 subject in Trial CI-0016 and 22 subjects in Trial CI-0017 may have qualified as anephric/anuric, but cannot be confirmed.

As expected, based on the study populations (correction of Hb versus conversion studies), there was a higher proportion of subjects in the correction of Hb studies (CI-0014 and CI-0016) in the lower baseline Hb strata. Baseline ferritin and baseline TSAT levels were higher in CI-0017 than the CI-0016 study and comparable in studies CI-0014 and CI-0015 (Table 5). In addition, baseline ferritin and TSAT levels were lower overall in PRO2TECT than in INNO2VATE reflecting less severe and shorter duration of kidney disease in PRO2TECT compared to INNO2VATE as well as more frequent IV iron administration in the dialysis population included in INNO2VATE. Of note, both the DD-CKD and NDD-CKD subjects were iron replete at Baseline as stipulated in study eligibility criteria.

Region-specific differences in the pooled CKD population were noted for several baseline characteristics. A history of CVD was more frequent in the US (53.0% of subjects) than in Europe (45.6% of subjects) and ROW (39.2% of subjects), but NYHA HF class II or III was more frequent in Europe (19.0% of subjects) than in the US (11.8% of subjects) and the ROW (13.5% of subjects). More subjects had diabetes mellitus in the US compared with Europe or ROW. This, in part, reflects the higher proportion of black patients and US patients with more extensive CV medical history enrolled in the US compared to Europe and ROW. Mean ESA dose at Baseline was lower and mean Baseline Hb was higher in Europe than in the US and ROW. The proportion of subjects with baseline ESA ≤90 U/kg/week was substantially higher in Europe (73.3%) compared with the US (53.7%) and ROW (56.2%). The proportion of subjects with baseline Hb considered high level (≥9.5 g/dL in CI-0014 and CI-0016 and ≥10.0 g/dL in CI-0015 and CI-0017) was highest in Europe (76.0%) compared to the US and ROW (50.3% and 62.7%, respectively).

Table 32 Demographic Characteristics - DD-CKD Population for the INNO$_2$VATE and NDD-CKD Population for the PRO$_2$TECT Global Phase 3 Studies (Randomized Population)

	INNO$_2$VATE						PRO$_2$TECT					
	Pooled		AKB-6548-CI-0016		AKB-6548-CI-0017		Pooled		AKB-6548-CI-0014		AKB-6548-CI-0015	
Characteristics Category/Statistic	Vada N=1958	Darbe N=1965	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=1741	Darbe N=1735	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Age[a] (Year), n	1958	1965	181	188	1777	1777	1741	1735	879	872	862	863
Mean (SD)	57.8 (13.95)	58.1 (13.94)	56.5 (14.80)	55.6 (14.60)	57.9 (13.86)	58.4 (13.84)	66.2 (13.76)	65.7 (13.64)	65.2 (14.27)	64.9 (13.71)	67.3 (13.14)	66.5 (13.52)
Age <65 years, n (%)	1289 (65.8)	1298 (66.1)	122 (67.4)	137 (72.9)	1167 (65.7)	1161 (65.3)	711 (40.8)	712 (41.0)	398 (45.3)	374 (42.9)	313 (36.3)	338 (39.2)
Age ≥65 years, n (%)	669 (34.2)	667 (33.9)	59 (32.6)	51 (27.1)	610 (34.3)	616 (34.7)	1030 (59.2)	1023 (59.0)	481 (54.7)	498 (57.1)	549 (63.7)	525 (60.8)
Sex, n (%)												
Male	1097 (56.0)	1117 (56.8)	107 (59.1)	113 (60.1)	990 (55.7)	1004 (56.5)	798 (45.8)	741 (42.7)	404 (46.0)	366 (42.0)	394 (45.7)	375 (43.5)
Female	861 (44.0)	848 (43.2)	74 (40.9)	75 (39.9)	787 (44.3)	773 (43.5)	943 (54.2)	994 (57.3)	475 (54.0)	506 (58.0)	468 (54.3)	488 (56.5)
Ethnicity, n (%)												
Hispanic or Latino	753 (38.5)	740 (37.7)	71 (39.2)	66 (35.1)	682 (38.4)	674 (37.9)	561 (32.2)	565 (32.6)	306 (34.8)	310 (35.6)	255 (29.6)	255 (29.5)
Not Hispanic or Latino	1147 (58.6)	1158 (58.9)	104 (57.5)	118 (62.8)	1043 (58.7)	1040 (58.5)	1150 (66.1)	1145 66.0)	566 (64.4)	554 (63.5)	584 (67.7)	591 (68.5)
Not Reported	41 (2.1)	50 (2.5)	5 (2.8)	3 (1.6)	36 (2.0)	47 (2.6)	10 (0.6)	10 (0.6)	2 (0.2)	5 (0.6)	8 (0.9)	5 (0.6)
Unknown	17 (0.9)	17 (0.9)	1 (0.6)	1 (0.5)	16 (0.9)	16 (0.9)	20 (1.1)	15 (0.9)	5 (0.6)	3 (0.3)	15 (1.7)	12 (1.4)
Race, n (%)												
American Indian or Alaska Native	20 (1.0)	30 (1.5)	1 (0.6)	0	19 (1.1)	30 (1.7)	54 (3.1)	49 (2.8)	22 (2.5)	23 (2.6)	32 (3.7)	26 (3.0)
Asian	88 (4.5)	107 (5.4)	12 (6.6)	8 (4.3)	76 (4.3)	99 (5.6)	110 (6.3)	92 (5.3)	48 (5.5)	37 (4.2)	62 (7.2)	55 (6.4)
Black or African American	470 (24.0)	479 (24.4)	38 (21.0)	35 (18.6)	432 (24.3)	444 (25.0)	281 (16.1)	303 (17.5)	188 (21.4)	172 (19.7)	93 (10.8)	131 (15.2)
Native Hawaiian or Other Pacific Islander	13 (0.7)	6 (0.3)	0	0	13 (0.7)	6 (0.3)	9 (0.5)	6 (0.3)	6 (0.7)	6 (0.7)	3 (0.3)	0
White	1264 (64.6)	1239 (63.1)	129 (71.3)	143 (76.1)	1135 (63.9)	1096 (61.7)	1177 (67.6)	1174 (67.7)	546 (62.1)	571 (65.5)	631 (73.2)	603 (69.9)
Not Reported	52 (2.7)	53 (2.7)	0	1 (0.5)	52 (2.9)	52 (2.9)	20 (1.1)	19 (1.1)	5 (0.6)	6 (0.7)	15 (1.7)	13 (1.5)
Other	42 (2.1)	46 (2.3)	0	1 (0.5)	42 (2.4)	45 (2.5)	83 (4.8)	80 (4.6)	58 (6.6)	48 (5.5)	25 (2.9)	32 (3.7)
Multiple	9 (0.5)	5 (0.3)	1 (0.6)	0	8 (0.5)	5 (0.3)	7 (0.4)	12 (0.7)	6 (0.7)	9 (1.0)	1 (0.1)	3 (0.3)
Region[b], n (%)												
US	1187 (60.6)	1188 (60.5)	97 (53.6)	102 (54.3)	1090 (61.3)	1086 (61.1)	862 (49.5)	864 (49.8)	532 (60.5)	529 (60.7)	330 (38.3)	335 (38.8)
Europe	280 (14.3)	297 (15.1)	26 (14.4)	16 (8.5)	254 (14.3)	281 (15.8)	296 (17.0)	289 (16.7)	71 (8.1)	68 (7.8)	225 (26.1)	221 (25.6)
Rest of the World	491 (25.1)	480 (24.4)	58 (32.0)	70 (37.2)	433 (24.4)	410 (23.1)	583 (33.5)	582 (33.5)	276 (31.4)	275 (31.5)	307 (35.6)	307 (35.6)
Country, n (%)												
Argentina	39 (2.0)	57 (2.9)	3 (1.7)	5 (2.7)	36 (2.0)	52 (2.9)	80 (4.6)	68 (3.9)	25 (2.8)	26 (3.0)	55 (6.4)	42 (4.9)
Australia	17 (0.9)	21 (1.1)	0	0	17 (1.0)	21 (1.2)	25 (1.4)	24 (1.4)	10 (1.1)	8 (0.9)	15 (1.7)	16 (1.9)
Austria	--	--	--	--	--	--	3 (0.2)	3 (0.2)	0	0	3 (0.3)	3 (0.3)
Brazil	173 (8.8)	172 (8.8)	18 (9.9)	20 (10.6)	155 (8.7)	152 (8.6)	102 (5.9)	104 (6.0)	62 (7.1)	58 (6.7)	40 (4.6)	46 (5.3)
Bulgaria	102 (5.2)	106 (5.4)	--	--	102 (5.7)	106 (6.0)	89 (5.1)	90 (5.2)	41 (4.7)	42 (4.8)	48 (5.6)	48 (5.6)
Canada	25 (1.3)	23 (1.2)	0	0	25 (1.4)	23 (1.3)	--	--	--	--	--	--
Chile	--	--	--	--	--	--	4 (0.2)	7 (0.4)	0	0	4 (0.5)	7 (0.8)
Colombia	--	--	--	--	--	--	9 (0.5)	11 (0.6)	0	0	9 (1.0)	11 (1.3)
Czech Republic	--	--	--	--	--	--	3 (0.2)	1 (0.1)	0	0	3 (0.3)	1 (0.1)
France	18 (0.9)	22 (1.1)	--	--	18 (1.0)	22 (1.2)	11 (0.6)	11 (0.6)	0	0	11 (1.3)	11 (1.3)
Germany	6 (0.3)	11 (0.6)	0	0	6 (0.3)	11 (0.6)	10 (0.6)	13 (0.7)	0	0	10 (1.2)	13 (1.5)
Hungary	--	--	--	--	--	--	39 (2.2)	40 (2.3)	7 (0.8)	8 (0.9)	32 (3.7)	32 (3.7)
Israel	14 (0.7)	18 (0.9)	--	--	14 (0.8)	18 (1.0)	9 (0.5)	3 (0.2)	2 (0.2)	2 (0.2)	7 (0.8)	1 (0.1)
Italy	10 (0.5)	9 (0.5)	6 (3.3)	1 (0.5)	4 (0.2)	8 (0.5)	18 (1.0)	17 (1.0)	7 (0.8)	9 (1.0)	11 (1.3)	8 (0.9)
Malaysia	--	--	--	--	--	--	10 (0.6)	16 (0.9)	0	0	10 (1.2)	16 (1.9)
Mexico	16 (0.8)	11 (0.6)	1 (0.6)	0	15 (0.8)	11 (0.6)	103 (5.9)	107 (6.2)	45 (5.1)	46 (5.3)	58 (6.7)	61 (7.1)
Poland	52 (2.7)	44 (2.2)	11 (6.1)	9 (4.8)	41 (2.3)	35 (2.0)	--	--	--	--	--	--

Characteristics Category/Statistic	INNO2VATE						PRO2TECT					
	Pooled		AKB-6548-CI-0016		AKB-6548-CI-0017		Pooled		AKB-6548-CI-0014		AKB-6548-CI-0015	
	Vada N=1958	Darbe N=1965	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=1741	Darbe N=1735	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Portugal	21 (1.1)	24 (1.2)	9 (5.0)	6 (3.2)	12 (0.7)	18 (1.0)	--	--	--	--	--	--
Republic of Korea	51 (2.6)	50 (2.5)	6 (3.3)	3 (1.6)	45 (2.5)	47 (2.6)	28 (1.6)	29 (1.7)	6 (0.7)	10 (1.1)	22 (2.6)	19 (2.2)
Romania	--	--	--	--	--	--	30 (1.7)	32 (1.8)	0	0	30 (3.5)	32 (3.7)
Russia Federation	57 (2.9)	45 (2.3)	4 (2.2)	6 (3.2)	53 (3.0)	39 (2.2)	24 (1.4)	22 (1.3)	7 (0.8)	10 (1.1)	17 (2.0)	12 (1.4)
Serbia	66 (3.4)	65 (3.3)	--	--	66 (3.7)	65 (3.7)	32 (1.8)	26 (1.5)	0	0	32 (3.7)	26 (3.0)
Slovak Republic	--	--	--	--	--	--	9 (0.5)	4 (0.2)	0	0	9 (1.0)	4 (0.5)
South Africa	--	--	--	--	--	--	72 (4.1)	65 (3.7)	52 (5.9)	51 (5.8)	20 (2.3)	14 (1.6)
Spain	--	--	--	--	--	--	21 (1.2)	27 (1.6)	5 (0.6)	5 (0.6)	16 (1.9)	22 (2.5)
Turkey	--	--	--	--	--	--	9 (0.5)	12 (0.7)	0	0	9 (1.0)	12 (1.4)
Ukraine	99 (5.1)	83 (4.2)	26 (14.4)	36 (19.1)	73 (4.1)	47 (2.6)	117 (6.7)	126 (7.3)	67 (7.6)	64 (7.3)	50 (5.8)	62 (7.2)
United Kingdom	5 (0.3)	16 (0.8)	--	--	5 (0.3)	16 (0.9)	22 (1.3)	13 (0.7)	11 (1.3)	4 (0.5)	11 (1.3)	9 (1.0)
United States	1187 (60.6)	1188 (60.5)	97 (53.6)	102 (54.3)	1090 (61.3)	1086 (61.1)	862 (49.5)	864 (49.8)	532 (60.5)	529 (60.7)	330 (38.3)	335 (38.8)
Height (cm), n	1927	1933	178	184	1749	1749	1701	1705	857	859	844	846
Mean (SD)	167.42 (10.824)	167.01 (10.444)	167.58 (10.684)	166.93 (8.961)	167.41 (10.841)	167.02 (10.591)	164.62 (10.498)	164.44 (10.325)	164.60 (10.452)	164.38 (10.235)	164.65 (10.551)	164.49 (10.420)
Weight (kg), n	1930	1946	177	184	1753	1762	1725	1723	872	867	853	856
Mean (SD)	80.07 (21.725)	79.75 (21.838)	77.93 (20.631)	77.55 (19.689)	80.29 (21.826)	79.98 (22.043)	79.97 (21.440)	80.63 (21.576)	80.65 (21.767)	81.07 (22.064)	79.27 (21.090)	80.18 (21.073)
BMI (kg/m^2), n	1904	1918	174	181	1730	1737	1698	1701	855	857	843	844
Mean (SD)	28.50 (7.142)	28.46 (7.099)	27.64 (6.087)	27.49 (6.003)	28.58 (7.235)	28.56 (7.198)	29.38 (7.129)	29.73 (7.246)	29.65 (7.181)	29.83 (7.240)	29.10 (7.068)	29.63 (7.254)

BMI: body mass index; CKD: chronic kidney disease; CRF: case report form; darbe: darbepoetin alfa; DD: dialysis-dependent; N: number of subjects; n: number of subjects within specific category; NDD: non-dialysis-dependent; SD: standard deviation; vada: vadadustat; --: not applicable.

a Reported age on the CRF.

b Across the 4 global studies, Europe included Bulgaria, France, Germany, Italy, Poland, Portugal, Serbia, and United Kingdom and the Rest of World included Argentina, Australia, Brazil, Canada, Israel, Mexico, Republic of Korea, Russian Federation, and Ukraine

Source: ISE Table 14.1.3.1a, CSR AKB-6548-CI-0016 Table 14.1.3.1, CSR AKB-6548-CI-0017 Table 14.1.3.1, ISE Table 14.1.3.1b, CSR AKB-6548-CI-0014 Table 14.1.3.1, CSR AKB-6548-CI-0015 Table 14.1.3.1

Table 33 Baseline Characteristics - DD-CKD Population for INNO2VATE and the NDD-CKD Population for the PRO2TECT Global Phase 3 Studies (Randomized Population)

Characteristics Category/ Statistics	INNO2VATE						PRO2TECT					
	Pooled		AKB-6548-CI-0016		AKB-6548-CI-0017		Pooled		AKB-6548-CI-0014		AKB-6548-CI-0015	
	Vada N=1958	Darbe N=1965	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=1741	Darbe N=1735	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Randomization stratification factors, n												
Enrolled in US	1187 (60.6)	1188 (60.5)	97 (53.6)	102 (54.3)	1090 (61.3)	1086 (61.1)	862 (49.5)	864 (49.8)	532 (60.5)	529 (60.7)	330 (38.3)	335 (38.8)
Enrolled in Europe	280 (14.3)	297 (15.1)	26 (14.4)	16 (8.5)	254 (14.3)	281 (15.8)	296 (17.0)	289 (16.7)	71 (8.1)	68 (7.8)	225 (26.1)	221 (25.6)
Enrolled in ROW	491 (25.1)	480 (24.4)	58 (32.0)	70 (37.2)	433 (24.4)	410 (23.1)	583 (33.5)	582 (33.5)	276 (31.4)	275 (31.5)	307 (35.6)	307 (35.6)
NYHA HF Class 0 (no HF) or Class I, n (%)	1707 (87.2)	1709 (87.0)	162 (89.5)	162 (86.2)	1545 (86.9)	1547 (87.1)	1497 (86.0)	1493 (86.1)	762 (86.7)	754 (86.5)	735 (85.3)	739 (85.6)
NYHA HF Class II or Class III, n (%)	251 (12.8)	256 (13.0)	19 (10.5)	26 (13.8)	232 (13.1)	230 (12.9)	244 (14.0)	242 (13.9)	117 (13.3)	118 (13.5)	127 (14.7)	124 (14.4)
Baseline Hb category[a] low, n (%)	714 (36.5)	718 (36.5)	94 (51.9)	99 (52.7)	620 (34.9)	619 (34.8)	837 (48.1)	842 (48.5)	564 (64.2)	563 (64.6)	273 (31.7)	279 (32.3)
Baseline Hb category[a] high, n	1244 (63.5)	1247 (63.5)	87 (48.1)	89 (47.3)	1157 (65.1)	1158 (65.2)	904 (51.9)	893 (51.5)	315 (35.8)	309 (35.4)	589 (68.3)	584 (67.7)
Has history of CVD[b]	NA	NA	69 (38.1)	73 (38.8)	868 (48.8)	932 (52.4)	NA	NA	406 (46.2)	412 (47.2)	375 (43.5)	402 (46.6)
No history of CVD[b]	NA	NA	112 (61.9)	115 (61.2)	909 (51.2)	845 (47.6)	NA	NA	473 (53.8)	460 (52.8)	487 (56.5)	461 (53.4)
Years since chronic dialysis initiated[c], n	NA	NA	179	186	1775	1777	NA	NA	NA	NA	NA	-NA
Mean (SD), years	NA	NA	0.138 (0.0883)	0.151 (0.2848)	4.004 (4.0224)	3.941 (4.0144)	NA	NA	NA	NA	NA	-NA

Characteristics Category/ Statistics	INNO2VATE Pooled Vada N=1958	INNO2VATE Pooled Darbe N=1965	INNO2VATE AKB-6548-CI-0016 Vada N=181	INNO2VATE AKB-6548-CI-0016 Darbe N=188	INNO2VATE AKB-6548-CI-0017 Vada N=1777	INNO2VATE AKB-6548-CI-0017 Darbe N=1777	PRO2TECT Pooled Vada N=1741	PRO2TECT Pooled Darbe N=1735	PRO2TECT AKB-6548-CI-0014 Vada N=879	PRO2TECT AKB-6548-CI-0014 Darbe N=872	PRO2TECT AKB-6548-CI-0015 Vada N=862	PRO2TECT AKB-6548-CI-0015 Darbe N=863
Has diabetes mellitus	1076 (55.0)	1094 (55.7)	105 (58.0)	96 (51.1)	971 (54.6)	998 (56.2)	1098 (63.1)	1117 (64.4)	581 (66.1)	599 (68.7)	517 (60.0)	518 (60.0)
No diabetes mellitus	882 (45.0)	871 (44.3)	76 (42.0)	92 (48.9)	806 (45.4)	779 (43.8)	643 (36.9)	618 (35.6)	298 (33.9)	273 (31.3)	345 (40.0)	345 (40.0)
Baseline ferritin, n	1957	1965	181	188	1776	1777	1741	1735	879	872	862	863
Mean (SD), ng/mL	811.91 (555.397)	810.72 (534.800)	469.72 (316.923)	527.76 (401.100)	846.78 (562.653)	840.65 (538.493)	368.28 (289.469)	371.66 (303.608)	368.08 (293.667)	360.25 (286.873)	368.48 (285.294)	383.18 (319.382)
Median, ng/mL	709.00	708.50	417.00	421.75	760.75	748.00	283.50	273.00	291.50	264.75	278.50	285.50
Q1, Q3	386.50, 1110.00	397.50, 1103.50	249.00, 587.00	259.75, 660.25	406.50, 1154.00	423.00, 1144.50	168.00, 469.50	172.00, 460.50	163.00, 466.00	166.00, 455.25	170.50, 471.00	179.50, 462.00
Baseline TSAT, n	1955	1965	181	188	1774	1777	1741	1735	879	872	862	863
Mean (SD), %	37.44 (13.272)	37.30 (13.154)	31.32 (9.446)	34.21 (12.679)	38.06 (13.449)	37.63 (13.165)	31.83 (9.709)	31.95 (10.342)	30.91 (9.623)	30.96 (10.042)	32.77 (9.711)	32.94 (10.549)
Median, %	34.50	34.50	28.50	31.00	35.00	34.50	30.00	30.00	28.50	29.00	31.00	30.50
Q1, Q3	28.00, 43.50	28.00, 43.00	24.50, 36.50	26.00, 38.00	29.00, 44.50	28.50, 43.50	25.00, 36.50	24.50, 36.50	24.50, 35.50	24.00, 35.00	26.00, 37.50	25.50, 38.00

CKD: chronic kidney disease; CVD: cardiovascular disease; darbe: darbepoetin alfa; DD: dialysis-dependent; Hb: hemoglobin; HF: heart failure; N: number of subjects; n: number of subjects within specific category; NA: not applicable; NDD: non-dialysis-dependent; NYHA: New York Heart Association; Q: quartile; ROW: Rest of World; SD: standard deviation; TSAT: transferrin saturation; vada: vadadustat.

a The low level of baseline Hb strata as measured by the central laboratory was defined as <9.5 g/dL for CI-0016 and <10.0 g/dL for CI-0017; the high baseline Hb strata was defined as ≥9.5 g/dL for CI-0016 and ≥10.0 g/dL for CI-0017. The low level of Baseline Hb as measured by the central laboratory was defined as <9.5 g/dL for CI-0014 and <10.0 g/dL for CI-0015; the high level of Baseline Hb is defined as ≥9.5 g/dL for CI-0014 and ≥10.0 g/dL for CI-0015.

b. CVD included coronary artery disease, myocardial infarction, stroke, and HF.

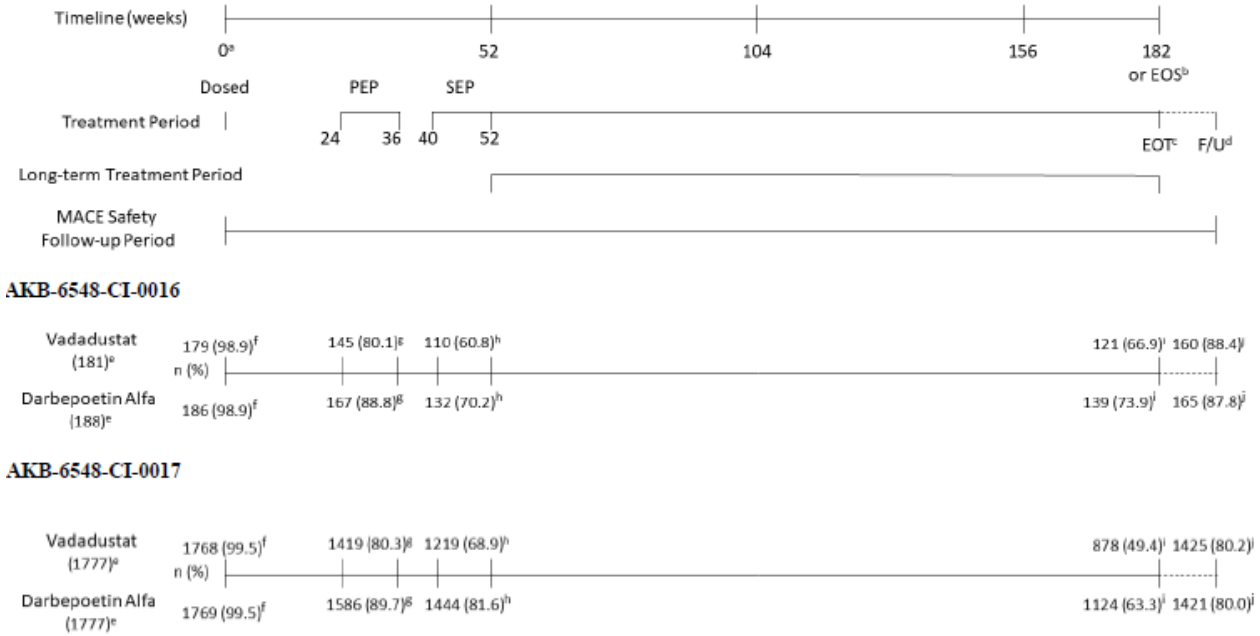
c. The handling of the partial date of chronic dialysis initiated: If day was missing, day was set to 15th of the month. If month was missing, month and day were set to Jul 1. If year was missing, date was missing. Years since chronic dialysis initiated was calculated based on date of chronic dialysis initiated and date of Screening 1.

Source: ISE Table 14.1.4.1a, CSR AKB-6548-CI-0016 Table 14.1.4.1, Table 14.1.5.1, CSR AKB-6548-CI-0017 Table 14.1.4.1, Table 14.1.5.1, ISE Table 14.1.4.1b, CSR AKB-6548-CI-0014 Table 14.1.4.1, Table 14.1.5.1, CSR AKB-6548-CI-0015 Table 14.1.4.1, Table 14.1.5.1.

- **Numbers analysed**

Figure 18 Timeline of Activities and Subject Numbers in the INNO2VATE and PRO2TECT Studies

(A) INNO2VATE Study Periods



(B) PRO2TECT Study Periods

AKB-6548-CI-0014

AKB-6548-CI-0015

EOS: end of study; EOT: end of treatment; F/U: follow-up; MACE: major adverse cardiovascular events; n: number of subjects within specific category; PEP: primary efficacy period; SEP: secondary efficacy period
Note: MACE information was collected beginning after Week 0 until EOS, regardless of subject treatment status.

a Randomization occurred at Week 0
b EOS occurred once 631 MACE events were recorded
c EOT occurred once subject permanently discontinued study drug, or upon announcement of global EOS
d F/U occurred 4 weeks after EOT
e Number of subjects randomized
f Number of subjects dosed
g Number of subjects on treatment during PEP
h Number of subjects on treatment during SEP
i Number of subjects on treatment at EOS
j Number of subjects who completed study (including MACE Safety Follow-up)

Source: CSR AKB-6548-CI-0016 Table 14.1.1, Table 14.1.9.4.1, CSR AKB-6548-CI-0017 Table 14.1.1, Table 14.1.9.4.1, CSR AKB-6548-CI-0014 Table 14.1.1, Table 14.1.9.4.1, CSR AKB-6548-CI-0015 Table 14.1.1, Table 14.1.9.4.1

- **Outcomes and estimation**

Primary Efficacy Endpoint of Mean Change from Baseline in Haemoglobin in the Primary Efficacy Period

The results of the analysis of the primary efficacy endpoint, the mean change in average Hb between baseline and the PEP (Week 24 to 36), are summarized in Table below for the INNO2VATE and PRO2TECT studies. The non-inferiority of vadadustat to darbepoetin alfa was demonstrated in the INNO2VATE CI-0016, and CI-0017 studies as well as the PRO2TECT CI-0014, and CI-0015 studies since the lower bound of the 95% CI (-0.53, -0.23, -0.04, and -0.09, respectively) for the LS mean difference in the change from baseline was above the prespecified non-inferiority margin of -0.75 g/dL in each study.

The pooled data in INNO2VATE and PRO2TECT were consistent with the findings of their respective individual studies.

Table 34 Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 24 to 36 (ANCOVA with Multiple Imputations) - INNO2VATE and PRO2TECT Global Phase 3 Studies (Randomized Population)

	INNO2VATE						PRO2TECT					
	Pooled		AKB-6548-CI-0016		AKB-6548-CI-0017		Pooled		AKB-6548-CI-0014		AKB-6548-CI-0015	
Visit/ Statistics	Vada N=1958	Darbe N=1965	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=1741	Darbe N=1735	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Baseline, n	1958	1965	181	188	1777	1777	1741	1735	879	872	862	863
Mean (SD)	10.17 (0.909)	10.13 (0.912)	9.37 (1.070)	9.19 (1.138)	10.25 (0.850)	10.23 (0.825)	9.76 (1.069)	9.76 (1.066)	9.11 (0.802)	9.14 (0.779)	10.42 (0.887)	10.39 (0.943)
Weeks 24 to 36 (obs), n	1730	1794	157	171	1573	1623	1534	1571	755	767	779	804
Mean (SD)	10.39 (1.005)	10.56 (0.950)	10.37 (1.096)	10.65 (0.921)	10.39 (0.996)	10.55 (0.953)	10.63 (0.982)	10.60 (1.016)	10.44 (0.969)	10.40 (1.017)	10.82 (0.959)	10.80 (0.977)
Weeks 24 to 36 (obs + imp), n	1958	1965	181	188	1777	1777	1741	1735	879	872	862	863
Mean (SD)	10.36 (1.018)	10.54 (0.961)	10.36 (1.133)	10.61 (0.940)	10.36 (1.006)	10.53 (0.963)	10.58 (1.004)	10.56 (1.030)	10.39 (0.994)	10.35 (1.031)	10.77 (0.978)	10.77 (0.985)
Change from Baseline, n	1958	1965	181	188	1777	1777	1741	1735	879	872	862	863
Mean (SD)	0.19 (1.153)	0.41 (1.183)	0.99 (1.276)	1.42 (1.414)	0.11 (1.108)	0.30 (1.103)	0.82 (1.096)	0.80 (1.103)	1.28 (1.005)	1.21 (1.055)	0.35 (0.982)	0.38 (0.990)
LS mean (SEM)	0.40 (0.038)	0.58 (0.038)	1.26 (0.109)	1.58 (0.108)	0.19 (0.032)	0.36 (0.032)	0.91 (0.028)	0.89 (0.028)	1.43 (0.046)	1.38 (0.047)	0.41 (0.036)	0.42 (0.037)
95% CI	0.33, 0.48	0.51, 0.66	1.05, 1.48	1.37, 1.79	0.12, 0.25	0.29, 0.42	0.86, 0.97	0.84, 0.95	1.34, 1.52	1.29, 1.47	0.34, 0.48	0.35, 0.49
LS mean (SEM) difference	-0.18 (0.031)		-0.31 (0.110)		-0.17 (0.033)		0.02 (0.032)		0.05 (0.048)		-0.01 (0.042)	
95% CI	-0.24, -0.12		-0.53, -0.10		-0.23, -0.10		-0.04, 0.08		-0.04, 0.15		-0.09, 0.07	

ANCOVA: analysis of covariance; CI: confidence interval; darbe: darbepoetin alfa; imp: imputed; N: number of subjects; n: number of subjects within specific category; obs: observed; SD: standard deviation; SEM: standard error of the mean; vada: vadadustat
Source: ISE Table 14.2.1.1a, CSR AKB-6548-CI-0016 Table 14.2.1.1, CSR AKB-6548-CI-0017 Table 14.2.1.1, ISE Table 14.2.1.1b, CSR AKB-6548-CI-0014 Table 14.2.1.1, and CSR AKB-6548-CI-0015 Table 14.2.1.1

Sensitivity Analyses of the Primary Endpoint

The consistency in the vadadustat treatment response with and without the context of ESA rescue therapy was confirmed with sensitivity analyses for the primary endpoint using an ANCOVA with multiple imputations and censoring for rescue therapy (considering narrow and broad-on-treatment rescue therapy) for each study. In INNO2VATE CI-0016 and CI-0017 studies and the PRO2TECT CI-0014 and CI-0015 studies, the lower bound of 95% CI was above -0.75 g/dL for both narrow and broad rescue therapy meeting the non-inferiority criteria.

Similarly, additional sensitivity analyses of the primary endpoint, including evaluation in the FAS and PP populations and an MMRM analysis performed utilizing the observed data confirmed these findings as did a tipping point analysis used to explore the consequences of assuming that data in the vadadustat treatment group are missing not at random.

Table 35 Sensitivity Analysis of Mean Change from Baseline in Hemoglobin to the Average Over Weeks 24 to 36 (ANCOVA with Multiple Imputations) Considering Narrow and Broad-on-Treatment Rescue Therapy – INNO2VATE Global Phase 3 Studies (Randomized Population)

	INNO2VATE			
	AKB-6548-CI-0016		AKB-6548-CI-0017	
Characteristics Category	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777
Narrow rescue therapy				
Change from Baseline at Week 24 and 36, n	181	188	1777	1777
Mean (SD)	1.02 (1.267)	1.42 (1.423)	0.07 (1.120)	0.31 (1.091)
LS mean (SEM)	1.29 (0.111)	1.59 (0.109)	0.15 (0.033)	0.37 (0.032)
95% CI	1.07, 1.51	1.37, 1.80	0.09, 0.21	0.31, 0.44
LS mean (SEM) difference	-0.30 (0.111)		-0.22 (0.034)	
95% CI	-0.51, -0.08		-0.29, -0.16	
Broad rescue therapy				
Change from Baseline at Week 24 and 36, n	181	188	1777	1777
Mean (SD)	0.98 (1.216)	1.42 (1.428)	0.08 (1.119)	0.32 (1.087)
LS mean (SEM)	1.25 (0.112)	1.58 (0.107)	0.16 (0.033)	0.38 (0.032)
95% CI	1.03, 1.47	1.37, 1.79	0.09, 0.22	0.32, 0.45

LS mean (SEM) difference	-0.34 (0.115)	-0.23 (0.035)
95% CI	-0.56, -0.11	-0.30, -0.16

ANCOVA: analysis of covariance; CI: confidence interval; darbe: darbepoetin alfa; LS: least squares; N: number of subjects; n: number of subjects within specific category; SD: standard deviation; SEM: standard error of the mean; vada: vadadustat

Source: CSR CI-0016 Tables 14.2.1.2.3.1 and 14.2.1.2.3.2, CSR AKB-6548-CI-0017 Tables 14.2.1.2.3.1 and 14.2.1.2.3.2

Table 36 Sensitivity Analysis of Mean Change from Baseline in Hemoglobin to the Average Over Weeks 24 to 36 (ANCOVA with Multiple Imputations) Considering Narrow and Broad-on-Treatment Rescue Therapy – PRO$_2$TECT Global Phase 3 Studies (Randomized Population)

	PRO$_2$TECT			
	AKB-6548-CI-0014		AKB-6548-CI-0015	
Characteristics/ Category	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Narrow rescue therapy				
Change from Baseline at Week 24 and 36, n	727	750	742	792
Mean (SD)	10.45 (0.941)	10.40 (1.004)	10.86 (0.938)	10.81 (0.965)
LS mean (SEM)	1.43 (0.046)	1.38 (0.046)	0.41 (0.038)	0.43 (0.037)
95% CI	1.34, 1.52	1.29, 1.47	0.33, 0.48	0.35, 0.50
LS mean (SEM) difference	0.04 (0.046)		-0.02 (0.042)	
95% CI	-0.05, 0.13		-0.10, 0.07	
Broad rescue therapy				
Change from Baseline at Week 24 and 36, n	722	750	735	790
Mean (SD)	10.45 (0.941)	10.40 (1.004)	10.86 (0.933)	10.82 (0.954)
LS mean (SEM)	1.42 (0.046)	1.38 (0.046)	0.43 (0.037)	0.44 (0.036)
95% CI	1.33, 1.51	1.29, 1.47	0.35, 0.50	0.37, 0.51
LS mean (SEM) difference	0.04 (0.046)		-0.02 (0.041)	
95% CI	-0.05, 0.13		-0.10, 0.06	

ANCOVA: analysis of covariance; CI: confidence interval; CKD: chronic kidney disease; darbe: darbepoetin alfa; DD: dialysis dependent; Q: quartile; SD: standard deviation; SEM: standard error of the mean; vada: vadadustat

Source: CSR AKB-6548-CI-0014 Tables 14.2.1.2.3.1 and 14.2.1.2.3.2, CSR AKB-6548-CI-0015 Tables 14.2.1.2.3.1 and 14.2.1.2.3.2

Secondary Efficacy Endpoint

As the primary endpoint met the non-inferiority margin, the key secondary endpoint was analyzed as specified in the SAP hierarchal analysis rules. The results of the analysis of the secondary efficacy endpoint, the mean change in average Hb between Baseline and the SEP (Week 40 to 52), are summarized in Table below. The non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the lower bound of the 95% CI (-0.34, -0.25, -0.06, and -0.10, respectively) for the LS mean difference in each study is above the prespecified non-inferiority margin of -0.75 g/dL.

The pooled data in INNO2VATE and PRO2TECT were consistent with the findings of their respective individual studies.

Table 37 Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 40 to 52 (ANCOVA with Multiple Imputations) - INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Studies (Randomized Population)

	INNO$_2$VATE						PRO$_2$TECT					
	Pooled		AKB-6548-CI-0016		AKB-6548-CI-0017		Pooled		AKB-6548-CI-0014		AKB-6548-CI-0015	
Visit/ Statistic	Vada N=1958	Darbe N=1965	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=1741	Darbe N=1735	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Baseline, n	1958	1965	181	188	1777	1777	1741	1735	879	872	862	863
Mean (SD)	10.17 (0.909)	10.13 (0.912)	9.37 (1.070)	9.19 (1.138)	10.25 (0.850)	10.23 (0.825)	9.76 (1.069)	9.76 (1.066)	9.11 (0.802)	9.14 (0.779)	10.42 (0.887)	10.39 (0.943)
Weeks 40 to 52 (obs), n	1584	1660	133	145	1451	1515	1287	1314	638	641	649	673
Mean (SD)	10.44 (1.041)	10.61 (0.977)	10.54 (1.111)	10.55 (1.094)	10.43 (1.034)	10.61 (0.965)	10.68 (1.011)	10.67 (1.005)	10.53 (0.998)	10.52 (0.977)	10.82 (1.004)	10.81 (1.013)
Weeks 40 to 52 (obs + imp), n	1958	1965	181	188	1777	1777	1741	1735	879	872	862	863
Mean (SD)	10.41 (1.059)	10.58 (0.999)	10.51 (1.192)	10.55 (1.137)	10.40 (1.044)	10.58 (0.984)	10.64 (1.056)	10.62 (1.045)	10.48 (1.053)	10.45 (1.014)	10.80 (1.035)	10.79 (1.050)
Change from Baseline, n	1958	1965	181	188	1777	1777	1741	1735	879	872	862	863
Mean (SD)	0.24 (1.228)	0.45 (1.216)	1.15 (1.345)	1.36 (1.568)	0.15 (1.178)	0.35 (1.131)	0.88 (1.171)	0.86 (1.191)	1.37 (1.080)	1.31 (1.111)	0.37 (1.040)	0.40 (1.087)
LS mean (SEM)	0.43 (0.043)	0.60 (0.042)	1.42 (0.132)	1.50 (0.136)	0.23 (0.035)	0.41 (0.033)	0.98 (0.033)	0.96 (0.033)	1.52 (0.052)	1.48 (0.053)	0.43 (0.044)	0.44 (0.044)
95% CI	0.34, 0.51	0.52, 0.68	1.17, 1.68	1.23, 1.76	0.16, 0.29	0.34, 0.48	0.92, 1.04	0.90, 1.03	1.42, 1.62	1.38, 1.59	0.35, 0.52	0.35, 0.52
LS mean (SEM) difference	-0.17 (0.034)		-0.07 (0.134)		-0.18 (0.035)		0.02 (0.036)		0.04 (0.052)		-0.00 (0.049)	
95% CI	-0.24, -0.11		-0.34, 0.19		-0.25, -0.12		-0.05, 0.09		-0.06, 0.14		-0.10, 0.09	

ANCOVA: analysis of covariance; CI: confidence interval; darbe: darbepoetin alfa; imp: imputed; LS: least squares; N: number of subjects; n: number of subjects within specific category; obs: observed; SD: standard deviation; SEM: standard error of the mean; vada: vadadustat.
Source: ISE Table 14.2.2.1a, CSR AKB-6548-CI-0016 Table 14.2.2.1, CSR AKB-6548-CI-0017 Table 14.2.2.1, ISE Table 14.2.2.1b, CSR AKB-6548-CI-0014 Table 14.2.2.1, CSR AKB-6548-CI-0015 Table 14.2.2.1

Sensitivity Analyses of the Key Secondary Endpoint

The consistency in the vadadustat treatment response with and without the context of ESA rescue therapy was confirmed with sensitivity analyses for the secondary endpoint using an ANCOVA with multiple imputations and censoring for rescue therapy (considering narrow and broad-on-treatment rescue therapy) for each study. In all studies, the lower bound of 95% CI was above -0.75 g/dL for both narrow and broad rescue therapy, meeting the non-inferiority criteria.

Similarly, additional sensitivity analyses of the key secondary endpoint, including evaluation in the FAS population and an MMRM analysis performed utilizing the observed data confirmed these findings.

Table 38 **Sensitivity Analysis of Mean Change from Baseline in Hemoglobin to the Average Over Weeks 40 to 52 Considering Narrow and Broad-on-Treatment Rescue Therapy (ANCOVA with Multiple Imputations) – INNO2VATE Global Phase 3 Studies (Randomized Population)**

	INNO2VATE			
	AKB-6548-CI-0016		AKB-6548-CI-0017	
Characteristics Category	Vada N= 181	Darbe N=188	Vada N=1777	Darbe N=1777
Narrow rescue therapy				
Change from Baseline at Week 40 and 52, n	181	188	1777	1777
Mean (SD)	1.02 (1.433)	1.34 (1.559)	0.10 (1.154)	0.37 (1.096)
LS mean (SEM)	1.33 (0.147)	1.51 (0.142)	0.19 (0.034)	0.44 (0.033)
95% CI	1.04, 1.62	1.23, 1.79	0.13, 0.26	0.38, 0.51
LS mean (SEM) difference	-0.18 (0.148)		-0.25 (0.036)	
95% CI	-0.47, 0.10		-0.32, -0.18	
Broad rescue therapy				
Change from Baseline at Week 40 and 52, n	181	188	1777	1777
Mean (SD)	1.03 (1.421)	1.36 (1.544)	0.11 (1.159)	0.38 (1.097)
LS mean (SEM)	1.34 (0.147)	1.54 (0.139)	0.21 (0.035)	0.46 (0.033)
95% CI	1.05, 1.63	1.27, 1.82	0.14, 0.28	0.39, 0.52
LS mean (SEM) difference	-0.20 (0.148)		-0.25 (0.036)	
95% CI	-0.49, 0.09		-0.32, -0.18	

ANCOVA: analysis of covariance; CI: confidence interval; darbe: darbepoetin alfa; LS: least squares; N: number of subjects; n: number of subjects within specific category; SD: standard deviation; SEM: standard error of the mean' vada: vadadustat

Source: CSR AKB-6548-CI-0016 Tables 14.2.2.2.3.1, 14.2.2.2.3.2, CSR AKB-6548-CI-0017 Tables 14.2.2.2.3.1, 14.2.2.2.3.2

Table 39 **Sensitivity Analysis of Mean Change from Baseline in Hemoglobin to the Average Over Weeks 40 to 52 (ANCOVA with Multiple Imputations) Considering Narrow and Broad-on-Treatment Rescue Therapy – PRO2TECT Global Phase 3 Studies (Randomized Population)**

	PRO2TECT			
	AKB-6548-CI-0014		AKB-6548-CI-0015	
Characteristics/ Category	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Narrow rescue therapy				
Change from Baseline at Week 40 and 52, n	879	872	862	863
Mean (SD)	1.36 (1.045)	1.29 (1.118)	0.38 (1.038)	0.39 (1.084)
LS mean (SEM)	1.53 (0.050)	1.47 (0.051)	0.43 (0.046)	0.43 (0.043)
95% CI	1.43, 1.62	1.37, 1.57	0.34, 0.52	0.35, 0.51
LS mean (SEM) difference	0.06 (0.051)		0.00 (0.051)	
95% CI	-0.04, 0.16		-0.10, 0.10	
Broad rescue therapy				
Change from Baseline at Week 40 and 52, n	879	872	862	863
Mean (SD)	1.36 (1.053)	1.29 (1.108)	0.38 (1.031)	0.40 (1.077)
LS mean (SEM)	1.53 (0.052)	1.47 (0.051)	0.44 (0.044)	0.44 (0.043)
95% CI	1.42, 1.63	1.37, 1.57	0.35, 0.52	0.36, 0.52
LS mean (SEM) difference	0.05 (0.055)		-0.00 (0.050)	
95% CI	-0.05, 0.16		-0.10, 0.10	

ANCOVA: analysis of covariance; CI: confidence interval; darbe: darbepoetin alfa; LS: least squares; SD: standard deviation; SEM: standard error of the mean; vada: vadadustat

Source: CSR AKB-6548-CI-0014 Tables 14.2.2.2.3.1, 14.2.2.2.3.2, CSR AKB-6548-CI-0015 Tables 14.2.2.2.3.1, 14.2.2.2.3.2

- **Ancillary analyses**

Other efficacy endpoints:

Mean change from baseline in Haemoglobin over time

The mean change from baseline Hb over time in the INNO2VATE CI-0016 and CI-0017 studies are illustrated in Figure 2 and for the PRO2TECT CI-0014 and CI-0015 studies in Figure 3.

In these studies, the initial period from Weeks 0 to 23 was for correction of Hb (CI-0014 and CI-0016) or conversion from prior ESA therapy (CI-0015 and CI-0017) while the PEP was from Weeks 24 to 36. As expected, there was a gradual increase in Hb during the correction period during Weeks 0 to 23 (CI-0014 and CI-0016). In the CI-0017 study, a slight decline in mean Hb was observed after conversion to vadadustat, likely reflecting the protocol-specified 4-week interval prior to further vadadustat dose adjustments along with a higher proportion of subjects in the higher baseline ESA dose strata (>90 U/kg/week) compared to the CI-0015 conversion study (47.5% versus 33.1%, respectively).

