Medicinrådet

Bilag til Medicinrådets anbefaling vedr. vadadustat til behandling af symptomatisk anæmi i forbindelse med kronisk nyresygdom hos voksne, der er i kronisk vedligeholdelsesdialyse

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. vadadustat
2. Forhandlingsnotat fra Amgros vedr. vadadustat
3. Ansøgers endelige ansøgning vedr. vadadustat

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Att: Medicinrådet

January 31, 2025

MEDICE's comments on the Danish Medicines Council assessment report for vadadustat for symptomatic anemia in dialysis-dependent CKD (DD-CKD)

MEDICE Arzneimittel Pütter GmbH & Co. KG sincerely appreciate the Danish Medicines Council (DMC) for its comprehensive evaluation of vadadustat and the productive dialogue throughout the process. While we align with the DMC on several key points, we would like to take this opportunity to reaffirm our position on the following matters.

Hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) inhibitors, including vadadustat, represent a novel treatment approach by mimicking the body's natural response to hypoxia. They have emerged as an alternative to erythropoiesis-stimulating agents (ESAs) for managing anaemia in CKD. This is further supported by the recently published guideline from the European Renal Best Practice (ERBP) board of the European Renal Association, which suggests that HIF-PH inhibitors (HIF-PHi) could be considered for specific patient groups in clinical practice.

For patients undergoing peritoneal dialysis (PD), vadadustat may be a preferred option, particularly when an oral treatment is desired. It offers key advantages, including better accessibility, convenience, and ease of administration without special storage requirements. This option is especially beneficial for patients who struggle with initiating or continuing ESA therapy, such as those with needle phobia or an inability to self-administer ESA injections. Additionally, vadadustat may be suitable in cases where iron administration is challenging or increased iron availability is desired, as well as for patients with ESA hyporesponsiveness, intolerance, or chronic inflammatory conditions characterized by a CRP level of ≥3 mg/L (Stoumpos et al., 2024).

For hemodialysis (HD) patients, HIF-PH inhibitors could also provide benefits, particularly for those who prefer oral treatment or are undergoing home hemodialysis. Their use should be considered in cases of hypersensitivity to intravenous iron or its unavailability, ESA hyporesponsiveness, intolerance, or chronic inflammation with a CRP level of ≥3 mg/L (Stoumpos et al., 2024). We urge that these diverse patient groups and their specific needs be appropriately considered in the assessment.

Furthermore, when assessing the additional cost of vadadustat in comparison to existing alternatives, we encourage the Medicines Council members to consider that the cost comparison presented in the draft assessment report is highly conservative. The analysis does not account for the benefits of an oral formulation. A survey conducted by TLV in Sweden found that 18% of patients undergoing ESA therapy require assistance with subcutaneous injections (TLV, 2022). The associated costs of patient training for ESA injections are not included in the comparative analysis of DMC.

Moreover, vadadustat offers unquantified cost savings by eliminating the need for cold chain logistics and ensuring appropriate storage conditions for ESA during patient transport and home storage for self-administration. According to the instructions, ESA must be kept cold but should not be injected at fridge temperature. This could mean that the nurse should wait 30 minutes or return later.

Below, we would like to provide our comment on the following passage in the draft report:

DMC: *"Medicinrådet vurderer, at administrationsomkostningerne forbundet med behovet for hjemmesygeplejerske til administration af darbepoetin alfa ikke bør indgå i hovedanalysen. Medicinrådet begrunder dette med, at alle patienter, som modtager hjemmedialyse, i forvejen har behov for besøg af en hjemmesygeplejerske til at dosere deres orale behandlinger, hvorfor yderligere besøg forbundet med administration af darbepoetin alfa ikke vil være gældende i dansk klinisk praksis. Derfor vil omkostningerne*

forbundet med forbruget af hjemmesygeplejerske være ens for begge behandlinger og dermed udgår denne omkostning af Medicinrådets hovedanalyse." (Side 34|51)

We note that the DMC's decision to exclude administration costs related to the need for a home nurse to administer darbepoetin alfa from the main analysis is a conservative approach, as it disregards the time and workload required of caregivers. Each administration of darbepoetin alfa involves preparation, administration, and post-administration care, all of which contribute to the overall burden. In contrast, vadadustat is taken orally, requiring significantly less time and effort. This becomes even more important given the shortage of nurses and home nurses in Denmark, which exacerbates the challenges associated with providing care in home settings (Birk et al., 2024). While the main model does not account for differences in administration costs, we strongly recommend considering these factors, along with the time savings for both patients and caregivers, when making a final decision.

According to data from the Danish National Patient Registry for the periods 2022/23 and 2023/24, more than 50% of all patients with CKD on home dialysis are under the age of 70 and are expected to be capable of self-administering vadadustat. Additionally, over 25% of these patients are under 60 years. Consequently, we do not expect that all patients will need assistance with the self-administration of their oral medications, including vadadustat.

A recommendation for vadadustat would expand the therapeutic options for a severely ill patient group and ensure future competition. In other countries, such as the United Kingdom, vadadustat has already been recommended by the National Institute for Health and Care Excellence (NICE) as an option for treating symptomatic anaemia caused by chronic kidney disease in adults having maintenance dialysis.

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04.02.2025

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.02.2025
Leverandør	Medice Arzneimittel Pütter GmbH & Co. KG
Lægemiddel	Vafseo (vadadustat)
Ansøgt indikation	Behandling af symptomatisk anæmi i forbindelse med kronisk nyresygdom (CKD) hos voksne, der er i kronisk vedligeholdelses-dialyse.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Vafseo (vadadustat):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabat ift. AIP
Vafseo	150 mg	28 tabletter	1.579,25	[redacted]	[redacted]
Vafseo	150 mg	98 tabletter	5.527,39	[redacted]	[redacted]
Vafseo	300 mg	28 tabletter	3.158,51	[redacted]	[redacted]
Vafseo	300 mg	98 tabletter	11.054,78	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Det nuværende valg af behandling er baseret på en behandlingsvejledning fra RADS, hvor alle erythropoietin stimulerende lægemidler (ESA-præparater) er ligestillede. Førstevalget til behandling af patienter i Danmark er på nuværende tidspunkt Aranesp (darbepoetin alfa) og Binocrit (epoetin alfa) er 2. valg.

[redacted]

Tabel 2 - Lægemiddeludgifter på udvalgte sammenlignelige lægemidler

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år***	Lægemiddeludgift pr. år (SAIP, DKK)****
Vafseo 300 mg	300 mg	28 stk	Opstart: 350 mg/dag Vedligehold: 385 mg/dag*	[redacted]	Opstartsår: [redacted] Vedligehold: [redacted]	Opstartsår: [redacted] Vedligehold: [redacted]
Evrenzo (Anbefalet af MR juni 2023)	150 mg	12 stk.	Opstart: 210 mg/uge** Vedligehold: 257,2 mg/uge	[redacted]	Opstartsår: [redacted] Vedligehold: [redacted]	Opstartsår: [redacted] Vedligehold: [redacted]
Aranesp (Nuværende 1. valg)	500 µg	1,0 ml inj.væske, opl., pen	Opstart: 29,1 µg/uge** Vedligehold: 44,4 µg/uge	[redacted]	Opstartsår: [redacted] Vedligehold: [redacted]	Opstartsår: [redacted] Vedligehold: [redacted]

*Jf. MR vurderingsrapport behandles med en gennemsnitsdosis på 350 mg i opstartsåret og 385 mg i vedligeholdelsesår. Dosis fluktuerer dog meget afhængig af patientens tilstand.
**Dosis titreres løbende (uge 1-24) op indtil vedligeholdelsesdosis nås.
***Antal pakninger er rundet op i henhold til antal åbnede pakninger.
****Lægemiddeludgiften er beregnet for det faktiske antal pakninger, dvs. uden oprunding til helt antal pakninger.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link
Sverige	Ikke ansøgt	Link
England	Under vurdering	Link

Konklusion

[redacted].

Application for the assessment of Vafseo® for the treatment of symptomatic anemia associated with CKD in adults on chronic maintenance dialysis

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
Name	[redacted]
Title	[redacted]
Phone number	[redacted]
E-mail	[redacted]
Name (External representation)	**N/A**
Title	
Phone number	N/A
E-mail	

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Tables and Figures

Abbreviations

Abbreviation	Term
µL	Microliter
AE	Adverse event
AESI	Adverse events of special interest
AIP	Pharmacies' purchase price
ATC	Anatomical Therapeutic Chemical
BIM	Budget impact model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic kidney disease
CMA	Cost-minimization analysis
CV	Cardiovascular
CVD	Cardiovascular disease
DD	Dialysis-dependent
DD-CKD	Dialysis-dependent chronic kidney disease
DMC	Danish Medicines Council
DNSL	National Registry of the Danish Nephrological Society
dL	Deciliter
DSA	Deterministic sensitivity analyses
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPO	Erythropoietin
EQ-5D	EuroQol Health Utility Index 5-Dimensional
EQ-5D-3L	EuroQol Health Utility Index 5-Dimensional 3 Level