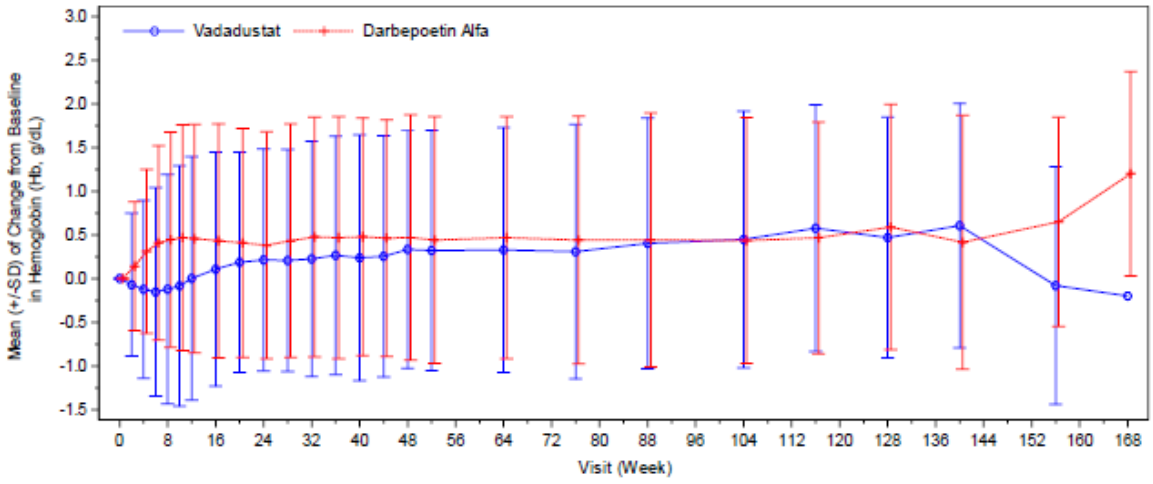
In all 4 studies, the mean Hb level gradually increased during the initial correction/conversion period and stabilized either before or by the start of the primary efficacy period.

In all 4 studies, the stable mean Hb level seen in the PEP was sustained throughout the SEP.

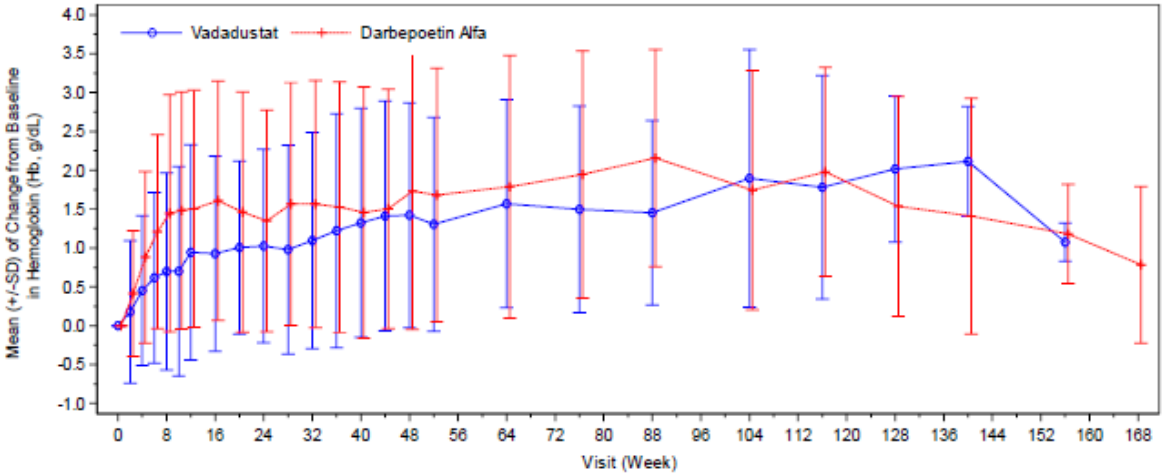
There were fewer dose adjustments and interruptions in vadadustat-treated subjects compared to darbepoetin alfa-treated subjects to maintain Hb levels within the geography-specific target range (37.2-44.1% and 30.4-36.4% of vadadustat subjects with dose change compared to 54.9-64.8% and 51.4-62.7% of darbepoetin alfa subjects with dose change during the primary efficacy period [Week 24 to 36] and key secondary efficacy period [Weeks 40 to 52], respectively).

Figure 19 Mean (SD) of Change from Baseline in Hemoglobin (g/dL) - INNO₂VATE Global Phase 3 Studies (Randomized Population)

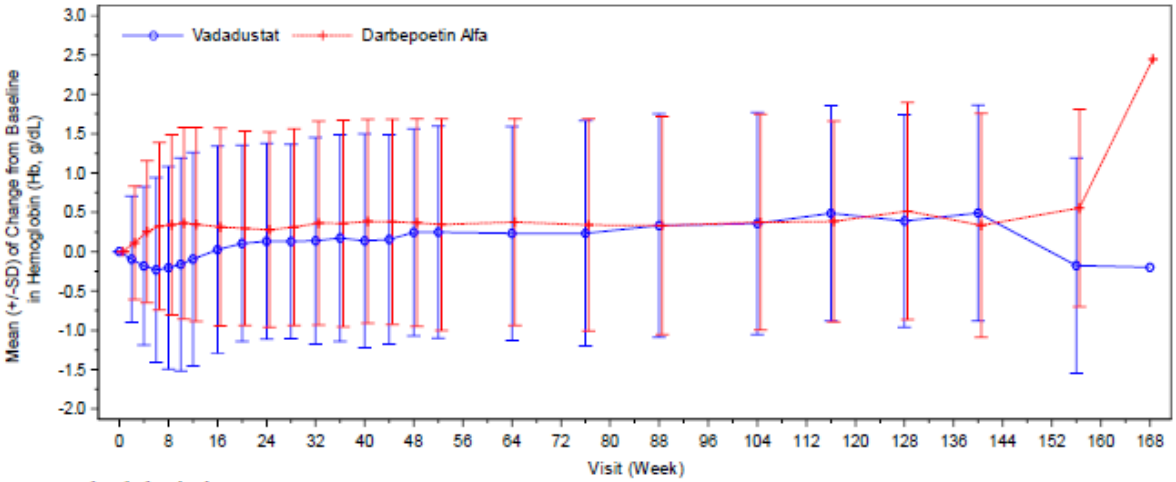
(A) INNO₂VATE Pooled Data



(B) AKB-6548-CI-0016 Data



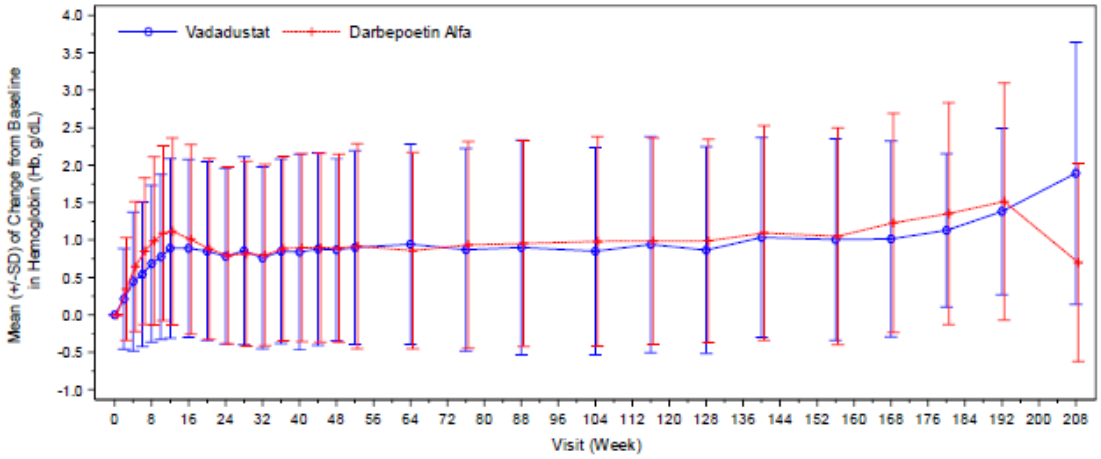
(C) AKB-6548-CI-0017 Data



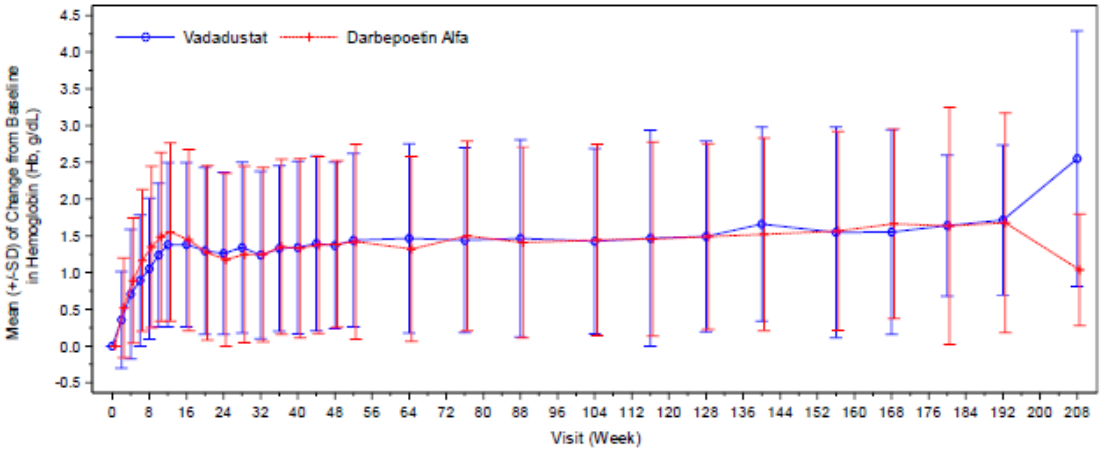
SD: standard deviation.
Note: Week 0 is Baseline.
Source: ISE Figure 14.2.1.1a, CSR AKB-6548-CI-0016 Figure 14.2.1.1, CSR AKB-6548-CI-0017 Figure 14.2.1.1

Figure 20 Mean (SD) of Change from Baseline in Hemoglobin (g/dL) - PRO2TECT Global Phase 3 Studies (Randomized Population)

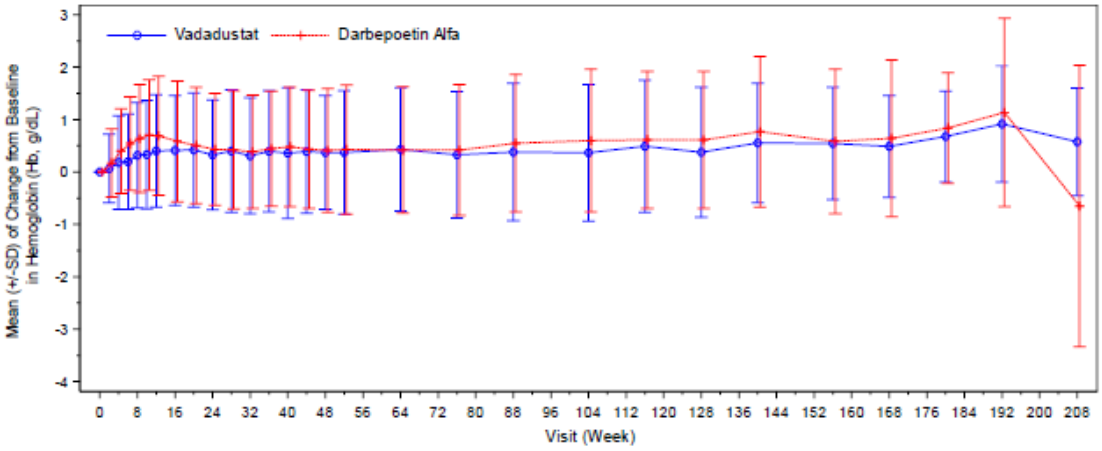
(A) PRO2TECT Pooled Data



(B) AKB-6548-CI-0014 Data

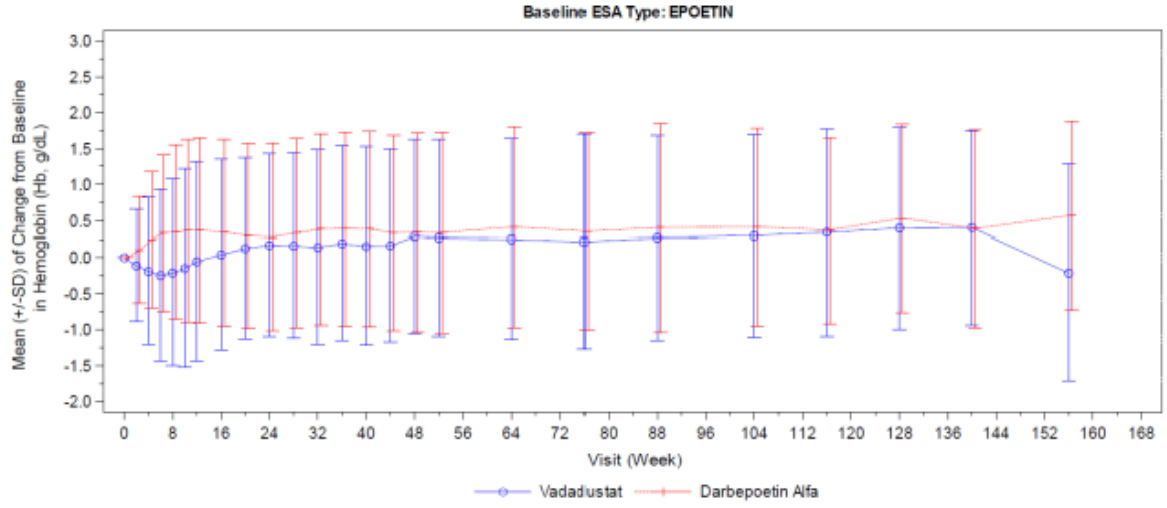


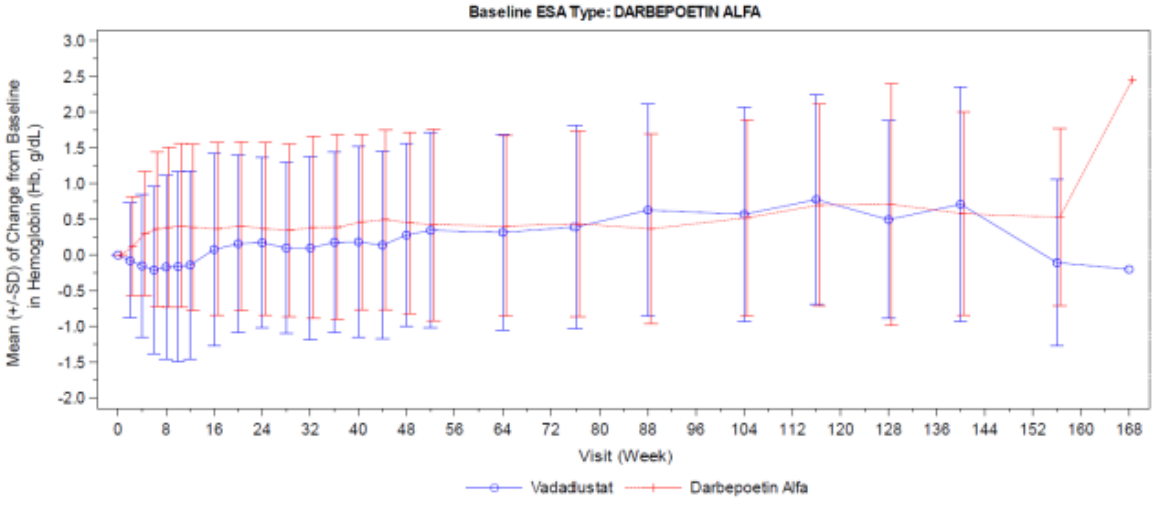
(C) AKB-6548-CI-0015 Data

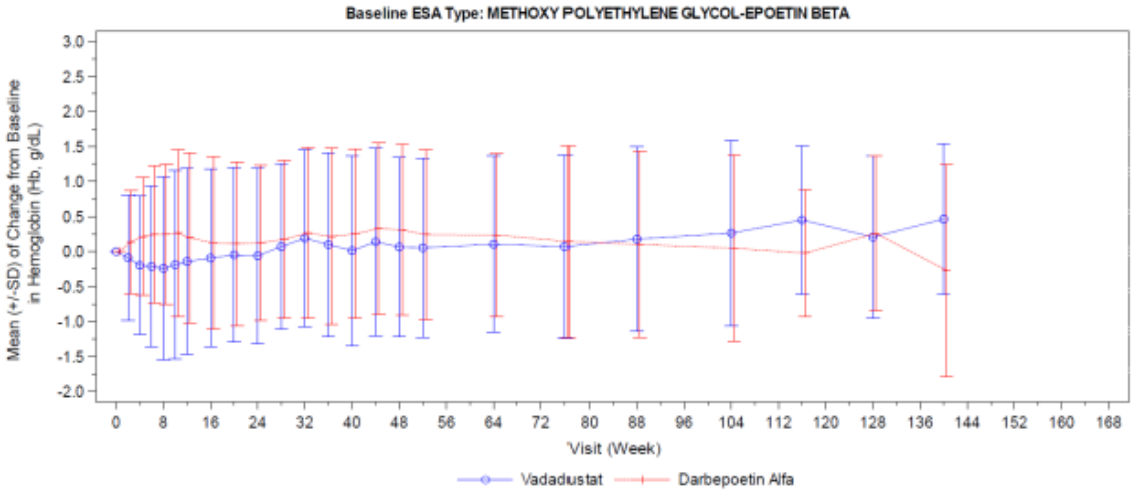


SD: standard deviation.
Note: Week 0 is Baseline.
Source: ISE Figure 14.2.1.1b, CSR AKB-6548-CI-0014 Figure 14.2.1.1, CSR AKB-6548-CI-0015 Figure 14.2.1.1

Figure 21 Mean (±SD) of Change from Baseline in Hemoglobin (Hb, g/dL) by Baseline ESA Type Randomized Population



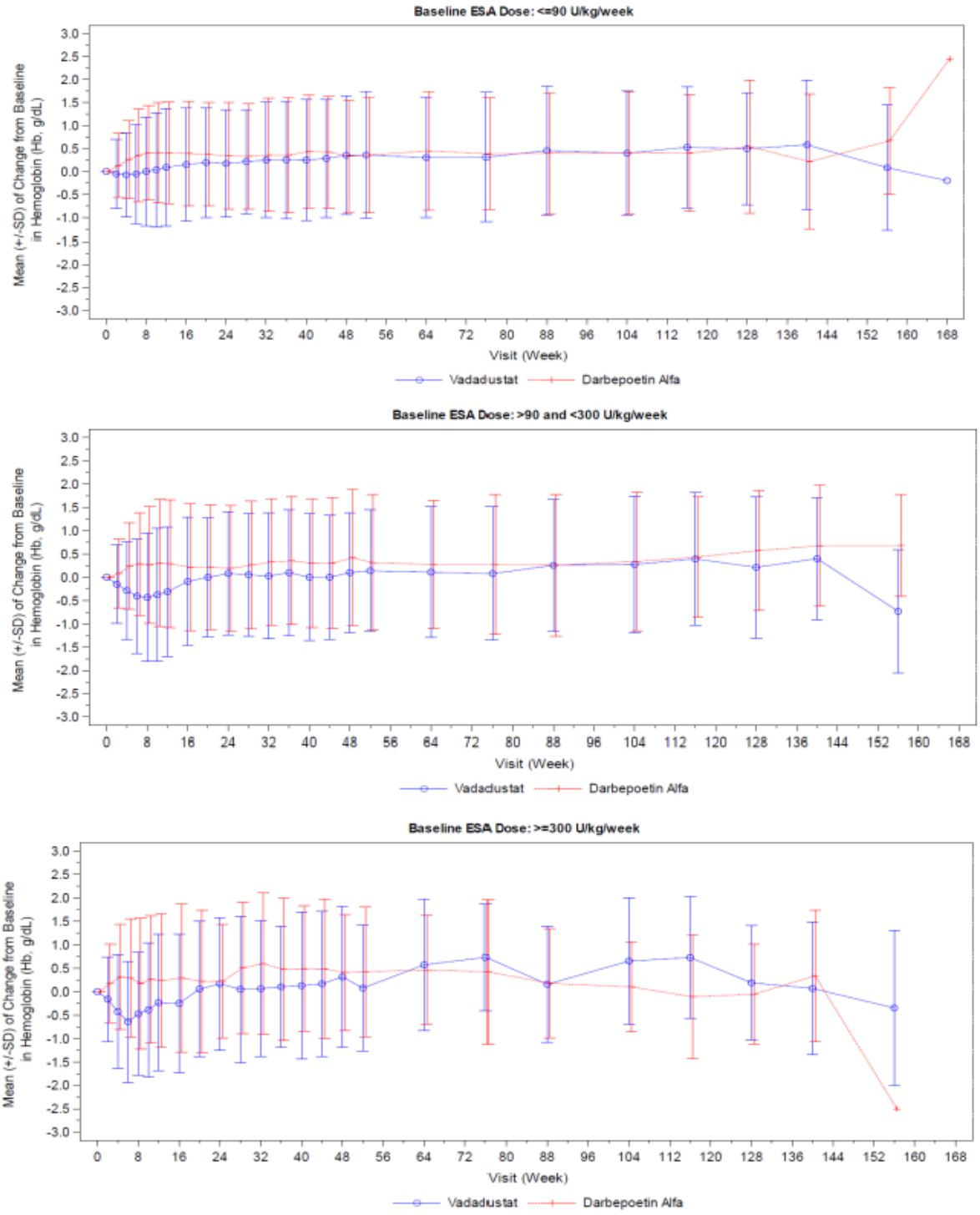




Mean change in Hb from baseline for the three different baseline ESA dose cohorts

Figure below presents the mean change in Hb from baseline for the three different baseline ESA dose cohorts: ≤ 90 U/kg/week (n = 1884; 53.8%), > 90 - < 300 U/kg/week (n = 1417; 40.5%), ≥ 300 U/kg/week (n = 199; 5.7%).

Figure 22 Mean (±SD) of Change from Baseline in Hemoglobin (Hb, g/dL) by Baseline ESA Dose Randomized Population



Please note that the initial dose of darbepoetin alfa was based on the prior dosing regimen for the subject's type of ESA dose (low or high). The mean change in Hb from baseline in response to the switch to vadadustat shows that the higher the baseline ESA dose, the deeper the initial decrease in Hb is, up to Week 16 to 20. This is because all subjects started at the same vadadustat dose of 300 mg/day. Dose adjustments for vadadustat were only allowed after Week 4 and therefore a rise in Hb occurred at a later time point.

A subgroup analyses of the primary endpoint by baseline ESA resistance (Yes or No) was conducted, where ESA resistance was defined as: "Within 8 weeks prior to or during screening, subjects have

epoetin >7700 units/dose 3 times per week or >23000 units per week; darbepoetin alfa >100 µg/week; methoxy polyethylene glycol-epoetin beta >100 µg every other week or >200 µg every month." The Applicant has also done analyses between treatment groups that are based on an ANCOVA model with the baseline Hb value, geographic region, NYHA Congestive HF class, treatment group, and baseline ESA treatment type (or baseline average weekly ESA dose) as fixed effects. The analyses only address the primary endpoint (Weeks 24 to 36). These data are presented in Tables below:

Table 40 **Primary Efficacy Analysis - Treatment Difference of Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Weeks 24 to 36 in Randomized Population**

	Least Squares Mean (SEM)	95% CI
Primary analysis*	-0.17 (0.033)	(-0.23, -0.10)
Adding "baseline average weekly ESA dose"	-0.16 (0.032)	(-0.23, -0.10)
Adding "baseline ESA treatment type"	-0.17 (0.033)	(-0.24, -0.11)

*The primary analysis model contains treatment group, baseline Hb level, and the 2 stratification factors (region and NYHA CHF class) as predictor variables.
Source: Appendix 17, Section 3.17, Table 14.2.1.1.3.1 and 14.2.1.1.3.2.

Table 41 **Subgroup Analysis of Primary Efficacy Analysis by Baseline ESA Resistance - Treatment Difference of Change from Baseline in Hemoglobin (Hb, g/dL) to the Average over Week 24 to 36 in Randomized Population**

ESA Resistance	Vadadustat (N)	Darbepoetin Alfa (N)	Least Squares Mean (SEM)	95% CI
No	870	883	-0.15 (0.048)	(-0.24, -0.06)
Yes	907	894	-0.19 (0.044)	(-0.27, -0.10)

Source: Appendix 17, Section 3.17, Table 14.2.5.1.1.

The subjects in Trial CI-0017 were defined as ESA-resistant at baseline, yes or no. In this analysis there is a minor treatment difference in the ESA-resistant subjects compared to the non-ESA-resistant subjects.

Average Haemoglobin Value in the Geography-specific Target Range

The proportion of subjects with an average Hb value within geography-specific target range was evaluated using a stratified Mantel-Haenszel method with multiple imputations (Tables below).

Table 42 **Proportion of Subjects with Average Hemoglobin Value Within Geography-Specific Target Range (Stratified Mantel-Haenszel Method with Multiple Imputations) – INNO$_2$VATE Global Phase 3 Studies (Randomized Population)**

	INNO$_2$VATE			
	AKB-6548-CI-0016		AKB-6548-CI-0017	
Efficacy Period Characteristics Category/Statistics	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777
Weeks 24 to 36				
Responders (obs), n (%)	79 (43.6)	107 (56.9)	874 (49.2)	946 (53.2)
95% CI	(36.30, 51.20)	(49.51, 64.10)	(46.83, 51.54)	(50.88, 55.58)
Responders (obs + imp), n (%)[a]	89 (49.0)	114 (60.8)	956 (53.8)	1016 (57.2)
95% CI[a]	46.96, 51.38	59.04, 62.77	53.07, 54.42	56.61, 57.96
Proportion difference (95% CI)[b]	-0.118 (-0.2246, -0.0119)		-0.033 (-0.0667, 0.0002)	
Odds ratio (vada/darbe) (95% CI)[b]	0.6 (0.40, 0.96)		0.9 (0.76, 1.00)	
Weeks 40 to 52				
Responders (obs), n (%)	72 (39.8)	77 (41.0)	787 (44.3)	905 (50.9)
95% CI	(32.59, 47.31)	(33.86, 48.35)	(41.96, 46.63)	(48.58, 53.28)
Responders (obs + imp), n (%)[a]	91 (50.1)	94 (49.9)	926 (52.1)	1029 (57.9)
95% CI[a]	46.96, 53.59	46.81, 53.72	51.15, 53.12	57.12, 58.69
Proportion difference (95% CI)[b]	0.002 (-0.1117, 0.1155)		-0.057 (-0.0909, -0.0229)	
Odds ratio (vada/darbe) (95% CI)[b]	1.0 (0.64, 1.59)		0.8 (0.68, 0.91)	

CI: confidence interval; darbe: darbepoetin alfa; imp: imputed; N: number of subjects; n: number of subjects within specific category; obs: observed; vada: vadadustat

a n (%) of responders was calculated as the average n (%) of responders based on 100 imputation datasets. 95% CI was calculated as the 2.5 percentile and 97.5 percentile of 100 values of percent of responders.

b From Mantel-Haenszel method stratified by the 3 randomization stratification factors based on multiply imputed data. Within any stratum, if there were no subjects in any treatment group or were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis.

Source: CSR AKB-6548-CI-0016 Tables 14.2.2.4, 14.2.2.5, CSR AKB-6548-CI-0017 Tables 14.2.2.4, 14.2.2.5

Table 43 roportion of Subjects with Average Hemoglobin Value within Geography-Specific Target Range (Stratified Mantel-Haenszel Method with Multiple Imputations) – PRO2TECT Global Phase 3 Studies (Randomized Population)

	PRO2TECT			
	AKB-6548-CI-0014		AKB-6548-CI-0015	
Characteristics/ Category	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Weeks 24 to 36				
Responders (obs), n (%)	443 (50.4)	438 (50.2)	518 (60.1)	524 (60.7)
95% CI	47.04, 53.75	46.86, 53.60	56.74, 63.38	57.37, 63.99
Responders (obs + imp), n (%)[a]	493 (56.1)	478 (54.9)	562 (65.2)	553 (64.1)
95% CI[a]	55.18, 57.34	53.78, 56.08	64.39, 65.89	63.50, 64.77
Proportion difference (95% CI)[b]	0.012 (-0.0372, 0.0603)		0.009 (-0.0360, 0.0533)	
Odds ratio (vada/darbe) (95% CI)[b]	1.0 (0.86, 1.28)		1.0 (0.84, 1.29)	
Weeks 40 to 52				
Responders (obs), n (%)	379 (43.1)	379 (43.5)	437 (50.7)	423 (49.0)
95% CI	(39.81, 46.47)	(40.14, 46.83)	(47.30, 54.08)	(45.63, 52.41)
Responders (obs + imp), n (%)[a]	486 (55.3)	479 (54.9)	556 (64.5)	524 (60.7)
95% CI[a]	(53.81, 56.54)	(53.21, 56.65)	(63.11, 66.47)	(59.21, 62.11)
Proportion difference (95% CI)[b]	0.004 (-0.0477, 0.0549)		0.036 (-0.0137, 0.0858)	
Odds ratio (vada/darbe) (95% CI)[b]	1.0 (0.82, 1.26)		1.2 (0.94, 1.49)	

CI: confidence interval; darbe: darbepoetin alfa; N: number of subjects; n: number of subjects within specific category; vada: vadadustat

a n (%) of responders was calculated as the average n (%) of responders based on 100 imputation datasets. 95% CI was calculated as the 2.5 percentile and 97.5 percentile of 100 values of percent of responders.

b From Mantel-Haenszel method stratified by the 3 randomization stratification factors based on multiply imputed data. Within any stratum, if there were no subjects in any treatment group or were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis.

Source: CSR AKB-6548-CI-0014 Tables 14.2.2.4, 14.2.2.5, CSR AKB-6548-CI-0015 Tables 14.2.2.4, 14.2.2.5

Change from Baseline in Iron-related Parameters

In CI-0017, CI-0014, and CI-0015, subjects in the vadadustat group had decreases from baseline in mean hepcidin compared with darbepoetin alfa over Weeks 24 to 36 and 40 to 52. In contrast in CI-0016, the LS mean change from baseline in hepcidin over Weeks 24 to 36 and 40 to 52 was not significantly different between treatment groups. Study CI-0016, however, had a smaller population than any of the other 3 global Phase 3 studies. In CI-0016, there were 181 and 188 subjects in the vadadustat and darbepoetin alfa treatment groups, respectively, compared with 1777 and 1777 subjects, respectively, in CI-0017, 879 and 872 subjects, respectively, in CI-0014, and 862 and 863 subjects, respectively, in CI-0015.

In CI-0016, there were no differences between treatment groups in terms of the change from baseline in mean ferritin over Weeks 24 to 36 and 40 to 52, whereas in CI-0017, CI-0014, and CI-0015, vadadustat-treated subjects had decreases from Baseline in mean ferritin compared with darbepoetin alfa in the PEP. This difference was maintained in the SEP for CI-0017 and CI-0014, but not for CI-0015.

In all 4 Phase 3 studies, vadadustat-treated subjects had increases from baseline in mean TIBC compared with darbepoetin alfa over Weeks 24 to 36 that were maintained at Weeks 40 to 52.

Across the Phase 3 studies, mean serum iron tended to decrease from baseline to a greater extent in the darbepoetin alfa treatment group compared to the vadadustat treatment group over Weeks 24 to 36 and 40 to 52.

For TSAT, there were greater decreases from baseline in mean TSAT in the vadadustat treatment group compared with darbepoetin alfa treatment group over Weeks 24 to 36 and Weeks 40 to 52 in the Phase 3 studies. This difference between the 2 treatment groups likely reflects the greater increase in mean TIBC observed in the vadadustat treatment group described above. After the SEP, iron-related parameters remained relatively stable through the EOS.

The sustained increase in TIBC induced by increases in HIF with vadadustat treatment in both the DD-CKD and NDD-CKD populations, suggests an increase in transferrin synthesis which, acting via the transferrin receptor, facilitates transport of iron into cells and is associated with the observed decrease in TSAT. Additionally, the decrease in serum ferritin and hepcidin with vadadustat treatment potentially increases gastrointestinal iron absorption and the release of iron from intracellular stores into the circulation. However, in vadadustat-treated patients, as there is no concomitant increase in serum iron concentrations, it suggests the vadadustat-induced increase in erythropoiesis utilizes the liberated iron, thereby maintaining iron homeostasis by balancing bioavailability and mobilization with utilization.

Iron Supplementation

A summary of the proportion of subjects with at least 1 administration of oral or IV elemental iron is presented in Table 15. There were greater percentage of vadadustat-treated subjects who received oral iron during Weeks 10 to 20 in CI-0015 and IV iron during Weeks 10 to 20 in CI-0014 and Weeks 40 to 52 in CI-0015.

Table 44 **Proportion of Subjects with at least 1 Administration of Elemental Iron by Administration Route and Baseline Iron Group (Stratified Mantel-Haenszel Method) for All Subjects - INNO2VATE and PRO2TECT Global Phase 3 Studies (Randomized Population)**

	INNO2VATE				PRO2TECT			
	AKB-6548-CI-0016		AKB-6548-CI-0017		AKB-6548-CI-0014		AKB-6548-CI-0015	
Study Period Route	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Weeks 2 to 8	179	186	1768	1769	878	870	861	862
IV Iron, n (%)	111 (62.0)	110 (59.1)	878 (49.7)	927 (52.4)	35 (4.0)	24 (2.8)	25 (2.9)	27 (3.1)
95% CI	54.47, 69.15	51.71, 66.28	47.30, 52.02	50.04, 54.75	2.79, 5.50	1.78, 4.08	1.89, 4.26	2.07, 4.52
Proportion difference (95% CI) [a]	0.029 (-0.0715, 0.1289)		-0.024 (-0.0569, 0.0079)		0.012 (-0.0046, 0.0292)		-0.002 (-0.0184, 0.0139)	
Odds ratio (vada/darbe) (95% CI)[a]	1.1 (0.74, 1.72)		0.9 (0.79, 1.03)		1.5 (0.86, 2.48)		0.9 (0.53, 1.61)	
Oral Iron, n (%)	40 (22.3)	29 (15.6)	239 (13.5)	232 (13.1)	467 (53.2)	492 (56.6)	456 (53.0)	421 (48.8)
95% CI	16.47, 29.16	10.70, 21.62	11.96, 15.20	11.58, 14.78	49.83, 56.53	53.18, 59.88	49.56, 56.34	45.45, 52.23
Proportion difference (95% CI) [a]	0.068 (-0.0127, 0.1478)		0.001 (-0.0210, 0.0232)		-0.034 (-0.0799, 0.0127)		0.042 (-0.0053, 0.0887)	
Odds ratio (vada/darbe) (95% CI)[a]	1.6 (0.92, 2.65)		1.0 (0.83, 1.23)		0.9 (0.72, 1.05)		1.2 (0.98, 1.43)	
Weeks 10 to 20	169	177	1647	1712	810	824	811	840
IV Iron, n (%)	117 (69.2)	114 (64.4)	892 (54.2)	937 (54.7)	59 (7.3)	33 (4.0)	46 (5.7)	50 (6.0)
95% CI	61.68, 76.09	56.88, 71.45	51.72, 56.59	52.34, 57.11	5.59, 9.30	2.77, 5.58	4.18, 7.49	4.45, 7.77
Proportion difference (95% CI) [a]	0.048 (-0.0508, 0.1473)		-0.003 (-0.0364, 0.0302)		0.033 (0.0104, 0.0551)		-0.003 (-0.0253, 0.0197)	
Odds ratio (vada/darbe) (95% CI)[a]	1.2 (0.79, 1.95)		1.0 (0.86, 1.13)		1.9 (1.22, 2.92)		1.0 (0.63, 1.44)	
Oral Iron, n (%)	37 (21.9)	27 (15.3)	242 (14.7)	249 (14.5)	454 (56.0)	493 (59.8)	448 (55.2)	420 (50.0)
95% CI	15.91, 28.89	10.30, 21.41	13.02, 16.50	12.91, 16.30	52.55, 59.50	56.39, 63.20	51.74, 58.70	46.56, 53.44
Proportion difference (95% CI) [a]	0.066 (-0.0154, 0.1482)		-0.001 (-0.0243, 0.0229)		-0.037 (-0.0848, 0.0104)		0.053 (0.0054, 0.1011)	
Odds ratio (vada/darbe) (95% CI)[a]	1.6 (0.90, 2.69)		1.0 (0.82, 1.21)		0.9 (0.70, 1.04)		1.2 (1.02, 1.51)	
Weeks 24 to 36	156	169	1473	1612	743	768	753	801
IV Iron, n (%)	109 (69.9)	109 (64.5)	825 (56.0)	903 (56.0)	64 (8.6)	69 (9.0)	56 (7.4)	44 (5.5)
95% CI	62.02, 76.95	56.78, 71.69	53.43, 58.56	53.55, 58.46	6.70, 10.87	7.06, 11.23	5.67, 9.55	4.02, 7.30
Proportion difference (95% CI) [a]	0.054 (-0.0482, 0.1557)		0.003 (-0.0318, 0.0376)		-0.004 (-0.0323, 0.0249)		0.020 (-0.0042, 0.0447)	
Odds ratio (vada/darbe) (95% CI)[a]	1.3 (0.80, 2.03)		1.0 (0.88, 1.17)		1.0 (0.67, 1.36)		1.4 (0.93, 2.11)	
Oral Iron, n (%)	36 (23.1)	27 (16.0)	218 (14.8)	245 (15.2)	427 (57.5)	464 (60.4)	415 (55.1)	403 (50.3)
95% CI	16.72, 30.49	10.80, 22.39	13.02, 16.72	13.48, 17.05	53.82, 61.06	56.86, 63.89	51.48, 58.71	46.79, 53.83
Proportion difference (95% CI) [a]	0.071 (-0.0151, 0.1572)		-0.005 (-0.0301, 0.0198)		-0.031 (-0.0803, 0.0184)		0.049 (-0.0005, 0.0983)	
Odds ratio (vada/darbe) (95% CI)[a]	1.6 (0.91, 2.75)		1.0 (0.78, 1.17)		0.9 (0.71, 1.08)		1.2 (1.00, 1.49)	

Weeks 40 to 52	125	140	1306	1486	629	649	620	669
IV Iron, n (%)	79 (63.2)	87 (62.1)	764 (58.5)	875 (58.9)	68 (10.8)	68 (10.5)	59 (9.5)	36 (5.4)
95% CI	54.11, 71.65	53.56, 70.20	55.77, 61.19	56.33, 61.40	8.49, 13.50	8.23, 13.09	7.32, 12.10	3.80, 7.37
Proportion difference (95% CI) [a]	0.011 (-0.1061, 0.1272)		-0.001 (-0.0371, 0.0354)		0.003 (-0.0310, 0.0365)		0.043 (0.0146, 0.0716)	
Odds ratio (vada/darbe) (95% CI)[a]	1.0 (0.64, 1.72)		1.0 (0.86, 1.16)		1.0 (0.72, 1.47)		1.9 (1.25, 2.98)	
Oral Iron, n (%)	28 (22.4)	20 (14.3)	196 (15.0)	230 (15.5)	369 (58.7)	397 (61.2)	346 (55.8)	354 (52.9)
95% CI	15.43, 30.72	8.95, 21.20	13.11, 17.06	13.67, 17.42	54.70, 62.54	57.30, 64.94	51.80, 59.76	49.05, 56.75
Proportion difference (95% CI) [a]	0.081 (-0.0121, 0.1744)		-0.005 (-0.0314, 0.0220)		-0.028 (-0.0816, 0.0257)		0.029 (-0.0250, 0.0831)	
Odds ratio (vada/darbe) (95% CI)[a]	1.7 (0.92, 3.26)		1.0 (0.78, 1.19)		0.9 (0.71, 1.11)		1.1 (0.90, 1.41)	
Weeks 64 to EOS	78	82	961	1185	479	504	470	526
IV Iron, n (%)	49 (62.8)	62 (75.6)	606 (63.1)	761 (64.2)	79 (16.5)	85 (16.9)	70 (14.9)	82 (15.6)
95% CI	51.13, 73.50	64.88, 84.42	59.92, 66.12	61.42, 66.95	13.28, 20.13	13.70, 20.43	11.80, 18.44	12.59, 18.98
Proportion difference (95% CI) [a]	-0.128 (-0.2698, 0.0140)		-0.008 (-0.0488, 0.0319)		-0.004 (-0.0510, 0.0426)		-0.006 (-0.0497, 0.0386)	
Odds ratio (vada/darbe) (95% CI)[a]	0.5 (0.28, 1.08)		1.0 (0.80, 1.15)		1.0 (0.69, 1.36)		1.0 (0.67, 1.36)	
Oral Iron, n (%)	18 (23.1)	15 (18.3)	161 (16.8)	198 (16.7)	290 (60.5)	322 (63.9)	292 (62.1)	309 (58.7)
95% CI	14.29, 34.00	10.62, 28.37	14.44, 19.27	14.63, 18.96	56.01, 64.95	59.52, 68.09	57.57, 66.53	54.40, 62.99
Proportion difference (95% CI) [a]	0.048 (-0.0776, 0.1733)		0.000 (-0.0313, 0.0322)		-0.037 (-0.0975, 0.0235)		0.037 (-0.0236, 0.0972)	
Odds ratio (vada/darbe) (95% CI)[a]	1.3 (0.62, 2.89)		1.0 (0.80, 1.26)		0.9 (0.66, 1.11)		1.2 (0.90, 1.51)	

CI: confidence interval; darbe: darbepoetin alfa; IV: intravenous; N: number of subjects; n: number of subjects within specific category; vada: vadadustat
Only subjects taking at least 1 dose are included in the analysis.
a From Mantel-Haenszel method stratified by the 3 randomization stratification factors based on multiply imputed data. Within any stratum, if there were no subjects in any treatment group or were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis.
Source: CSR AKB-6548-CI-0016 Table 14.2.4.3.2, CSR AKB-6548-CI-0017 Table 14.2.4.3.2, CSR AKB-6548-CI-0014 Table 14.2.4.3.2, CSR AKB-6548-CI-0015 Table 14.2.4.3.2

Red Blood Cell Transfusions

RBC transfusions as rescue therapy was defined as RBC transfusions grouped temporally into episodes, which may contain multiple administrations based on the gap in time between the end of 1 episode and the start of the next with the maximum gap for an episode of 7 days.

The proportion of subjects with RBC transfusions using the narrow rescue therapy criteria was generally higher in the vadadustat treatment group compared to the darbepoetin alfa treatment in each of the 4 studies at Weeks 2 to 8 (Table 17). This is possibly due to the fixed vadadustat starting dose during the first 4 weeks of the study that was inherent in the protocol design. Similar trends were seen for the proportion of subjects receiving RBC transfusions when the broad-on-treatment rescue criteria were considered (Table 18).

The episode rate per 100-subject years was slightly higher in the vadadustat treatment group in CI-0016 and CI-0017 using the narrow rescue therapy criteria and similar when using the broad-on-treatment rescue therapy criteria. The episode rate per 100-patient years was generally similar between treatment groups in CI-0014 and CI-0015 for both the narrow rescue therapy and broad-on-treatment rescue therapy criteria.