ERBP	European Renal Best Practice
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
EU	European Union
FAS	Full analysis set
g	Gram
GFR	Glomerular filtration rate
GI	Gastrointestinal
Hb	Hemoglobin
HCP	Health care professional
HD	Hemodialysis
HHD	Home hemodialysis
HIF	Hypoxia-inducible factor
HIF-PHI	Hypoxia-inducible factor prolyl hydroxylase inhibitor
HR	Hazard ratio
HRQoL	Health-related quality of life
HCRU	Healthcare resource utilization
ICER	Incremental cost-effectiveness ratio
ICHD	In-center hemodialysis
IU	International unit
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
kg	Kilogram
KRT	Kidney replacement therapy
LY	Life year
LS	Least-squares
MACE	Major adverse cardiovascular events
mg	Milligram
MI	Myocardial infarction
mL	Milliliter
mm	Millimeter
NDD	Non-dialysis-dependent
ng	Nanogram
NICE	National Institute for Health and Care Excellence
nM	Nanometer
NMB	Net monetary benefit
OAT	Organic anion transporter
OR	Odds ratio
PD	Peritoneal dialysis
PE	Pulmonary embolism
PT	Preferred term
QALY	Quality-adjusted life year
QoL	Quality of life

RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	System organ class
TE	Thromboembolic event
TEAE	Treatment-emergent adverse event
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation
UKKA	UK Kidney Association
US	United States
VAT	Vascular access thrombosis
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Vafseo
Generic name	Vadadustat
Therapeutic indication as defined by EMA	Treatment of symptomatic anemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis
Marketing authorization holder in Denmark	Medice Arzneimittel Pütter GmbH & Co. KG
ATC code	B03XA08
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	2023-04-24
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	N/A
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Package of 28 or 98 film-coated tablets of 150 / 300 mg

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Treatment of symptomatic anemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis
Dosage regiment and administration	Vadadustat is available as a film-coated tablet. The starting dose is 300 mg once daily, with an easy dose titration schedule, in increments of 150 mg.
Choice of comparator	Darbepoetin alfa
Prognosis with current treatment (comparator)	CKD is a progressive and irreversible disease. Anemia is the most common complication of CKD and is associated with an increased risk of cardiovascular (CV) events and mortality. It can also have a substantial impact on patients' health-related quality of life (HRQoL). Fluctuations in hemoglobin (Hb) (outside the target range) with current treatment with erythropoiesis-stimulating agent (ESA) might potentially lead to CV events.
Type of evidence for the clinical evaluation	Head-to-head studies (two phase 3 pivotal trials; INNO$_2$VATE CONVERSION and INNO$_2$VATE CORRECTION/CONVERSION)
Most important efficacy endpoints (Difference/gain compared to comparator)	**Primary efficacy endpoint:** Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36) **Key secondary efficacy endpoint:** Change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52) **INNO$_2$VATE INCIDENT dialysis dependent (DD)-CKD:** Primary: difference, LS mean (95% CI) −0.31 (−0.53, −0.10) Secondary: difference, LS mean (95% CI) −0.07 (−0.34, 0.19) **INNO$_2$VATE PREVALENT DD-CKD:** Primary: difference, LS mean (95% CI) −0.17 (−0.23, −0.10) Secondary: difference, LS mean (95% CI) −0.18 (−0.25, −0.12) Vadadustat demonstrated non-inferiority to darbepoetin alfa in both primary and key secondary efficacy endpoints in both trials.
Most important serious adverse events for the intervention and comparator	The hazard ratio (HR) (95% CI) for the time to first adjudicated MACE (primary safety endpoint) for vadadustat compared to darbepoetin alfa was 0.96 (0.833, 1.113). The upper bound of the 95% CI of the HR was below the prespecified non-inferiority margin of 1.30, thereby establishing non-inferiority of vadadustat to darbepoetin alfa. The most common serious treatment emergent adverse events (TEAEs) (>5%) resulting in hospitalisation were: peritonitis (n=17, 11.2%), pneumonia (n=13, 8.6%) and sepsis (n=8, 5.3%) in the vadadustat group, and peritonitis (n=31, 19.7%), pneumonia

Summary	
	(n=9, 5.7%), sepsis (n=9, 5.7%), acute myocardial infarction (n=8, 5.1%) and hyperkalaemia (n=8, 5.1%) in the darbepoetin alfa group.
Impact on health-related quality of life	Clinical documentation: N/A - HRQoL was not studied. Health economic model: N/A – HE-model does not include HRQoL
Type of economic analysis that is submitted	Cost-minimization analysis
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	[redacted] (for the three years of the analysis)
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	The below numbers represent 80% of all incident and prevalent dialysis patients in Denmark as this is the proportion of patients assumed to have anemia of CKD: Incidence: 496 Prevalence: 2,124
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Chronic kidney disease (CKD) is characterized by a progressive and irreversible loss of kidney function that may result in dialysis and/or renal transplantation. The KDIGO defines CKD as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified based on cause, glomerular filtration rate (GFR) category (G1-G5), and albuminuria category [1].