Table 45 **Proportion of Subjects with Red Blood Cell Transfusion by Study Period as Narrow Rescue Therapy (Stratified Mantel-Haenszel Method) - INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Studies (Randomized Population)**

	INNO$_2$VATE				PRO$_2$TECT			
	AKB-6548-CI-0016		AKB-6548-CI-0017		AKB-6548-CI-0014		AKB-6548-CI-0015	
Study Period	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Week 2 to 8, n	179	186	1768	1769	878	870	861	862
Subjects with any RBC Transfusion, n (%)	8 (4.5)	1 (0.5)	29 (1.6)	14 (0.8)	25 (2.8)	18 (2.1)	13 (1.5)	5 (0.6)
95% CI	1.95, 8.62	0.01, 2.96	1.10, 2.35	0.43, 1.32	1.85, 4.17	1.23, 3.25	0.81, 2.57	0.19, 1.35
Proportion difference (vada - darbe) (95% CI)[a]	0.039 (0.0073, 0.0714)		0.008 (0.0013, 0.0157)		0.008 (-0.0067, 0.0223)		0.009 (-0.0003, 0.0189)	
Odds ratio (vada/darbe) (95% CI)[a]	8.7 (1.07, 69.92)		2.1 (1.10, 3.97)		1.4 (0.75, 2.56)		2.6 (0.93, 7.40)	
Week 10 to 20, n	169	177	1647	1712	810	824	811	840
Subjects with any RBC Transfusion, n (%)	3 (1.8)	2 (1.1)	40 (2.4)	31 (1.8)	13 (1.6)	17 (2.1)	10 (1.2)	12 (1.4)
95% CI	0.37, 5.10	0.14, 4.02	1.74, 3.29	1.23, 2.56	0.86, 2.73	1.21, 3.28	0.59, 2.26	0.74, 2.48
Proportion difference (vada - darbe) (95% CI)[a]	0.006 (-0.0188, 0.0317)		0.006 (-0.0036, 0.0159)		-0.005 (-0.0176, 0.0084)		-0.002 (-0.0130, 0.0091)	
Odds ratio (vada/darbe) (95% CI)[a]	1.6 (0.26, 9.58)		1.3 (0.84, 2.17)		0.8 (0.37, 1.60)		0.9 (0.37, 2.00)	
Week 24 to 36, n	156	169	1473	1612	743	768	753	801
Subjects with any RBC Transfusion, n (%)	2 (1.3)	3 (1.8)	29 (2.0)	21 (1.3)	20 (2.7)	17 (2.2)	12 (1.6)	10 (1.2)
95% CI	0.16, 4.55	0.37, 5.10	1.32, 2.82	0.81, 1.98	1.65, 4.13	1.29, 3.52	0.83, 2.77	0.60, 2.28
Proportion difference (vada - darbe) (95% CI)[a]	-0.005 (-0.0315, 0.0217)		0.007 (-0.0023, 0.0157)		0.005 (-0.0108, 0.0204)		0.003 (-0.0083, 0.0152)	
Odds ratio (vada/darbe) (95% CI)[a]	0.7 (0.12, 4.36)		1.5 (0.86, 2.68)		1.2 (0.64, 2.35)		1.3 (0.55, 2.98)	
Week 40 to 52, n	125	140	1306	1486	629	649	620	669
Subjects with any RBC Transfusion, n (%)	3 (2.4)	1 (0.7)	26 (2.0)	28 (1.9)	15 (2.4)	14 (2.2)	15 (2.4)	13 (1.9)
95% CI	0.50, 6.85	0.02, 3.92	1.30, 2.90	1.26, 2.71	1.34, 3.90	1.18, 3.59	1.36, 3.96	1.04, 3.30
Proportion difference (vada - darbe) (95% CI)[a]	0.017 (-0.0134, 0.0471)		0.001 (-0.0092, 0.0113)		0.002 (-0.0141, 0.0186)		0.005 (-0.0112, 0.0208)	
Odds ratio (vada/darbe) (95% CI)[a]	3.4 (0.35, 33.29)		1.1 (0.62, 1.81)		1.1 (0.53, 2.31)		1.3 (0.59, 2.65)	
Week 64 to EOS, n	78	82	961	1185	479	504	470	526
Subjects with any RBC Transfusion, n (%)	0	3 (3.7)	36 (3.7)	37 (3.1)	19 (4.0)	26 (5.2)	16 (3.4)	23 (4.4)
95% CI	0.00, 4.62	0.76, 10.32	2.64, 5.15	2.21, 4.28	2.40, 6.13	3.40, 7.47	1.96, 5.47	2.79, 6.49
Proportion difference (vada - darbe) (95% CI)[a]	-0.037 (-0.0772, 0.0040)		0.006 (-0.0093, 0.0218)		-0.012 (-0.0380, 0.0141)		-0.010 (-0.0336, 0.0143)	
Odds ratio (vada/darbe) (95% CI)[a]	0.0 (--, --)		1.2 (0.76, 1.93)		0.8 (0.41, 1.39)		0.8 (0.40, 1.48)	

CI: confidence interval; darbe: darbepoetin alfa; EOS: end of study; N: number of subjects; n: number of subjects within specific category; RBC: red blood cell; vada: vadadustat; --: not applicable

Note: Only subjects taking at least 1 dose were included in the analysis.

a. From Mantel-Haenszel method stratified by the 3 randomization stratification factors. Within any stratum, if there were no subjects in any treatment group or there were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis

Source: CSR AKB-6548-CI-0016 Table 14.2.4.5.1.1, CSR AKB-6548-CI-0017 Table 14.2.4.5.1.1, CSR AKB-6548-CI-0014 Table 14.2.4.5.1.1, CSR AKB-6548-CI-0015 Table 14.2.4.5.1.1

Table 46 **Proportion of Subjects with Red Blood Cell Transfusion by Study Period as Broad-on-Treatment Rescue Therapy (Stratified Mantel-Haenszel Method) - INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Studies (Randomized Population)**

	INNO$_2$VATE				PRO$_2$TECT			
	AKB-6548-CI-0016		AKB-6548-CI-0017		AKB-6548-CI-0014		AKB-6548-CI-0015	
Study Period	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Week 2 to 8, n	179	186	1768	1769	878	870	861	862
Subjects with any RBC Transfusion, n (%)	8 (4.5)	3 (1.6)	51 (2.9)	29 (1.6)	35 (4.0)	31 (3.6)	17 (2.0)	9 (1.0)
95% CI	1.95, 8.62	0.33, 4.64	2.16, 3.78	1.10, 2.35	2.79, 5.50	2.43, 5.02	1.15, 3.14	0.48, 1.97
Proportion difference (vada - darbe) (95% CI)[a]	0.029 (-0.0067, 0.0638)		0.012 (0.0027, 0.0222)		0.004 (-0.0136, 0.0221)		0.009 (-0.0022, 0.0208)	
Odds ratio (vada/darbe) (95% CI)[a]	2.9 (0.74, 10.93)		1.8 (1.12, 2.83)		1.1 (0.69, 1.84)		1.9 (0.85, 4.31)	
Week 10 to 20, n	169	177	1647	1712	810	824	811	840
Subjects with any RBC Transfusion, n (%)	4 (2.4)	5 (2.8)	65 (3.9)	61 (3.6)	18 (2.2)	26 (3.2)	17 (2.1)	18 (2.1)
95% CI	0.65, 5.95	0.92, 6.47	3.06, 5.00	2.74, 4.55	1.32, 3.49	2.07, 4.59	1.23, 3.34	1.27, 3.37
Proportion difference (vada - darbe) (95% CI)[a]	-0.005 (-0.0381, 0.0289)		0.004 (-0.0090, 0.0167)		-0.009 (-0.0250, 0.0063)		-0.000 (-0.0144, 0.0134)	
Odds ratio (vada/darbe) (95% CI)[a]	0.8 (0.22, 3.16)		1.1 (0.78, 1.59)		0.7 (0.38, 1.28)		1.0 (0.50, 1.91)	
Week 24 to 36, n	156	169	1473	1612	743	768	753	801
Subjects with any RBC Transfusion, n (%)	3 (1.9)	6 (3.6)	59 (4.0)	53 (3.3)	27 (3.6)	28 (3.6)	21 (2.8)	20 (2.5)
95% CI	0.40, 5.52	1.31, 7.57	3.06, 5.14	2.47, 4.28	2.41, 5.24	2.44, 5.23	1.73, 4.23	1.53, 3.83
Proportion difference (vada - darbe) (95% CI)[a]	-0.016 (-0.0515, 0.0190)		0.007 (-0.0061, 0.0204)		-0.000 (-0.0190, 0.0188)		0.003 (-0.0131, 0.0189)	
Odds ratio (vada/darbe) (95% CI)[a]	0.5 (0.13, 2.17)		1.2 (0.84, 1.79)		1.0 (0.58, 1.71)		1.1 (0.60, 2.08)	
Week 40 to 52, n	125	140	1306	1486	629	649	620	669
Subjects with any RBC Transfusion, n (%)	7 (5.6)	6 (4.3)	54 (4.1)	70 (4.7)	25 (4.0)	23 (3.5)	26 (4.2)	23 (3.4)
95% CI	2.28, 11.20	1.59, 9.09	3.12, 5.36	3.69, 5.91	2.59, 5.81	2.26, 5.27	2.76, 6.08	2.19, 5.11
Proportion difference (vada - darbe) (95% CI)[a]	0.013 (-0.0393, 0.0656)		-0.006 (-0.0210, 0.0095)		0.004 (-0.0166, 0.0252)		0.008 (-0.0134, 0.0285)	
Odds ratio (vada/darbe) (95% CI)[a]	1.3 (0.43, 4.05)		0.9 (0.61, 1.25)		1.1 (0.63, 2.01)		1.2 (0.69, 2.18)	
Week 64 to EOS, n	78	82	961	1185	479	504	470	526
Subjects with any RBC Transfusion, n (%)	1 (1.3)	3 (3.7)	77 (8.0)	94 (7.9)	34 (7.1)	42 (8.3)	27 (5.7)	41 (7.8)
95% CI	0.03, 6.94	0.76, 10.32	6.37, 9.91	6.46, 9.62	4.97, 9.78	6.07, 11.10	3.82, 8.25	5.65, 10.43
Proportion difference (vada - darbe) (95% CI)[a]	-0.024 (-0.0715, 0.0239)		0.001 (-0.0223, 0.0239)		-0.012 (-0.0457, 0.0210)		-0.019 (-0.0496, 0.0117)	
Odds ratio (vada/darbe) (95% CI)[a]	0.3 (0.03, 3.36)		1.0 (0.74, 1.38)		0.8 (0.53, 1.35)		0.7 (0.44, 1.22)	

CI: confidence interval; darbe: darbepoetin alfa; EOS: end of study; N: number of subjects; n: number of subjects within specific category; RBC: red blood cell; vada: vadadustat;
Note: Only subjects taking at least 1 dose were included in the analysis.
a. From Mantel-Haenszel method stratified by the 3 randomization stratification factors. Within any stratum, if there were no subjects in any treatment group or there were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis
Source: CSR AKB-6548-CI-0016 Table 14.2.4.5.1.2, CSR AKB-6548-CI-0017 Table 14.2.4.5.1.2, CSR AKB-6548-CI-0014 Table 14.2.4.5.1.2, CSR AKB-6548-CI-0015 Table 14.2.4.5.1.2

Erythropoiesis-Stimulating Agent Rescue Therapy

For summaries of potential rescue therapies, exposure to the therapy was grouped temporally into episodes, which could contain multiple administrations based on the gap in time between the end of 1 episode and the start of the next. For ESA medication, the longest such gap within a single episode was 30 days.

In all pivotal trials, the proportion of subjects who received ESA rescue using the narrow rescue criteria was higher in the vadadustat treatment group compared with the darbepoetin alfa treatment groups at most time points during the study (Table below). In the vadadustat treatment group the proportion of subjects receiving ESA rescue was higher with vadadustat in the INNO2VATE studies CI-0016 and CI-0017 than in the PRO2TECT CI-0014 and CI-0015 studies during all treatment periods. Similar results were also seen when broad-on-treatment rescue therapy criteria were considered.

Using the narrow rescue therapy criteria, there was a higher rate of ESA rescue episodes per 100 patient years for the vadadustat treatment group compared with the darbepoetin alfa groups in all the

studies. Similar results were also seen when broad-on-treatment rescue therapy criteria were considered.

Table 47 **Proportion of Subjects With any Erythropoiesis-Stimulating Agent Rescue Medication by Study Period as Narrow Rescue Therapy (Stratified Mantel-Haenszel Method) - INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Studies (Randomized Population)**

	INNO$_2$VATE				PRO$_2$TECT			
	AKB-6548-CI-0016		AKB-6548-CI-0017		AKB-6548-CI-0014		AKB-6548-CI-0015	
Study Period	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
Week 2 to 8, n	179	186	1768	1769	878	870	861	862
n (%) of subjects with any ESA rescue medication	10 (5.6)	1 (0.5)	169 (9.6)	22 (1.2)	7 (0.8)	4 (0.5)	15 (1.7)	7 (0.8)
95% CI	2.71, 10.03	0.01, 2.96	8.23, 11.03	0.78, 1.88	0.32, 1.64	0.13, 1.17	0.98, 2.86	0.33, 1.67
Proportion difference (vada - darbe) (95% CI)[a]	0.050 (0.0152, 0.0857)		0.083 (0.0685, 0.0978)		0.003 (-0.0040, 0.0108)		0.009 (-0.0013, 0.0199)	
Odds ratio (vada/darbe) (95% CI)[a]	10.9 (1.39, 86.42)		8.4 (5.35, 13.15)		1.7 (0.51, 5.97)		2.2 (0.88, 5.34)	
Week 10 to 20, n	169	177	1647	1712	810	824	811	840
n (%) of subjects with any ESA rescue medication	25 (14.8)	3 (1.7)	297 (18.0)	58 (3.4)	21 (2.6)	9 (1.1)	35 (4.3)	4 (0.5)
95% CI	9.81, 21.06	0.35, 4.87	16.20, 19.98	2.58, 4.36	1.61, 3.94	0.50, 2.06	3.02, 5.95	0.13, 1.21
Proportion difference (vada - darbe) (95% CI)[a]	0.131 (0.0742, 0.1878)		0.146 (0.1260, 0.1669)		0.015 (0.0020, 0.0280)		0.038 (0.0237, 0.0531)	
Odds ratio (vada/darbe) (95% CI)[a]	10.1 (2.98, 34.03)		6.3 (4.69, 8.39)		2.4 (1.10, 5.29)		9.4 (3.33, 26.64)	
Week 24 to 36, n	156	169	1473	1612	743	768	753	801
n (%) of subjects with any ESA rescue medication	23 (14.7)	5 (3.0)	253 (17.2)	73 (4.5)	34 (4.6)	18 (2.3)	38 (5.0)	8 (1.0)
95% CI	9.58, 21.30	0.97, 6.77	15.28, 19.20	3.57, 5.66	3.19, 6.34	1.39, 3.68	3.60, 6.86	0.43, 1.96
Proportion difference (vada - darbe) (95% CI)[a]	0.118 (0.0566, 0.1791)		0.127 (0.1056, 0.1488)		0.022 (0.0039, 0.0408)		0.040 (0.0234, 0.0576)	
Odds ratio (vada/darbe) (95% CI)[a]	5.7 (2.10, 15.32)		4.5 (3.46, 5.98)		2.0 (1.12, 3.57)		5.3 (2.44, 11.37)	
Week 40 to 52, n	125	140	1306	1486	629	649	620	669
n (%) of subjects with any ESA rescue medication	19 (15.2)	4 (2.9)	273 (20.9)	95 (6.4)	35 (5.6)	18 (2.8)	32 (5.2)	10 (1.5)
95% CI	9.41, 22.71	0.78, 7.15	18.73, 23.21	5.20, 7.76	3.91, 7.65	1.65, 4.35	3.56, 7.21	0.72, 2.73
Proportion difference (vada - darbe) (95% CI)[a]	0.123 (0.0547, 0.1922)		0.147 (0.1219, 0.1721)		0.028 (0.0060, 0.0498)		0.037 (0.0170, 0.0564)	
Odds ratio (vada/darbe) (95% CI)[a]	6.1 (2.01, 18.45)		4.1 (3.17, 5.24)		2.1 (1.16, 3.69)		3.6 (1.75, 7.36)	
Week 64 to EOS, n	78	82	961	1185	479	504	470	526
n (%) of subjects with any ESA rescue medication	16 (20.5)	4 (4.9)	256 (26.6)	133 (11.2)	42 (8.8)	28 (5.6)	38 (8.1)	26 (4.9)
95% CI	12.20, 31.16	1.34, 12.02	23.87, 29.55	9.48, 13.16	6.39, 11.67	3.72, 7.93	5.78, 10.93	3.25, 7.16
Proportion difference (vada - darbe) (95% CI)[a]	0.156 (0.0553, 0.2574)		0.154 (0.1209, 0.1874)		0.032 (-0.0001, 0.0644)		0.031 (0.0006, 0.0623)	
Odds ratio (vada/darbe) (95% CI)[a]	5.0 (1.60, 15.82)		2.9 (2.28, 3.62)		1.6 (1.00, 2.68)		1.7 (1.01, 2.83)	

CI: confidence interval; darbe: darbepoetin alfa; EOS: end of study; ESA: erythropoiesis-stimulating agent; N: number of subjects; n: number of subjects within specific category; vada: vadadustat

Note: Only subjects taking at least 1 dose were included in the analysis.

a. From Mantel-Haenszel method stratified by the 3 randomization stratification factors. Within any stratum, if there were no subjects in any treatment group or there were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis

Source: CSR AKB-6548-CI-0016 Table 14.2.4.6.1.1, CSR AKB-6548-CI-0017 Table 14.2.4.6.1.1, CSR AKB-6548-CI-0014 Table 14.2.4.6.1.1, CSR AKB-6548-CI-0015 Table 14.2.4.6.1.1

The definitions of rescue therapy in the statistical analysis plans for the global Phase 3 studies represent a limitation that did impact the ability to demonstrate the full extent of efficacy for vadadustat. The administration of rescue for vadadustat-treated subjects was clearly defined. Conversely, dosing changes in darbepoetin alfa was not consistently defined as a rescue therapy in the protocols, but rather was classified as a protocol deviation, which led to underreporting of ESA rescue in this treatment group. In subjects randomized to darbepoetin alfa, the investigator was responsible for the proper reporting of reasons for changes in ESA dose. In practice, in the global clinical studies, dose increases of ≥50% and ≥100% were observed frequently in the darbepoetin alfa group. As the prescribing information recommends dose adjustments of ≤25%, the incremental changes in dose that are 2-fold to 4-fold higher than recommended fit the profile of rescue therapy in the darbepoetin alfa group. A post-hoc analysis was performed to explore this definition of rescue therapy, which demonstrated that a greater proportion of subjects taking darbepoetin alfa required rescue therapy (approximately 25% using the ≥50% criterion and approximately 10% using the ≥100% criterion) compared with subjects who received vadadustat (approximately 5% to 8%).

Progression of Chronic Kidney Disease in Pivotal Global PRO2TECT Studies

The time to progression of CKD was similar in the vadadustat and darbepoetin alfa treatment groups in CI-0014 where the hazard ratio was 1.1 (95% CI: 0.92, 1.22) and CI-0015 where the hazard ratio was 0.9 (95% CI: 0.80, 1.08) as shown in Figure below.

In the PRO2TECT studies, which enrolled subjects with NDD-CKD, progression of CKD was defined as a composite of:

• Transition to chronic dialysis, or

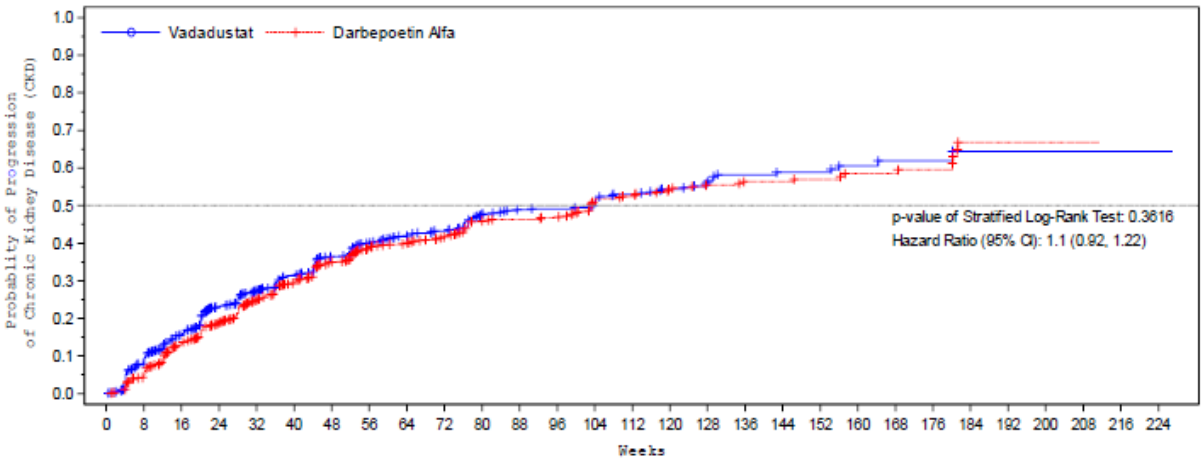
• Receipt of a kidney transplant, or

• eGFR <15 mL/min per 1.73 m² confirmed by another measurement at least 28 days later, or

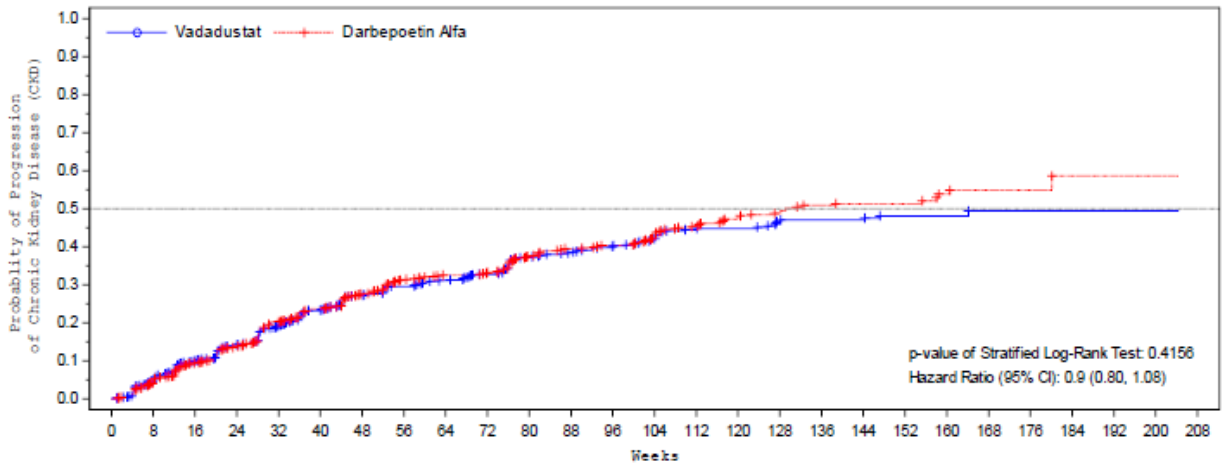
• Reduction in eGFR of 40% or more from baseline (confirmed by second measurement at least 28 days later).

Figure 23 **Kaplan-Meier Curve of Time to Progression of Chronic Kidney Disease (Stratified Log Rank Test) - PRO2TECT Global Phase 3 Studies (A) CI-0014 and (B) CI-0015 (Randomized Population)**

(A) AKB-6548-CI-0014 Data



(B) AKB-6548-CI-0015 Data



CI: confidence interval
Source: CSR AKB-6548-CI-0014 Table 14.2.3.8, Figure 14.2.3.2, CSR AKB-6548-CI-0015 Table 14.2.3.6, Figure 14.2.3.1

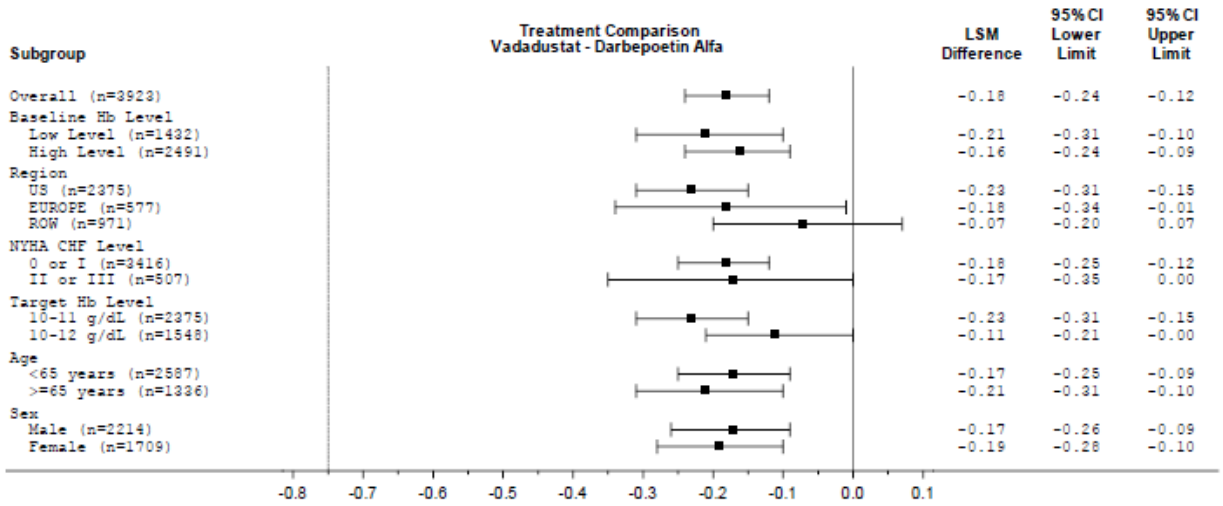
Subgroups:

Change from Baseline in Haemoglobin to the Average over Weeks 24 to 36 and Weeks 40 to 52

The Forest Plot of subgroup analyses of the change from baseline in Hb level the to the PEP (Weeks 24 to 36) for the INNO2VATE CI-0016 and CI-0017 studies and the PRO2TECT CI-0014 and CI-0015 studies are provided in Figures below, respectively. Similar trends were seen for the SEP (Weeks 40 to 52).

Figure 24 **Forest Plot of Subgroup Analysis of Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 24 to 36 (ANCOVA with Multiple Imputations) - Pooled DD-CKD Population for the INNO2VATE Global Phase 3 Studies (A), CI-0016 (B), and CI-0017 (C) (Randomized Population)**

(A) INNO$_2$VATE Pooled Data



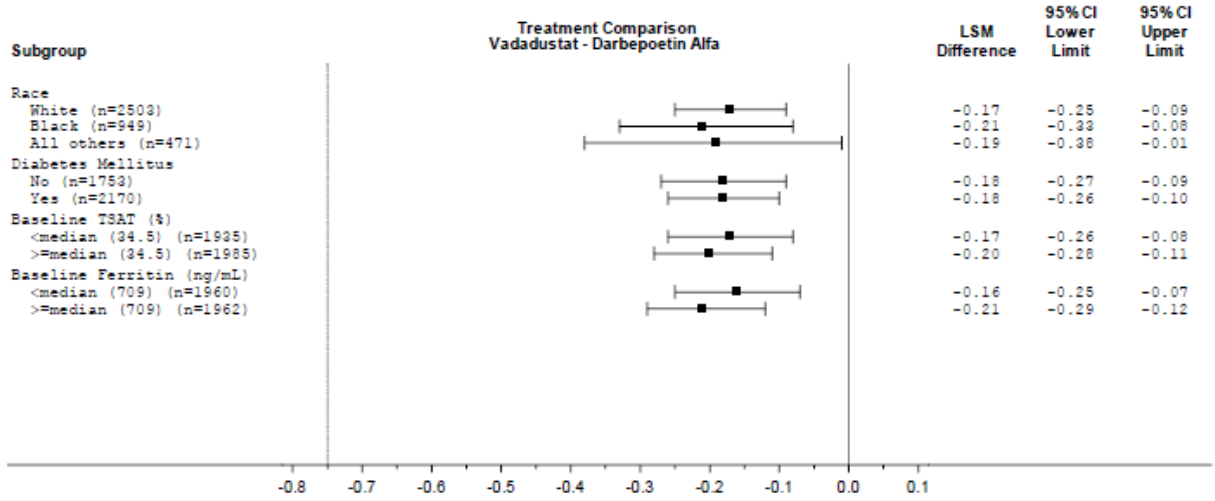
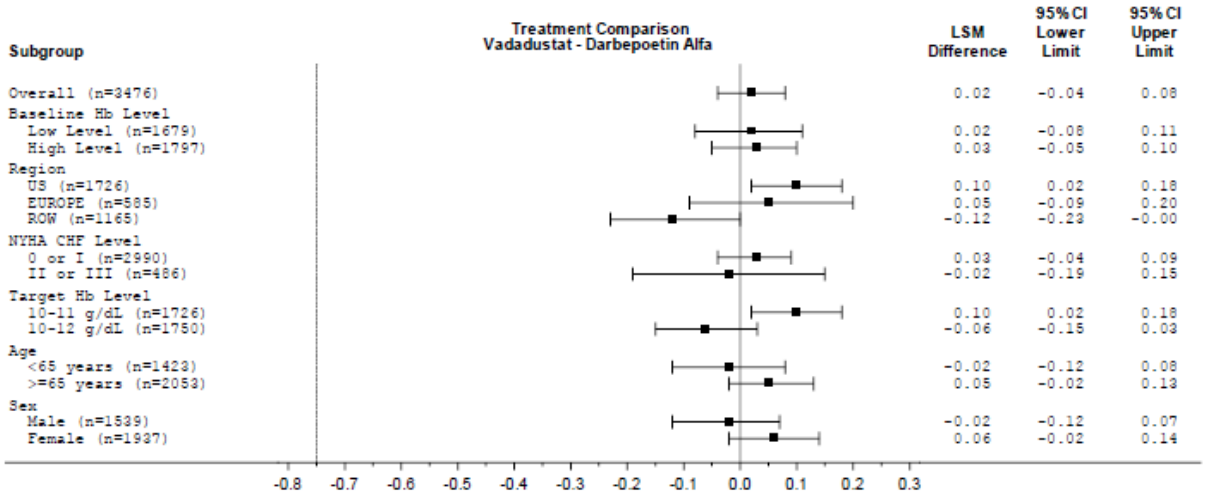
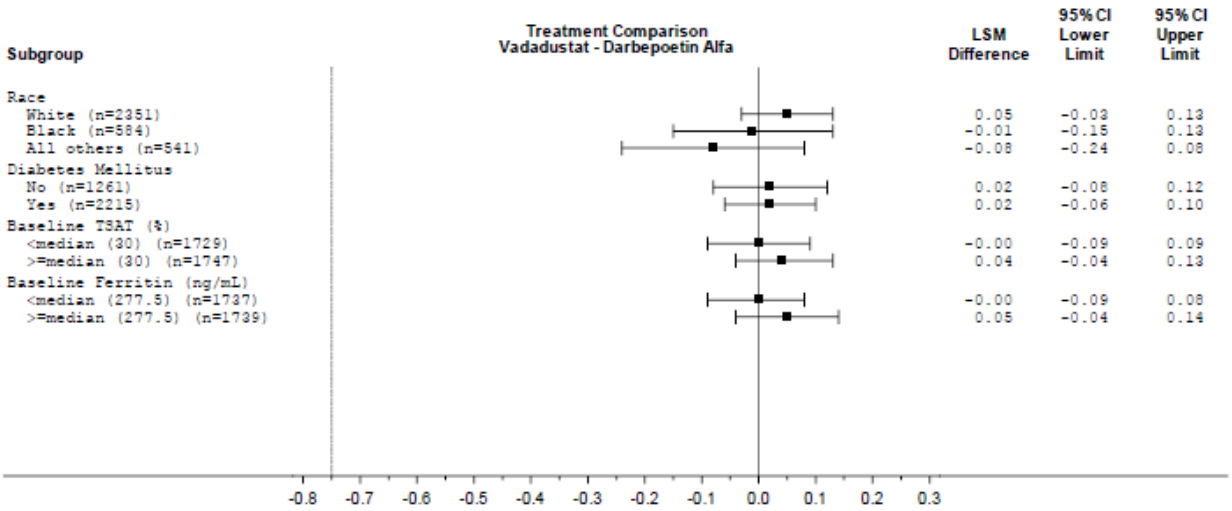


Figure 25 **Forest Plot of Subgroup Analysis of Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 24 to 36 (ANCOVA with Multiple Imputations) - Pooled NDD-CKD Population for the PRO2TECT Global Phase 3 Studies (A), CI-0014 (B), and CI-0015 (C) (Randomized Population)**

(A) PRO2TECT Pooled Data





In the pre-specified subgroup analyses for primary and secondary efficacy endpoints by eGFR < 15mL/min/1.73 m^2 and ≥ 15 mL/min/1.73 m^2 for CI-0014 and CI-0015, the results are consistent

and met NI margin for both endpoints. (CSR in-text Figure 7 and 8 for CI-0014; CSR in-text Figure 6 and 7 for CI-0015).

Figure 26 **Forest Plot of Subgroup Analysis of Change From Baseline in Hemoglobin (g/dL) to the Average over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population)**

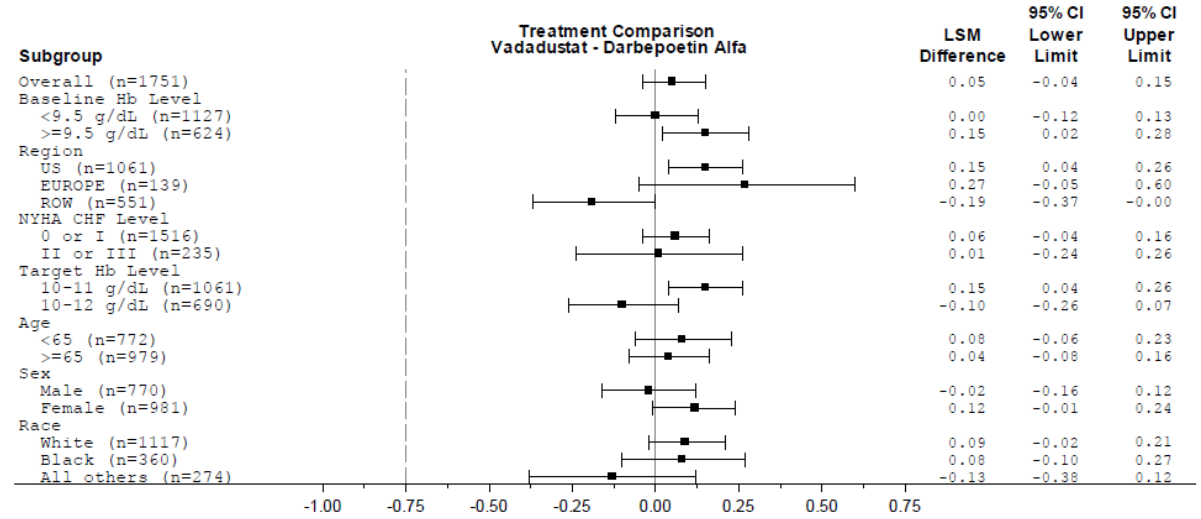


Figure 27 **Forest Plot of Subgroup Analysis of Change From Baseline in Hemoglobin (g/dL) to the Average over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population), cont.**

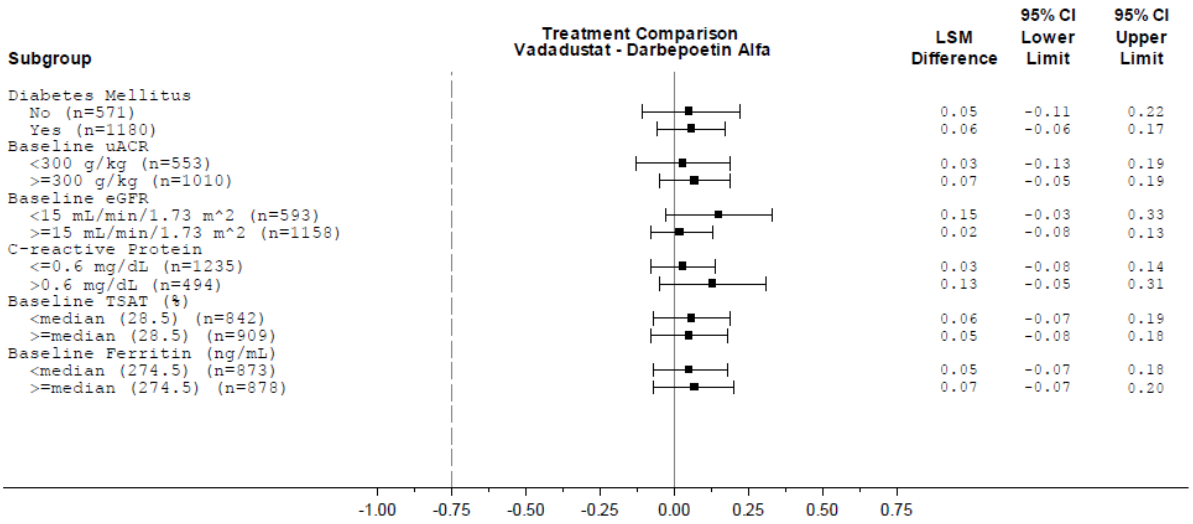


Figure 28 **Forest Plot of Subgroup Analysis of Change From Baseline in Hemoglobin (g/dL) to the Average over Weeks 40 to 52 (ANCOVA with Multiple Imputations) (Randomized Population)**

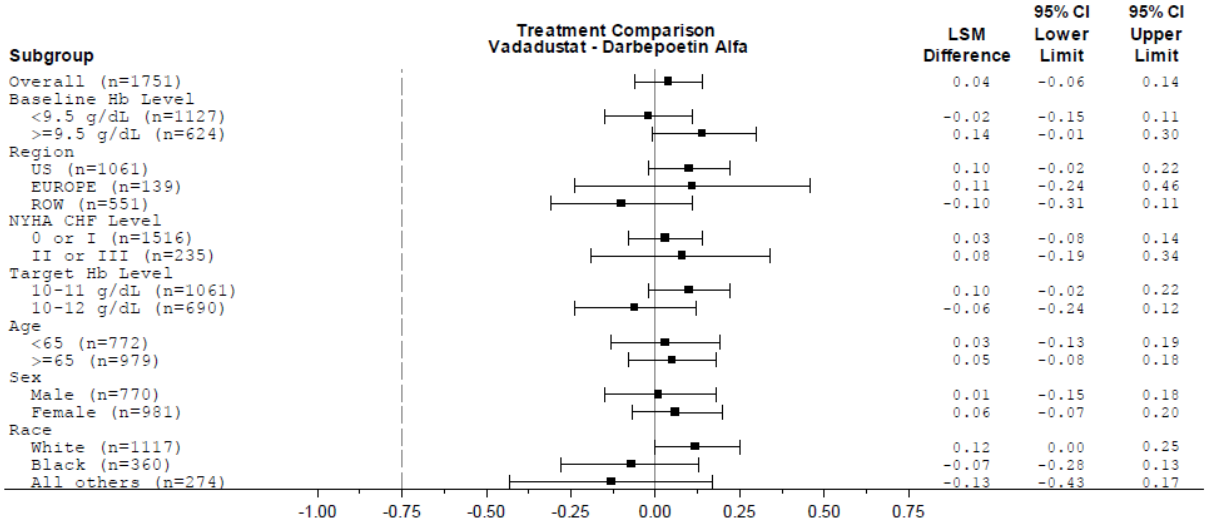


Figure 29 **Forest Plot of Subgroup Analysis of Change From Baseline in Hemoglobin (g/dL) to the Average over Weeks 40 to 52 (ANCOVA with Multiple Imputations) (Randomized Population), cont.**

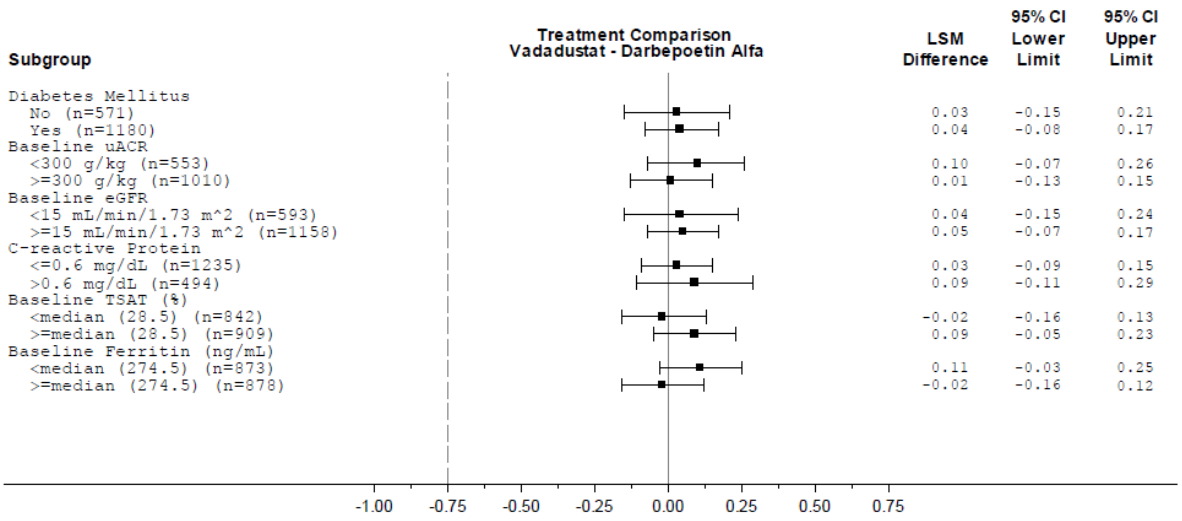


Figure 30 Forest Plot of Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population)

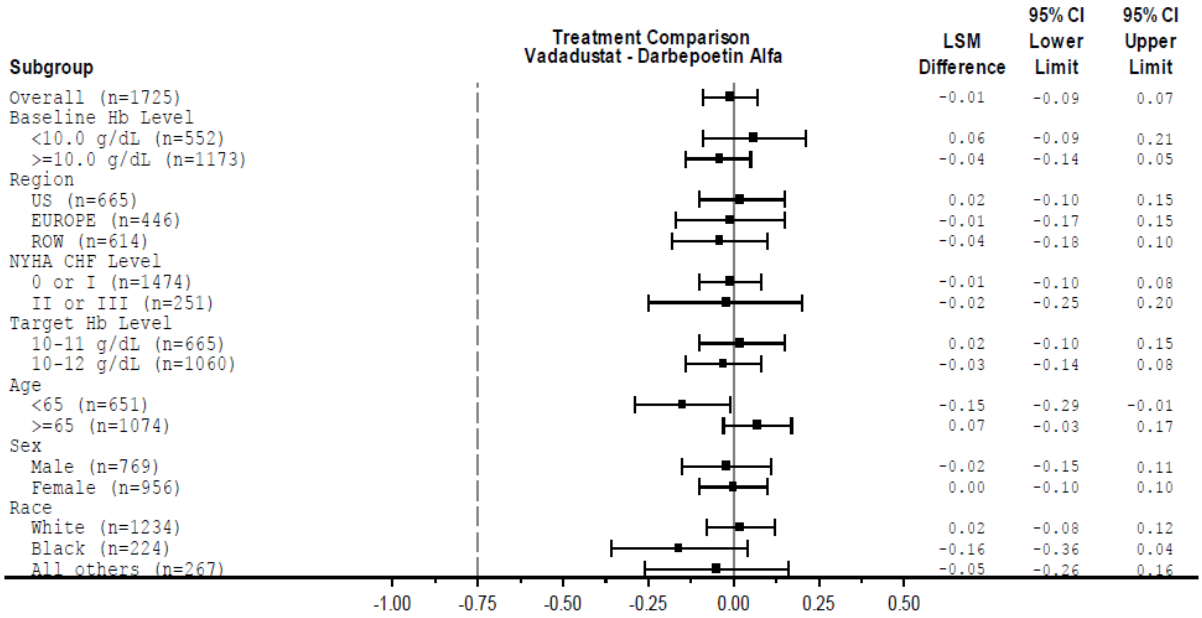
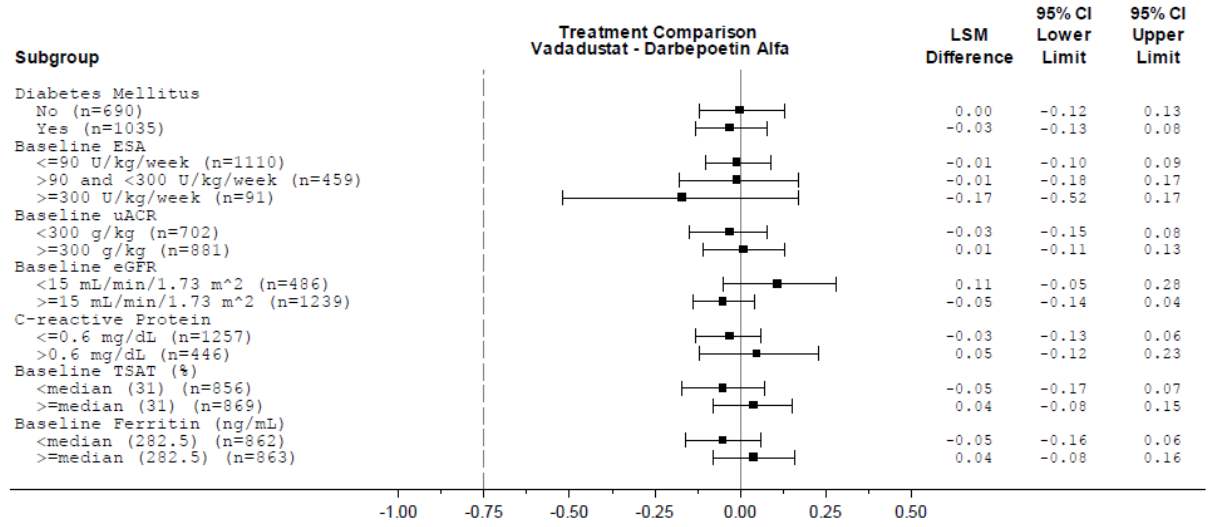


Figure 31 Forest Plot of Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population), cont.



CI: confidence interval; CHF: congestive heart failure; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulatingagent; Hb: hemoglobin; LSM: least squares mean; NYHA: New York Heart Association; ROW: rest of world; TSAT: transferrin saturation; uACR: urine albumin-to-creatinine ratio; US: United States
Source: Figure 14.2.5.1.1.

Figure 33 **Forest Plot of Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 40 to 52 (ANCOVA with Multiple Imputations) (Randomized Population)**

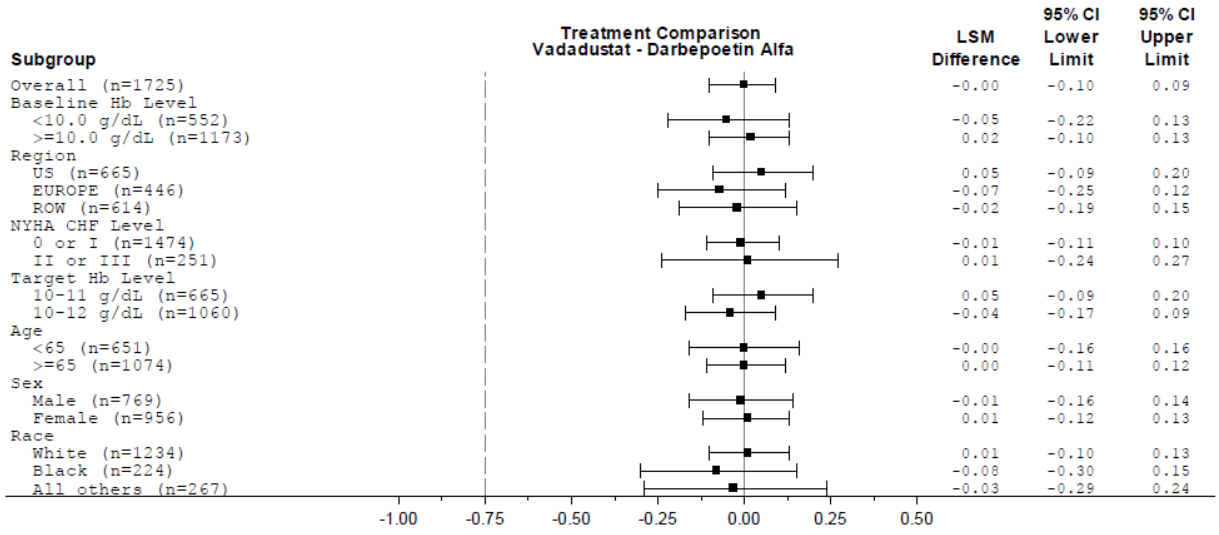
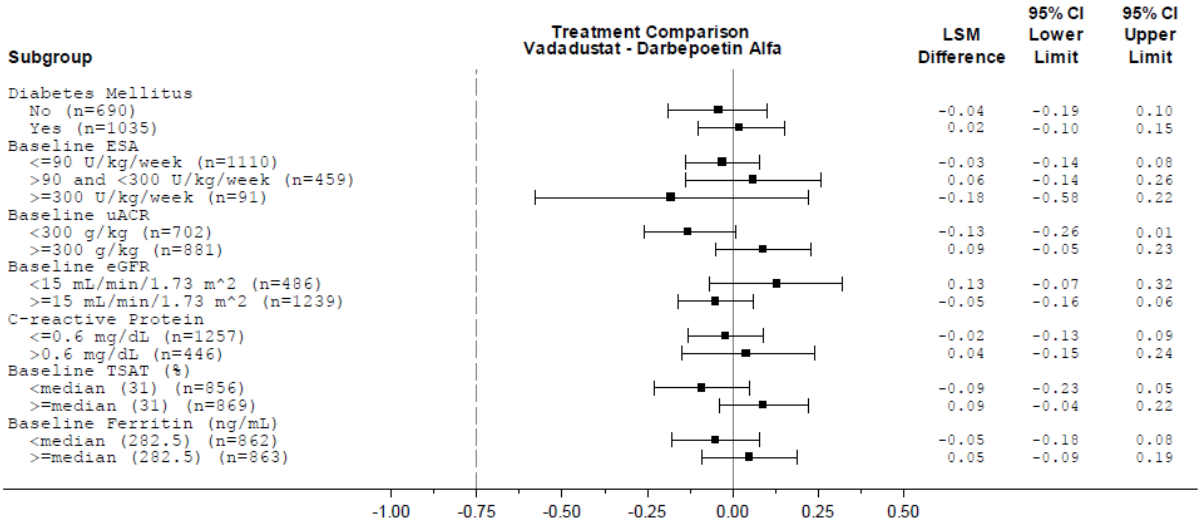


Figure 32 **Forest Plot of Change from Baseline in Hemoglobin (g/dL) to the Average over Weeks 40 to 52 (ANCOVA with Multiple Imputations) (Randomized Population), cont.**



In Trials CI-0014 and CI-0015, Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.1.3, and 14.2.1.1.4 (not reported here) illustrate the change from baseline in Hb (g/dL) to the average over Weeks 24 to 36 (ANCOVA with MI) for the randomized population in 4 cohorts of renal function.