There are several causes of CKD such as diabetes, hypertension, and long-term use of certain medications that can lead to a progressive destruction of nephrons in the kidney. The processes of blood pressure maintenance, red blood cell (RBC) production, and the removal of metabolic waste products from the blood are all affected in patients with CKD [2]. CKD is associated with decreased endogenous erythropoietin (EPO) synthesis, leading to erythroid progenitor cell apoptosis, which results in worsening anemia and a shortened half-life of erythrocytes [2-4].

The predictors of renal anemia include, but are not restricted to, female gender, advanced stage of CKD, diabetic nephropathy as etiology, non-smoking status, non-obese body habitus, low serum albumin, abnormal bone mineral levels (high phosphorus and low calcium levels), abnormal iron markers (transferrin saturation [TSAT] <20%), and low leukocyte count [5].

Anemia, the most common complication of CKD, is a condition that is characterized by a reduction in the quality and quantity of RBCs and hemoglobin (Hb) such that the oxygen-carrying capacity in the blood is insufficient to meet physiologic demands [2, 6, 7]. Anemia associated with CKD is a serious and debilitating condition that often leads to CV comorbidities, reduced quality of life (QoL), and higher mortality regardless of a patients' dependence on dialysis [8].

The main cause of anemia in CKD is a decreased production of EPO. EPO is a hormone that is primarily produced in the kidney and promotes RBC production in the bone marrow [9-11]. Under normal physiological conditions, EPO production is regulated by a highly sensitive feedback loop. Hypoxia (low oxygen levels) in the kidney stimulates the production of EPO, which in turn stimulates the bone marrow to produce RBCs, thus increasing oxygen-carrying capacity. The resulting increase in oxygen levels is sensed by the kidney and EPO production is decreased [10]. In CKD, the feedback loop is affected by damage to the renal tissue and the developing anemia is not adequately compensated by a sufficient increase in the EPO production [11].

Another important cause of anemia in CKD is iron deficiency (meaning that not enough iron is available for RBC production) [4, 11-13]. Iron deficiency can result from blood loss caused by platelet dysfunction, low-grade gastrointestinal (GI) bleeding, frequent blood sampling or malabsorption [4, 14]. In late-stage CKD patients, hemodialysis (HD) is the major cause of blood loss, as significant amounts of blood remain in the equipment after each dialysis [4, 11, 14, 15]. Dialysis dependent CKD (DD-CKD) patients also lose blood through anticoagulation and post-dialysis bleeding at vascular access sites [15, 16]. Other causes of anemia in CKD include inflammation, resistance to EPO and shortened RBC life span [4, 11-13, 15].

The clinical presentation of anemia in CKD is not different from that of anemia due to other causes. Common symptoms include shortness of breath, fatigue, weakness, headaches, and dizziness [17]. Common signs of anemia are pale skin, respiratory distress, tachycardia, chest pain, and heart failure. The pathophysiological response to anemia is increased cardiac output, the development of left ventricular hypertrophy, angina, and congestive heart failure and the progression of CKD and is one of the factors that contribute to the high morbidity and mortality in patients with chronic renal failure and their reduced survival [11]. Anemia also has an impact on mental health and QoL, including depression, anxiety, impaired activity levels, loss of libido, and decline in cognitive function [3, 18-21].

Anemia in CKD patients, particularly those on dialysis, is associated with increased mortality and morbidity. The impact of anemia in CKD patients is multifaceted, affecting various aspects of health and well-being.

Anemia in CKD can lead to complications such as CV events, which may result in hospitalisations. Anemia has been associated with an increased risk of CV events and all-cause mortality in a number of observational studies [22-24], and the American Heart Association considers anemia to be a non-traditional (non-Framingham) CV risk factor in patients with CKD [25]. A Danish study of patients with DD-CKD and NDD-CKD found that anemia was associated with increased risks of MACE, acute hospitalisation, and all-cause death [23].

Anemia in CKD can have a substantial impact on patients' health-related quality of life (HRQoL). This is exacerbated by reduced physical capacity and energy levels, which affect patients' ability to perform activities of daily living. The impact on patients' HRQoL may be similar to other chronic conditions, such as diabetes, epilepsy and certain forms of cancer [18].

3.2 Patient population

The below section aims to describe the Danish patient population relevant for the submission, i.e., DD-CKD patients with anemia.

According the latest annual report by the National Register of the Danish Nephrological Society (DNSL), in 2022, the incidence of DD-patients with CKD was 620 (387 HD patients and 233 PD patients), and the equivalent number for prevalent patients was 2,655 (2,119 HD patients and 536 PD patients) [26] (Table 1). Most of dialysis patients are expected to

have anemia and approximately 80% of the DD population is assumed to be treated with ESA [27].

Approximately 64% of the incident DD patients are men and the median age is 66. In the prevalent DD population, the percentage of males is 60% and the median age is 67 [26].

Denmark has the highest prevalence of home hemodialysis (HHD) in Europe [28]; approximately 40% of the incident DD population and about one quarter of the prevalent DD population. About 37% of the incident DD patients receive peritoneal dialysis (PD), and the remaining patients receive in-center hemodialysis (ICHD). For prevalent patients, the most common type of dialysis is in-center HD (68%) followed by approximately 20% on PD and 7% on HHD in 2022 [26]. This makes Denmark one of the European countries with the highest proportion of patients who can undergo dialysis at home [29].

Vadadustat's once-daily oral administration provides a non-invasive treatment drug delivery compared to IV or SC ESA therapy. There is evidence to suggest that there are a range of barriers (including injection fear, uncertainty, convenience and physical disabilities) that may influence patients' ability for self-injection [30]. A non-invasive oral drug administration could reduce these as well as barriers for patients to undergo dialysis at home, providing greater choice for patients as well as more independence (e.g., for travelling). It could also be particularly valuable for PD and home-HD (HHD) patients, as there is no need for training by health care professionals for invasive administration. The fact that no cool chain is required for handling and storing of vadadustat might also diminish some barriers for patients to undergo dialysis at home.

Table 1 below presents the incidence and prevalence of dialysis treatment in Denmark.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	582	648	701	620	620
Prevalence in Denmark	2,686	2,673	2,680	2,655	2,655

Source: 2019: [31], 2020-2022: [26], 2023: Assumption

The submission to DMC targets the same patient population as the label of vadadustat, i.e., "patients with symptomatic anemia associated with CKD in adults on chronic maintenance dialysis". This can include patients with any dialysis modality. As previously stated, approximately 80% of DD-CKD patients are assumed to have anemia [27]. The estimated number of patients eligible for treatment is presented in Table 2, which represents 80% of the summarized incident and prevalent DD-CKD Danish patients in 2022 (see Table 1, including 1,695 HD patients and 429 PD patients). It is important to note that the registered prevalent and incident patient numbers from the last 5 years (Table 1) have been constant, hence it was assumed that the eligible population for treatment with vadadustat in the next five years would also remain constant.

Table 2 Estimated number of patients eligible for treatment

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are eligible for treatment in the coming years	2,124	2,124	2,124	2,124	2,124

3.3 Current treatment options

Currently, treatment algorithm and treatment options for the anemic DD-CKD patients in Danish clinical practice follow international KDIGO guidelines [32].

The current standard of care for the management of CKD patients with anemia, as first line, is iron therapy (oral or IV) – to manage iron deficiencies. Iron therapy is an important step in the treatment of anemia in CKD patients, as both absolute and functional iron deficiencies are common. Iron is administered to increase iron and Hb levels when there is deficiency [33]. Oral iron tablets can cause gastrointestinal (GI) side effects (e.g., constipation, stomach pain, nausea) and patients are often non-compliant. IV iron therapy may be administered in patients who do not tolerate oral iron or in DD-CKD patients who can be easily administered IV iron during dialysis, and for this reason, a high proportion of DD patients are co-prescribed IV iron [2].

Nonetheless, when iron monotherapy is ineffective to treat anemia, IV or SC ESAs, along with oral or IV iron therapy, can be prescribed [7]. The choice of treatment and escalation of ESAs mainly relies on the dialysis-dependence of the patients and responsiveness to available therapies.

DMC has published treatment recommendations developed by Rådet for Anvendelse af Dyr Syghehusmedicin (RADS), regarding medical parenteral treatment of patients with CKD-anemia. Generally, treatment with ESA should be initiated at Hb <100 g/L, after optimal iron storage has been secured. The target Hb range is commonly 100-114.4 g/dL. The minimum interval between ESA dose adjustments is generally 2 weeks. The guidelines further state that switching type of dialysis from in-center HD to HHD, or to PD, may mean switching from a short-acting to a long-acting ESA. Based on drug acquisition price, the guidelines recommend darbepoetin alfa as a first line ESA treatment (should be prescribed to > 80% of new patients, on any dialysis type [34]).