Proportion of Subjects with Average Haemoglobin Values Within Geography-specific Target Range During Weeks 24 to 36 and Weeks 40 to 52

A subgroup analysis of the proportion of subjects with average Hb values within the geography-specific target range of 10.0 to 11.0 g/dL for the US and 10.0 to 12.0 g/dL for Europe and ROW was conducted for each of the INNO2VATE and PRO2TECT studies (Tables below).

Table 48 Subgroup Analysis of Proportion of Subjects with Average Hemoglobin Value within Geography-Specific Target Range During Weeks 24 to 36 (Stratified Mantel-Haenszel Method with Multiple Imputations) - INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Studies (Randomized Population)

	INNO$_2$VATE				PRO$_2$TECT			
	AKB-6548-CI-0016		AKB-6548-CI-0017		AKB-6548-CI-0014		AKB-6548-CI-0015	
Subgroup	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
US Target Range (Hb 10.0 to 11.0 g/dL), n	97	102	1090	1086	532	529	330	335
Responders, n (%)	33 (34.0)	46 (45.1)	450 (41.3)	514 (47.3)	251 (47.2)	233 (44.0)	147 (44.5)	151 (45.1)
95% CI	24.70, 44.34	35.22, 55.26	38.34, 44.27	44.32, 50.35	42.87, 51.52	39.76, 48.39	39.10, 50.09	39.66, 50.58
Proportion difference (vada/darbe) (95% CI) [a]	-0.119 (-0.2600, 0.0218)		-0.050 (-0.0942, -0.0064)		0.035 (-0.0293, 0.0987)		0.006 (-0.0717, 0.0846)	
Odds ratio (vada/darbe) (95% CI)[a]	0.60 (0.327, 1.105)		0.82 (0.685, 0.975)		1.15 (0.888, 1.490)		1.03 (0.748, 1.409)	
European Target Range (10.0 to 12.0 g/dL), n	26	16	254	281	71	68	225	221
Responders, n (%)	12 (46.2)	10 (62.5)	163 (64.2)	181 (64.4)	48 (67.6)	41 (60.3)	155 (68.9)	161 (72.9)
95% CI	26.59, 66.63	35.43, 84.80	57.94, 70.07	58.51, 70.01	55.45, 78.24	47.70, 71.97	62.40, 74.87	66.48, 78.60
Proportion difference (vada/darbe) (95% CI) [a]	-0.065 (-0.3833, 0.2538)		-0.021 (-0.1017, 0.0595)		0.076 (-0.0834, 0.2352)		-0.015 (-0.0980, 0.0677)	
Odds ratio (vada/darbe) (95% CI)[a]	0.76 (0.191, 3.014)		0.90 (0.616, 1.327)		1.43 (0.673, 3.039		0.92 (0.597, 1.428)	
ROW Target Range (10.0 to 12.0 g/dL), n	58	70	433	410	276	275	307	307
Responders, n (%)	34 (58.6)	51 (72.9)	261 (60.3)	251 (61.2)	144 (52.2)	164 (59.6)	216 (70.4)	212 (69.1)
95% CI	44.93, 71.40	60.90, 82.80	55.50, 64.92	56.31, 65.96	46.10, 58.20	53.58, 65.49	64.91, 75.41	63.56, 74.18
Proportion difference (vada/darbe) (95% CI) [a]	-0.135 (-0.3026, 0.0323)		0.003 (-0.0626, 0.0693)		-0.049 (-0.1342, 0.0357)		0.028 (-0.0424, 0.0992)	
Odds ratio (vada/darbe) (95% CI)[a]	0.52 (0.235, 1.172)		1.01 (0.756, 1.362)		0.81 (0.564, 1.165)		1.17 (0.795, 1.711)	

CI: confidence interval; darbe: darbepoetin alfa; Hb: hemoglobin; N: number of subjects; n: number of subjects within specific category; ROW: Rest of World; US: United States; vada: vadadustat

a From Mantel-Haenszel method stratified by the 3 randomization stratification factors based on multiply imputed data. Within any stratum, if there were no subjects in any treatment group or were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis.

Source: CI-0016 Table 14.2.5.2.2, CI-0017 Table 14.2.5.2.2, CI-0014 Table 14.2.5.2.2, CI-0015 Table 14.2.5.2.2

Table 49 Subgroup Analysis of Proportion of Subjects with Average Hemoglobin Value within Geography-Specific Target Range During Weeks 40 to 52 (Stratified Mantel-Haenszel Method with Multiple Imputations) - INNO$_2$VATE and PRO$_2$TECT Global Phase 3 Studies (Randomized Population)

	INNO$_2$VATE				PRO$_2$TECT			
	AKB-6548-CI-0016		AKB-6548-CI-0017		AKB-6548-CI-0014		AKB-6548-CI-0015	
Subgroup	Vada N=181	Darbe N=188	Vada N=1777	Darbe N=1777	Vada N=879	Darbe N=872	Vada N=862	Darbe N=863
US Target Range (Hb 10.0 to 11.0 g/dL), n	97	102	1090	1086	532	529	330	335
Responders, n (%)	32 (33.0)	34 (33.3)	398 (36.5)	483 (44.5)	218 (41.0)	205 (38.8)	131 (39.7)	130 (38.8)
95% CI	23.78, 43.27	24.31, 43.36	33.65, 39.45	41.49, 47.49	36.76, 45.29	34.58, 43.05	34.38, 45.20	33.56, 44.25
Proportion difference (vada/darbe) (95% CI)[a]	-0.017 (-0.1732, 0.1390)		-0.065 (-0.1095, -0.0210)		0.009 (-0.0576, 0.0753)		0.018 (-0.0669, 0.1028)	
Odds ratio (vada/darbe) (95% CI)[a]	0.93 (0.487, 1.784)		0.77 (0.643, 0.919)		1.04 (0.794, 1.352)		1.08 (0.762, 1.519)	
European Target Range (10.0 to 12.0 g/dL), n	26	16	254	281	71	68	225	221
Responders, n (%)	12 (46.2)	9 (56.3)	144 (56.7)	168 (59.8)	38 (53.5)	40 (58.8)	132 (58.7)	132 (59.7)
95% CI	26.59, 66.63	29.88, 80.25	50.35, 62.87	53.80, 65.57	41.29, 65.45	46.23, 70.63	51.93, 65.17	52.94, 66.25
Proportion difference (vada/darbe) (95% CI)[a]	-0.011 (-0.3430, 0.3203)		-0.042 (-0.1271, 0.0429)		-0.012 (-0.1741, 0.1504)		0.025 (-0.0645, 0.1137)	
Odds ratio (vada/darbe) (95% CI)[a]	0.96 (0.227, 4.013)		0.82 (0.556, 1.219)		0.94 (0.424, 2.099)		1.13 (0.719, 1.789)	
ROW Target Range (10.0 to 12.0 g/dL), n	58	70	433	410	276	275	307	307
Responders, n (%)	28 (48.3)	34 (48.6)	245 (56.6)	254 (62.0)	123 (44.6)	134 (48.7)	174 (56.7)	161 (52.4)
95% CI	34.95, 61.78	36.44, 60.83	51.77, 61.31	57.06, 66.67	38.61, 50.64	42.68, 54.80	50.93, 62.30	46.69, 58.14
Proportion difference (vada/darbe) (95% CI)[a]	0.039 (-0.1508, 0.2296)		-0.045 (-0.1119, 0.0225)		-0.003 (-0.0947, 0.0897)		0.064 (-0.0159, 0.1439)	
Odds ratio (vada/darbe) (95% CI)[a]	1.17 (0.547, 2.505)		0.81 (0.593, 1.111)		0.99 (0.663, 1.475)		1.38 (0.922, 2.056)	

CI: confidence interval; darbe: darbepoetin alfa; Hb: hemoglobin; N: number of subjects; n: number of subjects within specific category; ROW: Rest of World; US: United States; vada: vadadustat

a From Mantel-Haenszel method stratified by the 3 randomization stratification factors based on multiply imputed data. Within any stratum, if there were no subjects in any treatment group or were no responders in both treatment groups, unstratified Mantel-Haenszel method was used instead for analysis.

Source: CSR CI-0016 Table 14.2.5.2.3, CSR CI-0017 Table 14.2.5.2.3, CSR CI-0014 Table 14.2.5.2.3, CSR CI-0015 Table 14.2.5.2.3

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 50 Summary of efficacy for Trial AKB-6548-CI-0016

Title: Phase 3, randomized, open-label, active-controlled study evaluating the efficacy and safety of oral vadadustat for the correction or maintenance treatment of anaemia in subjects with incident dialysis-dependent chronic kidney disease (DD-CKD) ($INNO_2VATE$ – correction/conversion)			
Study identifier	Protocol Number: AKB-6548-CI-0016 EudraCT Number: 2016-000838-21		
Design	Randomized open-label, sponsor-blind, global, multi-centre, active-control trial to demonstrate efficacy and safety of vadadustat compared with darbepoetin alfa for correction and maintenance of haemoglobin in subjects with anaemia secondary to incident DD-CKD		
	Duration of Screening phase:		8-week screening period
	Duration of main phase:		Maintenance Phase: Week 24 to Week 52; Primary Efficacy Period: Week 24 to Week 36; Secondary Efficacy Period: Week 40 to Week 52 Long-term treatment period (Week 53 to end of
Hypothesis	The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anaemia after the correction of haemoglobin (Hb) or conversion from current ESA therapy, in subjects who have recently initiated dialysis treatment for DD-CKD.		
Treatments groups	Vadadustat		300 mg (2 × 150 mg tablet) daily starting dose with dose adjustment. Allowable dose levels of 150, 300, 450, or 600 mg daily was allowed during the study based on Hb level measurements every 4 weeks to maintain target Hb levels. Treatment up to Week 52. Number of subjects randomized = 181.
	Darbepoetin Alfa		Dose according to product labelling. Treatment up to Week 52, Number of subjects randomized = 188
Endpoints and definitions	Primary endpoint		The primary efficacy endpoint was to assess the change in average Hb between Baseline and the primary efficacy period (Weeks 24 to 36).
	Secondary endpoint		The key secondary efficacy endpoint of this study was to assess the change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52).
Database lock	Last patient last visit: 31 Jan 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The analysis populations were defined as follows: ·Randomized population: all subjects randomized. Analyses of this population was based on the randomized treatment. ·Full Analysis Set (FAS) population: all subjects in the Randomized population who received at least 1 dose of study drug and had at least 1 postdose Hb. Analyses of this population was based on the randomized treatment. ·Safety population: all subjects in the Randomized population who received at least 1 dose of study drug. Analysis of this population was based on the actual treatment received. Subjects who received in error both vadadustat and darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received study drug. ·Per Protocol (PP) population: all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least 1 Hb assessment during the primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviation affecting the primary endpoint analyses, ie, prior to Week 36. Analyses of this population was based on actual treatment received, as described for the Safety population.			
Descriptive statistics and estimate variability	Treatment group	Vadadustat	Darbepoetin Alfa	Total
	Number of subjects	181	188	369
	Change from Baseline in Haemoglobin (g/dL) to the Average Over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population)	0.99	1.42	-
	Standard Deviation	1.276	1.414	-
	Least squares mean (SEM)	1.26 (0.109)	1.58 (0.108)	
	95% Confidence Interval	1.05, 1.48	1.37, 1.79	
	Change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52). Mean	1.15	1.36	
	Standard Deviation	1.345	1.568	
	Least squares mean (SEM)	1.42 (0.132)	1.50 (0.136)	
	95% Confidence Interval	1.17, 1.68	1.23, 1.76	
Effect estimate per comparison	Primary endpoint	Comparison groups	Treatment group difference	
		Least squares mean (SEM)	-0.31 (0.110)	

		95% Confidence Interval	-0.53, -0.10
	Secondary endpoint	Comparison groups	Treatment group difference
		Least squares mean (SEM)	-0.07 (0.134)
		95% Confidence Interval	-0.34, 0.19

ANCOVA = analysis of covariance; CI = confidence interval; DD-CKD = dialysis-dependent chronic kidney disease; FAS = full analysis set; Hb = haemoglobin; MACE = major adverse cardiac event; PP = per protocol; QD = once daily; SEM = Least squares mean.

Table 51 Summary of efficacy for Trial AKB-6548-CI-0017

Title: Phase 3, randomized, open-label, active-controlled study evaluating the efficacy and safety of oral vadadustat for the maintenance treatment of anaemia in subjects with dialysis-dependent chronic kidney disease (DD-CKD) (INNO2VATE – conversion)			
Study identifier	Protocol Number: AKB-6548-CI-0017 EudraCT Number: 2016-001360-11		
Design	Randomized, open-label, sponsor-blind, global, multi-centre, active-control trial to demonstrate efficacy and safety of vadadustat compared to darbepoetin alfa for the maintenance treatment of anaemia in subjects with DD-CKD		
	Duration of Screening phase:	8-week screening period	
	Duration of main phase:	Maintenance Phase: Week 24 to Week 52; Primary Efficacy Period: Week 24 to Week 36; Secondary Efficacy Period: Week 40 to Week 52	
	Duration of Extension phase:	Long-term treatment period: Week 53 to end of treatment for the collection of safety data	
Hypothesis	The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anaemia in subjects with DD-CKD		
Treatments groups	Vadadustat		300 mg (2 × 150 mg tablet) daily starting dose with dose adjustment. Allowable dose levels of 150, 300, 450, or 600 mg daily was allowed during the study based on Hb level measurements every 4 weeks to maintain target Hb levels. Treatment up to Week 52. Number of subjects randomized = 1777
	Darbepoetin Alfa		Dose according to product labelling. Treatment up to Week 52, Number of subjects randomized = 1777
Endpoints and definitions	Primary endpoint		The primary efficacy endpoint was to assess the change in average Hb between Baseline and the primary efficacy period (Weeks 24 to 36).
	Secondary endpoint		The key secondary efficacy endpoint of this study was to assess the change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52).
Database lock	Last patient last visit: 16 Jan 2020		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	The analysis populations were defined as follows: ·Randomized population: all subjects randomized. Analyses of this population was based on the randomized treatment. ·Full Analysis Set (FAS) population: all subjects in the Randomized population who received at least 1 dose of study drug and had at least 1 postdose Hb. Analyses of this population was based on the randomized treatment. ·Safety population: all subjects in the Randomized population who received at least 1 dose of study drug. Analysis of this population was based on the actual treatment received. Subjects who received in error both vadadustat and darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received study drug. ·Per Protocol (PP) population: all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least 1 Hb assessment during the primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviation affecting the primary endpoint analyses, ie, prior to Week 36. Analyses of this population was based on actual treatment received, as described for the Safety population.			
Descriptive statistics and estimate variability	Treatment group	Vadadustat	Darbepoetin Alfa	Total
	Number of subjects	1777	1777	3554
	Change from Baseline in Haemoglobin (g/dL) to the Average Over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population) Mean	0.11	0.30	
	Standard Deviation	1.108	1.103	
	Least squares mean (SEM)	0.19 (0.032)	0.36 (0.032)	
	95% Confidence Interval	0.12, 0.25	0.29, 0.42	
	Change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52). (ANCOVA with Multiple Imputations) (Randomized Population) Mean	0.15	0.35	
	Standard Deviation	1.178	1.131	
	Least squares mean (SEM)	0.23 (0.035)	0.41 (0.033)	

	95% Confidence Interval	0.16, 0.29	0.34, 0.48	
Effect estimate per comparison	Primary endpoint	Comparison groups	Treatment Group Difference	
		Least squares mean (SEM)	-0.17 (0.033)	
		95% Confidence Interval	-0.23, -0.10	
	Secondary endpoint	Comparison groups	Treatment Group Difference	
		Least squares mean (SEM)	-0.18 (0.035)	
		95% Confidence Interval	(-0.25, -0.12)	
Notes	N/A			

Table 52 Summary of efficacy for Trial AKB-6548-CI-0014

Title: Phase 3, randomized, open-label, active-controlled study evaluating the efficacy and safety of oral vadadustat for the correction of anaemia in subjects with non-dialysis-dependent chronic kidney disease (NDD-CKD) (PRO_2TECT-correction)		
Study identifier	Protocol Number: AKB-6548-CI-0014 EudraCT Number: 2015-004265-81	
Design	Randomized, open-label, sponsor-blind, global, multi-centre, active-control trial to demonstrate efficacy and safety of vadadustat compared to darbepoetin alfa for correction and maintenance of Hb in subjects with anaemia secondary to NDD-CKD	
	Duration of Screening phase:	8-week screening period
	Duration of main phase:	Maintenance Phase: Week 24 to Week 52; Primary Efficacy Period: Week 24 to Week 36; Secondary Efficacy Period: Week 40 to Week 52
	Duration of Extension phase:	Long-term treatment period (Week 53 to end of treatment) for the collection of safety data
Hypothesis	The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the correction and maintenance of Hb in subjects with anaemia secondary to NDD-CKD	
Treatments groups	Vadadustat	300 mg (2 × 150 mg tablet) daily starting dose with dose adjustment. Allowable dose levels of 150, 300, 450, or 600 mg daily was allowed during the study based on Hb level measurements every 4 weeks to maintain target Hb levels. Treatment up to Week 52. Number of subjects randomized = 879
	Darbepoetin Alfa	Dose according to product labelling. Treatment up to Week 52, Number of subjects randomized = 872

Endpoints and definitions	Primary endpoint		The primary efficacy endpoint was to assess the change in average Hb between Baseline and the primary efficacy period (Weeks 24 to 36).
	Secondary endpoint		The key secondary efficacy endpoint of this study was to assess the change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52).
Database lock	Last Patient Last Visit Date: 04 Jun 2020		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The analysis populations were defined as follows: ·Randomized population: all subjects randomized. Analyses of this population was based on the randomized treatment. ·Full Analysis Set (FAS) population: all subjects in the Randomized population who received at least 1 dose of study drug and had at least 1 postdose Hb. Analyses of this population was based on the randomized treatment. ·Safety population: all subjects in the Randomized population who received at least 1 dose of study drug. Analysis of this population was based on the actual treatment received. Subjects who received in error both vadadustat and darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received study drug. ·Per Protocol (PP) population: all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least 1 Hb assessment during the primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviation affecting the primary endpoint analyses, ie, prior to Week 36. Analyses of this population was based on actual treatment received, as described for the Safety population.			
Descriptive statistics and estimate variability	Treatment group	Vadadustat	Darbepoetin Alfa	Total
	Number of subjects	879	872	1751
	Change from Baseline in Haemoglobin (g/dL) to the Average Over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population) Mean	1.28	1.21	
	Standard Deviation	1.005	1.055	
	Least squares mean (SEM)	1.43 (0.046)	1.38 (0.047)	
	95% Confidence Interval	(1.34, 1.52)	(1.29, 1.47)	

	Change From Baseline in Haemoglobin (g/dL) to the Average over Weeks 40 to 52 (ANCOVA with Multiple Imputations) (Randomized Population) Mean	1.37	1.31	
	Standard Deviation	1.080	1.111	
	Least squares mean (SEM)	1.52	1.48	
	95% Confidence Interval	0.052	0.053	

Effect estimate per comparison	Primary endpoint	Comparison groups	Treatment Group Difference
		Least squares mean (SEM)	0.05 (0.048)
		95% Confidence Interval	-0.04, 0.15
	Secondary endpoint	Comparison groups	Treatment Group Difference
		Least squares mean (SEM)	0.04 (0.052)
		95% Confidence Interval	-0.06, 0.14
Notes	N/A		

NDD-CKD = non-dialysis-dependent chronic kidney disease.

Table 53 Summary of efficacy for Trial AKB-6548-CI-0015

Title: Phase 3, randomized, open-label, active-controlled study evaluating the efficacy and safety of oral vadadustat for the maintenance treatment of anaemia in subjects with non-dialysis-dependent chronic kidney disease (NDD-CKD) (PRO_2TECT-correction)	
Study identifier	Protocol Number: AKB-6548-CI-0015 EudraCT Number 2015-004774-1
Design	Randomized, open-label, sponsor-blind, global, multi-centre, active-control trial to demonstrate efficacy and safety of vadadustat compared to darbepoetin alfa for maintenance treatment of anaemia in patients w/ NDD CKD

	Duration of Screening phase:		8-week screening phase
	Duration of main phase:		Maintenance Phase: Week 24 to Week 52; Primary Efficacy Period: Week 24 to Week 36; Secondary Efficacy Period: Week 40 to Week 52
	Duration of Extension phase:		Long-term treatment period (Week 53 to end of treatment) for the collection of safety data
Hypothesis	The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anaemia in subjects with NDD-CKD after conversion from current ESA therapy		
Treatments groups	Vadadustat		300 mg (2 × 150 mg tablet) daily starting dose with dose adjustment. Allowable dose levels of 150, 300, 450, or 600 mg daily was allowed during the study based on Hb level measurements every 4 weeks to maintain target Hb levels. Treatment up to Week 52. Number of subjects randomized = 862
	Darbepoetin Alfa		Dose according to product labelling. Treatment up to Week 52, Number of subjects randomized = 863
Endpoints and definitions	Primary endpoint		The primary efficacy endpoint was to assess the change in average Hb between Baseline and the primary efficacy period (Weeks 24 to 36).
	Secondary endpoint		The key secondary efficacy endpoint of this study was to assess the change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52).
Database lock	Last Patient Last Visit Date: 18 Jun 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The analysis populations were defined as follows: ·Randomized population: all subjects randomized. Analyses of this population was based on the randomized treatment. ·Full Analysis Set (FAS) population: all subjects in the Randomized population who received at least 1 dose of study drug and had at least 1 postdose Hb. Analyses of this population was based on the randomized treatment. ·Safety population: all subjects in the Randomized population who received at least 1 dose of study drug. Analysis of this population was based on the actual treatment received. Subjects who received in error both vadadustat and darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received study drug. ·Per Protocol (PP) population: all randomized subjects who received study drug during the primary efficacy period (Weeks 24 to 36), had at least 1 Hb assessment during the primary efficacy period (Weeks 24 to 36), and had no critical or major protocol deviation affecting the primary endpoint analyses, ie, prior to Week 36. Analyses of this population was based on actual treatment received, as described for the Safety population.			
Descriptive statistics and estimate variability	Treatment group	Vadadustat	Darbepoetin Alfa	Total
	Number of subjects	862	863	1725
	Change from Baseline in Haemoglobin (g/dL) to the Average Over Weeks 24 to 36 (ANCOVA with Multiple Imputations) (Randomized Population) Mean	0.35	0.38	
	Standard Deviation	0.982	0.990	
	Least squares mean (SEM)	0.41 (0.036)	0.42 (0.037)	
	95% Confidence Interval	(0.34, 0.48)	(0.35, 0.49)	
	Change From Baseline in Haemoglobin (g/dL) to the Average over Weeks 40 to 52 (ANCOVA with Multiple Imputations) (Randomized Population) Mean	0.37	0.40	
	Standard Deviation	1.040	1.087	
	Least squares mean (SEM)	0.43 (0.044)	0.44 (0.044)	
	95% Confidence Interval	(0.35, 0.52)	(0.35, 0.52)	

Effect estimate per comparison	Primary endpoint	Comparison groups	Treatment Group Difference
		Least squares mean (SEM)	-0.01 (0.042) g/dL
		95% Confidence Interval	(95% CI: -0.09, 0.07).
	Secondary endpoint	Comparison groups	Treatment Group Difference
		Least squares mean (SEM)	-0.00 (0.049)
		95% Confidence Interval	(-0.10, 0.09)
Notes	N/A		

2.6.5.3. Clinical studies in special populations

Table 54 Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials NDD-CKD	31.0 % (666/2151)	23.4 % (504/2151)	7.0% (150/2151)
Controlled Trials DD-CKD	24.9 % (554/2226)	11.3 % (251/2226)	1.1 % (24/2226)
Non Controlled trials NDD-CKD	25.0 % (8/32)	18.8 % (6/32)	0.0% (0/32)
Non Controlled trials DD-CKD	24.5 % (26/106)	3.8 % (4/106)	0.0% (0/106)

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

See efficacy section

2.6.5.6. Supportive studies

Additional data from 4 Phase 3 regional studies in subjects with DD-CKD and NDD-CKD conducted in Japan and 6 Phase 2 studies in subjects with DD-CKD and NDD-CKD conducted in the US support the efficacy conclusions from the pivotal global Phase 3 studies.

Table 55 Description of Supportive Clinical Efficacy Studies

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age in yr (SD)	Primary Endpoint
Phase 3, regional, active-controlled studies								
MT-6548-J03 (115 in Japan)	14 Feb 2018-10 Jul 2019	Double-blind, active-controlled, randomized, parallel groups efficacy and safety study	DD-CKD	≥20 yr and treated with dialysis for ≥12 wks prior to screening and received an ESA for prior 8 wks before screening, and with baseline Hb >9.5 to ≤12.0 g/dL	Vada initiated at 300 mg QD with adjustment to 150 to 600 mg QD Darbe given at 5 to 180 µg q1w, q2w, or q4w	24-wks in PEP and 52-wks to end of SEP	Vada[a]: 162 (64.2/35.8); 66.0 (11.3) Darbe[a]: 161 (67.7/32.3); 64.9 (11.7)	Mean Hb value at Wk 20 and Wk 24 of the PEP
MT-6548-J01 (86 in Japan)	30 Oct 2017-06 Aug 2019	Open-label, active-controlled randomized, parallel group efficacy, and safety study	NDD-CKD	≥20 yr and if no ESA use in prior 8 wks then baseline Hb ≥8.0 to ≤11.0 g/dL(Correction) or if ESA use in prior 8 wks then baseline Hb ≥9.0 to ≤12.5 g/dL (Conversion set)	Vada initiated at 300 mg QD, with dose adjustment to 150 to 600 mg QD based on Hb level Darbe: 30µg q2w with adjustment to 15 to 180 µg q2w (Correction set) or according to prior ESA dose as specified in protocol	24-wks in PEP and 52-wks to end of SEP	Vada[a]: 151 (49.7/50.3); 71.7 (10.3) Darbe[a]: 153 (47.7/52.3); 72.2 (9.5)	Mean Hb value at Wk 20 and Wk 24 of the PEP

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age in yr (SD)	Primary Endpoint
Phase 2 regional, active-controlled studies								
AKB-6548-CI-0025 (39 in US)	07 Jan 2019-05 Jun 2020	Open-label, active-controlled randomized, parallel group, efficacy, PK, PD, and safety study	DD-CKD	≥18 yr with HD given TIW for ≥12 wk prior to screening and <300 U/kg/wk for 8 wks prior to screening visit 2 and baseline Hb ≥8.5 and ≤11.0 g/dL for the Main Study and ≥300 U/kg/wk for 8 wks prior to screening visit 2 and baseline Hb ≥8.0 and ≤10.0 g/dL for the ESA Hyporesponder Parallel Study	Vada initiated at 300, 450 or 600 mg QD in Part 1 or TIW in Part 2 or epoetin alfa TIW in Main Study or 600 mg QD in Part 1 or TIW in Part 2 or epoetin alfa TIW in ESA Hyporesponder Study. In both, dose adjustment to 150 to 900 mg QD or TIW based on Hb level. Subjects were stratified into low epoetin alfa (≤90 U/kg/wk) or high epoetin alfa (>90 to <300 U/kg/wk) based on their ESA dose in the 8 wks prior to screening visit 2	20 wks (12-wks in Part 1 with QD dosing for vada and 8-wks in Part 2 with QD or TIW dosing for vada)	Main Study- Low epoetin alfa Group Vada 300 mg[d]: 35 (60.0/40.0); 61.3 (11.47) Vada 450 mg[d]: 34 (61.8/38.2); 58.6 (13.21) Epoetin alfa[d]: 23 (82.6/17.4); 59.2 (13.48) High epoetin alfa Group Vada 300 mg[d]: 18 (61.1/38.9); 62.4 (10.28) Vada 450 mg[d]: 21 (66.7/33.3); 51.6 (13.48) Vada 600 mg[d]: 21 (57.1/42.9); 57.0 (12.25) Epoetin alfa[d]: 13 (53.8/46.2); 61.6 (14.06) ESA Hyporesponder Parallel Study: Vada 600 mg[d]: 5 (20.0/80.0); 56.6 (7.33) Epoetin alfa[d]: 5 (40.0/60.0); 63.0 (11.18)	Change in mean Hb values between baseline and the PEP (average Hb value from wk 10 to 12)

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age in yr (SD)	Primary Endpoint
Phase 2 regional, placebo-controlled studies								
AKB-6548-CI-0022 (31 in Japan)	19 Dec 2016-24 Oct 2017	Double-blind, placebo-controlled, randomized, parallel group, dose-finding efficacy, PK, PD, and safety study	DD-CKD	≥20 yr and treated with dialysis for ≥8 wks prior to entry and baseline Hb <10.0 g/dL. If on ESA required to complete washout of up to 8 wks depending on ESA	Vada initiated at 150, 300 mg or 600 mg QD or placebo for 6-wks in PEP. After PEP, all given vada for 10 wks and dose adjusted to achieve Hb level of 10.0 to 12.0 g/dL	6-wks in PEP and 10-wks in SEP	Vada 150 mg[b]: 15 (66.7/33.3); 61.5 (11.01) Vada 300 mg[b]: 15 (86.7/13.3); 64.3 (8.02) Vada 600 mg[b]: 14 (64.3/35.7); 64.1 (8.50) Pbo to vada 150 mg[b]: 5 (60.0/40.0); 60.8 (12.85) Pbo to vada 300 mg[b]: 4 (50.0/50.0); 65.5 (13.77) Pbo to vada 600 mg[b]: 5 (60.0/40.0); 70.8 (8.23)	Mean change in Hb from pre-treatment to end of PEP (Wk 6)
AKB-6548-CI-0021 (30 in Japan)	19 Oct 2016-04 Jul 2017	Double-blind, placebo-controlled, randomized, parallel group, dose-finding efficacy, PK, PD, and safety study	NDD-CKD	≥20 yr and not treated with dialysis, no ESA use within 6 wk of screening, and baseline Hb <10.5 g/dL	Vada initiated at 150, 300 mg or 600 mg QD or Pbo for 6-wks in PEP. After PEP, all given vada for 10 wks and dose adjusted to achieve Hb level of 10.0 to 12.0 g/dL	6-wks in PEP and 10-wks in SEP	Vada 150 mg[b]: 12 (58.3/41.7); 71.9 (10.33) Vada 300 mg[b]: 12 (58.3/41.7); 65.8 (11.53) Vada 600 mg[b]: 13 (38.5/61.5); 71.5 (12.84) Pbo to vada 150 mg[b]: 5 (80.0/20.0); 73.4 (3.05)	Mean change in Hb from pre-treatment to end of PEP (Wk 6)

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age in yr (SD)	Primary Endpoint
							Pbo to vada 300 mg[b]: 4 (75.0/25.0);68.0 (21.21) Pbo to vada 600 mg[b]: 5 (60.0/40.0); 72.2 (8.64)	
AKB-6548-CI-0005 (29 in US)	15 Jun 2011-16 Feb 2012	Double-blind, placebo-controlled, randomized, parallel group, dose-finding PK, PD, and safety study	NDD-CKD	18 to 79 yr, no ESA use within 11 wks of screening, not ESA resistant, and had baseline Hb ≤10.5 g/dL	Vada initiated at 240, 370, 500, and 630 mg QD or Pbo with subsequent dose adjustment based on Hb level	6-wks	Vada 240 mg[c]: 18 (50.0/50.0); 64.2 (12.17) Vada 370 mg[c]: 18 (61.1/38.9); 68.9 (7.84) Vada 500 mg[c]: 17 (23.5/76.5); 64.7 (9.47) Vada 630 mg[c]: 19 (63.2/36.8); 64.9 (8.79) Pbo[c]: 19 (36.8/63.2); 64.9 (9.97)	Mean change in Hb from pre-treatment to EOT (wk 6)
AKB-6548-CI-0007 (61 in US)	23 Jul 2013-03 Sep 2014	Double-blind, placebo-controlled, randomized, parallel group, PD, and safety study	NDD-CKD	≥18 yr and no previous ESA use or ESA use was ≥11 wks prior to screening and both with baseline Hb ≤10.5 g/dL (naïve and previously	Vada initiated at 450 mg QD or Pbo with adjustment to 150 or 600 mg QD based on Hb level	20-wks	Naïve group-Vada[c]: 69 (49.3/50.7); 65.2 (9.22) Pbo[c]: 38 (47.4/52.6); 66.1 (11.43) Previously treated-Vada[c]: 42 (38.1/61.9);	Proportion who 1) achieved or maintained a mean Hb of ≥11.0 g/dL (average of wk 19 and 20) or 2) experienced an increase in Hb of ≥1.2 g/dL (average of wk

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age in yr (SD)	Primary Endpoint
				treated groups, respectively) or was actively treated with an ESA for >4 months prior to screening and had baseline Hb ≥9.5 and ≤12.0 g/dL at screening (actively treated group)			68.0 (10.87 Pbo[c]: 21 (66.7/33.3); 65.0 (14.81) Actively treated-Vada[c]: 27 (25.9/74.1); 68.1 (10.25) Pbo[c]: 13 (46.2/53.8); 66.7 (11.33)	19 and 20) over their predose average
Phase 3 regional, uncontrolled studies								
MT-6548-J02 (25 in Japan)	03 Jan 2018-06 Dec 2018	Open-label, uncontrolled, single arm	DD-CKD	≥20 yr and treated with peritoneal dialysis for ≥4 weeks, and not received an ESA for ≥8 wks prior to start or if had an ESA then completed 8 wk washout with baseline Hb >8.0 to ≤11.0 g/dL (Correction) or if taking stable ESA for ≥8wks prior to start with baseline Hb >9.0 to	Vada initiated at 300 mg QD with adjustment to 150 to 600 mg QD	24 wk	Vada[a]: 42 (71.4/28.6); 63.0 (12.6)	Mean Hb value at Wk 20 and Wk 24 of the treatment period, Hb at each timepoint, subjects within target range, time to reach target (Correction), and rate of increase of Hb value (Correction)
Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age in yr (SD)	Primary Endpoint
				≤12.5 g/dL (Conversion)				
MT-6548-J04 (25 in Japan)	05 Mar 2018-17 Dec 2018	Open-label, uncontrolled, single arm	DD-CKD	≥20 yr and treated with dialysis TIW, and not received an ESA or underwent ESA washout prior to entry and with baseline Hb ≥8.0 to ≤10.0 g/dL	Vada initiated at 300 mg QD with adjustment to 150 to 600 mg QD	24 wk	Vada[a]: 24 (79.2/20.8); 63.0 (12.4)	Mean Hb value at Wk 20 and Wk 24 of the treatment period, Hb at each timepoint, subjects within target range, time to reach target, and rate of increase of Hb value
Phase 2 regional, uncontrolled study								
AKB-6548-CI-0011 (22 in US)	10 Sep 2014-22 Jul 2015	Open-label, uncontrolled, randomized 3-cohort PD, efficacy, and safety study	DD-CKD	18 to 79 years, ≥3 months HD, >3 months ESA use, and baseline Hb ≥9.0 g/dL and ≤12.0 g/dL	Vada initiated at 300 mg QD, 450 mg QD, and 450 mg TIW. No increases during Wk 0 to 8, but from Wk 8 to 12 dose adjusted up to 600 mg based on Hb level	16 wk	Vada 300 mg[c]: 30 (56.7/43.3); 55.5 (12.44) Vada 450 mg QD[c]: 33 (54.5/45.5); 59.4 (11.62) 450 mg TIW[c]: 31 (61.3/38.7); 57.8 (8.26)	Change in Hb between 3 starting dose regimens for predose average and mid-study average, predose average and end-study average, and mid-study average and end-study average

CKD: chronic kidney disease; darbe: darbepoetin alfa; DD: dialysis-dependent; EOT: end of treatment; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; FPFV: first patient, first visit; Hb: hemoglobin; HD: hemodialysis; ITT: intention to treat; LPLV: last patient, last visit; mITT: modified ITT; NDD: non-dialysis-dependent; Pbo: placebo; PD: pharmacodynamic; PEP: primary efficacy period; PK: pharmacokinetic; q1w: once weekly; q2w: once every 2 weeks; q4w: once every 4 weeks; QD: once daily; SD: standard deviation; SEP: secondary efficacy period; TIW: 3 times weekly; United States; vada: vadadustat; wk(s): week(s); yr: year(s)

Phase/ Study Number (Sites and Location)	Dates FPFV-LPLV	Trial Design	Population	Main Inclusion Criteria	Treatment Arm	Duration of Treatment	No. Subjects (M/F%); Mean Age in yr (SD)	Primary Endpoint

a FAS population
b mITT population
c ITT population
d randomized population

MT-6548-J03: Primary analysis in PPS (using MMRM)

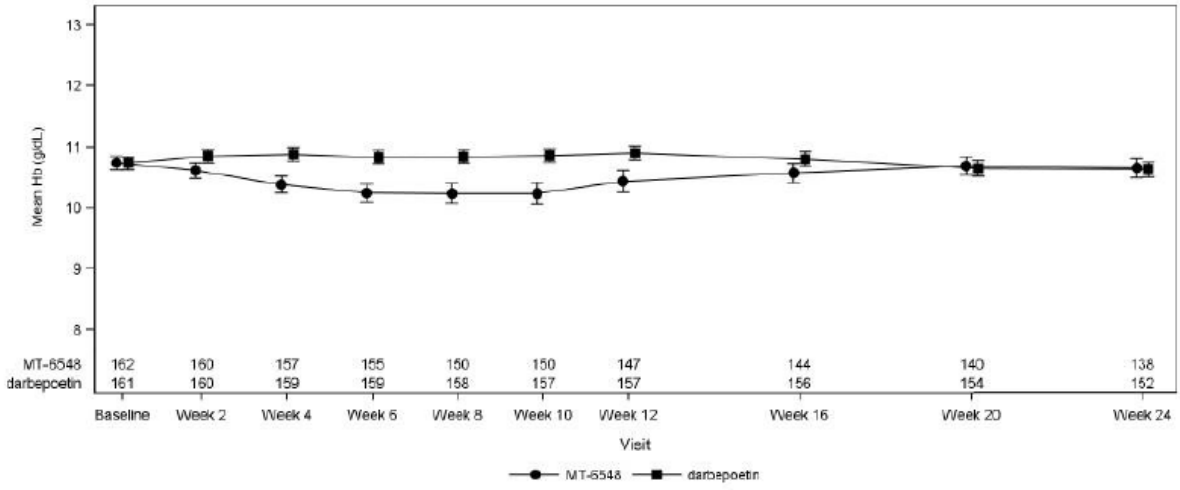
Table 56 Hb Average of week 20 and week 24 by MMRM (PPS)

Treatment Group	Visit	N	Mean at Baseline (SD)	LSMean	SE	95% CI
MT-6548	Week 20 and Week 24	152	10.73 (0.72)	10.58	0.08	(10.42, 10.73)
darbepoetin	Week 20 and Week 24	151	10.76 (0.73)	10.63	0.08	(10.48, 10.78)
Difference MT-6548 - darbepoetin	Week 20 and Week 24			-0.05	0.11	(-0.26, 0.17)

Note(s): Hb (g/dL).
Note(s): N: number of subjects who was used in MMRM model (i.e. number of subjects with Hb at least one visit after baseline).
Note(s): This MMRM model includes treatment group, visits, interaction of treatment group and visits as a fixed effect, baseline value as covariate effect, and subject as random effect. (covariance matrix: unstructured)
Data Source: Listing 16.2.4.1
Source: t_14_2_1_2_2.sas

MT-6548-J03: Changes in the mean Hb value

Figure 34 Changes in the mean Hb value



Note(s): Mean Hb (g/dL): mean and 95% confidence interval of the mean.
Data Source: Table 14.2.2.1.1
Source: f_14_2_1_1_1.sas

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The global Phase 3 clinical program for vadadustat consisted of 4 randomized, open-label, sponsor-blinded studies to support the proposed indication for treatment of anaemia associated with CKD in adults who were new to dialysis, those who required dialysis for survival (DD-CKD) and those who were not yet dependent on dialysis (NDD-CKD). This cross-section of CKD subjects included those who

were naïve to erythropoietin-stimulating agents (ESAs) as well as those treated with ESAs. The global Phase 3 clinical studies were designed to test the non-inferiority for efficacy and safety (MACE) of vadadustat against the active comparator, darbepoetin alfa.

There were 4 additional supportive regional Phase 3 studies that included subjects in Japan; 3 in subjects with DD-CKD (MT-6548-J03, MT-6548-J04, and MT-6548-J02) and 1 in subjects with NDD-CKD (MT-6548-J01). These Phase 3 studies were conducted by the Mitsubishi Tanabe Pharma Corporation (MTPC) and are not discussed in full due to the differences in subject characteristics and endpoints analyzed in comparison to the pivotal global studies. Only data from MT-6548-J03 is of special interest as it is a study with double blind double dummy design, adequately powered for the primary efficacy analyses at 24 weeks and conducted in Japan in subjects with DD-CKD (the population for which efficacy results from the pivotal program need further discussion). Additional data from 6 Phase 2 studies in subjects with DD-CKD and NDD-CKD support the efficacy conclusions from the pivotal global Phase 3 studies.

Two of the global Phase 3 studies (INNO2VATE: Studies CI-0016 and CI-0017) were conducted in adult DD-CKD subjects with baseline Hb values between 8.0 to 11.0 g/dL in Study CI-0016 and between 8.0 to 11.0 g/dL in the US and 9.0 to 12.0 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 and was considered a correction (correction of Hb) and conversion (from current ESA therapy) study. Study CI-0017 included subjects on chronic maintenance dialysis for more than 12 weeks and were being treated with an ESA for anaemia, as such this was considered a conversion study as subjects were randomized to vadadustat or darbepoetin alfa.

Two of the global Phase 3 studies (PRO2TECT: Studies CI-0014 and CI-0015) were conducted in adult NDD-CKD subjects with an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m2 during screening. There were 13 patients in Study CI-0014, and 20 patients in Study CI-0015 who did not meet this inclusion criterion at baseline. Study CI-0014 included subjects diagnosed with CKD with baseline Hb values less than 10.0 g/dL and who were not being treated with an ESA, as such this was considered a correction study with all subjects randomized to vadadustat or darbepoetin alfa. Study CI-0015 included subjects diagnosed with CKD with baseline Hb levels between 8.0 and 11.0 g/dL in the US and between 9.0 and 12.0 g/dL outside of the US who were being treated with an ESA for anaemia (dosed within 6 weeks prior to or during screening). Study CI-0015 was considered a conversion study.

In general, inclusion and exclusion criteria are appropriate for the individual studies and intended population for enrolment. While similar, there were important differences in the inclusion and exclusion criteria for the 2 INNO2VATE studies consistent with the incident dialysis nature of study CI-0016 and the prevalent dialysis nature of study CI-0017. In CI-0016, subjects that met the criteria of ESA resistance within 8 weeks prior to or during screening were excluded from the study (epoetin >7700 units/dose 3 times per week or >23000 units per week; darbepoetin alfa >100 µg/week; methoxy polyethylene glycol-epoetin beta >100 µg every other week or >200 µg every month). Anemic incident DD-CKD subjects with superimposed ESA resistance were excluded, as these subjects likely represent a medically unstable and acutely ill subject population unlikely to be suitable for enrolment into this long-term trial. Trial CI-0017 required subjects to be maintained on variable doses of ESA therapy at screening, with a dose received within 6 weeks prior to or during screening. Trial CI-0017 included 90.6% of the totality of subjects dependent on hemodialysis or peritoneal dialysis (3554 / [3554 + 369]). Therefore, this trial provides efficacy data on the totality of subjects on renal replacement therapy and treated with different types of ESAs and with variable doses of ESA. The Applicant was asked to discuss if patients who meet ESA resistance criteria in the protocol should also be excluded from conversion to vadadustat treatment in clinical practice, however, they see no reason to exclude due to additional sensitivity analyses of primary endpoint for these subjects. This is agreed, and it is

communicated to the treating physician in SmPC as a warning that the mean change in Hb from baseline in response to the switch to vadadustat shows a deeper initial decrease in Hb, up to Week 16 to 20 in parallel with the higher baseline ESA dose, and these patients might require higher vadadustat doses and more frequent rescue therapies.

CI-0014 was a correction of Hb study in which ESA use was prohibited within 8 weeks prior to randomization while CI-0015 was a conversion study in which subjects were required to be currently maintained on ESA therapy, with a dose received within 6 weeks prior to or during screening. Concomitant use of an ESA with study drug was strictly prohibited in all 4 pivotal studies although ESAs could be given as rescue. The impact of ESA rescue and the interpretability of the primary and key secondary outcomes was investigated in sensitivity analyses.

The mean Hb levels for eligibility were different in the 4 pivotal global studies, reflective of the different subject populations enrolled. In all studies, Serum ferritin ≥100 ng/mL, Transferrin saturation (TSAT) ≥20%, Folate and vitamin B12 measurements ≥ lower limit of normal were requirements to avoid confounding effects of vitamin or iron deficiency on RBC production. Subjects presenting with anaemia due to a cause other than CKD or with active bleeding or recent blood loss, RBC transfusion within 8 weeks prior to Randomization, as well as those with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anaemia, thalassemia, or pure red cell aplasia were excluded from the studies. This requirement for evaluation of other causes for anaemia is included as a recommendation at the beginning of section 4.2 of SmPC.

Subjects were stratified by geographic region (United States versus Europe versus Rest of World, New York Heart Association Heart Failure Class (0 or Class I versus Class II or III), and by baseline Hb level at study entry. In studies CI-0014 and CI-0016 a baseline Hb of <9.5 versus ≥9.5 g/dL was chosen while in CI-0015 and CI-0017 a baseline Hb level of <10.0 versus ≥10.0 g/dL was selected. Stratification for geographic region is in line with previous scientific advice and differences in clinical practice between regions. There was no stratification of subjects by eGFR/CKD stages. The results for G3, G4, G5 stages do not raise any concerns in post-hoc analyses, while no benefit was observed in G2 groups who are not meeting inclusion criteria either (using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation at screening and not expected to start dialysis within 6 months of screening) this group should be considered in the B/R discussion for vadadustat.

The pivotal global INNO2VATE and PRO2TECT studies used a starting dose of 300 mg QD and maintenance doses of between 150 and 600 mg QD, with dose adjustments made every 4 weeks to maintain Hb levels as specified by the Dose Adjustment Algorithm provided with the study protocol. The starting dose and the proposed dosing algorithm for these studies were designed to maintain Hb in a predictable and controlled manner while minimizing abrupt increases or excessive rises in Hb levels. The dosing is queried in PK/PD section and further below in efficacy discussion.