In addition, DMC recommends the treatment with roxadustat (another HIF-PHI) for treatment of CKD-anemia in patients who are not (or have been for maximum 4 months) on dialysis, before treatment initiation. The efficacy and safety of roxadustat was accepted to be comparable to ESAs [35].

A Cochrane review compared the efficacy and safety of ESAs to treat anemia in adults with CKD and showed that there is insufficient evidence to suggest the superiority of any ESA formulation (i.e., epoetin alfa, epoetin beta, darbepoetin alfa, or methoxy polyethylene

glycol-epoetin beta, and biosimilars) over the others based on available safety and efficacy data [36]. This is supported by the KDIGO guidelines, which state that the likelihood of differences in clinical outcomes among ESA brands is low, and the National Institute for Health and Care Excellence (NICE) guidelines, which highlight that there is no evidence to distinguish between ESAs in terms of efficacy [2, 7]. This is also stated by DMC in previous assessments in CKD-anemia [37].

The most recent recommendations from the UK Kidney Association (UKKA) 2024 Clinical Practice Guideline suggest that treatment with HIF-PHI should be considered, after iron repletion, in DD-CKD and symptomatic anemia (Hb <105 g/L) patients who are likely to benefit in terms of QoL and physical function and to avoid blood transfusion, especially in people considered suitable for transplantation [38].

3.4 The intervention

Vafseo (vadadustat) is included in a pharmacotherapeutic group of other anti-anemic preparations (ATC code: B03XA08) [39]. Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that mimics hypoxia by stabilising hypoxia-inducible factor (HIF), which leads to increased endogenous EPO production and iron mobilisation, and subsequently, increased erythropoiesis.

Table 3 Overview of intervention

Overview of intervention [40]	
Therapeutic indication relevant for the assessment	Treatment of symptomatic anemia associated with CKD in adults on chronic maintenance dialysis
Method of administration	Oral
Dosing	**Starting dose:** 300 mg once daily. Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. **Converting from ESA:** starting dose is 300 mg once daily. **Dose titration:** Dose adjustment in increments of 150 mg within the range of 150 mg to a maximum recommended daily dose of 600 mg to achieve/ maintain Hb levels of 10 – 12 g/dL.
Dosing in the health economic model (including relative dose intensity)	Dosing is informed by INNO$_2$VATE clinical trials. Average weekly dose in year 1: [redacted] (corresponding to daily dose of [redacted]) Average weekly dose in year 2 and beyond: [redacted] (corresponding to daily dose of [redacted])
Should the medicine be administered with other medicines?	No

Overview of intervention [40]	
Treatment duration / criteria for end of treatment	Chronic treatment. Treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved [39].
Necessary monitoring, both during administration and during the treatment period	When initiating or adjusting therapy, monitor Hb levels every two weeks until stable, then monitor at least monthly. ALT, AST, and bilirubin must be evaluated prior to the initiation of Vafseo, monthly for three months after initiation and as clinically indicated thereafter.
Need for diagnostics or other tests (e.g., companion diagnostics). How are these included in the model?	Iron status should be evaluated in all patients before and during treatment (serum ferritin and serum transferrin saturation), which is currently used in Danish clinical practice. Note: costs for blood work are not included in the CMA
Package size(s)	Package of 28 or 98 film-coated tablets of 150 / 300 mg

3.4.1 The intervention in relation to Danish clinical practice

According to both international (KDIGO) and national guidelines (RADS), ESAs are a key treatment option for patients with CKD-anemia, with long-acting ESA (darbepoetin alfa) being recommended as first line treatment [1, 34]. Currently, the only available oral formulation targeted at CKD-anemia is roxadustat, which is limited for use, by recommendation by DMC, in patients that are not on dialysis (or have been on dialysis for less than 4 months) [35].

Vadadustat has been studied in CKD-anemia in both incident and prevalent DD populations and is assumed to be used in Danish clinical practice for both populations (including patients on dialysis for more than 4 months). An advantage of vadadustat is the non-invasive formulation, compared to injectable ESAs, and for patients receiving HHD and PD, vadadustat is a treatment option that can be provided at home, without training by healthcare professional. The RADS guidelines state that for patients changing the modality of the dialysis, a switch in ESA might be appropriate, e.g., from short-acting to long-acting, when switching from in-center HD to HHD or to PD. This is understood to be for the benefit of convenience of the patient, which could also be achieved with a tablet formulation, with a simple dosing schedule.

Lastly, for patients not achieving the target Hb with current ESA treatment, i.e., are hyporesponsive to treatment, vadadustat could also provide a possible treatment alternative meeting an important unmet need and potentially preventing RBC transfusions, which are the last treatment option [41]. There are no particular warnings or precautions for switching from ESA to vadadustat.