The pivotal studies used the active comparator, darbepoetin alfa as it is marketed and available globally and it has a well-characterized safety profile. For darbepoetin alfa, the initial dose was based on the current PI for investigational sites in the US and the SmPC for all other investigational sites (ex-US) for adult patients with DD-CKD and NDD-CKD. Due to practical considerations to execute a double blind, double dummy design (the potential for dosing errors and inappropriate dose adjustments, delays in dosing, discomfort and risks inherent in repeated injections of placebo, extensive coordination to maintain the blind, the endpoints both efficacy and safety were outcomes that required laboratory and/or diagnostic measurements) the Applicant did not comply with the CHMP advice for either double-blind design or as a minimum to ensure blinding of the person(s) responsible for drug dosing to the treatment allocation (which was in line with the EMA/CHMP guideline (EMEA/CHMP/BWP/301636/2008)). The Applicant used an open-label study design with measures to keep only key sponsor personnel and external adjudication committee blinded. The use of a blinded

double dummy design was not impossible and was highly preferred in a study with an endpoint such as Haemoglobin and titrated dosing. Although the reasons as provided by the applicant are reasonable, challenges due to different administration route, the open label design is considered as a factor creating difficulties in assessment of issues with discontinuations, need for rescue treatments, non-inferiority and sensitivity analyses of primary and key secondary endpoints. It is acknowledged that roxadustat which is approved in EU for a similar indication was studied in a clinical development program with double-blind placebo controlled studies and open-label ESA controlled studies.

Blocked randomisation as a form of restriction in randomisation process was performed in all four pivotal trials, so a good balance of participant characteristics within each group is likely to be achieved.

RBC transfusion and ESA were used as rescue therapies. Investigators used their local institution's transfusion guidelines when determining whether to transfuse a study subject. Study drug (vadadustat or darbepoetin alfa) could be continued during the transfusion period. Starting at Week 6, subjects in both treatment groups were allowed to have their Hb rescued with ESA therapy. When possible, a subject on vadadustat had to be on the maximum dose of vadadustat for 2 weeks prior to ESA rescue. A subject on darbepoetin alfa could be rescued with another ESA per the standard of care. To qualify for ESA rescue, a subject had to experience worsening of the symptoms of anaemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared to Baseline and have a Hb of <9.5 g/dL. ESA rescue was also permitted when medically necessary at the discretion of the investigator. Following ESA rescue, the study drug was resumed at the same dose as previously used or 1 dose higher and adjusted according to the Dose Adjustment Algorithms.

In general, the primary and secondary efficacy endpoints are acceptable. Safety endpoints including cardiovascular safety and risk of RCC are assessed in relevant sections. Hb was selected as an objective measure of efficacy that was determined via a central laboratory and is a standard, objective laboratory assessment that is not subject to bias. The primary efficacy endpoint in the INNO2VATE and PRO2TECT studies was the change in average Hb between baseline and Weeks 24 to 36 (primary evaluation period, PEP) and the common key secondary efficacy endpoint was the change in average Hb value between baseline and Weeks 40 to 52 (secondary evaluation period, SEP). Other efficacy endpoints included Hb, iron, rescue treatment, dose adjustment and disease progression related endpoints. As the primary and key secondary endpoints were kept similar between all 4 pivotal studies, this allows for better comparison of data from different trials and different CKD populations.

The selected primary endpoint is a validated and well-established marker for the evaluation of anaemia therapies, for which expedient and reliable test methods are available in the clinical environment. It has also been used as primary endpoint for all the ESAs approved by CHMP (e.g., Aranesp (darbepoetin alfa), Biopoin/Eporatio (epoetin theta), Mircera (methoxy polyethylene glycol-epoetin beta), NeoRecormon (epoetin beta)). The specific time frame for the assessment of this primary endpoint (i.e. between Week 24 and Week 36, primary efficacy period, PEP) was selected based on the clinical development of approved ESAs and to be generally consistent with CHMP Guidelines on clinical development of similar biological medicinal products containing recombinant Erythropoietin (Revision) (EMEA/CHMP/BWP/301636/2008 Corr., dated 18 March 2010) (appropriate for analysing true effect of new treatment in case of changes from before). The handling of the primary endpoint in subjects treated with vadadustat who received ESA or transfusion rescue was queried (if they were counted as treatment failures for efficacy) and new analyses supported the primary analysis.

Per scientific advice, the secondary efficacy endpoints also test stability of attained haemoglobin levels. Initial treatment period was at least 36 weeks and was followed by long-term treatment period which adds up to at least 52 weeks (up to 104 weeks) allowing for an appropriate period for evaluation of efficacy and stability of effect. The secondary efficacy period (SEP) which was used for key secondary endpoint analyses was from Week 40 to 52.

The non-inferiority margin was changed to -0.75 g/dL from -0.5 g/dL against active comparator. Given the open label design of the pivotal studies and the timing of change in NI margin, there was a concern that the decision to change the NI margin was data driven, potentially threatening the integrity of study results. The Applicant retrospectively checked a number of patients who would have at least one Hb measurement during the primary efficacy period (PEP) prior to 31 Dec 2017, when change of NI margin was introduced. Less than 10% of the subjects were enrolled in Trial CI-0016 and only ~25% subjects were enrolled in other trials. Due to low numbers enrolled at the time of the change, the extend of possible clinical variability in real life, and the fact that 3 out of 4 trials (except for the smallest trial CI-0016) met the stringent NI margins, the change is considered acceptable.

The Applicant provided tabular overview of the major clinical study protocol amendments of the four pivotal clinical studies, together with potential impact and number of participants recruited by protocol version in the responses to D120 LoQ. Although changes were numerous, it can be concluded that they were done to align inclusion/exclusion criteria with available guidelines, and to provide more robust data and analyses eventually. It is unfortunate that number of those changes were not thought of during the planning stage of concerned studies. SAP changes were few, and happened prior to database lock. Overall, it seems that the clinical study protocol and SAP amendments did not affect the integrity of the results.

In summary, the clinical development program for vadadustat for treatment of anaemia in DD-CKD and NDD-CKD populations are acceptable for the size of the trials, use of active control, stratification for geographic region and baseline Hb level at study entry, duration of treatment, set up of primary and key secondary endpoints and their evaluation periods.

Efficacy data and additional analyses

The global Phase 3 clinical studies randomized 3476 subjects not on dialysis and 3923 subjects on dialysis. In the pooled INNO2VATE studies, a total of 1047 (53.8%) subjects were exposed to vadadustat for ≥52 weeks, 275 (14.1%) subjects in this group were exposed for ≥104 weeks. The number of subjects exposed to vadadustat in the pooled PRO2TECT studies was 964 (55.5%) for ≥52 weeks, 420 (24.2%) of these subjects were exposed for ≥104 weeks. The dose adjustments and interruptions to maintain subjects within target Hb range were less frequent in the vadadustat treatment group compared to the darbepoetin alfa treatment group (During Weeks 24 to 36 37.2% versus % 57.4 in CI-0017, 37.5% and 64.8% in CI-0016, 44.1% and 59.6% in CI-0014, and 38.6% and 54.9% in CI-0015, respectively. During Weeks 40 to 52, these percentages were 36.4% and 62.7% in CI-0017, 30.4% and 51.4% in CI-0016, 34.8% and 55.8% in CI-0014, and 30.8% and 52.0% in CI-0015, respectively.). However, discontinuations up to end of primary efficacy period (26 or 39 weeks) seem to be higher for vadadustat groups than active control groups across studies (46.8% vs 40.7%, 39.3% vs 32.3%, 33.1% vs 26.1%, and 50.6% vs 36.7% in the vadadustat and darbepoetin alfa treatment groups in CI-0014, CI-0015, CI-0016, and CI-0017, respectively). The posthoc sensitivity analyses show no significant impact of missing data due to discontinuations on the results.

So called important protocol deviations were reported more frequently in participants in vadadustat group (21-46%) compared to control group (6-20%) in all pivotal studies. High proportion of participants were excluded from the PP analysis set (30-40% in vadadustat groups, and 15-25% in control groups). Greater proportions of participants receiving vadadustat had dosing errors compared to control group. Nevertheless, it is expected that clear SmPC guidance can mitigate potential errors.

Treatment compliance was apparently high throughout the pivotal studies.

All the pivotal studies were global with European sites and thus potentially representative for the EU setting. However, EU enrolment was 14.3% and 17% of the pooled DD-CKD and NDD-CKD populations, respectively, which is below the recommended numbers in previous scientific advice (at least 30-40% of the total subjects in the pivotal studies). Subjects from the ROW region, treated per protocol according to European Hb target of 10.0-12.0 g/dL, accounted for between 24.4 to 33.5 percent of the randomized population in the Phase 3 studies. Altogether, patients from EU and ROW could be considered as %30-40 of the population who were treated according to the "European" haemoglobin target.

Other baseline characteristics have demonstrated some differences which were expected due to regional and disease severity related differences. The population studied in pivotal trials are considered as representative of the population in sought indication.

In the randomized population, vadadustat was shown to be non-inferior to darbepoetin alfa at the PEP (Weeks 24 to 36) in treating anaemia associated with CKD in both subjects on dialysis and not on dialysis since the lower bound of the 95% CI (-0.53, -0.23, and -0.04, -0.09, respectively) for the LS mean difference in the change from baseline was above the prespecified non-inferiority margin of -0.75 g/dL in each study. Except for INNO2VATE CI-0016 study which has shown widest 95% CI which passed beyond initially defined and agreed NI margin of 0.5 g/dL, all other studies met the more stringent NI margin also. For CI-0016 study, secondary analysis of HGB within normal range yields an odds ratio that reinforces the impression of ambiguous non-inferiority: OR = 0.6 (CI: 0.40, 0.96). NI margin of 0.5 g/dL being met for 3 out of 4 studies is reassuring as this value could be considered a diurnal variation level change, and is not clinically significant. In the NDD-CKD population, vadadustat treatment is considered non-inferior to darbepoetin alfa. In the DD-CKD population, primary endpoint is met, however, the upper limit of the 2-sided 95% CI for the difference between the mean in the vadadustat group and the mean in the darbepoetin alfa group was below zero for both DD-CKD trials.

The Applicant claims that EPO is produced primarily, but not exclusively, by the kidney. EPO is also synthetized in the liver and brain. The Applicant also claims that phase 2 data show no clear differentiation of the efficacy of the drug vs. the status of the patient's kidney function. In all studies, vadadustat is claimed to be efficacious regardless of baseline renal function. To support these claims in the absence of stratification for renal function at baseline or subgroup analysis for renal status, the Applicant was requested to submit subgroup analysis of primary and key secondary endpoints by the baseline renal function/CKD stage and in nephrectomised versus not nephrectomised subgroups. The percentage of subjects with a preferred term "Nephrectomy" was 1.9% in Trial CI-0016 and 3.1% in Trial CI-0017. Number of patients with bilateral nephrectomy is unknown but considered to be 22.

In NDD trials, eGFR was used as a prespecified dichotomic analysis of < 15mL/min/1.73 m^2 and ≥ 15 mL/min/1.73 m^2. According to this sensitivity analysis the NI margins are kept although the results may favour darbopoetin in some subgroups. For patients in G3, G4, G5 stages, the results are in line with the primary analysis. In Trial CI-0014, Least squares mean Hb change (95% CI) for G5 (n= 301 AKB300 and 292 DALFA) is 0.15 (-0.03, 0.33), for G4 (n= 384 AKB300 and 381 DALFA) is 0.03 (-0.10, 0.16), for G3 (n= 207 AKB300 and 200 DALFA) is 0.01 (-0.17, 0.18), for G2 (in/exclusion criterion at baseline) (n= 5 AKB300 and 8 DALFA) is 0.13 (-0.87, 1.12). In Trial CI-0015, Least squares mean Hb change (95% CI) for G5 (n= 244 AKB300 and 242 DALFA) is 0.11 (-0.05, 0.28), for G4 (n= 406 AKB300 and 413 DALFA) is 0.01 (-0.10, 0.13), for G3 (n= 187 AKB300 and 186 DALFA) is -0.17 (-0.33, -0.02), for G2 (in/exclusion criterion at baseline) (n= 7 AKB300 and 13 DALFA) is -0.21 . G2 population were not supposed to be treated with vadadustat in the trials, and according to very limited numbers enrolled there is no proven benefit in this population.

Non-inferiority of vadadustat to darbepoetin alfa for the primary efficacy endpoint was also demonstrated in the FAS and the PP population analyses. For the PP population, in the INNO2VATE CI-

0016, CI-0017, and the PRO2TECT CI-0014, CI-0015 studies, the lower bound of the 95% CI were -0.54, -0.21, 0, and -0.04, respectively. For the FAS population, the lower bound of the 95% CI were -0.54, -0.23, -0.04, and -0.09, respectively. Similar to the results with the randomized population analyses, all studies except for INNO2VATE CI-0016 study met NI margin of 0.5 g/dL for both the FAS and PP populations. As stated in the previous scientific advice and referred guidelines, consistency of results in FAS, RP and PP populations was required and is reassuring.

All pivotal studies comparing the treatment of vadadustat with ESA therapy in DD/NDD patients were open-label which may be subject to bias in particular to endpoints with treatment management decisions (e.g. rescue therapy, iv iron use). The primary analysis included patients who did not receive treatment, discontinued treatment, or used rescue therapy. However, sensitivity analyses of the primary endpoint demonstrated consistency in the vadadustat treatment response with and without the context of ESA rescue therapy. Sensitivity analyses censored at the time of rescue medication and handled the resulting missing data with multiple imputation (MI). For DD patients the most extreme CI lower limit produced was -0.56 (for CI-0016), and for NDD patients -0.10 (for CI-0015). To better represent the 'failure' of treatment, new sensitivity analyses were performed with missing values replaced by the Hb value preceding rescue medication (as per last-observation-carried-forward) or the worst Hb in previous time period, which supported the primary analysis.

As the primary endpoint met the non-inferiority margin, the key secondary endpoint was analyzed as specified in the SAP hierarchal analysis rules. The initial effect, observed in the randomized population between weeks 24 to 36, was sustained through Weeks 40 to 52 (key secondary efficacy endpoint). The non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the lower bound of the 95% CI (-0.34, -0.25, -0.06, and -0.10, respectively) for the LS mean difference in each study is above the prespecified non-inferiority margin of -0.75 g/dL or even the -0.5 g/dL margin. This result is reassuring and is in line with the hypothesis that vadadustat induces a slower and more controlled erythropoiesis in a longer term for these patients. Non-inferiority of vadadustat to darbepoetin alfa for the key secondary efficacy endpoint was also demonstrated in the FAS population analyses. For CI-0016 study, during the tipping point analysis the conclusion of vadadustat non-inferiority to darbepoetin alfa is tipped when the shift is -1.4, where the lower bound of 95% CI (-0.77) is below -0.75 g/dL. The Applicant pointed out the differences between two DD trials and is of the opinion that these results in slightly different populations but proposes the small size of the study as the only explanation for different results. This issue is not pursued as CI-0017 is a large enough study to evaluate efficacy of vadadustat in DD population with broader criteria for use of ESA.

The consistency in the vadadustat treatment response with and without the context of ESA rescue therapy was confirmed with sensitivity analyses for the secondary endpoint using an ANCOVA with multiple imputations and censoring for rescue therapy (considering narrow and broad-on-treatment rescue therapy) for each study.

The mean change from baseline Hb over time was evaluated as secondary endpoint. In all 4 studies, the mean Hb level gradually increased during the initial correction/conversion period and stabilized by the primary efficacy period, and was maintained throughout the secondary efficacy period. The level of Hb in Study CI-0017 initially decreased in the vadadustat treatment group as subjects converted from the ESA on which they had been stabilized for at least 12 weeks prior to baseline, likely reflecting the protocol not allowing dose increases for the first 4 weeks following the start of treatment. This decrease in Hb was not observed in the darbepoetin alfa group, likely due to the fact that subjects either continued on their baseline dose of darbepoetin alfa or the well-established conversion algorithms for ESAs were implemented in subjects who converted to darbepoetin alfa from their baseline ESA. This initial slower response in Hb (with vadadustat in comparison to darbepoetin alfa observed in the pivotal trials) tended to correct itself by the end of study periods in long term. The Applicant presented phase 2 studies which supported the choice of the 4 weeks period recommended

for dose increase. The Applicant maintains their opinion that the initiation dose of vadadustat should be independent of the previous ESA treatment dose, and a warning on initial Hb decrease and higher risk of need for rescue therapy will be communicated in the SmPC.

The proportion of subjects with RBC transfusions using the narrow rescue therapy criteria was generally higher in the vadadustat treatment group compared to the darbepoetin alfa treatment group in each of the 4 studies at Weeks 2 to 8. Similarly, the proportion of subjects who received ESA rescue using the narrow and broad rescue criteria were higher in the vadadustat treatment group compared with the darbepoetin alfa treatment groups at most time points during the study. Potential impact of different handling of rescue treatment for vadadustat and EPO arms is proposed as the only explanation by the Applicant. There were no protocol prespecified dose-related criteria to define ESA rescue with darbepoetin alfa in subjects randomized to the darbepoetin alfa treatment group. The sponsor conducted post-hoc analyses of ESA rescue that in addition to the prespecified narrow and broad-on-treatment ESA rescue definitions, also included subjects who received ≥50% or ≥100% increase in the dose of darbepoetin alfa from the previous closest reported dose. When the Applicant considered ≥100% dose increases in darbepoetin alfa group as rescue treatment, the post-hoc analyses showed a higher proportion of subjects in the darbepoetin alfa treatment group requiring ESA rescue compared with the vadadustat treatment group in the NDD-CKD population, and similar proportions in DD-CKD population.

The changes in the iron-related parameters are variable over time and there is no benefit with vadadustat use over EPO use in terms of decrease in need for iron supplementation.

Time to progression of CKD was similar for vadadustat and darbepoetin alfa for the NDD-CKD patients.

Number of pre-specified other secondary endpoints are not presented in the submitted dossier, and explanations were provided in the responses to D120 LoQ. Of note, proportions of subjects with Hb increase of >1.0 g/dL in studies CI-0015 and CI-0017 were lower in vadadustat groups compared to ESA groups and Times to achieve Hb increase of >1.0 g/dL from Baseline in studies CI-0015 and CI-0017 were lower in vadadustat groups compared to ESA groups, while numbers were comparable between groups in studies CI-0014 and CI-0016.

Dose adjustments were done according to the pre-specified dose adjustment algorithms (by study, and by region). Dose decrease or dose increase was observed in majority of participants (84 – 88%) receiving vadadustat in all pivotal studies, with roughly comparable numbers in darbepoetin alfa groups. More participants had dosing interrupted due to ESA rescue, dose decreased due to AE and dosing interrupted due to AE in vadadustat groups compared to darbepoetin alfa groups among the pivotal trials. Fewer participants had dosing interrupted due to elevated Hb in vadadustat compared to darbepoetin alfa groups among the pivotal trials. Those results suggest that vadadustat performed inconsistently over time and that vadadustat has increased number of AEs leading to dose adjustments compared to darbepoetin alfa.

There was no information registered on subject reported outcomes in the 4 pivotal trials in NDD-CKD and DD-CKD. Subject reported outcomes were collected in one Phase 2 trial (CI-0025); however, the results were inconclusive.

2.6.7. Conclusions on the clinical efficacy

Vadadustat gradually increased Hb to targeted ranges according to clinical practice guidelines in adult patients with CKD both on dialysis and not on dialysis. Hb levels stabilized by the weeks 24-36

(primary efficacy period) and was sustained through Weeks 40 to 52 (key secondary efficacy endpoint).

From an efficacy point of view, the benefit-risk can be considered positive. However as explained in the next section due to safety issues the indication was restricted only to the DD-CKD patients.

2.6.8. Clinical safety

The evaluation of the safety of vadadustat includes the results of nonclinical studies, consideration of potential risk due to an effect of hypoxia-inducible factor (HIF) prolyl-4-hydroxylase (PH) enzyme inhibitors on vascular endothelial growth factor (VEGF), the known risks of erythropoiesis-stimulating agents (ESA)s in patients with chronic kidney disease (CKD), potential risks of the new class of HIF inhibitors, and the assessment of treatment-emergent adverse events (TEAEs) in the vadadustat clinical development program.

Four Pivotal Phase 3 studies have been included in this safety assessment of Vadadustat. However as the approved indication is restricted only to the DD-CKD patients due to safety issues only the relevant studies are reflected in the SmPC.

All phase 3 studies were randomized, open-label, active-controlled studies that evaluated the efficacy and safety of vadadustat for the treatment of anaemia in subjects with DD-CKD or NDD-CKD compared with the standard erythropoiesis-stimulating agent darbepoetin alfa.

2.6.8.1. Patient exposure

From the initiation of the development program on 19 Aug 2009 to the data cutoff date of 15 Oct 2020, 5374 subjects have been exposed to vadadustat in completed studies in subjects with anaemia associated with CKD, in healthy subjects, and in subjects with moderate hepatic impairment:

- CKD population: 4686 subjects with CKD (DD-CKD and NDD-CKD) have been exposed to vadadustat, of which 3686 subjects have been exposed to vadadustat in completed global Phase 3 studies in the CKD population.
    - DD-CKD population: 2503 subjects with DD-CKD have been exposed to vadadustat, of which 1947 subjects have been exposed to vadadustat in completed global Phase 3 studies in the DD-CKD population.
    - NDD-CKD population: 2183 subjects with NDD-CKD have been exposed to vadadustat, of which 1739 subjects have been exposed to vadadustat in completed global Phase 3 studies in the NDD-CKD population.
- Healthy subject population: 717 healthy subjects and 8 subjects with moderate hepatic impairment have been exposed to vadadustat.

In the ongoing Study 404-201-00012 in subjects with DD-CKD, data are still blinded. At the data cutoff date of 15 Oct 2020, 209 subjects had been exposed to either vadadustat or darbepoetin alfa.

For the purpose of this document, results for the 4 pooled global Phase 3 studies in subjects with anaemia associated with CKD are presented herein as the primary safety analyses.

The safety database was grouped into three pooling blocks: Pooled DD-CKD population, Pooled NDD-CKD population and Pooled CKD population.

The Applicant states that the regional Japanese studies were not designed to assess MACE outcomes, instead were focused on evaluating mean Hb levels and overall safety of vadadustat. Due to this reason, Japanese phase 3 studies were not pooled with the global Phase 3 studies.

However, as 4 Phase 3 trials performed in Japan could not be included in the pooled safety evaluation due to differences in study designs, the Applicant was asked to provide a summary of safety information from these studies. The 4 Phase 3 trials performed in Japan (MT-6548-J03, MT-6548-J04, MT-6548-J02 and MT-6548-J01) included 379 patients with CKD treated with vadadustat. No new safety concerns were identified from these Phase 3 trials.

The studies included in the pooled CKD population for global Phase 3 studies are presented by study and by treatment group (Table below). Subjects were included in the safety population if they received at least 1 dose of study drug and analysis was based on the actual treatment received.

Table 57 **Number of Subjects by Study and Treatment – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

Study	Vadadustat N = 3686 n (%)	Darbepoetin Alfa N = 3687 n (%)	Total N = 7373 n (%)
CI-0014[a]	878 (23.8)	870 (23.6)	1748 (23.7)
CI-0015[a]	861 (23.3)	862 (23.4)	1723 (23.3)
CI-0016[b]	179 (4.9)	186 (5.0)	365 (5.0)
CI-0017[b]	1768 (48.0)	1769 (48.0)	3537 (48.0)
Total	3686 (100.0)	3687 (100.0)	7373 (100.0)

CKD: chronic kidney disease; DD-CKD: dialysis-dependent chronic kidney disease N: number of subjects; n: number of subjects within specific category; NDD-CKD: non-dialysis-dependent chronic kidney disease
a. Studies included in the NDD-CKD population for global Phase 3 Studies.
b. Studies included in the DD-CKD population for global Phase 3 Studies.
Source: ISS Table 14.1.1.1c

In the pooled CKD population, the proportion of subjects who completed the studies was similar for vadadustat-treated subjects (80.2% of subjects) and darbepoetin alfa-treated subjects (80.4% of subjects, Table 6). All 4 of the global Phase 3 studies had a minimum of 4 weeks of follow-up period (end of treatment + 4 weeks) for post-treatment visit for safety (either in person or via telephone).

Table 58 **Subject Disposition (Study Completion) – Pooled DD-CKD, NDD-CKD, and CKD Populations for Global Phase 3 Studies (Safety Population)**

Category	DD-CKD Population		NDD-CKD Population		CKD Population	
	Vadadustat N = 1947 n (%)	Darbepoetin Alfa N = 1955 n (%)	Vadadustat N = 1739 n (%)	Darbepoetin Alfa N = 1732 n (%)	Vadadustat N = 3686 n (%)	Darbepoetin Alfa N = 3687 n (%)
Completed study	1583 (81.3)	1582 (80.9)	1373 (79.0)	1384 (79.9)	2956 (80.2)	2966 (80.4)
Discontinued study	364 (18.7)	373 (19.1)	366 (21.0)	348 (20.1)	730 (19.8)	721 (19.6)
Primary reason for discontinuation from study						
Death	277 (14.2)	295 (15.1)	311 (17.9)	303 (17.5)	588 (16.0)	598 (16.2)
Withdrawal of informed consent	47 (2.4)	45 (2.3)	33 (1.9)	18 (1.0)	80 (2.2)	63 (1.7)
Lost to follow-up	40 (2.1)	33 (1.7)	22 (1.3)	27 (1.6)	62 (1.7)	60 (1.6)

CKD: chronic kidney disease; DD-CKD: dialysis-dependent chronic kidney disease; N: number of subjects; n: number of subjects within specific category; NDD-CKD: non-dialysis-dependent chronic kidney disease
Completed study for an individual subject was defined as a subject who received study drug treatment at any time during the study, was alive, had not withdrawn consent, and was not lost to follow-up at the global end-of-study Follow up Visit.
Source: ISS Tables 14.1.2.2a, b, and c

The proportion of subjects who completed study drug treatment was lower in the vadadustat treatment group (54.0%) compared to the darbepoetin alfa treatment group (64.1%, Table below).

Table 59 Subject Disposition (Study Drug Treatment Completion) – Pooled DD-CKD, NDD-CKD, and CKD Populations for Global Phase 3 Studies (Safety Population)

	DD-CKD Population		NDD-CKD Population		CKD Population	
Category	Vadadustat N = 1947 n (%)	Darbepoetin Alfa N = 1955 n (%)	Vadadustat N = 1739 n (%)	Darbepoetin Alfa N = 1732 n (%)	Vadadustat N = 3686 n (%)	Darbepoetin Alfa N = 3687 n (%)
Completed treatment	999 (51.3)	1263 (64.6)	990 (56.9)	1100 (63.5)	1989 (54.0)	2363 (64.1)
Discontinued study drug treatment	948 (48.7)	692 (35.4)	748 (43.0)	631 (36.4)	1696 (46.0)	1323 (35.9)
Subjects with missing status of treatment compliance	0	0	1 (0.1)	1 (0.1)	1 (0.0)	1 (0.0)
Primary reason for discontinuation from study drug treatment						
Unacceptable toxicity, drug intolerability, or adverse event	114 (5.9)	61 (3.1)	214 (12.3)	170 (9.8)	328 (8.9)	231 (6.3)
Investigator's decision	104 (5.3)	44 (2.3)	73 (4.2)	56 (3.2)	177 (4.8)	100 (2.7)
Subject became pregnant	2 (0.1)	2 (0.1)	1 (0.1)	0	3 (0.1)	2 (0.1)
Kidney transplant	120 (6.2)	105 (5.4)	34 (2.0)	23 (1.3)	154 (4.2)	128 (3.5)
Lack of efficacy	64 (3.3)	5 (0.3)	26 (1.5)	6 (0.3)	90 (2.4)	11 (0.3)
Subject no longer wanted to receive study drug	232 (11.9)	113 (5.8)	172 (9.9)	130 (7.5)	404 (11.0)	243 (6.6)
Death[a]	148 (7.6)	191 (9.8)	68 (3.9)	81 (4.7)	216 (5.9)	272 (7.4)
Other[a]	164 (8.4)	171 (8.7)	160 (9.2)	165 (9.5)	324 (8.8)	336 (9.1)

CKD: chronic kidney disease; DD-CKD: dialysis-dependent chronic kidney disease; N: number of subjects; n: number of subjects within specific category; NDD-CKD: non-dialysis-dependent chronic kidney disease
Completed treatment for an individual subject was defined as a subject that was on study drug treatment at the time of study closure.
a. "Death" was identified from the UTDIAE collected on the case report forms and summarized separately.
Source: ISS Tables 14.1.2.2a, b, and c

Since 4 different definitions of the outcome 'death' are used across the Dossier, the Applicant provided an additional table summarising deaths per each definition (additional table below).

Table 60 Definition of death and frequencies in the three pooling blocks in the phase 3 clinical trials of vadadustat.

Definitions of deaths	pooled DD-CKD population		pooled NDD-CKD population		pooled CKD population	
	Vadadustat N = 1947	Darbepoetin alfa N = 1955	Vadadustat N = 1739	Darbepoetin alfa N = 1732	Vadadustat N = 3686	Darbepoetin alfa N = 3687
Death in 'Primary reason for discontinuation from study drug treatment'	148 (7.6)	191 (9.8)	68 (3.9)	81 (4.7)	216 (5.9)	272 (7.4)
Death in 'Primary reason for discontinuation from study'	277 (14.2)	295 (15.1)	311 (17.9)	303 (17.5)	588 (16.0)	598 (16.2)
Any TEAE leading to death	281 (14.4)	294 (15.0)	312 (17.9)	302 (17.4)	593 (16.1)	596 (16.2)
All deaths	291 (14.9)	310 (15.9)	319 (18.3)	307 (17.7)	610 (16.5)	617 (16.7)

Source: 2.7.4 Summary of Clinical Safety Table 6 (Primary reason for discontinuation from study), Table 7 (Primary reason for discontinuation from study drug), Table 13, Table 14, and Table 15 (TEAE leading to death, all deaths).

Table 61 **Study Drug Exposure – Pooled DD-CKD, and NDD-CKD, and CKD Populations for Global Phase 3 Studies (Safety Population)**

Parameter Statistics	DD-CKD Population		NDD-CKD Population		CKD Population	
	Vadadustat N = 1947	Darbepoetin Alfa N = 1955	Vadadustat N = 1739	Darbepoetin Alfa N = 1732	Vadadustat N = 3686	Darbepoetin Alfa N = 3687
Total duration of exposure (weeks)[a]						
Mean (SD)	59.45 (37.568)	71.25 (36.729)	69.24 (47.739)	75.46 (48.518)	64.06 (42.943)	73.23 (42.720)
Median	55.86	71.71	59.43	67.00	56.71	70.00
Q1, Q3	28.86, 85.00	43.86, 96.14	33.29, 101.86	36.14, 112.14	31.86, 91.71	39.86, 102.14
Min – Max	0.1 – 163.1	0.1 – 169.1	0.1 – 204.1	0.1 – 208.1	0.1 – 204.1	0.1 – 208.1
Total duration category, n (%)						
<4 weeks	73 (3.7)	29 (1.5)	56 (3.2)	39 (2.3)	129 (3.5)	68 (1.8)
≥4 and <13 weeks	182 (9.3)	89 (4.6)	135 (7.8)	104 (6.0)	317 (8.6)	193 (5.2)
≥13 and <26 weeks	178 (9.1)	122 (6.2)	139 (8.0)	95 (5.5)	317 (8.6)	217 (5.9)
≥26 and <39 weeks	196 (10.1)	158 (8.1)	238 (13.7)	252 (14.5)	434 (11.8)	410 (11.1)
≥39 and <52 weeks	271 (13.9)	240 (12.3)	207 (11.9)	191 (11.0)	478 (13.0)	431 (11.7)
≥52 and <78 weeks	461 (23.7)	519 (26.5)	315 (18.1)	315 (18.2)	776 (21.1)	834 (22.6)
≥78 and <104 weeks	311 (16.0)	395 (20.2)	229 (13.2)	252 (14.5)	540 (14.7)	647 (17.5)
≥104 weeks	275 (14.1)	403 (20.6)	420 (24.2)	484 (27.9)	695 (18.9)	887 (24.1)

CKD: chronic kidney disease; DD-CKD: dialysis-dependent chronic kidney disease; Max: maximum; Min: minimum; N: number of subjects; n: number of subjects within specific category; NDD-CKD: non-dialysis-dependent chronic kidney disease; Q1: first quartile; Q3: third quartile; SD: standard deviation

a. Duration (weeks) = (last treatment date – first treatment date + 1)/7.

Source: ISS Tables 14.1.4.2a, b, and c

In the pooled CKD population a total of 2923 (79,5%) subjects were exposed to vadadustat for at least 6 months, a total of 2011 (54,6%) subjects were exposed to vadadustat for a least 1 year and a total of 695 (18,9%) subjects were exposed to vadadustat for at least 2 years (Table above).

2.6.8.2. Adverse events

Analysis of Treatment-Emergent Adverse Events

Pooled Global Phase 3 DD-CKD Population

A summary of TEAEs reported for subjects in the pooled DD-CKD population for global Phase 3 studies is presented by treatment group in Table below.

Table 62 **Overall Summary of Treatment-Emergent Adverse Events – Pooled DD-CKD Population for Global Phase 3 Studies (Safety Population)**

Category	Vadadustat N = 1947 PY = 3222.0		Darbepoetin Alfa N = 1955 PY = 3245.8		Total N = 3902 PY = 6467.8	
	n (%)	E (E × 100/PY)	n (%)	E (E × 100/PY)	n (%)	E (E × 100/PY)
Any TEAE	1712 (87.9)	14478 (449.3)	1739 (89.0)	15247 (469.7)	3451 (88.4)	29725 (459.6)
Any drug-related TEAE[a]	176 (9.0)	275 (8.5)	73 (3.7)	89 (2.7)	249 (6.4)	364 (5.6)
Any severe TEAE	767 (39.4)	2357 (73.2)	813 (41.6)	2642 (81.4)	1580 (40.5)	4999 (77.3)
Any treatment-emergent SAE	1062 (54.5)	3718 (115.4)	1137 (58.2)	3991 (123.0)	2199 (56.4)	7709 (119.2)
Any drug-related treatment-emergent SAE[a]	30 (1.5)	35 (1.1)	31 (1.6)	38 (1.2)	61 (1.6)	73 (1.1)
Any TEAE leading to discontinuation from study drug	96 (4.9)	114 (3.5)	22 (1.1)	23 (0.7)	118 (3.0)	137 (2.1)
Any drug-related TEAE[a] leading to discontinuation from study drug	44 (2.3)	54 (1.7)	5 (0.3)	5 (0.2)	49 (1.3)	59 (0.9)
Any TEAEs leading to death	281 (14.4)	281 (8.7)	294 (15.0)	295[b] (9.1)	575 (14.7)	576 (8.9)
All deaths[c]	291 (14.9)	291 (9.0)	310 (15.9)	310 (9.6)	601 (15.4)	601 (9.3)

DD-CKD: dialysis-dependent chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event

A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.

MedDRA version 23.0

a. Relatedness as assessed by investigator and/or sponsor.

b. In Study CI-0017, 1 subject in the darbepoetin alfa treatment group had 2 TEAEs (coronary artery disease and sepsis) that led to death. Additional details are presented in CSR AKB-6548-CI-0017.

c. All deaths were collected during the study and presented in this table irrespective of whether a preceding TEAE was recorded.

Source: ISS Table 14.3.1.2a

Pooled Global Phase 3 NDD-CKD Population

A summary of TEAEs reported for subjects in the pooled NDD-CKD population for global Phase 3 studies is presented by treatment group in Table below.

Table 63 **Overall Summary of Treatment-Emergent Adverse Events – Pooled NDD-CKD Population for Global Phase 3 Studies (Safety Population)**

	Vadadustat N = 1739 PY = 3113.3		Darbepoetin Alfa N = 1732 PY = 3174.3		Total N = 3471 PY = 6287.7	
Category	n (%)	E (E × 100/PY)	n (%)	E (E × 100/PY)	n (%)	E (E × 100/PY)
Any TEAE	1565 (90.0)	12939 (415.6)	1553 (89.7)	13093 (412.5)	3118 (89.8)	26032 (414.0)
Any drug-related TEAE	195 (11.2)	301 (9.7)	101 (5.8)	129 (4.1)	296 (8.5)	430 (6.8)
Any severe TEAE	815 (46.9)	2222 (71.4)	783 (45.2)	1991 (62.7)	1598 (46.0)	4213 (67.0)
Any treatment-emergent SAE	1077 (61.9)	3263 (104.8)	1049 (60.6)	3168 (99.8)	2126 (61.3)	6431 (102.3)
Any drug-related treatment-emergent SAE	36 (2.1)	40 (1.3)	24 (1.4)	26 (0.8)	60 (1.7)	66 (1.0)
Any TEAE leading to discontinuation from study drug	163 (9.4)	207 (6.6)	104 (6.0)	136 (4.3)	267 (7.7)	343 (5.5)
Any drug-related TEAE leading to discontinuation from study drug	29 (1.7)	31 (1.0)	6 (0.3)	7 (0.2)	35 (1.0)	38 (0.6)
Any TEAEs leading to death	312 (17.9)	312 (10.0)	302 (17.4)	302 (9.5)	614 (17.7)	614 (9.8)
All deaths[a]	319 (18.3)	319 (10.2)	307 (17.7)	307 (9.7)	626 (18.0)	626 (10.0)

E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; NDD-CKD: non-dialysis-dependent chronic kidney disease; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
a. All deaths were collected during the study and presented in this table irrespective of whether a preceding TEAE was recorded.
Source: ISS Table 14.3.1.2b

Pooled Global Phase 3 CKD Population

A summary of TEAEs reported for subjects in the pooled CKD population for global Phase 3 studies is presented by treatment group in Table below.

Table 64 **Overall Summary of Treatment-Emergent Adverse Events – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

	Vadadustat N = 3686 PY = 335.3		Darbepoetin Alfa N = 3687 PY = 6420.1		Total N = 7373 PY = 12755.5	
Category	n (%)	E (E × 100/PY)	n (%)	E (E × 100/PY)	n (%)	E (E × 100/PY)
Any TEAE	3277 (88.9)	27417 (432.8)	3292 (89.3)	28340 (441.4)	6569 (89.1)	55757 (437.1)
Any drug-related TEAE	371 (10.1)	576 (9.1)	174 (4.7)	218 (3.4)	545 (7.4)	794 (6.2)
Any severe TEAE	1582 (42.9)	4579 (72.3)	1596 (43.3)	4633 (72.2)	3178 (43.1)	9212 (72.2)
Any treatment-emergent SAE	2139 (58.0)	6981 (110.2)	2186 (59.3)	7159 (111.5)	4325 (58.7)	14140 (110.9)
Any drug-related treatment-emergent SAE	66 (1.8)	75 (1.2)	55 (1.5)	64 (1.0)	121 (1.6)	139 (1.1)
Any TEAE leading to discontinuation from study drug	259 (7.0)	321 (5.1)	126 (3.4)	159 (2.5)	385 (5.2)	480 (3.8)
Any drug-related TEAE leading to discontinuation from study drug	73 (2.0)	85 (1.3)	11 (0.3)	12 (0.2)	84 (1.1)	97 (0.8)
Any TEAEs leading to death	593 (16.1)	593 (9.4)	596 (16.2)	597[a] (9.3)	1189 (16.1)	1190 (9.3)
All deaths[b]	610 (16.5)	610 (9.6)	617 (16.7)	617 (9.6)	1227 (16.6)	1227 (9.6)

CKD: chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
a. In Study CI-0017, 1 subject in the darbepoetin alfa treatment group had 2 TEAEs (coronary artery disease and sepsis) that led to death. Additional details are presented in CSR AKB-6548-CI-0017.
b. All deaths were collected during the study and presented in this table irrespective of whether a preceding TEAE was recorded.
Source: ISS Table 14.3.1.2c

Common Treatment-Emergent Adverse Events

Pooled Global Phase 3 DD-CKD Population

A summary of TEAEs reported in ≥5% of subjects in any treatment group in the pooled DD-CKD population for global Phase 3 studies is presented by SOC and PT in Table below.

Table 65 **Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in Any Treatment Group – Pooled DD-CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 1947 PY = 3222.0 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 1955 PY = 3245.8 n (%)	 E (E × 100/PY)	Total N = 3902 PY = 6467.8 n (%)	 E (E × 100/PY)
Any TEAE	1712 (87.9)	14478 (449.3)	1739 (89.0)	15247 (469.7)	3451 (88.4)	29725 (459.6)
Infections and infestations	974 (50.0)	2325 (72.2)	1039 (53.1)	2464 (75.9)	2013 (51.6)	4789 (74.0)
Pneumonia	208 (10.7)	276 (8.6)	187 (9.6)	217 (6.7)	395 (10.1)	493 (7.6)
Urinary tract infection	121 (6.2)	144 (4.5)	133 (6.8)	191 (5.9)	254 (6.5)	335 (5.2)
Upper respiratory tract infection	104 (5.3)	125 (3.9)	121 (6.2)	137 (4.2)	225 (5.8)	262 (4.1)
Sepsis	95 (4.9)	103 (3.2)	110 (5.6)	120 (3.7)	205 (5.3)	223 (3.4)
Nasopharyngitis	102 (5.2)	142 (4.4)	92 (4.7)	116 (3.6)	194 (5.0)	258 (4.0)
Bronchitis	72 (3.7)	82 (2.5)	102 (5.2)	120 (3.7)	174 (4.5)	202 (3.1)
Gastrointestinal disorders	786 (40.4)	1808 (56.1)	724 (37.0)	1707 (52.6)	1510 (38.7)	3515 (54.3)
Diarrhoea	248 (12.7)	295 (9.2)	196 (10.0)	249 (7.7)	444 (11.4)	544 (8.4)
Nausea	163 (8.4)	209 (6.5)	147 (7.5)	183 (5.6)	310 (7.9)	392 (6.1)
Vomiting	133 (6.8)	160 (5.0)	134 (6.9)	167 (5.1)	267 (6.8)	327 (5.1)
Injury, poisoning, and procedural complications	733 (37.6)	1651 (51.2)	741 (37.9)	1781 (54.9)	1474 (37.8)	3432 (53.1)
Fall	161 (8.3)	215 (6.7)	168 (8.6)	234 (7.2)	329 (8.4)	449 (6.9)
Dialysis-related complication	105 (5.4)	148 (4.6)	132 (6.8)	242 (7.5)	237 (6.1)	390 (6.0)
Arteriovenous fistula site complication	102 (5.2)	161 (5.0)	129 (6.6)	173 (5.3)	231 (5.9)	334 (5.2)
Arteriovenous fistula thrombosis	112 (5.8)	141 (4.4)	88 (4.5)	116 (3.6)	200 (5.1)	257 (4.0)
Vascular disorders	631 (32.4)	1165 (36.2)	676 (34.6)	1246 (38.4)	1307 (33.5)	2411 (37.3)
Hypertension	216 (11.1)	287 (8.9)	266 (13.6)	353 (10.9)	482 (12.4)	640 (9.9)
Hypotension	153 (7.9)	229 (7.1)	157 (8.0)	220 (6.8)	310 (7.9)	449 (6.9)
Metabolism and nutrition disorders	590 (30.3)	1099 (34.1)	640 (32.7)	1183 (36.4)	1230 (31.5)	2282 (35.3)
Hyperkalaemia	168 (8.6)	223 (6.9)	201 (10.3)	258 (7.9)	369 (9.5)	481 (7.4)
Fluid overload	169 (8.7)	244 (7.6)	179 (9.2)	238 (7.3)	348 (8.9)	482 (7.5)
Hypoglycaemia	97 (5.0)	138 (4.3)	87 (4.5)	127 (3.9)	184 (4.7)	265 (4.1)
Respiratory, thoracic, and mediastinal disorders	486 (25.0)	970 (30.1)	568 (29.1)	1085 (33.4)	1054 (27.0)	2055 (31.8)
Cough	110 (5.6)	136 (4.2)	126 (6.4)	149 (4.6)	236 (6.0)	285 (4.4)
Dyspnoea	105 (5.4)	128 (4.0)	129 (6.6)	154 (4.7)	234 (6.0)	282 (4.4)
Cardiac disorders	463 (23.8)	915 (28.4)	537 (27.5)	1108 (34.1)	1000 (25.6)	2023 (31.3)
Atrial fibrillation	74 (3.8)	92 (2.9)	101 (5.2)	114 (3.5)	175 (4.5)	206 (3.2)
Nervous system disorders	486 (25.0)	908 (28.2)	464 (23.7)	803 (24.7)	950 (24.3)	1711 (26.5)
Headache	168 (8.6)	342 (10.6)	146 (7.5)	219 (6.7)	314 (8.0)	561 (8.7)
Musculoskeletal and connective tissue disorders	429 (22.0)	785 (24.4)	468 (23.9)	823 (25.4)	897 (23.0)	1608 (24.9)
Pain in extremity	99 (5.1)	125 (3.9)	123 (6.3)	142 (4.4)	222 (5.7)	267 (4.1)
Back pain	83 (4.3)	103 (3.2)	103 (5.3)	123 (3.8)	186 (4.8)	226 (3.5)

DD-CKD: dialysis-dependent chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
Source: ISS Table 14.3.1.3a

Pooled Global Phase 3 NDD-CKD Population

A summary of TEAEs reported in ≥5% of subjects in any treatment group in the pooled NDD-CKD population for global Phase 3 studies is presented by SOC and PT in Table below.

Table 66 **Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in Any Treatment Group – Pooled NDD-CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 1739 PY = 3113.3 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 1732 PY = 3174.3 n (%)	 E (E × 100/PY)	Total N = 3471 PY = 6287.7 n (%)	 E (E × 100/PY)
Any TEAE	1565 (90.0)	12939 (415.6)	1553 (89.7)	13093 (412.5)	3118 (89.8)	26032 (414.0)
Infections and infestations	899 (51.7)	2022 (64.9)	903 (52.1)	2132 (67.2)	1802 (51.9)	4154 (66.1)
Urinary tract infection	218 (12.5)	301 (9.7)	229 (13.2)	350 (11.0)	447 (12.9)	651 (10.4)
Pneumonia	172 (9.9)	211 (6.8)	159 (9.2)	199 (6.3)	331 (9.5)	410 (6.5)
Upper respiratory tract infection	107 (6.2)	128 (4.1)	116 (6.7)	144 (4.5)	223 (6.4)	272 (4.3)
Nasopharyngitis	103 (5.9)	125 (4.0)	109 (6.3)	139 (4.4)	212 (6.1)	264 (4.2)
Renal and urinary disorders	755 (43.4)	1055 (33.9)	750 (43.3)	1071 (33.7)	1505 (43.4)	2126 (33.8)
End-stage renal disease	542 (31.2)	566 (18.2)	551 (31.8)	590 (18.6)	1093 (31.5)	1156 (18.4)
Acute kidney injury	120 (6.9)	147 (4.7)	109 (6.3)	126 (4.0)	229 (6.6)	273 (4.3)
Metabolism and nutrition disorders	684 (39.3)	1580 (50.8)	696 (40.2)	1521 (47.9)	1380 (39.8)	3101 (49.3)
Hyperkalaemia	189 (10.9)	235 (7.5)	221 (12.8)	269 (8.5)	410 (11.8)	504 (8.0)
Hypoglycaemia	106 (6.1)	158 (5.1)	104 (6.0)	137 (4.3)	210 (6.1)	295 (4.7)
Fluid overload	107 (6.2)	133 (4.3)	96 (5.5)	134 (4.2)	203 (5.8)	267 (4.2)
Hyperphosphataemia	104 (6.0)	106 (3.4)	93 (5.4)	96 (3.0)	197 (5.7)	202 (3.2)
Metabolic acidosis	101 (5.8)	116 (3.7)	76 (4.4)	81 (2.6)	177 (5.1)	197 (3.1)
Gastrointestinal disorders	697 (40.1)	1512 (48.6)	573 (33.1)	1291 (40.7)	1270 (36.6)	2803 (44.6)
Diarrhoea	241 (13.9)	301 (9.7)	163 (9.4)	206 (6.5)	404 (11.6)	507 (8.1)
Nausea	161 (9.3)	184 (5.9)	129 (7.4)	157 (4.9)	290 (8.4)	341 (5.4)
Constipation	119 (6.8)	132 (4.2)	114 (6.6)	124 (3.9)	233 (6.7)	256 (4.1)
Vomiting	100 (5.8)	119 (3.8)	94 (5.4)	115 (3.6)	194 (5.6)	234 (3.7)
Vascular disorders	509 (29.3)	774 (24.9)	537 (31.0)	859 (27.1)	1046 (30.1)	1633 (26.0)
Hypertension	279 (16.0)	359 (11.5)	320 (18.5)	421 (13.3)	599 (17.3)	780 (12.4)
Hypotension	100 (5.8)	120 (3.9)	89 (5.1)	107 (3.4)	189 (5.4)	227 (3.6)
General disorders and administration site conditions	483 (27.8)	700 (22.5)	417 (24.1)	612 (19.3)	900 (25.9)	1312 (20.9)
Oedema peripheral	195 (11.2)	234 (7.5)	178 (10.3)	204 (6.4)	373 (10.7)	438 (7.0)
Musculoskeletal and connective tissue disorders	414 (23.8)	651 (20.9)	427 (24.7)	735 (23.2)	841 (24.2)	1386 (22.0)
Arthralgia	93 (5.3)	100 (3.2)	95 (5.5)	107 (3.4)	188 (5.4)	207 (3.3)
Back pain	95 (5.5)	104 (3.3)	82 (4.7)	88 (2.8)	177 (5.1)	192 (3.1)
Nervous system disorders	394 (22.7)	591 (19.0)	428 (24.7)	637 (20.1)	822 (23.7)	1228 (19.5)
Headache	69 (4.0)	77 (2.5)	88 (5.1)	98 (3.1)	157 (4.5)	175 (2.8)
Respiratory, thoracic, and mediastinal disorders	416 (23.9)	733 (23.5)	398 (23.0)	769 (24.2)	814 (23.5)	1502 (23.9)
Cough	88 (5.1)	97 (3.1)	96 (5.5)	104 (3.3)	184 (5.3)	201 (3.2)
Dyspnoea	76 (4.4)	103 (3.3)	89 (5.1)	113 (3.6)	165 (4.8)	216 (3.4)
Injury, poisoning, and procedural complications	355 (20.4)	678 (21.8)	391 (22.6)	768 (24.2)	746 (21.5)	1446 (23.0)
Fall	153 (8.8)	191 (6.1)	152 (8.8)	203 (6.4)	305 (8.8)	394 (6.3)

E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; NDD-CKD: non-dialysis-dependent chronic kidney disease; PY: patient-year; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
Source: ISS Table 14.3.1.3b

Pooled Global Phase 3 CKD Population

A summary of TEAEs reported in ≥5% of subjects in any treatment group in the pooled CKD population for global Phase 3 studies is presented by SOC and PT in Table 18.

Table 67 **Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in Any Treatment Group – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 3686 PY = 6335.3 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 3687 PY = 6420.1 n (%)	 E (E × 100/PY)	Total N = 7373 PY = 12755.5 n (%)	 E (E × 100/PY)
Any TEAE	3277 (88.9)	27417 (432.8)	3292 (89.3)	28340 (441.4)	6569 (89.1)	55757 (437.1)
Infections and infestations	1873 (50.8)	4347 (68.6)	1942 (52.7)	4596 (71.6)	3815 (51.7)	8943 (70.1)
Pneumonia	380 (10.3)	487 (7.7)	346 (9.4)	416 (6.5)	726 (9.8)	903 (7.1)
Urinary tract infection	339 (9.2)	445 (7.0)	362 (9.8)	541 (8.4)	701 (9.5)	986 (7.7)
Upper respiratory tract infection	211 (5.7)	253 (4.0)	237 (6.4)	281 (4.4)	448 (6.1)	534 (4.2)
Nasopharyngitis	205 (5.6)	267 (4.2)	201 (5.5)	255 (4.0)	406 (5.5)	522 (4.1)
Bronchitis	150 (4.1)	171 (2.7)	185 (5.0)	208 (3.2)	335 (4.5)	379 (3.0)
Gastrointestinal disorders	1483 (40.2)	3320 (52.4)	1297 (35.2)	2998 (46.7)	2780 (37.7)	6318 (49.5)
Diarrhoea	489 (13.3)	596 (9.4)	359 (9.7)	455 (7.1)	848 (11.5)	1051 (8.2)
Nausea	324 (8.8)	393 (6.2)	276 (7.5)	340 (5.3)	600 (8.1)	733 (5.7)
Vomiting	233 (6.3)	279 (4.4)	228 (6.2)	282 (4.4)	461 (6.3)	561 (4.4)
Constipation	206 (5.6)	229 (3.6)	207 (5.6)	231 (3.6)	413 (5.6)	460 (3.6)
Metabolism and nutrition disorders	1274 (34.6)	2679 (42.3)	1336 (36.2)	2704 (42.1)	2610 (35.4)	5383 (42.2)
Hyperkalaemia	357 (9.7)	458 (7.2)	422 (11.4)	527 (8.2)	779 (10.6)	985 (7.7)
Fluid overload	276 (7.5)	377 (6.0)	275 (7.5)	372 (5.8)	551 (7.5)	749 (5.9)
Hypoglycaemia	203 (5.5)	296 (4.7)	191 (5.2)	264 (4.1)	394 (5.3)	560 (4.4)
Vascular disorders	1140 (30.9)	1939 (30.6)	1213 (32.9)	2105 (32.8)	2353 (31.9)	4044 (31.7)
Hypertension	495 (13.4)	646 (10.2)	586 (15.9)	774 (12.1)	1081 (14.7)	1420 (11.1)
Hypotension	253 (6.9)	349 (5.5)	246 (6.7)	327 (5.1)	499 (6.8)	676 (5.3)
Injury, poisoning, and procedural complications	1088 (29.5)	2329 (36.8)	1132 (30.7)	2549 (39.7)	2220 (30.1)	4878 (38.2)
Fall	314 (8.5)	406 (6.4)	320 (8.7)	437 (6.8)	634 (8.6)	843 (6.6)
Respiratory, thoracic, and mediastinal disorders	902 (24.5)	1703 (26.9)	966 (26.2)	1854 (28.9)	1868 (25.3)	3557 (27.9)
Cough	198 (5.4)	233 (3.7)	222 (6.0)	253 (3.9)	420 (5.7)	486 (3.8)
Dyspnoea	181 (4.9)	231 (3.6)	218 (5.9)	267 (4.2)	399 (5.4)	498 (3.9)
General disorders and administration site conditions	984 (26.7)	1526 (24.1)	883 (23.9)	1408 (21.9)	1867 (25.3)	2934 (23.0)
Oedema peripheral	255 (6.9)	311 (4.9)	252 (6.8)	305 (4.8)	507 (6.9)	616 (4.8)
Nervous system disorders	880 (23.9)	1499 (23.7)	892 (24.2)	1440 (22.4)	1772 (24.0)	2939 (23.0)
Headache	237 (6.4)	419 (6.6)	234 (6.3)	317 (4.9)	471 (6.4)	736 (5.8)
Musculoskeletal and connective tissue disorders	843 (22.9)	1436 (22.7)	895 (24.3)	1558 (24.3)	1738 (23.6)	2994 (23.5)
Back pain	178 (4.8)	207 (3.3)	185 (5.0)	211 (3.3)	363 (4.9)	418 (3.3)
Pain in extremity	164 (4.4)	202 (3.2)	194 (5.3)	230 (3.6)	358 (4.9)	432 (3.4)
Renal and urinary disorders	872 (23.7)	1209 (19.1)	860 (23.3)	1210 (18.8)	1732 (23.5)	2419 (19.0)
End-stage renal disease	558 (15.1)	582 (9.2)	563 (15.3)	602 (9.4)	1121 (15.2)	1184 (9.3)

CKD: chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
Source: ISS Table 14.3.1.3c

2.6.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

Pooled Global Phase 3 DD-CKD Population

Table 68 **Treatment-Emergent Serious Adverse Events Reported in ≥2% of Subjects in Any Treatment Group – Pooled DD-CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 1947 PY = 3222.0 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 1955 PY = 3245.8 n (%)	 E (E × 100/PY)	Total N = 3902 PY = 6467.8 n (%)	 E (E × 100/PY)
Any treatment-emergent SAE	1062 (54.5)	3718 (115.4)	1137 (58.2)	3991 (123.0)	2199 (56.4)	7709 (119.2)
Infections and infestations	531 (27.3)	908 (28.2)	545 (27.9)	977 (30.1)	1076 (27.6)	1885 (29.1)
Pneumonia	148 (7.6)	195 (6.1)	126 (6.4)	150 (4.6)	274 (7.0)	345 (5.3)
Sepsis	79 (4.1)	86 (2.7)	94 (4.8)	102 (3.1)	173 (4.4)	188 (2.9)
Septic shock	45 (2.3)	47 (1.5)	48 (2.5)	50 (1.5)	93 (2.4)	97 (1.5)
Cellulitis	47 (2.4)	52 (1.6)	40 (2.0)	44 (1.4)	87 (2.2)	96 (1.5)
Osteomyelitis	35 (1.8)	39 (1.2)	43 (2.2)	51 (1.6)	78 (2.0)	90 (1.4)
Cardiac disorders	319 (16.4)	546 (16.9)	378 (19.3)	622 (19.2)	697 (17.9)	1168 (18.1)
Acute myocardial infarction	84 (4.3)	101 (3.1)	82 (4.2)	93 (2.9)	166 (4.3)	194 (3.0)
Cardiac failure congestive	55 (2.8)	67 (2.1)	67 (3.4)	82 (2.5)	122 (3.1)	149 (2.3)
Cardiac arrest	51 (2.6)	54 (1.7)	63 (3.2)	64 (2.0)	114 (2.9)	118 (1.8)
Atrial fibrillation	47 (2.4)	52 (1.6)	41 (2.1)	48 (1.5)	88 (2.3)	100 (1.5)
Injury, poisoning, and procedural complications	247 (12.7)	340 (10.6)	255 (13.0)	369 (11.4)	502 (12.9)	709 (11.0)
Arteriovenous fistula thrombosis	59 (3.0)	69 (2.1)	44 (2.3)	52 (1.6)	103 (2.6)	121 (1.9)
Metabolism and nutrition disorders	209 (10.7)	308 (9.6)	219 (11.2)	301 (9.3)	428 (11.0)	609 (9.4)
Fluid overload	108 (5.5)	154 (4.8)	100 (5.1)	137 (4.2)	208 (5.3)	291 (4.5)
Hyperkalaemia	60 (3.1)	68 (2.1)	80 (4.1)	93 (2.9)	140 (3.6)	161 (2.5)
Respiratory, thoracic, and mediastinal disorders	194 (10.0)	281 (8.7)	201 (10.3)	295 (9.1)	395 (10.1)	576 (8.9)
Acute respiratory failure	49 (2.5)	54 (1.7)	54 (2.8)	59 (1.8)	103 (2.6)	113 (1.7)
Respiratory failure	27 (1.4)	32 (1.0)	42 (2.1)	42 (1.3)	69 (1.8)	74 (1.1)
Blood and lymphatic system disorders	73 (3.7)	83 (2.6)	76 (3.9)	94 (2.9)	149 (3.8)	177 (2.7)
Anaemia	37 (1.9)	40 (1.2)	39 (2.0)	43 (1.3)	76 (1.9)	83 (1.3)

DD-CKD: dialysis-dependent chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
Source: ISS Table 14.3.1.6a

Pooled Global Phase 3 NDD-CKD Population

Table 69 **Treatment-Emergent Serious Adverse Events Reported in ≥2% of Subjects in Any Treatment Group – Pooled NDD-CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 1739 PY = 3113.3 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 1732 PY = 3174.3 n (%)	 E (E × 100/PY)	Total N = 3471 PY = 6287.7 n (%)	 E (E × 100/PY)
Any treatment-emergent SAE	1077 (61.9)	3263 (104.8)	1049 (60.6)	3168 (99.8)	2126 (61.3)	6431 (102.3)
Renal and urinary disorders	631 (36.3)	734 (23.6)	631 (36.4)	727 (22.9)	1262 (36.4)	1461 (23.2)
End-stage renal disease	524 (30.1)	540 (17.3)	530 (30.6)	546 (17.2)	1054 (30.4)	1086 (17.3)
Acute kidney injury	76 (4.4)	92 (3.0)	72 (4.2)	78 (2.5)	148 (4.3)	170 (2.7)
Infections and infestations	327 (18.8)	586 (18.8)	339 (19.6)	527 (16.6)	666 (19.2)	1113 (17.7)
Pneumonia	116 (6.7)	136 (4.4)	98 (5.7)	110 (3.5)	214 (6.2)	246 (3.9)
Sepsis	45 (2.6)	51 (1.6)	35 (2.0)	36 (1.1)	80 (2.3)	87 (1.4)
Urinary tract infection	39 (2.2)	45 (1.4)	33 (1.9)	37 (1.2)	72 (2.1)	82 (1.3)
Cardiac disorders	281 (16.2)	471 (15.1)	292 (16.9)	484 (15.2)	573 (16.5)	955 (15.2)
Cardiac failure congestive	69 (4.0)	89 (2.9)	70 (4.0)	91 (2.9)	139 (4.0)	180 (2.9)
Acute myocardial infarction	66 (3.8)	70 (2.2)	51 (2.9)	56 (1.8)	117 (3.4)	126 (2.0)
Cardiac failure acute	36 (2.1)	42 (1.3)	40 (2.3)	44 (1.4)	76 (2.2)	86 (1.4)
Metabolism and nutrition disorders	185 (10.6)	261 (8.4)	168 (9.7)	236 (7.4)	353 (10.2)	497 (7.9)
Fluid overload	51 (2.9)	60 (1.9)	34 (2.0)	49 (1.5)	85 (2.4)	109 (1.7)
Hyperkalaemia	33 (1.9)	41 (1.3)	35 (2.0)	39 (1.2)	68 (2.0)	80 (1.3)
General disorders and administration site conditions	98 (5.6)	111 (3.6)	67 (3.9)	74 (2.3)	165 (4.8)	185 (2.9)
Death	43 (2.5)	43 (1.4)	32 (1.8)	32 (1.0)	75 (2.2)	75 (1.2)
Blood and lymphatic system disorders	58 (3.3)	76 (2.4)	66 (3.8)	78 (2.5)	124 (3.6)	154 (2.4)
Anaemia	34 (2.0)	41 (1.3)	42 (2.4)	48 (1.5)	76 (2.2)	89 (1.4)

E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; NDD-CKD: non-dialysis-dependent chronic kidney disease; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
Source: ISS Table 14.3.1.6b

Pooled Global Phase 3 CKD Population

Table 70 **Treatment-Emergent Serious Adverse Events Reported in ≥2% of Subjects in Any Treatment Group – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 3686 PY = 6335.3 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 3687 PY = 6420.1 n (%)	 E (E × 100/PY)	Total N = 7373 PY = 12755.5 n (%)	 E (E × 100/PY)
Any treatment-emergent SAE	2139 (58.0)	6981 (110.2)	2186 (59.3)	7159 (111.5)	4325 (58.7)	14140 (110.9)
Infections and infestations	858 (23.3)	1494 (23.6)	884 (24.0)	1504 (23.4)	1742 (23.6)	2998 (23.5)
Pneumonia	264 (7.2)	331 (5.2)	224 (6.1)	260 (4.0)	488 (6.6)	591 (4.6)
Sepsis	124 (3.4)	137 (2.2)	129 (3.5)	138 (2.1)	253 (3.4)	275 (2.2)
Renal and urinary disorders	684 (18.6)	790 (12.5)	667 (18.1)	763 (11.9)	1351 (18.3)	1553 (12.2)
End-stage renal disease	539 (14.6)	555 (8.8)	541 (14.7)	557 (8.7)	1080 (14.6)	1112 (8.7)
Acute kidney injury	80 (2.2)	96 (1.5)	75 (2.0)	81 (1.3)	155 (2.1)	177 (1.4)
Cardiac disorders	600 (16.3)	1017 (16.1)	670 (18.2)	1106 (17.2)	1270 (17.2)	2123 (16.6)
Acute myocardial infarction	150 (4.1)	171 (2.7)	133 (3.6)	149 (2.3)	283 (3.8)	320 (2.5)
Cardiac failure congestive	124 (3.4)	156 (2.5)	137 (3.7)	173 (2.7)	261 (3.5)	329 (2.6)
Cardiac arrest	83 (2.3)	86 (1.4)	95 (2.6)	96 (1.5)	178 (2.4)	182 (1.4)
Atrial fibrillation	74 (2.0)	86 (1.4)	62 (1.7)	72 (1.1)	136 (1.8)	158 (1.2)
Metabolism and nutrition disorders	394 (10.7)	569 (9.0)	387 (10.5)	537 (8.4)	781 (10.6)	1106 (8.7)
Fluid overload	159 (4.3)	214 (3.4)	134 (3.6)	186 (2.9)	293 (4.0)	400 (3.1)
Hyperkalaemia	93 (2.5)	109 (1.7)	115 (3.1)	132 (2.1)	208 (2.8)	241 (1.9)
Respiratory, thoracic, and mediastinal disorders	307 (8.3)	449 (7.1)	336 (9.1)	480 (7.5)	643 (8.7)	929 (7.3)
Acute respiratory failure	78 (2.1)	95 (1.5)	81 (2.2)	90 (1.4)	159 (2.2)	185 (1.5)
Blood and lymphatic system disorders	131 (3.6)	159 (2.5)	142 (3.9)	172 (2.7)	273 (3.7)	331 (2.6)
Anaemia	71 (1.9)	81 (1.3)	81 (2.2)	91 (1.4)	152 (2.1)	172 (1.3)

CKD: chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
Source: ISS Table 14.3.1.6c

Most of the treatment-emergent SAEs were assessed not related to study drug by the investigator and/or sponsor; 1.5% and 1.6% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively, had treatment-emergent SAEs that were considered to be related to study drug in the pooled DD-CKD population. In the pooled NDD-CKD population slightly more in the vadadustat treatment groups were considered to be related to study drug compared to the darbepoetin alfa treatment group (2.1% and 1.4%, respectively).

Deaths due to Treatment-Emergent Adverse Events

Pooled Global Phase 3 DD-CKD Population

Table 71 **Treatment-Emergent Adverse Events That Led to Death in >0.1% of Subjects in Any Treatment Group – Pooled DD-CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 1947 PY = 3222.0 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 1955 PY = 3245.8 n (%)	 E (E × 100/PY)	Total N = 3902 PY = 6467.8 n (%)	 E (E × 100/PY)
Any TEAE leading to death[a]	281 (14.4)	281 (8.7)	294 (15.0)	295 (9.1)	575 (14.7)	576 (8.9)
Cardiac disorders	109 (5.6)	109 (3.4)	111 (5.7)	111 (3.4)	220 (5.6)	220 (3.4)
Cardiac arrest	36 (1.8)	36 (1.1)	39 (2.0)	**39 (1.2)**	75 (1.9)	75 (1.2)
Cardio-respiratory arrest	23 (1.2)	23 (0.7)	23 (1.2)	23 (0.7)	46 (1.2)	46 (0.7)
Acute myocardial infarction	15 (0.8)	15 (0.5)	7 (0.4)	7 (0.2)	22 (0.6)	22 (0.3)
Cardiac shock	5 (0.3)	5 (0.2)	9 (0.5)	9 (0.3)	14 (0.4)	14 (0.2)
Cardiopulmonary failure	7 (0.4)	7 (0.2)	5 (0.3)	5 (0.2)	12 (0.3)	12 (0.2)
Myocardial infarction	4 (0.2)	4 (0.1)	3 (0.2)	3 (0.1)	7 (0.2)	7 (0.1)
Cardiac failure acute	4 (0.2)	4 (0.1)	1 (0.1)	1 (0.0)	5 (0.1)	5 (0.1)
Cardiac failure congestive	1 (0.1)	1 (0.1)	3 (0.2)	3 (0.1)	4 (0.1)	4 (0.1)
Coronary artery disease	1 (0.1)	1 (0.1)	3 (0.2)	3 (0.1)	4 (0.1)	4 (0.1)
Infections and infestations	50 (2.6)	50 (1.6)	61 (3.1)	61 (1.9)	111 (2.8)	111 (1.7)
Septic shock	24 (1.2)	24 (0.7)	23 (1.2)	23 (0.7)	47 (1.2)	47 (0.7)
Sepsis	13 (0.7)	13 (0.4)	15 (0.8)	15 (0.5)	28 (0.7)	28 (0.4)
Pneumonia	7 (0.4)	7 (0.2)	6 (0.3)	6 (0.2)	13 (0.3)	13 (0.2)
Endocarditis	0	0	3 (0.2)	3 (0.1)	3 (0.1)	3 (0.0)
General disorders and administration site conditions	36 (1.8)	36 (1.1)	32 (1.6)	32 (1.0)	68 (1.7)	68 (1.1)
Death	25 (1.3)	25 (0.8)	15 (0.8)	15 (0.5)	40 (1.0)	40 (0.6)
Sudden death	3 (0.2)	3 (0.1)	9 (0.5)	9 (0.3)	12 (0.3)	12 (0.2)
Multiple organ dysfunction syndrome	2 (0.1)	2 (0.1)	6 (0.3)	6 (0.2)	8 (0.2)	8 (0.1)
Sudden cardiac death	4 (0.2)	4 (0.1)	1 (0.1)	1 (0.0)	5 (0.1)	5 (0.1)
Respiratory, thoracic, and mediastinal disorders	13 (0.7)	13 (0.4)	20 (1.0)	20 (0.6)	33 (0.8)	33 (0.5)
Acute respiratory failure	7 (0.4)	7 (0.2)	6 (0.3)	6 (0.2)	13 (0.3)	13 (0.2)
Respiratory failure	2 (0.1)	2 (0.1)	9 (0.5)	9 (0.3)	11 (0.3)	11 (0.2)
Renal and urinary disorders	19 (1.0)	19 (0.6)	12 (0.6)	12 (0.4)	31 (0.8)	31 (0.5)
End-stage renal disease	11 (0.6)	11 (0.3)	8 (0.4)	8 (0.2)	19 (0.5)	19 (0.3)
Azotaemia	4 (0.2)	4 (0.1)	1 (0.1)	1 (0.0)	5 (0.1)	5 (0.1)
Nervous system disorders	14 (0.7)	14 (0.4)	16 (0.8)	16 (0.5)	30 (0.8)	30 (0.5)
Ischaemic stroke	1 (0.1)	1 (0.0)	5 (0.3)	5 (0.2)	6 (0.2)	6 (0.1)
Haemorrhagic stroke	1 (0.1)	1 (0.0)	3 (0.2)	3 (0.1)	4 (0.1)	4 (0.1)
Vascular disorders	12 (0.6)	12 (0.4)	11 (0.6)	11 (0.3)	23 (0.6)	23 (0.4)
Arteriosclerosis	2 (0.1)	2 (0.1)	5 (0.3)	5 (0.2)	7 (0.2)	7 (0.1)
Shock	3 (0.2)	3 (0.1)	2 (0.1)	2 (0.1)	5 (0.1)	5 (0.1)
Gastrointestinal disorders	11 (0.6)	11 (0.3)	9 (0.5)	9 (0.3)	20 (0.5)	20 (0.3)
Gastrointestinal haemorrhage	3 (0.2)	3 (0.1)	2 (0.1)	2 (0.1)	5 (0.1)	5 (0.1)
Intestinal ischaemia	3 (0.2)	3 (0.1)	1 (0.1)	1 (0.0)	4 (0.1)	4 (0.1)

DD-CKD: dialysis-dependent chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; TEAE: treatment-emergent adverse event

A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.

MedDRA version 23.0

a. Deaths not due to TEAEs are not presented in this table.

Source: ISS Table 14.3.1.10a

Pooled Global Phase 3 NDD-CKD Population

Table 72 **Treatment-Emergent Adverse Events That Led to Death in >0.1% of Subjects in Any Treatment Group – Pooled NDD-CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 1739 PY = 3113.3 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 1732 PY = 3174.3 n (%)	 E (E × 100/PY)	Total N = 3471 PY = 6287.7 n (%)	 E (E × 100/PY)
Any TEAE leading to death[a]	312 (17.9)	312 (10.0)	302 (17.4)	302 (9.5)	614 (17.7)	614 (9.8)
Cardiac disorders	94 (5.4)	94 (3.0)	94 (5.4)	94 (3.0)	188 (5.4)	188 (3.0)
Cardiac arrest	28 (1.6)	28 (0.9)	24 (1.4)	24 (0.8)	52 (1.5)	52 (0.8)
Cardio-respiratory arrest	10 (0.6)	10 (0.3)	14 (0.8)	14 (0.4)	24 (0.7)	24 (0.4)
Acute myocardial infarction	5 (0.3)	5 (0.2)	12 (0.7)	12 (0.4)	17 (0.5)	17 (0.3)
Myocardial infarction	9 (0.5)	9 (0.3)	7 (0.4)	7 (0.2)	16 (0.5)	16 (0.3)
Cardiac failure	8 (0.5)	8 (0.3)	7 (0.4)	7 (0.2)	15 (0.4)	15 (0.2)
Cardiac failure acute	5 (0.3)	5 (0.2)	6 (0.3)	6 (0.2)	11 (0.3)	11 (0.2)
Cardiac failure congestive	5 (0.3)	5 (0.2)	6 (0.3)	6 (0.2)	11 (0.3)	11 (0.2)
Cardiogenic shock	6 (0.3)	6 (0.2)	2 (0.1)	2 (0.1)	8 (0.2)	8 (0.1)
Cardiac failure chronic	2 (0.1)	2 (0.1)	4 (0.2)	4 (0.1)	6 (0.2)	6 (0.1)
Arrhythmia	3 (0.2)	3 (0.1)	0	0	3 (0.1)	3 (0.0)
Cardiopulmonary failure	3 (0.2)	3 (0.1)	0	0	3 (0.1)	3 (0.0)
Renal and urinary disorders	49 (2.8)	49 (1.6)	55 (3.2)	55 (1.7)	104 (3.0)	104 (1.7)
End-stage renal disease	30 (1.7)	30 (1.0)	40 (2.3)	40 (1.3)	70 (2.0)	70 (1.1)
Azotaemia	5 (0.3)	5 (0.2)	3 (0.2)	3 (0.1)	8 (0.2)	8 (0.1)
Renal failure	6 (0.3)	6 (0.2)	2 (0.1)	2 (0.1)	8 (0.2)	8 (0.1)
Chronic kidney disease	3 (0.2)	3 (0.1)	4 (0.2)	4 (0.1)	7 (0.2)	7 (0.1)
Acute kidney injury	2 (0.1)	2 (0.1)	3 (0.2)	3 (0.1)	5 (0.1)	5 (0.1)
General disorders and administration site conditions	53 (3.0)	53 (1.7)	40 (2.3)	40 (1.3)	93 (2.7)	93 (1.5)
Death	43 (2.5)	43 (1.4)	32 (1.8)	32 (1.0)	75 (2.2)	75 (1.2)
Multiple organ dysfunction syndrome	4 (0.2)	4 (0.1)	2 (0.1)	2 (0.1)	6 (0.2)	6 (0.1)
Infections and infestations	37 (2.1)	37 (1.2)	33 (1.9)	33 (1.0)	70 (2.0)	70 (1.1)
Septic shock	11 (0.6)	11 (0.4)	7 (0.4)	7 (0.2)	18 (0.5)	18 (0.3)
Pneumonia	7 (0.4)	7 (0.2)	8 (0.5)	8 (0.3)	15 (0.4)	15 (0.2)
Sepsis	7 (0.4)	7 (0.2)	4 (0.2)	4 (0.1)	11 (0.3)	11 (0.2)
Peritonitis	3 (0.2)	3 (0.1)	2 (0.1)	2 (0.1)	5 (0.1)	5 (0.1)
Staphylococcal sepsis	1 (0.1)	1 (0.0)	3 (0.2)	3 (0.1)	4 (0.1)	4 (0.1)
Nervous system disorders	27 (1.6)	27 (0.9)	13 (0.8)	13 (0.4)	40 (1.2)	40 (0.6)
Uraemic encephalopathy	5 (0.3)	5 (0.2)	1 (0.1)	1 (0.0)	6 (0.2)	6 (0.1)
Cerebrovascular accident	3 (0.2)	3 (0.1)	1 (0.1)	1 (0.0)	4 (0.1)	4 (0.1)
Haemorrhagic stroke	3 (0.2)	3 (0.1)	1 (0.1)	1 (0.0)	4 (0.1)	4 (0.1)
Ischaemic stroke	4 (0.2)	4 (0.1)	0	0	4 (0.1)	4 (0.1)
Respiratory, thoracic, and mediastinal disorders	15 (0.9)	15 (0.5)	21 (1.2)	21 (0.7)	36 (1.0)	36 (0.6)
Acute respiratory failure	3 (0.2)	3 (0.1)	6 (0.3)	6 (0.2)	9 (0.3)	9 (0.1)
Pneumonia aspiration	3 (0.2)	3 (0.1)	5 (0.3)	5 (0.2)	8 (0.2)	8 (0.1)
Respiratory failure	3 (0.2)	3 (0.1)	1 (0.1)	1 (0.0)	4 (0.1)	4 (0.1)
Metabolism and nutrition disorders	9 (0.5)	9 (0.3)	8 (0.5)	8 (0.3)	17 (0.5)	17 (0.3)
Hypoglycaemia	4 (0.2)	4 (0.1)	0	0	4 (0.1)	4 (0.1)

E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; NDD-CKD: non-dialysis-dependent chronic kidney disease; PY: patient-year; TEAE: treatment-emergent adverse event

A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.

MedDRA version 23.0

a. Deaths not due to TEAEs are not presented in this table.

Source: ISS Table 14.3.1.10b

Pooled Global Phase 3 CKD Population

Table 73 **Treatment-Emergent Adverse Events That Led to Death in >0.1% of Subjects in Any Treatment Group – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

MedDRA System Organ Class Preferred Term	Vadadustat N = 3686 PY = 6335.3 n (%)	 E (E × 100/PY)	Darbepoetin Alfa N = 3687 PY = 6420.1 n (%)	 E (E × 100/PY)	Total N = 7373 PY = 12755.5 n (%)	 E (E × 100/PY)
Any TEAE leading to death[a]	593 (16.1)	593 (9.4)	596 (16.2)	597 (9.3)	1189 (16.1)	1190 (9.3)
Cardiac disorders	203 (5.5)	203 (3.2)	205 (5.6)	205 (3.2)	408 (5.5)	408 (3.2)
Cardiac arrest	64 (1.7)	64 (1.0)	63 (1.7)	63 (1.0)	127 (1.7)	127 (1.0)
Cardio-respiratory arrest	33 (0.9)	33 (0.5)	37 (1.0)	37 (0.6)	70 (0.9)	70 (0.5)
Acute myocardial infarction	20 (0.5)	20 (0.3)	19 (0.5)	19 (0.3)	39 (0.5)	39 (0.3)
Myocardial infarction	13 (0.4)	13 (0.2)	10 (0.3)	10 (0.2)	23 (0.3)	23 (0.2)
Cardiogenic shock	11 (0.3)	11 (0.2)	11 (0.3)	11 (0.2)	22 (0.3)	22 (0.2)
Cardiac failure	9 (0.2)	9 (0.1)	9 (0.2)	9 (0.1)	18 (0.2)	18 (0.1)
Cardiac failure acute	9 (0.2)	9 (0.1)	7 (0.2)	7 (0.1)	16 (0.2)	16 (0.1)
Cardiac failure congestive	6 (0.2)	6 (0.1)	9 (0.2)	9 (0.1)	15 (0.2)	15 (0.1)
Cardiopulmonary failure	10 (0.3)	10 (0.2)	5 (0.1)	5 (0.1)	15 (0.2)	15 (0.1)
Infections and infestations	87 (2.4)	87 (1.4)	94 (2.5)	94 (1.5)	181 (2.5)	181 (1.4)
Septic shock	35 (0.9)	35 (0.6)	30 (0.8)	30 (0.5)	65 (0.9)	65 (0.5)
Sepsis	20 (0.5)	20 (0.3)	19 (0.5)	19 (0.3)	39 (0.5)	39 (0.3)
Pneumonia	14 (0.4)	14 (0.2)	14 (0.4)	14 (0.2)	28 (0.4)	28 (0.2)
General disorders and administration site conditions	89 (2.4)	89 (1.4)	72 (2.0)	72 (1.1)	161 (2.2)	161 (1.3)
Death	68 (1.8)	68 (1.1)	47 (1.3)	47 (0.7)	115 (1.6)	115 (0.9)
Sudden death	5 (0.1)	5 (0.1)	11 (0.3)	11 (0.2)	16 (0.2)	16 (0.1)
Multiple organ dysfunction syndrome	6 (0.2)	6 (0.1)	8 (0.2)	8 (0.1)	14 (0.2)	14 (0.1)
Renal and urinary disorders	68 (1.8)	68 (1.1)	67 (1.8)	67 (1.0)	135 (1.8)	135 (1.1)
End-stage renal disease	41 (1.1)	41 (0.6)	48 (1.3)	48 (0.7)	89 (1.2)	89 (0.7)
Azotaemia	9 (0.2)	9 (0.1)	4 (0.1)	4 (0.1)	13 (0.2)	13 (0.1)
Chronic kidney disease	5 (0.1)	5 (0.1)	6 (0.2)	6 (0.1)	11 (0.1)	11 (0.1)
Renal failure	7 (0.2)	7 (0.1)	3 (0.1)	3 (0.0)	10 (0.1)	10 (0.1)
Respiratory, thoracic, and mediastinal disorders	28 (0.8)	28 (0.4)	41 (1.1)	41 (0.6)	69 (0.9)	69 (0.5)
Acute respiratory failure	10 (0.3)	10 (0.2)	12 (0.3)	12 (0.2)	22 (0.3)	22 (0.2)
Respiratory failure	5 (0.1)	5 (0.1)	10 (0.3)	10 (0.2)	15 (0.2)	15 (0.1)
Vascular disorders	18 (0.5)	18 (0.3)	14 (0.4)	14 (0.2)	32 (0.4)	32 (0.3)
Arteriosclerosis	3 (0.1)	3 (0.0)	6 (0.2)	6 (0.1)	9 (0.1)	9 (0.1)

CKD: chronic kidney disease; E (E × 100/PY): number of events (events rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
a. Deaths not due to TEAEs are not presented in this table.
Source: ISS Table 14.3.1.10c

Major Adverse Cardiovascular Events (MACE)

The primary safety endpoint of time to first MACE (all-cause mortality, non-fatal MI, or non-fatal stroke) was assessed in the DD-CKD population and NDD-CKD population from subjects enrolled in the global Phase 3 studies, this endpoint was adequately powered for the pooled data with a non-inferiority margin of 1.3.

Each of the key secondary endpoints were assessed separately either from pooled data from the DD-CKD studies or from pooled data from the NDD-CKD studies. These endpoints are presented in Table below. Analysis of time to first MACE for both DD-CKD and NDD-CKD was based on a stratified Cox regression model with study as a stratification factor for each analysis.

Table 74 Major Adverse Cardiac Events Endpoints for Global Phase 3 Studies

Endpoint	Description
Primary Safety Endpoint	• Time to first occurrence of EAC-adjudicated MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke
Key Secondary Safety Endpoints	• Time to first MACE plus hospitalization for HF or thromboembolic event, excluding vascular access thrombosis (MACE+) • Time to CV mortality, non-fatal MI, or non-fatal stroke • Time to CV mortality • Time to all-cause mortality
Other Adjudicated Safety Endpoints	• Time to first individual components of MACE o Non-fatal MI o Non-fatal stroke • Time to non-CV mortality • Time to first individual component of MACE+ o MACE plus thromboembolic event o MACE plus thromboembolic event, excluding vascular access failure o MACE plus hospitalization for HF o MACE plus hospitalization for HF or thromboembolic event

CV: cardiovascular; EAC: Endpoint Adjudication Committee; HF: heart failure; MACE: major adverse cardiac events; MI: myocardial infarction

Source: $INNO_2VATE$ MACE Report, PRO_2TECT MACE Report, and Combined MACE Report: PRO_2TECT MACE and $INNO_2VATE$

Pooled Global Phase 3 DD-CKD Population

The HR (95% CI) from the multivariate Cox model for the time to first MACE in the DD-CKD population for vadadustat compared to darbepoetin alfa was 0.96 (0.833, 1.113), which met the prespecified non-inferiority margin of 1.3, thereby establishing non-inferiority of vadadustat to darbepoetin alfa (Table below).

Table 75 $INNO_2VATE$ Primary and Key Secondary MACE Endpoints (Global and by Region)

	Global HR (95% CI)	US HR (95% CI)	Europe HR (95% CI)	ROW HR (95% CI)
Primary MACE Endpoint				
Time to first MACE	0.96 (0.833, 1.113)	1.00 (0.842, 1.184)	0.89 (0.570, 1.394)	0.87 (0.605, 1.256)
Key Secondary MACE Endpoint				
Time to first Expanded MACE[a]	0.96 (0.840, 1.096)	0.99 (0.848, 1.154)	0.93 (0.612, 1.428)	0.86 (0.603, 1.214)
Time to All-Cause Mortality	0.95 (0.812, 1.118)	0.97 (0.804, 1.174)	0.91 (0.567, 1.472)	0.93 (0.625, 1.381)
Time to CV MACE	0.95 (0.795, 1.144)	0.98 (0.799, 1.214)	0.73 (0.413, 1.308)	0.97 (0.599, 1.580)
Time to Cardiovascular Deaths	0.96 (0.766, 1.195)	0.96 (0.743, 1.246)	0.78 (0.396, 1.536)	1.10 (0.617, 1.965)

CI: confidence interval; CV: cardiovascular; HR: Hazard ratio; MACE: major adverse cardiovascular event; ROW: rest of world; US: United States

a Expanded MACE: MACE plus Hospitalization for Heart Failure or Thromboembolic Events Excluding Vascular Access Thrombosis

Source: $INNO_2VATE$ MACE Report After-text Tables 2.1, 2.2.1, 2.2.2, 2.2.3, 2.2.4, 5, 6.1-6.4

Pooled Global Phase 3 NDD-CKD Population

The HR (95% CI) from the multivariate Cox model for the time to first MACE for vadadustat compared to darbepoetin alfa was 1.17 (1.012, 1.355) in the NDD-CKD population (Table below). The upper bound of the 95% CI of the HR (1.355) exceeded the prespecified non-inferiority margin of 1.3, and therefore, the non-inferiority of vadadustat compared to darbepoetin alfa was not demonstrated (Table below).

Table 76 PRO_2TECT Primary and Key Secondary MACE Endpoints (Global and by Region)

	Global HR (95% CI)	US[a] HR (95% CI)	Europe[a] HR (95% CI)	ROW[a] HR (95% CI)
Primary MACE Endpoint				
Time to first MACE	1.17 (1.012, 1.355)	1.06 (0.872, 1.292)	1.56 (1.039, 2.350)	1.25 (0.960, 1.618)
Key Secondary MACE Endpoint				
Time to first Expanded MACE[b]	1.11 (0.972, 1.267)	1.02 (0.856, 1.212)	1.31 (0.917, 1.875)	1.23 (0.956, 1.590)
Time to All-Cause Mortality	1.09 (0.930, 1.274)	0.92 (0.743, 1.151)	1.64 (1.064, 2.522)	1.20 (0.920, 1.577)
Time to CV MACE	1.16 (0.947, 1.420)	1.20 (0.920, 1.553)	1.20 (0.688, 2.106)	1.05 (0.704, 1.558)
Time to Cardiovascular Deaths	1.01 (0.792, 1.293)	0.96 (0.684, 1.343)	1.29 (0.684, 2.416)	0.96 (0.623, 1.492)

CI: confidence interval; CV: cardiovascular; HR: Hazard ratio; MACE: major adverse cardiovascular event; ROW: rest of world; US: United States

a Hb target range for US region was 10.0-11.0 g/dL. Hb target range for Europe and ROW was 10.0-12.0 g/dL.

b Expanded MACE: MACE plus Hospitalization for Heart Failure or Thromboembolic Events Excluding Vascular Access Thrombosis

Source: PRO_2TECT MACE Report After-text Tables 2.1, 2.2.1, 2.2.2, 2.2.3, 2.2.4, 5, 6.1-6.4

Investigations of Major Adverse Cardiovascular Events in NDD-CKD by baseline characteristics and region

There was a higher proportion of subjects with NYHA Heart Failure Class II and III in Europe (22.3%) compared to ROW (15.5%) and US (10.2%), as well as a higher proportion of subjects with previous CVD (Table below).

Table 77 **Baseline Characteristics by Region (Safety Population)**

Characteristics Category/Statistic	United States Vadadustat N=861 (n%)	United States Darbepoetin Alfa N=862 (n%)	United States Total N=1723 (n%)	Europe Vadadustat N=295 (n%)	Europe Darbepoetin Alfa N=288 (n%)	Europe Total N=583 (n%)	Rest of World Vadadustat N=583 (n%)	Rest of World Darbepoetin Alfa N=582 (n%)	Rest of World Total N=1165 (n%)
Randomization Stratification Factors, n (%)									
NYHA Heart Failure Class, n (%)									
Class 0 (no Heart Failure) or I	774 (89.9)	774 (89.8)	1548 (89.8)	229 (77.6)	224 (77.8)	453 (77.7)	492 (84.4)	492 (84.5)	984 (84.5)
II or III	87 (10.1)	88 (10.2)	175 (10.2)	66 (22.4)	64 (22.2)	130 (22.3)	91 (15.6)	90 (15.5)	181 (15.5)
Central Laboratory Baseline Hb Category[a], n (%)									
Low Level	512 (59.5)	519 (60.2)	1031 (59.8)	73 (24.7)	73 (25.3)	146 (25.0)	251 (43.1)	250 (43.0)	501 (43.0)
High Level	349 (40.5)	343 (39.8)	692 (40.2)	222 (75.3)	215 (74.7)	437 (75.0)	332 (56.9)	332 (57.0)	664 (57.0)
Baseline ESA Dose Use (U/kg/week)[b]									
n	317	324	641	220	218	438	295	300	595
Epoetin	227 (71.6)	238 (73.5)	465 (72.5)	55 (25.0)	57 (26.1)	112 (25.6)	228 (77.3)	228 (76.0)	456 (76.6)
Darbepoetin Alfa	90 (28.4)	86 (26.5)	176 (27.5)	130 (59.1)	137 (62.8)	267 (61.0)	41 (13.9)	50 (16.7)	91 (15.3)
Methoxy Polyethylene Glycol-Epoetin Beta	--	--	--	35 (15.9)	24 (11.0)	59 (13.5)	26 (8.8)	22 (7.3)	48 (8.1)
n	315	319	634	218	216	434	290	300	590
Mean	149.29 (192.273)	130.48 (140.461)	139.82 (168.340)	56.65 (64.601)	60.72 (98.033)	58.68 (82.871)	92.80 (104.836)	109.16 (327.359)	101.12 (244.664)
≤90 U/kg/week	174 (55.2)	164 (51.4)	338 (53.3)	182 (83.5)	185 (85.6)	367 (84.6)	194 (66.9)	209 (69.7)	403 (68.3)
>90 and <300 U/kg/week	102 (32.4)	127 (39.8)	229 (36.1)	35 (16.1)	28 (13.0)	63 (14.5)	84 (29.0)	83 (27.7)	167 (28.3)
≥300 U/kg/week	39 (12.4)	28 (8.8)	67 (10.6)	1 (0.5)	3 (1.4)	4 (0.9)	12 (4.1)	8 (2.7)	20 (3.4)
Diabetes Mellitus									
Yes	612 (71.1)	616 (71.5)	1228 (71.3)	151 (51.2)	139 (48.3)	290 (49.7)	335 (57.5)	360 (61.9)	695 (59.7)
No	249 (28.9)	246 (28.5)	495 (28.7)	144 (48.8)	149 (51.7)	293 (50.3)	248 (42.5)	222 (38.1)	470 (40.3)
History of Cardiovascular Disease[c]									
Yes	423 (49.1)	434 (50.3)	857 (49.7)	152 (51.5)	153 (53.1)	305 (52.3)	206 (35.3)	226 (38.8)	432 (37.1)
No	438 (50.9)	428 (49.7)	866 (50.3)	143 (48.5)	135 (46.9)	278 (47.7)	377 (64.7)	356 (61.2)	733 (62.9)

ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; IV: intravenous; N: number of subjects; n: number of subjects within specific category; NYHA: New York Heart Association; SC: subcutaneous

The percentage is calculated based on the number of subjects with non-missing data.

Characteristics Category/Statistic	United States Vadadustat N=861 (n%)	United States Darbepoetin Alfa N=862 (n%)	United States Total N=1723 (n%)	Europe Vadadustat N=295 (n%)	Europe Darbepoetin Alfa N=288 (n%)	Europe Total N=583 (n%)	Rest of World Vadadustat N=583 (n%)	Rest of World Darbepoetin Alfa N=582 (n%)	Rest of World Total N=1165 (n%)

a The low level of baseline Hb is defined as <9.5 g/dL for CI-0014 and <10.0 g/dL for CI-0015; the high level of baseline Hb is defined as ≥9.5 g/dL for CI-0014 and ≥10.0 g/dL for CI-0015.

b ESA doses are converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin Alfa to IV epoetin is 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin is 1:220; SC epoetin to IV epoetin is 1:1.25. The summary is based on the data of Study CI-0015 only.