3.5 Choice of comparator(s)

For the clinical trial program, darbepoetin alfa was chosen as an active comparator as it is a globally available ESA which has an extensive safety profile including CV safety data. This treatment has been approved for use in patients with anemia associated with CKD. As stated previously (3.3), there is no evidence to support a difference in efficacy or safety of one ESA to another, thus the results from the comparison to darbepoetin alfa are considered to be representative as a comparison of the ESA treatment class. Darbepoetin alfa was also used in the cost-minimization model associated with this submission. According to treatment recommendations by RADS, darbepoetin alfa is the first line choice of ESA, which is also reflected in sales numbers, where darbepoetin alfa is absolutely dominant in both value and volume (approximately 97-99% of the total market) [42].

Table 4 Overview of comparator

Overview of comparator	
Generic name	Darbepoetin alfa
ATC code	B03XA02
Mechanism of action	Human erythropoietin is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Production of endogenous erythropoietin is impaired in patients with chronic renal failure and the primary cause of their anemia is due to erythropoietin deficiency [43].
Method of administration	Subcutaneous and intravenous injection
Dosing	The dosing below concerns DD-patients: Correction phase: Starting dose is 0.45 µg/kg body weight, once weekly (e.g. 33.75 µg/kg, for a patient of 75 kg). Dose can be adjusted. Maintenance phase: Dosing once weekly or once per two weeks (double the once weekly dose)
Dosing in the health economic model (including relative dose intensity)	Dosing is informed by pooled INNO$_2$VATE clinical trials. Average weekly dose in year 1: [redacted] Average weekly dose in year 2 and beyond: [redacted]
Should the medicine be administered with other medicines?	No

Treatment duration/ criteria for end of treatment	Chronic treatment.
Need for diagnostics or other tests (i.e., companion diagnostics)	Hb levels to be monitored regularly to make appropriate dose adjustments to keep Hb at desired level.
Package size(s)	**Pre-filled syringe / pen:** 1 and 4 pack of 10mcg, 15mcg, 20mcg, 30mcg, 40mcg, 50mcg, 60mcg, 80mcg, 100mcg, 130mcg, 150mcg, 300mcg, 500mcg **Injection vial:** 1 and 4 pack of 25mcg, 40mcg, 60mcg, 100mcg, 200mcg, 300mcg

3.6 Cost-effectiveness of the comparator(s)

Darbepoetin alfa is recommended in the treatment guidelines by RADS, which are approved by DMC [34]. Additionally, darbepoetin alfa was also accepted as a comparator in DMCs assessment of Roxadustat [35].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The primary and key secondary efficacy outcomes relevant and necessary to evaluate the effect of vadadustat vs. darbepoetin alfa were change in average Hb between baseline as well as both primary (week 24-36) and secondary (week 40-52) efficacy period, which were deemed to be appropriate for establishing non-inferiority in both INNO$_2$VATE trials. For more information refer to Table 5. Other endpoints included in the health economic analysis (proportion of patients with >1 administration of IV iron, and average dose of elemental iron used) are described in Appendix B.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Primary efficacy outcome [AKB-6548-CI-0016 & -17]	Weeks 24 – 36	Change in average Hb between baseline and the primary efficacy period.	Study visits occurred at baseline and every 2 weeks through week 12, every 4 weeks from weeks 13 to 52 and then every 12 weeks until the end of treatment. Blood samples were taken via a central laboratory for all efficacy endpoints. Samples for laboratory assays were sent to a central laboratory for analysis. If blood was collected on a hemodialysis day, blood was drawn prior to dialysis, if applicable. The investigator was responsible for reviewing laboratory results for clinical significance.
Key secondary efficacy endpoint [AKB-6548-CI-0016 & -17]	Weeks 40 – 52	Change in average Hb between baseline and the secondary efficacy period.	

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

Change in Hb is a common outcome measure in trials regarding treatment of CKD-anemia, as exemplified in DMC's previous assessment of Roxadustat, for which change in Hb was primary outcomes measure in the studies referred to in that submission [37].

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 [44].

The selected primary endpoint is a validated and well-established marker for the evaluation of anemia 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 Committee for Medicinal Products for Human Use (CHMP). The specific time frame for the assessment of this primary endpoint (i.e. between week 24 and week 36, primary efficacy period) 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 [44].

Per scientific advice, the secondary efficacy endpoints also test stability of attained Hb 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 which was used for key secondary endpoint analyses was from week 40 to 52 [44].

4. Health economic analysis

4.1 Model structure

A cost-minimization analysis (CMA) was deemed appropriate considering the available data from the INNO$_2$VATE clinical trial program, in which vadadustat demonstrated non-inferiority to darbepoetin alfa on the primary and key secondary endpoints [45, 46].