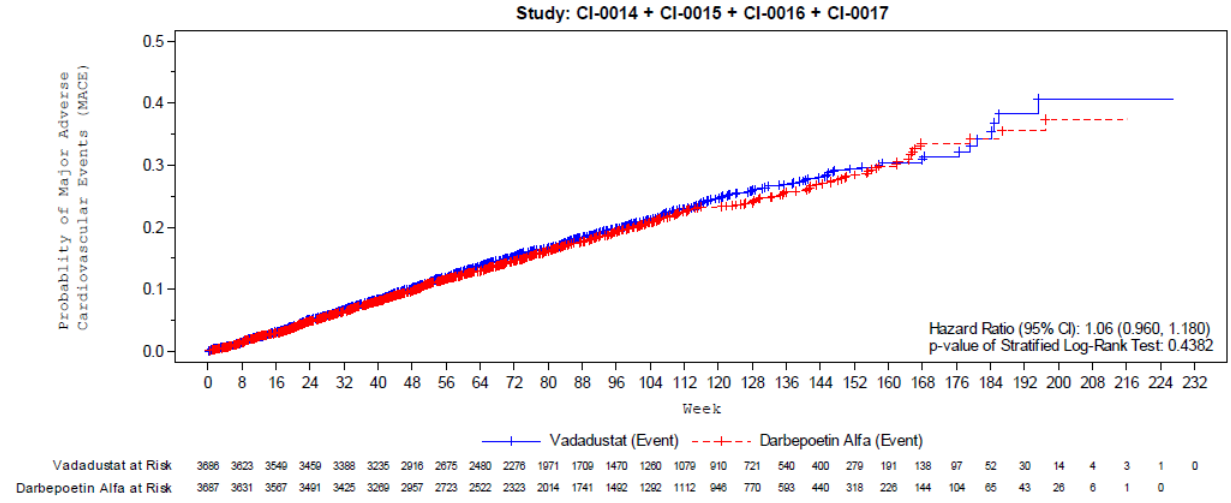
c Cardiovascular disease includes coronary artery disease, myocardial infarction, stroke and heart failure.

Source: After-text Table 7.3a, After-text Table 7.3c, and After-text Table 7.3d

Pooled Global Phase 3 CKD Population

Post-hoc MACE analyses pooled MACE from the pooled DD-CKD and NDD-CKD populations for global Phase 3 studies. The HR (95% CI) for the time to first MACE for vadadustat compared to darbepoetin alfa was 1.06 (0.960, 1.180;) and the lower limit of the 95% CI was below the prespecified non-inferiority margin of 1.30 as required by the EMA, establishing the non-inferiority of vadadustat compared to darbepoetin alfa in the CKD population for global Phase 3 studies.

Figure 35 **Kaplan-Meier Curve of Time to First Major Adverse Cardiovascular Events – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**



CI: confidence interval; CKD: chronic kidney disease; MACE: major adverse cardiovascular events
Source: Combined MACE Report: INNO$_2$VATE and PRO$_2$TECT After-text Figure 2.1

After the consultation with the Methodology Working Party (MWP), the Applicant was also asked to submit two additional analyses: the OT and OT+1 day for both MACE and all-cause mortality.

The additional analyses were submitted on 24 November. The results are as follows:

Table 78 **PRO$_2$TECT (NDD-CKD): Comparison of Analysis for Risk of MACE**

PRO2TECT (NDD- CKD) Primary MACE	Vadadustat N = 1739 n (%)	Darbepoetin alfa N = 1732 n (%)	Overall HR (95%CI)
OT	137 (7.9)	128 (7.4)	1.21 (0.950, 1.541)
OT +1 day	172 (9.9)	138 (8.0)	1.42 (1.134, 1.778)
OT + 28 days	245 (14.1)	214 (12.4)	1.30 (1.078, 1.558)
OT + dosing frequency	172 (9.9)	198 (11.4)	1.03 (0.835, 1.259)
OT + dosing frequency +28 days	245 (14.1)	247 (14.3)	1.14 (0.954, 1.360)

Source: Ad hoc Table 15.1.1, Ad hoc Table 15.1.2, PRO$_2$TECT MACE report After text Table 3.1.1, Ad hoc Table 1.1.1 and Ad hoc Table 1.1.2

Model description = all analyses used the exact COX modeling with the same covariates as described in the MACE SAP, section 4.4 of Primary MACE Analysis.

n (%) = number of subjects with events (percentage).

Dosing frequency = The majority of subjects had 1 to 4 weeks of additional follow up time to the darbepoetin alfa subjects based upon the individual frequency of darbepoetin alfa dosing: 1 week for a subject receiving darbepoetin alfa weekly, 2 weeks for a subject receiving darbepoetin alfa every 2 weeks and 4 weeks for subjects receiving darbepoetin alfa every 4 weeks. A few subjects had >4 weeks of additional follow time.

CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiovascular event, NDD-CKD = non dialysis dependent chronic kidney disease., OT = on treatment.

Table 79 **PRO$_2$TECT (NDD-CKD): Comparison of Analysis for Risk of All-Cause Mortality**

PRO$_2$TECT (NDD-CKD) All-Cause Mortality	Vadadustat N = 1739 n (%)	Darbepoetin alfa N = 1732 n (%)	Overall HR (95%CI)
OT	77 (4.4)	90 (5.2)	0.99 (0.726, 1.337)
OT + 1 day	103 (5.9)	101 (5.8)	1.19 (0.904, 1.570)
OT + 28 days	180 (10.4)	174 (10.0)	1.19 (0.964, 1.465)
OT + dosing frequency	103 (5.9)	159 (9.2)	0.78 (0.610, 1.005)
OT + dosing frequency +28 days	180 (10.4	208 (12.0)	1.01 (0.824, 1.229)

Source: Ad hoc Table 15.2.1, Ad hoc Table 15.2.2, PRO$_2$TECT MACE report After text Table 1.3 and Ad-hoc Table 1.3.1 and Ad hoc Table 1.3.2

Model description = all analyses used the exact COX modeling with the same covariates as described in the MACE SAP, section 4.4 of Primary MACE Analysis.

n (%) = number of subjects with events (percentage).

Dosing frequency = The majority of subjects had 1 to 4 weeks of additional follow up time to the darbepoetin alfa subjects based upon the individual frequency of darbepoetin alfa dosing: 1 week for a subject receiving darbepoetin alfa weekly, 2 weeks for a subject receiving darbepoetin alfa every 2 weeks and 4 weeks for subjects receiving darbepoetin alfa every 4 weeks. A few subjects had >4 weeks of additional follow time.

CI = confidence interval, HR = hazard ratio, NDD-CKD = non dialysis dependent chronic kidney disease., OT = on treatment

Table 80 – Summary of Primary MACE endpoint - Positively Adjudicated Safety Population per region (NDD-CKD population); Assessor's table, Source: MACE report for the PRO2TECT studies

US		**N=861**	**N=862**
	MACE	23.7%	22.7%
	All-cause mortality	18%	19.7%
	Non-fatal MI	6%	4.1%
	Non-fatal stroke	2.6%	2.1%
Europe		**N=295**	**N=288**
	MACE	19%	14.2%
	All-cause mortality	17.3%	12.5%
	Non-fatal MI	2.4%	2.1%
	Non-fatal stroke	1.7%	1.7%
ROW		**N=583**	**N=582**
	MACE	20.9%	18.4%
	All-cause mortality	19.4%	17.4%
	Non-fatal MI	1.4%	1.2%
	Non-fatal stroke	1.2%	0.9%

Adverse Events of Special Interest

Overall AESIs were reported more frequently in the darbepoetin alfa treatment groups compared to the vadadustat treatment groups in both the pooled DD-CKD-, NDD-CKD- and CKD population (45.2% and 41.1% of subjects, respectively in the pooled CKD population). In the pooled CKD population, the most frequent reported AESIs by SOC were hypertension, hyperkalaemia and congestive heart failure (21.0%, 11.9% and 11.5% of subjects, respectively in the darbepoetin alfa population and 18.0%, 9.9% and 10.3% of subjects, respectively in the vadadustat treatment group). There were no major differences between the pooled DD-CKD and NDD-CKD population.

Adrenal disorders

Adrenal disorders were reported in ≤0.1% of subjects in the vadadustat and darbepoetin alfa treatment groups in all three pooling blocks. Within Adrenal Disorder medical topic, a total of 4 cases of adrenal mass were seen in the vadadustat treatment group. All events were assessed by the investigators as not related. In addition, a total of 2 serious events of adrenal insufficiency were seen in the vadadustat treatment group. Both events were assessed as unrelated by the investigator as they were attributed to low cortisol at baseline or weaning of cortisol treatment.

Cardiac valve disorders

Cardiac valve disorders (CVD) were reported less frequent in the vadadustat treatment group compared to the darbepoetin alfa treatment group in DD-CKD population (2.4% and 2.9% of subjects, respectively). In the NDD-CKD population CVD were reported more frequent in the vadadustat treatment group compared to the darbepoetin alfa treatment group (2.1% and 1.6% of subjects, respectively). The most frequent PTs were mitral valve incompetence and tricuspid valve in all three pooling blocks for both the darbepoetin alfa and vadadustat treatment groups (mitral valve incompetence: 1.1% and 1.2% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively; and tricuspid valve incompetence: 0.8% of subjects in each of the vadadustat and darbepoetin alfa treatment groups in the pooled CKD population). All the cardiac valve disorders events were assessed as not related to either drug as most patients had a history of hypertension, advanced age, worsening of CKD, previous history of cardiac related issues-cardiomyopathy or pre-existing valvular disorders. With the inconclusive non-clinical findings, comorbidities in CKD subjects and balance in the frequencies of cardiac valve disorders in the pooled CKD population.

Congestive heart failure

Congestive heart failure was reported for 10.3% of subjects in the vadadustat treatment group and 11.5% of subjects in the darbepoetin alfa treatment group in the pooled CKD population. The distribution was similar in the pooled DD-CKD and NDD-CKD population with a little overweight of events in the darbepoetin alfa treatment groups compared to the vadadustat treatment groups. The most frequent PTs were cardiac failure congestive in all three pooling blocks, with a higher frequency in the vadadustat treatment group compared to the darbepoetin alfa treatment group in the pooled NDD-CKD population (4.7% and 4.4% of subjects, respectively). The opposite pattern was seen in the pooled CC-CKD population (3.3% and 4.2% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively).

Hepatotoxicity

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 the pooled CKD population, with a little higher frequency in the darbepoetin alfa treatment group compared to the vadadustat treatment group in the DD-CKD population (relative risk [95% CI], vadadustat/darbepoetin alfa: 0.954 [0.7597, 1.1986]) and the opposite in the NDD-CKD population (relative risk [95% CI], vadadustat/darbepoetin alfa: 1.199

[0.9252, 1.5545]). The most frequent PTs were similar in all three pooling blocks (transaminases increased: 1.3% and 1.2% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively; ALT increased: 1.0% and 1.1% of subjects, respectively; and AST increased: 0.7% and 1.2% of subjects, respectively in the CKD population). 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.

One subject on vadadustat developed elevated hepatic parameters assessed to have met the biochemical criteria for Hy's law during the phase 2 study AKB-6548-CI-0007. Later upon re-assessment by the Hepatic Expert Committee, it was determined that this case was suggestive of mixed type hepatobiliary injury with a cholestatic component and was assessed as a non-classic case of Hy's Law. After the Global Phase 3 clinical development for vadadustat completed, a Blinded Expert Committee re-adjudicated this case and determined it as a 'severe hepatic injury event' probably related to vadadustat, but not a Hy's Law case.

Hyperkalemia

Hyperkalemia was reported for 9.9% of subjects in the vadadustat treatment group and 11.9% of subjects in the darbepoetin alfa treatment group in the pooled CKD population with similar patterns in the DD-CKD and NDD-CKD populations. The applicant suggests hyperkalemia is an electrolyte imbalance associated with the underlying medical condition of CKD, especially in the dialysis population set.

Hypersensitivity

Hypersensitivity were reported for 7.7% of subjects in the vadadustat treatment group and 7.9% of subjects in the darbepoetin alfa treatment group in the pooled CKD population. The most frequent PTs were face edema (1.4% and 1.2% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively) and rash (1.4% and 1.1% of subjects, respectively. Anaphylactic reactions 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 1 with vadadustat where possibility of reasonable causal relationship could not be ruled out.

Malignancies Including Renal Cell Carcinoma

Malignancies were reported for 3.3% of subjects in the vadadustat treatment group and 4.0% of subjects in the darbepoetin alfa treatment group. Cases of renal cell carcinoma were reported rarely (< 0.1%) for subjects in both the vadadustat and darbepoetin alfa groups. Overall, no pattern of malignancy type was observed, as these were reported in very small numbers.

Pulmonary hypertension

Pulmonary hypertension was reported for 2.4% of subjects in the vadadustat treatment group and 2.6% of subjects in the darbepoetin alfa treatment group in the pooled CKD population.

Retinal-Related Treatment-Emergent Adverse Events

Retinal-related effects were reported for 2.0% of subjects in the vadadustat treatment group and 2.1% of subjects in the darbepoetin alfa treatment group in the CKD population. The most frequent PT was diabetic retinopathy (1.0% and 0.9% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively). The Applicant states that no evidence was found to support an association between vadadustat and retinal-related TEAEs.

Thrombotic Events (Including Myocardial Infarction and Stroke)

In the pooled CKD population for the Phase 3 studies, the incidence rate of thromboembolic events (which includes preferred terms acute MI, arteriovenous fistula thrombosis, arteriovenous graft thrombosis, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, and transient ischaemic attack) was 10.5% with vadadustat versus 9.5% with darbepoetin alfa. The most frequent PTs described in the individual MACE reports were vascular access thrombosis and deep vein thrombosis.

Thromboembolic events (positively adjudicated vascular access thrombosis, arterial thrombosis, deep vein thrombosis and pulmonary embolism) were reported in 8.7% (7.5/100 patient-years) and 7.6% (7.7/100 patient-years) of subjects in the pooled DD-CKD population for the vadadustat and darbepoetin alfa treated patients, respectively. In the pooled NDD-CKD population 1.9% of subjects in the vadadustat treatment group and 2.2% of subjects in the darbepoetin alfa treatment group reported thrombotic events. Since Hb increases to >14.0 g/dL were overall more frequent in the vadadustat treatment group compared to the darbepoetin alfa treatment group in the DD-CKD population (3.9% and 3.4%, respectively), the Applicant was asked to discuss if the events were related. A total of 11 TEAEs with positively adjudicated thromboembolic events were reported in 8 subjects with any Hb value > 14.0 g/dL in the pooled DD-CKD population. The temporal relationship between the occurrence of thromboembolic events and the increase of Hb to values > 14 g/dL was investigated for these 11 cases. No correlation between the thromboembolic events and Hb >14.0 g/dL could be found.

Thromboembolic events is listed in the tabulated list of adverse reactions in the SmPC.

Worsening of Hypertension

Hypertension was reported for 18.0% of subjects in the vadadustat treatment group and 21.0% of subjects in the darbepoetin alfa treatment group in the pooled CKD population. Equal frequencies were reported in the DD-CKD and NDD-CKD population. The most frequently reported PTs for hypertension AESI were hypertension, hypertensive urgency, hypertensive crisis and increased blood pressure. Changes in mean blood pressure observed during the study were similar in the vadadustat and darbepoetin alfa treatment groups (see Vital Signs section).

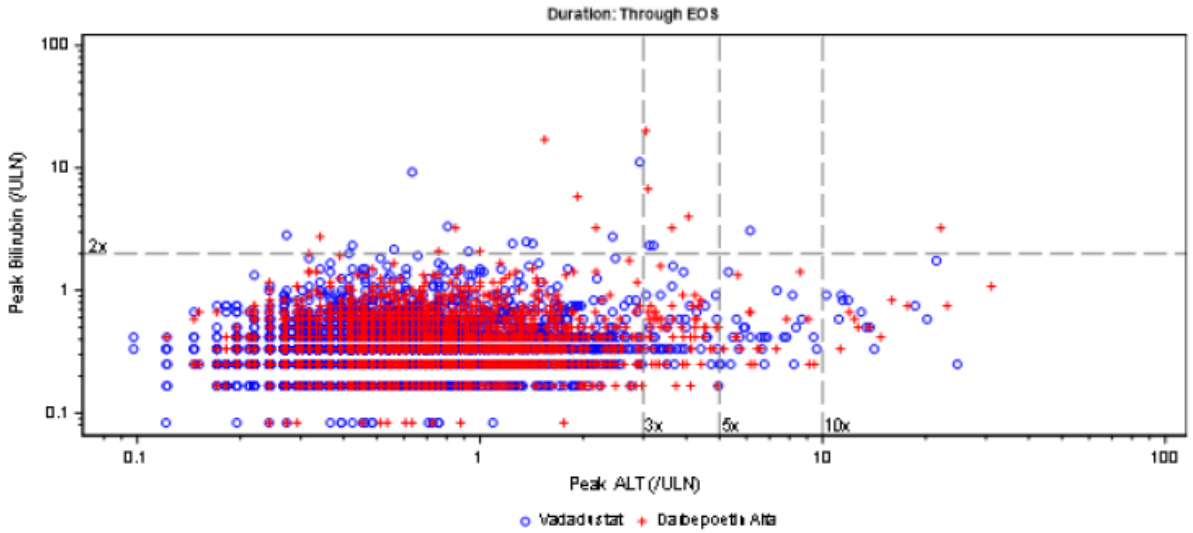
2.6.8.4. Laboratory findings

Hepatic Parameters

Pooled Global Phase 3 CKD Population

The mean changes from baseline in hepatic parameters (ie, ALT, AST, and total bilirubin) in the pooled CKD population for global Phase 3 studies were small and not clinically meaningful. Most of the hepatic parameter changes were due to increased transaminases without significant changes in bilirubin. eDISH plots for ALT versus bilirubin are presented in Figure below. The symbols on the figures are representative of a peak value at any time during the study.

Figure 36 **eDISH Plots (Hy's Law: Alanine Aminotransferase Versus Bilirubin) Through End of Study – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**



ALT: alanine aminotransferase; CKD: chronic kidney disease; eDISH: evaluation of drug-induced serious hepatotoxicity; ULN: upper limit of normal
The symbols are representative of a peak value at any time during the study.
There were no subjects in the vadadustat treatment group with abnormal hepatic parameters that satisfied Hy's law criteria. One subject in the vadadustat treatment group with ALT >3× ULN and bilirubin >2× ULN experienced acute cholecystitis. There was >1 year between the ALT >3× ULN and the bilirubin >2× ULN. The ALT elevation occurred 29 days after start of administration of vadadustat. On Day 526, the subject was diagnosed with acute cholecystitis (upgraded from worsening of cholelithiasis) associated with elevated bilirubin (as well as milder elevations of ALT and alkaline phosphatase) 8 days later (CSR AKB-6548-CI-0017 Table 14.3.5.10.1).
Source: ISS Figure 14.3.5.4.1c

Overall, the mean changes from baseline in hepatic parameters in the pooled CKD population for global Phase 3 studies were small and comparable between the two treatment groups. Even though the frequencies of TEAEs were comparable between treatment groups, more of the TEAEs were related to the study drug in the vadadustat treatment group and therefore described in the SmPC section 4.8.

In the pooled DD-CKD population one subject in the vadadustat treatment group had ALT >3× ULN and bilirubin >2× ULN, the increased hepatic parameters was assessed related to acute cholecystitis. There was >1 year between the ALT >3× ULN and the bilirubin >2× ULN, hence no Hy's law was observed

In the NDD-CKD population two subjects had ALT or AST >3× and ≤5× ULN and total bilirubin >2× ULN in the vadadustat treatment group. In one subject it was assessed related to lithiasis of common bile duct and a history of cholangitis and in the other subject a mild liver injury with jaundice was observed which was assessed likely related to a biliary event and unlikely related to vadadustat. Two subjects had ALT or AST >10× ULN and total bilirubin >2× ULN. One subject was assessed attributed to transient biliary obstruction due to cholelithiasis and hepatitis C and was considered unrelated to study drug. The other subject was determined as a 'severe hepatic injury event' probably related to vadadustat, but not a Hy's Law case.

Haemoglobin Outliers

Pooled Global Phase 3 CKD Population

The Hb-related safety endpoints in the pooled CKD population for global Phase 3 studies are presented by treatment group in Table below.

Table 81 **Hemoglobin-Related Safety Endpoints – Pooled CKD Population (Safety Population)**

Study Period Hemoglobin Category	Vadadustat N = 3686 n (%)	Darbepoetin Alfa N = 3687 n (%)
Overall		
n	3650	3661
Hb >12.0 g/dL	1569 (43.0)	1868 (51.0)
Hb >13.0 g/dL	488 (13.4)	573 (15.7)
Hb >14.0 g/dL	129 (3.5)	133 (3.6)
Hb increase >1.0 g/dL within any 2-week interval	937 (25.7)	1128 (30.8)
Hb increase >2.0 g/dL within any 4-week interval	676 (18.5)	722 (19.7)
Hb <8.0 g/dL	768 (21.0)	666 (18.2)
Hb <9.0 g/dL	1862 (51.0)	1737 (47.4)
Weeks 2 to 8		
n	3645	3654
Hb >12.0 g/dL	451 (12.4)	617 (16.9)
Hb >13.0 g/dL	78 (2.1)	143 (3.9)
Hb >14.0 g/dL	13 (0.4)	15 (0.4)
Hb increase >1.0 g/dL within any 2-week interval	523 (14.3)	690 (18.9)
Hb increase >2.0 g/dL within any 4-week interval	142 (3.9)	197 (5.4)

Study Period Hemoglobin Category	Vadadustat N = 3686 n (%)	Darbepoetin Alfa N = 3687 n (%)
Hb <8.0 g/dL	319 (8.8)	168 (4.6)
Hb <9.0 g/dL	1024 (28.1)	683 (18.7)
Weeks 10 to 20		
n	3494	3550
Hb >12.0 g/dL	650 (18.6)	869 (24.5)
Hb >13.0 g/dL	129 (3.7)	174 (4.9)
Hb >14.0 g/dL	22 (0.6)	25 (0.7)
Hb increase >1.0 g/dL within any 2-week interval	363 (10.4)	365 (10.3)
Hb increase >2.0 g/dL within any 4-week interval	246 (7.0)	198 (5.6)
Hb <8.0 g/dL	269 (7.7)	180 (5.1)
Hb <9.0 g/dL	838 (24.0)	607 (17.1)
Weeks 24 to 36		
n	3264	3365
Hb >12.0 g/dL	599 (18.4)	698 (20.7)
Hb >13.0 g/dL	127 (3.9)	138 (4.1)
Hb >14.0 g/dL	27 (0.8)	28 (0.8)
Hb increase >1.0 g/dL within any 2-week interval	66 (2.0)	123 (3.7)
Hb increase >2.0 g/dL within any 4-week interval	166 (5.1)	189 (5.6)
Hb <8.0 g/dL	213 (6.5)	178 (5.3)
Hb <9.0 g/dL	660 (20.2)	625 (18.6)
Weeks 40 to 52		
n	2871	2974
Hb >12.0 g/dL	581 (20.2)	662 (22.3)
Hb >13.0 g/dL	130 (4.5)	154 (5.2)
Hb >14.0 g/dL	29 (1.0)	32 (1.1)
Hb increase >1.0 g/dL within any 2-week interval	62 (2.2)	105 (3.5)
Hb increase >2.0 g/dL within any 4-week interval	171 (6.0)	163 (5.5)
Hb <8.0 g/dL	184 (6.4)	174 (5.9)
Hb <9.0 g/dL	614 (21.4)	559 (18.8)
Week 64 to end-of-study		
n	2150	2322
Hb >12.0 g/dL	614 (28.6)	710 (30.6)
Hb >13.0 g/dL	190 (8.8)	188 (8.1)
Hb >14.0 g/dL	54 (2.5)	56 (2.4)
Hb increase >1.0 g/dL within any 2-week interval	73 (3.4)	130 (5.6)
Hb increase >2.0 g/dL within any 4-week interval	106 (4.9)	123 (5.3)
Hb <8.0 g/dL	175 (8.1)	212 (9.1)
Hb <9.0 g/dL	584 (27.2)	652 (28.1)

CKD: chronic kidney disease; Hb: hemoglobin; N: number of subjects; n: number of subjects within specific category
The percentage is calculated based on n.
All central laboratory values in the database starting from first dose date to last visit are included.
Source: ISS Table 14.3.5.1c

Vital signs

Evaluation of vital signs for vadadustat in the three pooled populations showed similar mean changes from baseline across the vadadustat and darbepoetin alfa treatment groups. The proportion of SBP and DBP outliers were similar across the vadadustat and darbepoetin alfa treatment groups in all three pooled populations.

Vadadustat did not cause clinically relevant changes in electrocardiogram (ECG), including QTc interval changes. Therefore, no post-baseline ECG was collected in the global Phase 3 studies.

2.6.8.5. In vitro biomarker test for patient selection for safety

There are no in vitro biomarker tests relevant for patient selection for safety.

2.6.8.6. Safety in special populations

Age

Overall summary of TEAEs by age group for the pooled CKD population are presented in Table below.

Table 82 **Overall Summary of Treatment-Emergent Adverse Events by Age Group – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

	<65 Years of Age		≥65 to <75 Years of Age		≥75 to <85 Years of Age		≥85 Years of Age	
	Vadadustat N = 1989 PY = 3476.7	Darbepoetin Alfa N = 2002 PY = 3543.1	Vadadustat N = 953 PY = 1638.3	Darbepoetin Alfa N = 990 PY = 1756.3	Vadadustat N = 588 PY = 975.2	Darbepoetin Alfa N = 564 PY = 932.7	Vadadustat N = 156 PY = 245.1	Darbepoetin Alfa N = 131 PY = 188.1
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	1765 (88.7)	1775 (88.7)	835 (87.6)	892 (90.1)	533 (90.6)	507 (89.9)	144 (92.3)	118 (90.1)
Any drug-related TEAE	191 (9.6)	95 (4.7)	96 (10.1)	38 (3.8)	62 (10.5)	33 (5.9)	22 (14.1)	8 (6.1)
Any severe TEAE	793 (39.9)	809 (40.4)	410 (43.0)	445 (44.9)	290 (49.3)	265 (47.0)	89 (57.1)	77 (58.8)
Any treatment-emergent SAE	1099 (55.3)	1152 (57.5)	562 (59.0)	604 (61.0)	375 (63.8)	338 (59.9)	103 (66.0)	92 (70.2)
Any drug-related treatment-emergent SAE	33 (1.7)	27 (1.3)	16 (1.7)	12 (1.2)	15 (2.6)	12 (2.1)	2 (1.3)	4 (3.1)
Any TEAE leading to discontinuation from study drug	135 (6.8)	62 (3.1)	71 (7.5)	32 (3.2)	46 (7.8)	28 (5.0)	7 (4.5)	4 (3.1)
Any drug-related TEAE leading to discontinuation from study drug	40 (2.0)	7 (0.3)	18 (1.9)	2 (0.2)	13 (2.2)	1 (0.2)	2 (1.3)	1 (0.8)
Any TEAEs leading to death	231 (11.6)	222 (11.1)	154 (16.2)	172 (17.4)	146 (24.8)	149 (26.4)	62 (39.7)	53 (40.5)
All deaths[a]	237 (11.9)	227 (11.3)	158 (16.6)	182 (18.4)	151 (25.7)	155 (27.5)	64 (41.0)	53 (40.5)

CKD: chronic kidney disease; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
a. All deaths were collected during the study and presented in this table irrespective of whether a preceding TEAE was recorded.
Source: ISS Table 14.3.1.2.1c

Sex

A summary of TEAEs reported for subjects in the pooled CKD population for global Phase 3 studies is presented by sex in Table below.

Table 83 **Overall Summary of Treatment-Emergent Adverse Events by Sex – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

	Male		Female	
	Vadadustat N = 1886 PY = 3156.1	Darbepoetin Alfa N = 1848 PY = 3151.4	Vadadustat N = 1800 PY = 3179.2	Darbepoetin Alfa N = 1839 PY = 3268.7
Category	n (%)	n (%)	n (%)	n (%)
Any TEAE	1668 (88.4)	1636 (88.5)	1609 (89.4)	1656 (90.0)
Any drug-related TEAE	178 (9.4)	83 (4.5)	193 (10.7)	91 (4.9)
Any severe TEAE	855 (45.3)	824 (44.6)	727 (40.4)	772 (42.0)
Any treatment-emergent SAE	1120 (59.4)	1106 (59.8)	1019 (56.6)	1080 (58.7)
Any drug-related treatment-emergent SAE	36 (1.9)	26 (1.4)	30 (1.7)	29 (1.6)
Any TEAE leading to discontinuation from study drug	135 (7.2)	56 (3.0)	124 (6.9)	70 (3.8)
Any drug-related TEAE leading to discontinuation from study drug	38 (2.0)	5 (0.3)	35 (1.9)	6 (0.3)
Any TEAEs leading to death	335 (17.8)	319 (17.3)	258 (14.3)	277 (15.1)
All deaths[a]	342 (18.1)	333 (18.0)	268 (14.9)	284 (15.4)

CKD: chronic kidney disease; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event
A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.
MedDRA version 23.0
a. All deaths were collected during the study and presented in this table irrespective of whether a preceding TEAE was recorded.
Source: ISS Table 14.3.1.2.2c

Race

In the ethnobridging study performed in Japanese and Caucasian subjects (Study CI-0020), the pharmacokinetics (PK) of vadadustat was confirmed to be similar between the 2 populations.

A summary of TEAEs reported for subjects in the pooled CKD population for global Phase 3 studies is presented by race in Table below.

Table 84 **Overall Summary of Treatment-Emergent Adverse Events by Race – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

	White		Black		All Others	
	Vadadustat N = 2432 PY = 4149.1	Darbepoetin Alfa N = 2403 PY = 4095.9	Vadadustat N = 750 PY = 1429.7	Darbepoetin Alfa N = 780 PY = 1504.2	Vadadustat N = 504 PY = 756.5	Darbepoetin Alfa N = 504 PY = 820.0
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any TEAE	2129 (87.5)	2120 (88.2)	699 (93.2)	716 (91.8)	449 (89.1)	456 (90.5)
Any drug-related TEAE	225 (9.3)	102 (4.2)	80 (10.7)	47 (6.0)	66 (13.1)	25 (5.0)
Any severe TEAE	991 (40.7)	1001 (41.7)	388 (51.7)	397 (50.9)	203 (40.3)	198 (39.3)
Any treatment-emergent SAE	1364 (56.1)	1396 (58.1)	498 (66.4)	499 (64.0)	277 (55.0)	291 (57.7)
Any drug-related treatment-emergent SAE	36 (1.5)	31 (1.3)	19 (2.5)	20 (2.6)	11 (2.2)	4 (0.8)
Any TEAE leading to discontinuation from study drug	163 (6.7)	81 (3.4)	49 (6.5)	34 (4.4)	47 (9.3)	11 (2.2)
Any drug-related TEAE leading to discontinuation from study drug	43 (1.8)	8 (0.3)	14 (1.9)	3 (0.4)	16 (3.2)	0
Any TEAEs leading to death	396 (16.3)	404 (16.8)	115 (15.3)	122 (15.6)	82 (16.3)	70 (13.9)
All deaths[a]	408 (16.8)	420 (17.5)	118 (15.7)	123 (15.8)	84 (16.7)	74 (14.7)

CKD: chronic kidney disease; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event

A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.

MedDRA version 23.0

a. All deaths were collected during the study and presented in this table irrespective of whether a preceding TEAE was recorded.

Source: ISS Table 14.3.1.2.3c

Renal Insufficiency

Because CKD was the underlying disease of the patient population, no individual study was designed to investigate the effect of renal insufficiency on vadadustat safety. The predominant route of elimination of vadadustat is by hepatic metabolism and renal excretion of the metabolites.

By nature of the population cohorts under investigation, all subjects in the global Phase 3 studies by definition, had various degrees of renal insufficiency. Within the patient population, subjects with NDD-CKD would be expected to have more preserved renal function (eGFR ≤60 mL/min/1.73 m2 predialysis) compared with patients with DD-CKD.

The frequency of treatment-emergent SAEs was higher in vadadustat treatment group compared to the darbepoetin alfa-treated subjects in the pooled NDD-CKD population (61.9% and 60.6% of subjects, respectively) and lower in the pooled DD-CKD population (54.5% and 58.2% of subjects, respectively). Any TEAEs that led to death were reported more frequent in the NDD-CKD population (17.9% and 17.5% of subjects, respectively) than the DD-CKD population (14.2% and 15.1% of subjects, respectively). Overall, no evidence that renal insufficiency is correlated with an increased risk with vadadustat treatment compared with darbepoetin alfa treatment.

Hepatic Impairment

In the global Phase 3 studies, subjects were excluded from participation if AST, ALT, or bilirubin levels were >2.0× ULN during Screening. Subjects were not excluded if they had a history of Gilbert's syndrome.

In Study CI-0024, there was no significant difference in the proportion of subjects or type of TEAEs reported for subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic function (Table 100). No treatment-emergent SAEs or deaths were reported during this study. Vadadustat has not been studied in severe hepatic impairment (Child-Pugh Class C).

Overall, no increased risk of moderate hepatic impairment related to vadadustat was seen and there is no data in patients with severe hepatic impairment.

Patients with Diabetes Mellitus

Overall, the data suggest that there is no specific risk to diabetes mellitus control from vadadustat, and no greater risk of adverse outcomes from vadadustat in diabetics compared to non-diabetics (Table below).

Table 85 **Overall Summary of Treatment-Emergent Adverse Events by Diabetes Mellitus at Time of Study Entry – Pooled CKD Population for Global Phase 3 Studies (Safety Population)**

	No		Yes	
	Vadadustat N = 1518 PY = 2540.3	Darbepoetin Alfa N = 1484 PY = 2543.9	Vadadustat N = 2168 PY = 3795.1	Darbepoetin Alfa N = 2203 PY = 3876.2
Category	n (%)	n (%)	n (%)	n (%)
Any TEAE	1318 (86.8)	1277 (86.1)	1959 (90.4)	2015 (91.5)
Any drug-related TEAE	167 (11.0)	78 (5.3)	204 (9.4)	96 (4.4)
Any severe TEAE	505 (33.3)	519 (35.0)	1077 (49.7)	1077 (48.9)
Any treatment-emergent SAE	749 (49.3)	753 (50.7)	1390 (64.1)	1433 (65.0)
Any drug-related treatment-emergent SAE	28 (1.8)	19 (1.3)	38 (1.8)	36 (1.6)
Any TEAE leading to discontinuation from study drug	105 (6.9)	42 (2.8)	154 (7.1)	84 (3.8)
Any drug-related TEAE leading to discontinuation from study drug	33 (2.2)	7 (0.5)	40 (1.8)	4 (0.2)
Any TEAEs leading to death	208 (13.7)	181 (12.2)	385 (17.8)	415 (18.8)
All deaths[a]	213 (14.0)	187 (12.6)	397 (18.3)	430 (19.5)

CKD: chronic kidney disease; MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects with events; PY: patient-year; SAE: serious adverse event; TEAE: treatment-emergent adverse event

A TEAE was an adverse event that started (or a preexisting adverse event that worsened) on or after the first dose of study drug.

MedDRA version 23.0

a. All deaths were collected during the study and presented in this table irrespective of whether a preceding TEAE was recorded.

Source: ISS Table 14.3.1.2.5c

Geographic Region (US/Europe/ROW)

In the pooled CKD population for global Phase 3 studies, TEAEs were reported in a higher proportion of subjects in the US (90.2% of subjects in the vadadustat treatment group and 90.9% of subjects in the darbepoetin alfa treatment group) and ROW (90.2% and 90.3% of subjects, respectively) than Europe (82% and 81.6% of subjects, respectively; Data not shown here, but available in ISS Tables 14.3.1.2.4a, 14.3.1.2.4b, and 14.3.1.2.4c).

Some differences in reported TEAEs related to geographic region were seen in the pivotal studies; In the vadadustat treatment group, TEAEs were reported in a higher proportion of subjects in the US (90.2%) and ROW (90.2%) than Europe (82%). Drug-related TEAEs were reported more frequent in ROW (13.1%) compared to US (9.2%) and Europe (7.3%). Treatment-emergent SAEs were reported more frequent in the US (65.7%) compared to ROW (48.8%) and Europe (47.9%). Further, TEAEs that led to death were reported more frequently in US (17.3%) compared to Europe (14.2%) and ROW (14.8%). The regional differences in TEAEs, serious TEAEs, drug-related TEAEs, and fatal TEAEs for vadadustat is also observed for darbepoetin alfa.

2.6.8.7. Immunological events

Vadadustat is not a monoclonal antibody, therefore no data is available.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Drug-drug interactions

Use of concomitant medications were not evaluated in the pooled global Phase 3 populations.

From the pharmacological studies, vadadustat was found to have interactions with iron-containing phosphate binders, iron supplements and non-iron containing phosphate binders. Co-administration reduced vadadustat exposure from 50% up to 90% for Cmax. The Applicant states, that the interaction can be reduced by administering vadadustat 1 hour prior to or 2 hours after binder administration.

Vadadustat is an inhibitor of the drug transporter BCRP. The interaction of vadadustat when co-administered with the BCRPs substrates simvastatin or rosuvastatin was investigated in healthy subjects. Exposures of simvastatin and its active metabolite (beta-hydroxy acid) were increased approximately 2-fold with co-administration of vadadustat in healthy subjects. Exposure (maximum observed plasma concentration of rosuvastatin was increased 2- to 3-fold when co-administered with vadadustat in healthy subjects. For subjects in the global Phase 3 clinical studies taking vadadustat who were concomitantly taking simvastatin or rosuvastatin, their dose of statin was limited to 20 mg simvastatin daily or 10 mg rosuvastatin daily. The frequency of AEs in general and of AEs expected in subjects receiving statins is higher in subjects receiving concomitant statins compared to those receiving only vadadustat or darbepoetin alone.

Vadadustat is an inhibitor of the organic anion transporter (OAT)3. Exposure of furosemide, an OAT3 substrate, increased 2-fold when co-administered with vadadustat in healthy subjects.

Further, vadadustat is an OAT1/3 substrate. Exposure of vadadustat increased approximately 2-fold when co-administered with probenecid, an OAT1/3 and glucuronidase inhibitor.

Alcohol and Tobacco Use

The interaction of alcohol and tobacco use on vadadustat has not been studied.

Use in Pregnancy and Lactation

Eligible participants from the Global phase 3 studies were required to use contraception. Safety database search identified 5 cases of exposure to vadadustat during pregnancy. Of those, 3 cases were associated with treatment-emergent SAEs in the mother receiving vadadustat – 1 case of spontaneous abortion, 1 case of pre-eclampsia that resulted in elective termination and 1 case of cervical insufficiency and breech presentation that resulted in a premature live birth at 32 weeks. The two remaining cases were partner pregnancies, 1 with a favourable outcome and another that was progressing uneventfully but the outcome is unknown.

Overdose

Overall, more special situations of overdose were presented in the vadadustat treatment group compared to the darbepoitin alfa treatment group. None of the special situations of overdose led to TEAEs.

Drug Abuse

Overall, more special situations of drug abuse were presented in the vadadustat treatment group compared to the darbepoitin alfa treatment group. None of the special situations of suspected abuse/misuse led to TEAEs. Even though no TEAEs were related to misuse in the phase 3 studies, 15 events of misuse were reported and since HIF-activating agents are listed in the prohibited list of the International Standard World Anti-Doping Code.

Withdrawal and Rebound

No formal withdrawal and rebound assessments after vadadustat administration is discontinued have been conducted in human subjects.

Effect of Ability to Drive or Operate Machinery

Overall, TEAEs of somnolence were reported for 0.2% of subjects in both treatment groups, and there was no evident difference between the treatment groups in the reporting of dizziness or other neurological disorders, or eye disorders including TEAEs of vision blurred or visual impairment in the pooled CKD population.

2.6.8.9. Discontinuation due to adverse events

As previously mentioned, TEAEs that led to discontinuation from study drug were reported more frequent in the vadadustat treatment group compared to the darbepoetin alfa treatment group in all three pooled populations (7.0% and 3.4% of subjects, respectively in the CKD population). TEAEs that led to discontinuation from study were higher in both treatment groups in the NDD-CKD population compared to the DD-CKD population (9.4% and 6.0% of subjects, respectively in the NDD-CKD population and 4.9% and 1.1% of subjects, respectively in the DD-CKD population). Drug-related TEAEs that led to discontinuation from study drug had the same pattern with more frequent reporting in the vadadustat treatment group compared to the darbepoetin alfa treatment group (2.0% and 0.3% of subjects, respectively in the CKD population.

In the CKD population, the most frequent TEAEs that led to discontinuation from study drug in the vadadustat treatment group were within the SOCs Renal and urinary disorders (ESRD [1.7% of subjects]) and Gastrointestinal disorders (diarrhoea [0.7% of subjects], nausea [0.4% of subjects], and vomiting [0.2% of subjects]). The most frequent TEAEs that led to discontinuation from study drug in the darbepoetin alfa treatment group were within the SOCs Renal and urinary disorders (ESRD [1.7% of subjects]).

2.6.8.10. Post marketing experience

A total of 297 AEs has been reported for 237 patients from post marketing surveillance in Japan, until 25 Feb 2021. Of these events, 79 events were serious. There were 41 serious events with fatal outcome, of which 9 events with fatal outcome in 5 patients were assessed as related to vadadustat. The 9 fatal events assessed as related, in 5 subjects over the age of 80 years old both male and female, included PTs blood pressure decreased, acute myeloid leukemia and decreased appetite in an patient; cardiac failure and hyponatremia in; myocardial ischemia in an; sepsis, and abdominal pain in an, and death in a. Of the non-serious events, 159 events were considered related to vadadustat.

Adverse Drug Reactions

For the purpose of product labeling, ADRs for vadadustat as presented in Table below, are based upon a best-evidence assessment of all observed TEAEs and laboratory investigations from pooled CKD population for global Phase 3 studies and accumulated post marketing safety data.

Table 86 **Summary of Adverse Drug Reactions Identified in Global Phase 3 CKD Subjects**

Adverse Reaction		Vadadustat N = 3686		Darbepoetin Alfa N = 3687
SOC	PT	Incidence Rate	Frequency	Incidence Rate
Nervous systems disorders	Headache	6.4%	Common	6.3%
Vascular disorders	Hypertension	13.4%	Very common	15.9%
	Thromboembolic events[a]	10.5%	Very common	9.5%
	Hypotension	6.9%	Common	6.7%
Respiratory, thoracic, and mediastinal disorders	Cough	5.4%	Common	6.0%
Gastrointestinal disorders	Diarrhoea	13.3%	Very common	9.7%
	Constipation	5.6%	Common	5.6%
	Nausea	8.8%	Common	7.5%
	Vomiting	6.3%	Common	6.2%
Hepatobiliary disorders	Elevated liver enzymes[b]	3.0%	Common	3.2%
	Blood bilirubin increased	0.1%	Uncommon	<0.1%

CKD: chronic kidney disease; N: number of subjects; PT: preferred term

a. Includes Preferred Terms of acute myocardial infarction, cerebrovascular accident, transient ischaemic attack, deep vein thrombosis, pulmonary embolism, arteriovenous fistula thrombosis, arteriovenous graft thrombosis.

b. Includes transaminases increased, ALT increased, AST increased, hepatic enzyme increased, liver function test abnormal.

Source: Integrated Summary of Safety Tables 14.3.1.11.1c, 14.3.1.3c, 14.3.1.5c, and 14.3.1.3.1.2c

2.6.9. Discussion on clinical safety

Safety data

With regard to the safety exposure, the primary safety analyses for this submission was based on 4 pivotal phase 3 clinical studies. All studies were randomized, open-label, active-controlled studies that evaluated the efficacy and safety of vadadustat for the treatment of anaemia in subjects with DD-CKD and NDD-CKD compared with the standard erythropoiesis-stimulating agent (ESA) darbepoetin alfa. As stated in the scientific advice EMA/CHMP/SAWP/818714/2015, CHMP did not agree with the study design. In line with the EMA/CHMP guideline (EMEA/CHMP/BWP/301636/2008), the Applicant should have, as an absolute minimum, considered a design where the person(s) responsible for drug dosing is blinded to the treatment allocation. The Applicant has justified the open-label design due to the different dosing regimens and ethics related to the safety risk for the study participants and clarified procedures to minimize bias.

Overall, the primary clinical safety database included 3686 subjects receiving vadadustat. The safety database was grouped into three pooling blocks: Pooled DD-CKD population, Pooled NDD-CKD population and Pooled CKD population.

Four Phase 3 studies performed on Japanese subjects with CKD were not included in the pooled analyses due to differences in design. No new safety information was identified in those studies.

The proportion of subjects who completed study drug treatment was lower in the vadadustat treatment group (54.0%) compared to the darbepoetin alfa treatment group (64.1%) and the mean (SD) total duration of exposure (weeks) was longer for the Darbepoetin alfa group compared to the vadadustat group for all three pooling blocks; 73.23 (42.720) for Darbepoetin alfa compared to 64.06 (42.943) for vadadustat in the CKD population. It has been clarified that the different duration of exposure had no impact on the safety data.

The DD-CKD and NDD-CKD subjects exposed to vadadustat for at least 6 months, at least 1 year, and at least 2 years met the requirements of the ICH E1 guideline for safety evaluation of drugs intended for long-term treatment of non-life-threatening diseases.

Some differences in baseline characteristics are observed between the DD and the NDD pooled populations. The mean age in DD-CKD population is lower compared to the NDD-CKD population (approximately 58 years vs 66 years, respectively). The DD population is mainly composed of patients from the US (around 60%), while US patients account for about 50% of the NDD population. In addition, patients from the DD population less frequently had diabetes mellitus compared to patients from the NDD population (around 55-56% vs 63-64%, respectively).

In the pooled CKD population a total of 2923 (79,5%) subjects were exposed to vadadustat for at least 6 months, a total of 2011 (54,6%) subjects were exposed to vadadustat for a least 1 year and a total of 695 (18,9%) subjects were exposed to vadadustat for at least 2 years.

Overall, 55.4% of the subjects enrolled in the United States (US), 15.7% from Europe and 28.9% from the Rest of World (ROW). The proportion of enrolled subjects in Europe and ROW is acceptable for being representative for the practice in the European Union as discussed in the Scientific advice EMA/CHMP/SAWP/818714/2015, since the European Hb target range were used in ROW. In both Europe and US the median duration of follow-up was 60 weeks for vadadustat in the CKD population. For ROW the median duration of follow-up was 52 weeks in the pooled CKD population for vadadustat. The percentage of subjects on vadadustat with an exposure of more than 52 weeks were similar in Europe and US (57% and 56%) in the pooled CKD population.

Adverse events

The proportion of TEAEs, severe TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs and TEAEs that lead to death were comparable in the two treatment groups, with a tendency to have a slightly higher frequency in the vadadustat treatment group compared to darbepoitin alfa treatment group in the pooled NDD-CKD population and the opposite tendency in the pooled DD-CKD population. The proportion of subjects with drug-related TEAEs, TEAEs that led to discontinuation from study drug, and drug-related TEAEs that led to discontinuation from study drug were higher in the vadadustat treatment group compared to the darbepoetin alfa treatment group.

In the pooled CKD pooling population, the proportion of subjects with drug-related TEAEs, TEAEs that led to discontinuation from study drug, and drug-related TEAEs that led to discontinuation from study drug were higher in the vadadustat treatment group compared to the darbepoetin alfa treatment group throughout all three pooling blocks (10.1%, 7.0%, and 2.0% of subjects compared to 4.7%, 3.4%, and 0.3% of subjects, respectively). The difference in early discontinuations between vadadustat and darbepoetin alfa, can be due to the open-label design. The most frequent reasons for discontinuations suggest that subjects may have preferred to switch to a product which effect and dosing were well known (standard of care). Even though discontinuations were more frequent in the vadadustat treatment group, the frequency of subjects completing the trial was similar for vadadustat and darbepoetin alfa, showing that subjects in both groups were followed-up for MACE and TEAEs even though they discontinued. The potential missing data didn’t have an impact on the overall number of

reported TEAEs, serious TEAEs, and TEAEs leading to death in the CKD population, since they were similar.

With regard to common adverse events, the most frequent adverse reactions in patients treated with vadadustat were hypertension (13.4%), diarrhoea (13.3%) and thromboembolic events (10.5%). Overall, TEAEs within the SOCs Gastrointestinal disorders and General disorders and administration site conditions were reported more frequent in the vadadustat treatment group compared to the darbepoetin alfa treatment group. All the common adverse events are reflected in section 4.8 of the PI. The most frequent drug-related TEAEs reported for subjects in the vadadustat treatment group were in the SOC Gastrointestinal disorders (5.0% of subjects), and by PT: diarrhoea (2.2% of subjects) and nausea (1.2% of subjects). This could be due to the oral route of administration.

Severe TEAEs were reported for 42.9% of subjects in the vadadustat treatment group and 43.3% of subjects in the darbepoetin alfa treatment group in the pooled CKD population.

Serious adverse events and Deaths

In the pooled DD-CKD population, treatment-emergent SAEs were reported less frequently in the vadadustat treatment groups compared to the darbepoetin alfa treatment groups (54.5% and 58.2% of subjects respectively). Contrary, in the pooled NDD-CKD population, treatment-emergent SAEs were reported slightly more frequently in the vadadustat treatment groups compared to the darbepoetin alfa treatment groups (61.9% and 60.6% of subjects, respectively).

Most of the treatment-emergent SAEs were assessed not related to study drug by the investigator and/or sponsor;

Acute myocardial disease (AMI) and pneumonia were reported more frequently in the vadadustat treatment groups compared to darbepoetin alfa in all pooling blocks. The difference was most clear in the NDD-CKD population. Further, In the NDD-CKD population acute kidney disease, sepsis, UTI, fluid overload and death were reported more frequently in the vadadustat treatment group compared to the darbepoetin alfa treatment group. Regarding AMI, vascular thrombosis is a theoretical risk from stabilization of HIF-α and the resulting increase in erythropoiesis. Thromboembolic events including acute myocardial infraction (AMI) and stroke is considered as important identified risk for vadadustat in the RMP. The risk pertaining to AMI and thromboembolic events well reflected in the SmPC. Regarding UTI, sepsis and pneumonia, it is not completely clear whether the phenomenon of HIF-1α activation in infections has a protective or detrimental effect for the host. However, overall no signal was raised for infections in the clinical development program of vadadustat. Activation of HIF-1α has strong renal protective effects in acute kidney injury, whereas inappropriate activation of HIF-1α in tubules promotes the progression of kidney diseases, as evidenced by genetic and pharmacological modulation in animal models. No theoretical mechanism could be established between fluid overload and HIF-PHD inhibitors.

Overall, treatment-emergent SAEs were reported slightly more frequently and assessed more frequently related to study drug in the vadadustat treatment groups compared to darbepoetin alfa in the NDD-CKD population. This was considered in the overall benefit-risk assessment for the NDD-CKD population which was not included in the approved indication.

Overall, TEAEs leading to deaths were comparable between the two treatment groups, with a slightly higher frequency in the NDD-CKD population in the vadadustat treatment group compared to the darbepoetin alfa treatment group (17.9% and 17.4% of subjects, respectively). The opposite pattern was seen the DD-CKD population (14.4% and 15.0% of subjects, respectively).

Overall, TEAEs leading to death were comparable between the two treatment groups. Nevertheless, some differences requiring justification are noted, primarily regarding the higher frequency of death in the NDD-CKD population. The most frequent reason given for discontinuation in each study in both treatment groups was death (CI-0016 8.3% vs 10.1%; CI-0017 14.7% vs 15.6%; CI-0014 19.8% vs 19.2%; CI-0015 15.9 vs 15.9). Overall, the incidences of death were higher in NDD-CKD setting, and the study CI-0014 had highest incidence of death of almost 20%. The Applicant provided a discussion for the observed differences, highlighted the difficulties of inter-trial comparisons and the fact that the NDD-CKD population enrolled more subjects from ROW (33.6% of subjects in the NDD-CKD population versus 24.8% subjects in the DD-CKD population), including developing countries in which renal replacement therapy is more difficult to obtain than in the US or Europe. The NDD-CKD had a higher proportion of subjects with diabetes mellitus and subjects who were on statins at time of enrolment compared to the DD-CKD population.

Major Adverse Cardiovascular Events

The primary safety endpoint of time to first MACE (all-cause mortality, non-fatal MI, or non-fatal stroke) was assessed in the DD-CKD population and NDD-CKD population from subjects enrolled in the global Phase 3 studies, with a non-inferiority margin of 1.3, endorsed by an CHMP scientific advice. All MACE events were adjudicated and confirmed by a blinded adjudication committee. MACE were required to be achieved in each of the INNO2VATE and PRO2TECT studies, respectively. In total 887 MACE was achieved in the DD-CKD population and 825 MACE in the NDD-CKD population.

In the pooled DD-CKD population, non-inferiority of vadadustat to darbepoetin alfa was shown, for time to first MACE for vadadustat compared to darbepoetin alfa: HR (95% CI) 0.96 (0.833, 1.113), with upper bound of the 95% CI of the HR was below the prespecified non-inferiority margin of 1.30. The results were supported by the results from the secondary endpoints. However, in the sub analyses for Europe, the non-inferiority margin of 1.3 was exceeded for the primary safety endpoint (HR [95% CI] 0.89 [0.570, 1.394]). The same pattern was seen in the key secondary endpoints. However, the point estimates of the HRs and 95% CIs are 0.86 (0.652, 1.143) for target Hb level 10-12 g/dL used in Europe. This was supported by the key secondary MACE endpoints for the for target Hb level 10-12 g/dL used in Europe. All the upper bounds of 95% CI are below the NI margin of 1.3 for both target ranges, except the endpoint of cardiovascular death (HR 0.94 (0.602, 1.453). The reason of the larger confidence interval for cardiovascular death is the small number of events, 38 (5.0%) in the vadadustat group and 43 (5.6%) in the darbepoetin alfa group. This justify the indication in the DD-CKD population in Europe. The additional analysis requested by the CHMP (OT+DF+28 days) were in line with the pre-defined analyses (HR 0.91 (0.769, 1.086).

In the pooled NDD-CKD population, for the two pre-specified analyses, the upper bound of the 95% CI of the HR exceeded the prespecified non-inferiority margin of 1.3 (ITT: HR (95% CI): 1.17 (1.012, 1.355); OT+28: HR (95%CI: 1.30 (1.08, 1.56)), therefore the non-inferiority of vadadustat compared to darbepoetin alfa for time to first MACE was not demonstrated in this population, rather the results indicate an increased risk of MACE in NDD-CKD patients with vadadustat treatment. The key secondary endpoints supported the results. In the sub analyses for Europe, the exceedance of the non-inferiority margin was more pronounced (HR (95% CI) 1.56 (1.039, 2.350)).

The Applicant states that the submitted on-treatment analysis did not consider the different dosing regimens used with the comparator darbepoetin alfa (dosed once weekly, every other week or once monthly (different half-lives) and that the submitted on-treatment analysis +28 days is confounded by variations in the darbepoetin alfa treatment schedule. The Applicant has therefore undertaken a new on-treatment analysis that considers the different follow-up periods for darbepoetin alfa. This is done according to a paper published in New England Journal of Medicine for daprodustat, another HIF-PH inhibitor. The new on-treatment+ dosing frequency analysis shows a HR of 1.03 (95% CI

0.835;1.259), hence no increase in MACE risk compared to darbepoetin alfa is evident using this approach accounting for the different follow-up periods. In this analysis, there was a substantial drop in number of events, especially in the vadadustat arm due to the shorter follow-up period (1 day compared to 1-4 weeks in the comparator arm). There was an increase in MACE events in the 0-30 days after the EOT in both the NDD and DD population. For the NDD population 21.7% and 24.3%, for vadadustat and darbepoetin alfa, respectively. The corresponding numbers for the DD population were 8.4% and 13.9%. The Applicant believes that the poor health of some patients was the explanation for the immediate increase in MACE events following EOT and not switching to ESA. The basis for this hypothesis is that the Applicant has looked at the patients who had a MACE event in the subsequent 90 days following end-of-treatment (EOT) and then looked at how many of those patients were treated with an ESA in that period. It was observed that only a small proportion of patients were shifted to an ESA in the period of 90 days after EOT. For NDD: 6.8% and 6.1% and for DD: 18.5% and 10%, in the vadadustat and darbepoetin arm, respectively. In addition, the Applicant clarified that the immediate increase in events in the 0-30 days EOT period is due to a large number of events actually causing the discontinuation of the study drug treatment.

The additional analysis requested by CHMP, where the follow-up period was on-treatment (OT)+dosing frequency (DF) + 28 days, showed a HR of 1.14 (0.954, 1.360), and two additional on-treatment analyses (OT+1day and OT) were in line with the pre-defined analyses. In the Kaplan-Meier figure the curves diverge and then merge and cross. It is not unusual for composites to show non-proportional hazards (NPH). The concern is that the estimated hazard ratio is conservative under NPH and thus anti-conservative in the context of non-inferiority testing (especially when the censoring rate is as high as 50%). The Applicant has addressed the concern of non-proportional hazards and the implied ambiguity with regards to specifying the hazard rate. In the data collected there were no clear indications on non-proportional hazards, when looking at residuals and likewise the estimated restricted mean survival times, which do not depend on the proportional hazards assumption, were consistent with the Cox modelling. In conclusion, the results from the Cox modelling are considered appropriate to capture the difference between treatments.

It has been clarified that there are negligible differences in the results for the OT analyses when using Region as a stratification factor in the Cox models compared with Region being a covariate. For some of the individual components for the MACE, numbers were so small for Region that the model could not converge and thus no estimates provided.

The Applicant has investigated whether the risk of MACE was different in the NDD population according to eGFR <15 and >15 ml/min/1.73m2 in the two post-hoc OT analyses (OT+DF and OT+DF+28 days). Apart from fewer events in the <15 eGFR group for vadadustat in the OT+DF analysis, there is no indication that baseline eGFR can predict a worse outcome regarding MACE in the NDD population.

The Applicant provided a descriptive analysis of the darbepoetin alfa treatment schedule as requested. For the NDD-CKD population, the mean number of days to last dose was 21.97 days and for the DD-CKD population, it was 13.44 days.

Both baseline and last Hb values before the event and the relation to the MACE event were evaluated. Baseline Hb: HRs for time to first MACE was 1.11 (95% CI 0.913; 1.342) for low baseline Hb values (< 9.5g/dL for CI-0014 and < 10 g/dL for CI-0015) and 1.29 (95% CI 1.027; 1.610) for high baseline Hb (≥ 9.5g/dL for CI-0014 and ≥ 10 g/dL for CI-0015).

For both NDD trials 0014 and 0015, the majority of MACE events were seen in patients with Hb values <12, and no apparent differences were seen between vadadustat and darbepoetin alfa. For the first MACE events, around 40-50% of patients had Hb values <10. This was comparable to darbepoetin alfa. Few MACE events were seen in patients that had a Hb value above 12 g/dL, and this was also comparable to darbepoetin alfa. Hence, the presented subgroup data according to baseline and pre-

MACE Hb, suggest that the impact of Hb values were comparable to darbepoetin alfa, and that lower Hb values were associated with more MACE events.

The Applicant performed an analysis to determine the impact of the baseline ESA dose ≤ 90 U/kg/week in the conversion study CI-0015 on MACE. In study CI-0015 the subgroup of subjects with a baseline ESA dose ≤ 90 U/kg/week the subjects randomized to vadadustat had a higher MACE rate compared to the subjects continued on darbepoetin alfa (HR of MACE: 0.49 (1.1, 2.0). Further the Applicant performed Kaplan-Meier curve of time to first MACE for Trial CI-0015 and CI-0014 with the exclusion of all subjects on a baseline ESA dose of ≤ 90 U/kg/week, showing similar MACE risks in the two treatment groups.

When looking at individual components of the MACE endpoint across regions, the unfavourable results in Europe are driven by a large difference in all-cause mortality in vadadustat compared to darbepoetin groups (17.3% vs 12.5%, respectively). The Applicant proposes an explanation for these excess deaths based on healthcare disparities since the 4 top enrolling countries in study 0015 are former Eastern Bloc countries with 'different healthcare systems' than the US and other EU member states (Bulgaria, Hungary, Romania and Serbia). This argument is not considered valid, since treatment allocation was randomised. Assuming similar numbers of subjects allocated to each treatment arm within each country, the subjects had equal chances of dying due to 'different' healthcare systems in both treatment arms. In addition, the Applicant provides no data to substantiate claims that mortality rates in those 4 countries differ from the mortality rates observed.

Several differences in baseline characteristics observed in the European population compared to the US and ROW (higher frequency of NYHA II and III, previous CVD, high baseline Hb) do disfavour the EU population, but they equally disfavour European population receiving vadadustat and darbepoetin. Given the importance of optimal performance of the comparator in non-inferiority trials, the lower performance of darbepoetin in the US might be questioned, rather than the good performance of darbepoetin in Europe.

For ROW, the majority of deaths in study CI-0014 were non-CV deaths. The narratives of the MACE and additional clinical data indicated that many of the subjects in these 2 countries had very low eGFRs and did not receive renal replacement therapy resulting in death. In trial CI-0014, subjects in the vadadustat treatment group in South Africa and Brazil by had lower mean and median eGFR and a higher proportion of subjects with eGFR ≤ 10 mL/min/1.73m2 at baseline than subjects in the darbepoetin alfa treatment group. This imbalance was not observed in trial CI-0015.

In conclusion, in the NDD population, failure to show non-inferiority was seen for both the pre-specified ITT and OT+28 days analyses, and the post-hoc OT+DF+28 days, OT and OT+1 das analyses. One post-hoc analysis, provided by the Applicant, that account for the difference in the dosing regimen provided a result that showed non-inferiority to darbepoetin alfa. However, this analysis disfavoured the darbepoetin arm in relation to longer follow-up time after end-of-treatment. A number of additional subgroup analyses were requested in relation to the impact on MACE risk from baseline Hb, Hb over time and Hb achieved at the primary endpoint. As expected, higher haemoglobin was also associated with higher risk of MACE, but it seemed to more pronounced in the vadadustat treatment group. Although the Applicant provided some explanations as to why non-inferiority could not be shown in the NDD population, it cannot be assumed that these are the sole explanations, and also these would be hypotheses that cannot be confirmed. Hence, a residual increased risk of MACE cannot be ruled out for the NDD population. In addition, some of the explanations would presumably also pertain to the DD population, for which non-inferiority was shown consistently.

In the latest response, the Applicant reiterated the issue of confounders: healthcare disparities in South Africa and Brazil in ESA-naïve Study CI-0014 and a design bias against vadadustat in Europe in the ESA-treated Study CI-0015.

In a new analysis of data from Study CI-0014, the Applicant excluded data from South Africa and Brasil, and replaced age as a dichotomous variable (< 65 years and > 65 years) with age as a continuous variable. This post-hoc analysis yielded MACE HR of 1.08 (0.929, 1.265). Although, the upper limit of the 95%CI in this analysis is just below the NIM, it is a single post-hoc analysis giving a non-inferior result and cannot be considered sufficiently robust to overturn the results from the pre-planned primary analyses.

In a new analysis of data from Study CI-0015, the Applicant added ESA rescue as a covariate in the MACE analysis, as this would account for Hb instability during conversion. ESA rescue was defined as any exogenous ESA in the vadadustat group or another ESA in the darbepoetin alfa group or any dose increase of darbepoetin alfa of ≥ 100% from the prior dose. This data shows that ESA rescue was associated with an increased rate of MACE, particularly in vadadustat arm (23.5% in ESA-rescue vadadustat group compared to 16.4% in ESA-rescue darbepoetin group). The low rate of MACE events in Europe among participants without ESA rescue does indicate more stable clinical course. However, within Europe, there is again a striking difference in vadadustat compared to darbepoetin even among those patients who did not require ESA rescue – MACE rate was 17.9% in vadadustat compared to 8% in darbepoetin among stable patients. A comparable difference was observed within Europe also among patients requiring ESA rescue – 25% in vadadustat compared to 17.1% in darbepoetin group. It seems again that an increased CV risk with vadadustat appears. In this analysis, the need for ESA rescue was interpreted as a consequence of Hb instability and the hypothesis that more patients switching to vadadustat would have unstable levels of Hb and therefore have a greater need for ESA rescue is not backed up by the numbers. According to provided data, only 85/861 (9.9%) of patients in the vadadustat group needed ESA rescue, while this was the case for 341/862 (39.6%) in the darbepoetin group. Therefore, need for ESA rescue does not appear to be the sole explanation for the observed increased risk of MACE.

Adding ESA rescue as a covariate in the MACE analysis for PROTECT programme, yielded MACE HR of 1.05 (0.903, 1.227). The same analysis was not done for the INNO2VATE programme.

The Applicant further presents a new pooling strategy, pooling conversion subjects from CI-0015 (NDD-CKD) subjects with the subset of conversion subjects from Study CI-0016 (incident DD-CKD) and subjects from Study CI-0017 (prevalent DD-CKD). This analysis results in a HR with the 95% CI below the NIM.

Although additional analyses and explanations for the observed increased MACE risk compared to darbepoetin in the NDD-CKD population provided by the Applicant could be plausible, given their post-hoc nature, they cannot be considered sufficiently robust to overrule the results of the primary analysis. In conclusion, as the provided data points towards an increased cardiovascular risk of vadadustat compared to darbepoetin, the B/R balance in the NDD-CKD population is negative.

The failure to show non-inferiority of time to first MACE for vadadustat compared to darbepoetin alfa observed in the NDD-CKD population does not allow to conclude a positive B/R of vadadustat in this subpopulation and the Applicant has excluded the NDD-CKD patients from the indication of vadadustat.

Adverse events of special interest

Overall AESIs were reported more frequently in the darbepoetin alfa treatment groups compared to the vadadustat treatment groups in both the pooled DD-CKD-, NDD-CKD- and CKD population (45.2% and 41.1% of subjects, respectively in the pooled CKD population).

Adrenal disorders: In the EMA scientific advice EMA/CHMP/SAWP/818714/2015, it was noted that alterations of the HIF-signaling pathway have been linked to functional abnormalities of the adrenal

gland, including pheochromocytoma. Therefore, it was deemed necessary by CHMP to perform functional studies of the adrenal gland in patients receiving study drug. The Applicant has justified not providing functional studies of the adrenal gland in patients receiving study drug. Alterations of the HIF-signaling pathway have been linked to functional abnormalities of the adrenal gland, including pheochromocytoma and non-adverse adrenal gland histopathology findings were observed in dogs. Based on the justification of the Applicant, the observed effects seem to be isolated observations not linked to pathological changes in systems or organs regulated by the adrenal or to correlate with adrenal gland insufficiency, and further, they seem to be reversible. In the clinical trials adrenal disorders were reported in ≤0.1% of subjects in the vadadustat and darbepoetin alfa treatment groups. Thus, the findings are not considered of clinical concern.

Cardiac valve disorders: With the inconclusive non-clinical findings, comorbidities in CKD subjects and balance in the frequencies of cardiac valve disorders in the pooled CKD population. It is agreed that cardiac valve disorders are not a concern for vadadustat.

Congestive heart failure: Congestive heart failure was reported for 10.3% of subjects in the vadadustat treatment group and 11.5% of subjects in the darbepoetin alfa treatment group in the pooled CKD population. The Applicant's conclusion of no evidence to support an association between vadadustat and congestive heart failure is endorsed.

Hepatotoxicity: 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. Even though there was an imbalance in DILI between treatment arms in the unblinded assessment, the absence of imbalance in the blinded assessment between vadadustat and darbepoetin alfa is reassuring. Hence, it is agreed to have a statement on elevated lever enzymes in the SmPC section 4.8. The Applicant has added hepatotoxicity to the RMP as an important potential risk as requested. In addition, routine risk minimisation measures have been added to the SmPC in 4.2, 4.4 and 4.8.

Hyperkalaemia: No imbalances were seen between the two treatment groups.

Hypersensitivity: Anaphylactic reactions were rare in both the vadadustat and darbepoetin alfa treatment. All reported anaphylactic reactions were assessed as unrelated, except 1 with vadadustat where possibility of reasonable causal relationship could not be ruled out. The Applicant suggest, hypersensitivity will continue to be monitored as an identified risk with vadadustat. This is endorsed. The Applicant has added hypersensitivity to the tabulated list of adverse reaction with the frequency "common" as requested.

Malignancies: Overall, no pattern of malignancy type was observed, as these were reported in very small numbers. 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. The Applicant suggests, that malignancies are considered as an important potential risk for vadadustat. This is endorsed. According to the Scientific Advice EMA/CHMP/SAWP/818714/2015, sufficiently long follow-up of all patients/healthy volunteers who have been exposed to vadadustat is essential. Malignancies will continue to be monitored through routine pharmacovigilance. This is considered acceptable since no pattern of malignancy type was observed and since malignancies overall were reported less frequent in the vadadustat treatment group.

Pulmonary hypertension: Pulmonary hypertension was reported for 2.4% of subjects in the vadadustat treatment group and 2.6% of subjects in the darbepoetin alfa treatment group in the pooled CKD population. The applicant argues that the above findings were not suggestive of an association between vadadustat with pulmonary hypertension, but rather supported the association of the

pulmonary hypertension with the underlying disease and comorbidities that are common characteristics of the CKD population. This is endorsed.

Retinal-related effects: The Applicant states that no evidence was found to support an association between vadadustat and retinal-related TEAEs. This is endorsed, since the frequencies were equivalent between the two treatment groups and the underlying disease and comorbidities is associated with the retinal-related events.

Thromboembolic events: Thromboembolic events (positively adjudicated vascular access thrombosis, arterial thrombosis, deep vein thrombosis and pulmonary embolism) were reported in 8.7% (7.5/100 patient-years) and 7.6% (7.7/100 patient-years) of subjects in the pooled DD-CKD population for the vadadustat and darbepoetin alfa treated patients, respectively. In the pooled NDD-CKD population the opposite was the case with 1.9% of subjects in the vadadustat treatment group and 2.2% of subjects in the darbepoetin alfa treatment group with thrombotic events. Since Hb increases to >14.0 g/dL were overall more frequent in the vadadustat treatment group compared to the darbepoetin alfa treatment group in the DD-CKD population (3.9% and 3.4%, respectively), the Applicant was asked to discuss if the events were related. A total of 11 TEAEs with positively adjudicated thromboembolic events were reported in 8 subjects with any Hb value > 14.0 g/dL in the pooled DD-CKD population. The temporal relationship between the occurrence of thromboembolic events and the increase of Hb to values > 14 g/dL was investigated for these 11 cases. No correlation between the thromboembolic events and Hb >14.0 g/dL could be found. Thromboembolic events is listed in the tabulated list of adverse reactions in the SmPC. This is endorsed.

Hypertension: Changes in mean blood pressure observed during the study were similar in the vadadustat and darbepoetin alfa treatment groups. The Applicant states that hypertension is considered an identified risk and hypertension is listed in the tabulated list of adverse reactions in the SmPC. This is endorsed.

Laboratory values: Overall, the mean changes from baseline in hepatic parameters in the pooled CKD population for global Phase 3 studies were small and comparable between the two treatment groups. Even though the frequencies of TEAEs were comparable between treatment groups, more of the TEAEs were related to the study drug in the vadadustat treatment group.

Vital signs and ECG Evaluation of vital signs for vadadustat in the three pooled populations showed similar mean changes from baseline across the vadadustat and darbepoetin alfa treatment groups. The proportion of SBP and DBP outliers were similar across the vadadustat and darbepoetin alfa treatment groups in all three pooled populations.

Safety in special populations

Age: Drug-related TEAEs, severe TEAEs, treatment-emergent SAEs and TEAEs that led to death were more frequently reported for each step up in the age groups in both treatment groups in the pooled CKD population, showing the elderly being more vulnerable in general. In the SmPC it is stated that no dose adjustment is recommended for elderly patients. This is acceptable based on the pharmacokinetic findings and on a similar pattern of adverse events in both treatment groups.

Sex: Overall, there were no trends implying that sex was a factor in the reporting of TEAEs with vadadustat in any of the pooled populations.

Race: The slightly higher reporting of TEAEs that led to death, in white subjects appears to be due to by the frequency of cardiac disorders leading to death, which were reported in 6.1% of white subjects in both the vadadustat and darbepoetin alfa treatment groups compared to black subjects (5.1% and 4.7% of subjects, respectively) and all other subjects (3.4% and 4.4% of subjects, respectively).

Body Weight: There was no safety analysis performed on the effect of body weight in vadadustat.

Renal Insufficiency: Overall, no evidence that renal insufficiency is correlated with an increased risk with vadadustat treatment compared with darbepoetin alfa treatment. In the SmPC it is stated that no dose adjustment is needed in patients with renal impairment. This is agreed.

Hepatic Impairment: Overall, no increased risk of moderate hepatic impairment related to vadadustat was seen and there was no data in patients with severe hepatic impairment.

Patients with Diabetes Mellitus: TEAEs, severe TEAEs, treatment-emergent SAEs, and TEAEs that led to death were generally more frequent in subjects with diabetes mellitus at baseline, than in subjects without diabetes in the CKD population in both treatment groups. As the Applicant states, the differences are expected due to the co-morbidities associated with diabetes mellitus. Drug-related treatment emergent SAEs were similar in subjects with diabetes mellitus at baseline and subjects without diabetes. Overall, the data showed that there was no greater risk to diabetes mellitus control from vadadustat compared to darbepoetin alfa, and no greater risk of adverse outcomes from vadadustat in diabetics compared to non-diabetics.

Geographic Region (US/Europe/ROW): The difference in frequencies reported is not considered to have an impact on the interpretation of the safety profile of vadadustat compared to darbepoetin alfa.

Other Issues

Drug-drug interactions and other interactions: Use of concomitant medications were not evaluated in the pooled global Phase 3 populations. The possible interactions with phosphate binders, BCRPs substrates (statins), OAT3 substrates (furosemide), OAT1/3 and glucuronidase inhibitor (probenecid), and CYP2B6 substrates are reflected ins SmPC section 4.5. The Applicant in order to provide further data regarding DDI has accepted the recommendation to conduct: a) an in vitro DDI CYP inhibition study on the glucuronide metabolite to evaluate the inhibitory effects of the metabolite vadadustat-O-glucuronide on CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5, b) an in vivo study on CYP2B6 induction.

Use in Pregnancy and Lactation: Safe use of vadadustat during pregnancy or lactation has not been established; therefore, the use of vadadustat in pregnancy, in nursing mothers, or in women of childbearing potential should avoid using vadadustat due to the possible risks to mother and child. The effects of exposure during pregnancy and lactation are considered as missing information. The currently proposed wording in Section 4.6 (it is preferable to avoid the use of vadadustat during pregnancy is acceptable. The Applicant confirms there were no additional cases with exposure during pregnancy reported from the clinical trials or post-marketing setting.

Drug Abuse Overall, more special situations of drug abuse were presented in the vadadustat treatment group compared to the darbepoetin alfa treatment group. None of the special situations of suspected abuse/misuse led to TEAEs. Even though no TEAEs were related to misuse in the phase 3 studies, 15 events of misuse were reported and since HIF-activating agents are listed in the prohibited list of the International Standard World Anti-Doping Code. The Applicant has added a section in 4.4 regarding misuse as requested.

Discontinuations: As renal and urinary disorders leading to discontinuation were reported in the same frequency in the two treatment groups, gastrointestinal disorders were the predominant reasons for discontinuation of the study in the vadadustat treatment group, that was not seen in the darbepoetin alfa group. Gastrointestinal disorders are included in the tabulated list of adverse reactions in the SmPC. This is endorsed. The Applicant was also asked to add "abdominal pain upper" to the table in the SmPC section 4.8 with the frequency "common".

Post Marketing Experience: Overall, the post marketing data support the safety findings from the pivotal studies, however it is difficult to estimate the frequencies since the exact exposure is unknown.

2.6.10. Conclusions on the clinical safety

Overall, the primary clinical safety database included 3686 subjects receiving vadadustat. The DD-CKD and NDD-CKD subjects exposed to vadadustat for at least 6 months, at least 1 year, and at least 2 years were acceptable.

Overall, the safety profile of vadadustat were comparable to darbepoetin alfa in the DD-CKD population. The failure to show non-inferiority of time to first MACE for vadadustat compared to darbepoetin alfa observed in the NDD-CKD population does not allow to conclude a positive B/R of vadadustat in this subpopulation and the Applicant has excluded the NDD-CKD patients from the indication of vadadustat. As the approved indication is restricted only to the DD-CKD patients due to safety issues only results of the relevant studies are reflected in the SmPC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 87 SVIII-1: Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	• Hepatotoxicity
Missing Information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.7.3. Risk minimisation measures

Table 88 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	**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.	**Routine pharmacovigilance activities: beyond adverse reactions reporting and signal detection:** • Specific clinical measures for hepatotoxicity • Targeted follow-up questionnaire for hepatotoxicity

Table 88 V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	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	
Important Missing Information		
None		

2.7.4. Conclusion

The CHMP considers that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 29.06.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vafseo (vadadustat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for by the Applicant is for the treatment of anaemia associated with chronic kidney disease (CKD) in adults. However as explained previously the indication is restricted only to the DD-CKD patients due to safety issues, therefore only the relevant studies are reflected in the B/R discussion and the SmPC.

The approved indication is for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.

3.1.2. Available therapies and unmet medical need

Goal of therapy in Europe is to maintain Hb levels between 10.0 and 12.0 g/dL. A more recent analysis of 9220 CKD patients receiving ESA showed that the rate of Hb rise greater than 0.125 g/dL/month increases CV incidence rates (Fusco 2017).

Treatments for anaemia associated with dialysis dependent (DD) patients with CKD include iron supplementation, RBC transfusions, treatment with erythropoiesis-stimulating agents (ESA) and/or hypoxia-inducible factor prolyl-hydroxylase inhibitor (roxadustat).

ESA is the current standard of care. All ESAs are administered either intravenously or subcutaneously and have complex dosing schedules. Slowly increasing Hb levels and maintaining Hb levels within target range, without cardiovascular or thrombotic complications is challenging for some patients.

Roxadustat is approved in EU as the first hypoxia-inducible factor prolyl-hydroxylase inhibitor. Roxadustat has been associated with cardiovascular or thrombotic events, or inadequate response (similar to ESAs), an increased risk of seizures, and serious infection.

3.1.3. Main clinical studies

The main evidence of efficacy in DD-CKD patients submitted is two global studies (INNO2VATE studies) which are randomised, open-label, active-controlled (darbepoetin alfa), non-inferiority efficacy and safety cardiovascular outcomes studies (AKB-6548-CI-0016 and AKB-6548-CI-0017, the INNO2VATE studies). This cross-section of CKD subjects included those who were naïve to erythropoietin-stimulating agents (ESAs) as well as those treated with ESAs.

In these pivotal global studies 3923 subjects on chronic dialysis were randomized and the starting dose of vadadustat was 300 mg once daily (QD), with up-and-down titration to 150 mg to 600 mg QD to achieve target Hb levels (10.0 to 11.0 g/dL in US and 10.0 to 12.0 g/dL ex-US).

The primary efficacy endpoint was the change in average Hb between baseline and Weeks 24 to 36 (primary evaluation period, PEP) and the common key secondary efficacy endpoint was the change in average Hb value between baseline and Weeks 40 to 52 (secondary evaluation period, SEP). The selected primary endpoint is a validated and well-established marker for the evaluation of anaemia therapies and the specific time frame for the assessment of this primary endpoint is appropriate for analysing true effect of new treatment in case of changes from before and consistent with CHMP

Guidelines on clinical development of similar biological medicinal products containing recombinant Erythropoietin (Revision) and the clinical development of approved ESAs.

3.2. Favourable effects

Non-inferiority of vadadustat to darbepoetin alfa for the primary efficacy endpoint was demonstrated in the Randomized, FAS and the PP population analyses. In the randomized population, vadadustat was shown to be non-inferior to darbepoetin alfa at the PEP (Weeks 24 to 36) in treating anaemia associated with CKD in subjects on chronic dialysis since the lower bound of the 95% CI (-0.53, -0.23) for the LS mean difference in the change from baseline was above the prespecified non-inferiority margin of -0.75 g/dL in each study. INNO2VATE CI-0016 study showed the widest 95% CI that passed beyond the initially defined and agreed NI margin of 0.5 g/dL, but INNO2VATE CI-0017 study met the more stringent NI margin also.

The initial effect, observed in the randomized population between weeks 24 to 36, was sustained through Weeks 40 to 52 (key secondary efficacy endpoint).

In both studies, the mean Hb level (secondary endpoint) gradually increased during the initial correction/conversion period and stabilized by the primary efficacy period, and was maintained throughout the secondary efficacy period. The lower bound of the 95% CI) for the LS mean difference is above the NI margin of -0.75 g/dL (-0.34 in CI-0016 and -0.25 CI-0017).

3.3. Uncertainties and limitations about favourable effects

Both pivotal studies comparing the treatment of vadadustat with ESA therapy in DD patients were open-label which may be subject to bias in particular to endpoints with treatment management decisions (e.g. rescue therapy, iv iron use). The primary analysis included patients who did not receive treatment, discontinued treatment, or used rescue therapy. However, sensitivity analyses of the primary endpoint supported primary analysis.

EU enrolment was 14.3% of the pooled DD-CKD population, which is below the recommended numbers in previous scientific advice (at least 30-40% of the total subjects in the pivotal studies). Subjects from the ROW region, treated per protocol according to European Hb target of 10.0-12.0 g/dL, accounted for between 24-25 percent of the randomized population in the two Phase 3 studies. Altogether, patients from EU and ROW could be considered as %30-40 of the population who were treated according to the "European" haemoglobin target.

Discontinuations up to end of primary efficacy period (26 or 39 weeks) are higher for vadadustat groups than active control groups across studies (33.1% vs 26.1%, and 50.6% vs 36.7% in the vadadustat and darbepoetin alfa treatment groups in CI-0016 and CI-0017, respectively).

The proportion of subjects with RBC transfusions using the narrow rescue therapy criteria was generally higher in the vadadustat treatment group compared to the darbepoetin alfa treatment group in both studies at Weeks 2 to 8. Similarly, the proportion of subjects who received ESA rescue using the narrow and broad rescue criteria were higher in the vadadustat treatment group compared with the darbepoetin alfa treatment groups at most time points during the study.

There is no guidance on how to identify patients not responding to vadadustat treatment. The clinical relevance and consequences of the observed mean Hb decline during first 4 weeks of vadadustat treatment in conversion setting were questioned. An initial lower to similar response with vadadustat in comparison to darbepoetin alfa was observed in pivotal trials which tended to become similar by the end of study periods in long term. For converting from other treatments, the treating physician should

be aware of initial Hb decrease which is parallel in magnitude with previous ESA dose, and a higher risk of rescue therapy use and higher dose of vadadustat needed for these subjects.

The changes in the iron-related parameters are variable over time and there is no benefit with vadadustat use over EPO use in terms of decrease in need for iron supplementation. In CI-0017, the decreases in mean hepcidin with vadadustat from baseline over Weeks 24 to 36 and 40 to 52 could be noted as supportive although similar trend was not seen in CI-0016.

3.4. Unfavourable effects

The proportion of subjects with drug-related TEAEs, TEAEs that led to discontinuation from study drug and drug-related TEAEs that led to discontinuation from study drug were 9.0, 4.9 and 2.3 % for vadadustat versus 3.7, 1.1 and 0.3 for darbepoetin alfa.

The most frequently reported PTs in the AESIs per were hypertension (16.3% and 19.3% of subjects, respectively) and CHF (9.5% and 10.8% of subjects, respectively). The most frequent AESIs by PT reported for subjects in the vadadustat and darbepoetin alfa treatment groups were hypertension (11.1% and 13.6% of subjects, respectively) and hyperkalemia (8.6% and 10.3% of subjects, respectively). In the pooled DD-CKD population, the only SOC reported more frequently in the vadadustat treatment group compared to the darbepoetin alfa treatment group was Gastrointestinal disorders with 40.4% of subjects in the vadadustat treatment group compared to 37.0% of subjects in the darbepoetin alfa treatment group. Gastrointestinal disorders were the predominant reason for discontinuation of the study in the vadadustat treatment group.

With regard to serious adverse events, acute myocardial disease (AMI) (4.3% vs 4.2%) and pneumonia (7.6% vs 6.4%) were reported respectively for vadadustat and darbepoetin alfa.

In the pooled DD-CKD population, non-inferiority of vadadustat to darbepoetin alfa was shown, for time to first MACE: HR (95% CI) 0.96 (0.833, 1.113), with upper bound of the 95% CI of the HR was below the prespecified non-inferiority margin of 1.30.

The events of the components of the first MACE included all cause death: 253 (13.0%) versus 253 (12.9%) for patients in the vadadustat and darbepoetin alfa treatment groups, respectively; non-fatal MI 76 (3.9%) versus 87 (4.5%), and non-fatal stroke: 26 (1.3%) versus 37 (1.9%) for vadadustat and darbepoetin alfa treatment groups, respectively. The prespecified OT+30 days showed a HR (95% CI) 0.95 (0.801, 1.137). The number of subjects with events (percentage) within 4 weeks of the end of treatment was 224 (11.5%) with vadadustat versus 285 (14.6%) with darbepoetin alfa. There was an increase in MACE events in the 0-30 days after the EOT: 8.4% and 13.9% for vadadustat and darbepoetin alfa, respectively.

Thromboembolic events (positively adjudicated vascular access thrombosis, arterial thrombosis, deep vein thrombosis and pulmonary embolism) were reported in 8.7% (7.5/100 patient-years) and 7.6% (7.7/100 patient-years) of subjects in the pooled DD-CKD population for the vadadustat and darbepoetin alfa treated patients, respectively.

Hepatotoxicity was reported for 6.9% of subjects in the vadadustat treatment group and 7.2% of subjects in the darbepoetin alfa treatment group in the pooled DD population. The most frequent PTs were transaminases increased: 1.1% and 1.2% of subjects in the vadadustat and darbepoetin alfa treatment groups, respectively (ALT increased: 1.0% and 0.8% of subjects, respectively). 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.

One subject on vadadustat developed elevated hepatic parameters assessed to have met the biochemical criteria for Hy's law during the phase 2 study AKB-6548-CI-0007. Later upon re-assessment by the Hepatic Expert Committee, it was determined that this case was suggestive of mixed type hepatobiliary injury with a cholestatic component and was assessed as a non-classic case of Hy's Law. After the Global Phase 3 clinical development for vadadustat completed, a Blinded Expert Committee re-adjudicated this case and determined it as a 'severe hepatic injury event' probably related to vadadustat, but not a Hy's Law case. Hepatotoxicity has been added as an important potential risk to the RMP.

3.5. Uncertainties and limitations about unfavourable effects

The primary safety endpoint was time to first MACE. Both primary analyses (ITT and OT-30 days) met the non-inferiority success criterion in terms of HR within a margin below 1.3. Additional analyses were requested to evaluate the most appropriate follow-up time after the MACE event. According to recommendations of the Methodology Working Party (MWP), the cleanest output of treatment associated MACE risk would be to consider an OT analysis without additional days, as this has the least interpretational issues, with least potential to capture events under a possible altered risk profile following the intercurrent event of treatment discontinuation. This analysis (OT) also showed non-inferiority to darbepoetin alfa on the risk of MACE.

Another HIF-PHI compound, roxadustat, is authorised for the treatment of anaemia in CKD patients. An increased risk of MACE in DD patients in the conversion setting was found. (ref. SmPC and EPAR for Evrenzo) Some of the apparently contrasting results between roxadustat and the current dossier are currently not understood.

Overall, no pattern of malignancy type was observed, as these were reported in very small numbers. 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.

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. Even though no TEAEs were related to misuse in the phase 3 studies, 15 events of misuse were reported.

Use of concomitant medications were not evaluated in the pooled global Phase 3 populations. The possible interactions with phosphate binders, BCRPs substrates (statins), OAT3 substrates (furosemide), OAT1/3 and glucuronidase inhibitor (probenecid), and CYP2B6 substrates are listed in the RMP as "Potential Risks with minimal clinical impact on patients" and are also reflected in SmPC section 4.5. The Applicant in order to provide further data regarding DDI has accepted the recommendation to conduct: a) an in vitro DDI CYP inhibition study on the glucuronide metabolite to evaluate the inhibitory effects of the metabolite vadadustat-O-glucuronide on CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5, b) an in vivo study on CYP2B6 induction.

3.6. Effects Table

Table 89 Effects Table for Vadadustat in treatment of anaemia in DD-CKD (DLP 31 and 16 Jan 2020).

Effect	Short Description	Unit	Group difference	95% CI	Uncertainties/ Strength of evidence	References
	Favourable Effects					
Hb Change in **DD-CKD**	Change from Baseline in Haemoglobin (g/dL) to the Average Over Weeks 24 to 36 (**Randomized Population**)	Least squares mean (SEM)	-0.31	**-0.53**, -0.10	**Primary endpoint** N=369 NI margin=0.50, then changed to 0.75. Does not meet NI criteria for earlier NI margin of 0.5. Vadadustat is strictly inferior but within NI margin which was changed late during the open label trial	AKB-6548-**CI-0016** p18, summary clin eff
	(Per protocol population)	Least squares mean (SEM)	-0.32	**-0.54** -0.09	N=249 More conservative approach	CSR, p539
	Change from Baseline in Haemoglobin (g/dL) to the Average Over Weeks 24 to 36 (**Randomized Population**)	Least squares mean (SEM)	-0.17	-0.23 -0.10	Primary endpoint N=3554	AKB-6548-**CI-0017** P19, summary clin eff
	(Per protocol population)	Least squares mean (SEM)	-0.15	-0.21 -0.08	N=2557	CSR, p668, tables: 14.2.1.2.2
	Change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52)	Least squares mean (SEM)	-0.07	-0.34, 0.19	**Key secondary endpoint**	AKB-6548-CI-0016
	Change in average Hb value between Baseline and the secondary efficacy period (Weeks 40 to 52)	Least squares mean (SEM)	-0.18	-0.25, -0.12	Key secondary endpoint	AKB-6548-CI-0017
	Unfavourable Effects					
DD-CKD	**Short Description**	**Unit**	**Vadadustat**	**Darbepoetin alfa**	**Uncertainties/ Strength of evidence**	Ref
	Drug-related TEAEs	%	9.0	3.7		(1)
	TEAE leading to discontinuation from study drug	%	4.9	1.1		(1)

	Drug-related TEAE leading to discontinuation from study drug	%	2.3	0.3		(1)
	Gastrointestinal disorders (SOC)	%	40.4	37.0		(1)
	AMI (SAE)	%	4.3	4.2		(1)
	Pneumonia (SAE)	%	7.6	6.4		(1)
	Time to first MACE	HR (95% CI)	0.96	0.833, 1.113	Primary safety endpoint Non-inferiority margin 1.3	(2)
	Thrombotic events (AESI)	%	8.7	7.6		(1)
	Hb increases to >14.0 g/dL	%	3.9	3.4		(1)
	Hepatotoxicity	%	6.9	7.2		(1)

Abbreviations:
Notes: (1) Pooled DD-CKD population for global Phase 3 studies

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Noninferiority of vadadustat in comparison to darbepoetin alfa is demonstrated in DD-CKD patients according to defined NI margin (-0.75 g/dL) on primary and secondary efficacy endpoints. Primary and key secondary endpoints are considered as clinically relevant with suitable time window for testing and appropriate for studying change of Hb in these populations.

Despite concluded as non-inferior according to the NI margin, the primary endpoint analyses for the DD-CKD population provided a point estimate and the 95% CI margins which are below 0. For study CI-0016 (incident dialysis patients), the 95% CI margin also crosses the initially agreed NI margin of 0.5 g/dL and secondary analysis of Hb within normal range yields an odds ratio that reinforces the impression of ambiguous non-inferiority: OR = 0.6 (CI: 0.40, 0.96). However, trial CI-0017 included 90.6% of the totality of subjects dependent on hemodialysis or peritoneal dialysis (3554 / [3554 + 369]). Therefore, this trial provides efficacy data on the totality of subjects on renal replacement therapy and treated with different types of ESAs and with variable doses of ESA.

Thromboembolic events were reported more frequently in the vadadustat treatment group compared to the darbepoetin alfa treatment group in the pooled DD-CKD population: 8.7% (7.5/100 patient-years) and 7.6% (7.7/100 patient-years) of subjects, respectively, although the IR were comparable. Information on thromboembolic events is included in sections 4.4 and 4.8 in the SmPC.

Vadadustat was shown to be non-inferior to darbepoetin alfa for the primary safety endpoint time to first MACE in the DD patients. Additional on-treatment analyses were requested and did overall support the primary analyses and the conclusion for the DD-CKD population, that non-inferiority for time to first MACE was shown.

Gastrointestinal disorders were the predominant reason for discontinuation of the study in the vadadustat treatment group and therefore an important safety concern. Hepatotoxicity is identified as an important potential risk.

3.7.2. Balance of benefits and risks

The benefit-risk balance is positive for the DD-CKD population.

3.8. Conclusions

The overall benefit/risk balance of Vafseo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vafseo is favourable in the following indication(s):

Vafseo is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that vadadustat is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).