4.2 Model features

Table 6 summarizes the model features for the presented CMA.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Symptomatic anemia associated with CKD in adults on chronic maintenance dialysis	Same patient population as presented in Section 3.2.
Perspective	Limited societal perspective	As per guidelines by DMC.
Time horizon	3 years	The CMA uses a 3-year time horizon which was deemed appropriate as it captures the variability in dosing in the initiation phase and the maintenance phase.
Cycle length	13 weeks	A quarterly cycle length was implemented in the model.
Half-cycle correction	No	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years.
Intervention	Vadadustat	
Comparator(s)	Darbepoetin alfa	According to treatment guideline. Most used ESA, according to sales data. See more details in Section 3.5.
Outcomes	Drug acquisition costs, drug administration costs, IV iron rescue costs, and patient time and transport costs	Other costs were not considered relevant for this CMA.

Abbreviations: CKD, Chronic kidney disease; CMA, Cost-minimization analysis.

5. Overview of literature

The clinical assessment and the health economic analysis are exclusively informed by the head-to-head studies in the INNO$_2$VATE trial program comparing vadadustat to darbepoetin alfa, which is the comparator relevant in Danish clinical practice. In addition, the health economic analysis deemed relevant is a CMA, so no HRQoL is included. Thus, no further literature searches have been performed and the following subsections to chapter 5 are thus not applicable.

5.1 Literature used for the clinical assessment

N/A

Table 7 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
N/A	N/A	N/A	N/A	N/A

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

N/A

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economic model

N/A

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of vadadustat compared to darbepoetin alfa for anemic DD-CKD patients

6.1.1 Relevant studies

This section focuses on the key pivotal trials of the INNO$_2$VATE program (Incident DD-CKD [Correction/Conversion, AKB-6548-CI-0016] and Prevalent DD-CKD [Conversion, AKB-6548-CI-0017]) documenting the effect of vadadustat compared to darbepoetin alfa. Since the presented data comes from head-to-head trials, literature search for comparative evidence was omitted. For more details refer to Table 10 and Appendix A.

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
$INNO_2VATE$ – Correction/Conversion, (AKB-6548-CI-0016), NCT02865850, Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Correction or Maintenance Treatment of Anemia in Subjects with Incident DD-CKD [45, 47]	Randomized phase III, open-label, active comparator-control	3.5 years (2016-07-18 – 2020-01-31) Screening: up to 8 weeks Correction/conversion: week 0-23 Maintenance: week 24-52 Long-term treatment: week 53 – end of treatment Follow-up: 4 weeks	Adult CKD-DD subjects on incident dialysis (initiation of chronic maintenance dialysis within 16 weeks prior to screening)	Vadadustat 150 mg tablets for oral administration; starting dose of 300 mg/day, up-and-down titration to 150, 300, 450, 600 mg was allowed during the study based on Hb level measurement every 4 weeks to maintain target Hb level of 10-12g/dL.	Darbepoetin alfa, pre-filled syringe as an injectable solution for IV or SC administration; starting dose based on the prior dose for patients already on darbepoetin alfa and based on the product label for those not on darbepoetin alfa prior to randomization, up-and-down titration based on protocol-specified dose adjustment guideline algorithms to maintain target Hb level of 10-12g/dL.	Primary efficacy endpoint: Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36) Key secondary efficacy endpoint: change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52)
$INNO_2VATE$ – Conversion (AKB-6548-CI-0017), NCT02892149, Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with DD-CKD [46, 47]	Randomized phase III, open-label, active comparator-control	3.5 years (2016-08-17 – 2020-01-16) Screening: up to 8 weeks Conversion: week 0-23 Maintenance: 24-52 Long-term treatment: week 53 – end of treatment Follow-up: 4 weeks	Adult DD-CKD patients on dialysis after conversion from ESA therapy	Vadadustat 150 mg tablets for oral administration; starting dose of 300 mg/day, up-and-down titration to 150, 300, 450, 600 mg was allowed during the study based on Hb level measurement every 4 weeks to maintain target Hb level of 10-12g/dL.	Darbepoetin alfa, pre-filled syringe as an injectable solution for IV or SC administration; starting dose based on the prior dose for patients already on darbepoetin alfa and based on the product label for those not on darbepoetin alfa prior to randomization, up-and-down titration based on protocol-specified dose adjustment guideline algorithms to maintain target Hb level of 10-12g/dL.	Primary efficacy endpoint: Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36) Key secondary efficacy endpoint: change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52)

6.1.2 Comparability of studies

N/A since efficacy of vadadustat was assessed in head-to-head trials. Both trials were similar in design (randomized, open-label, active-controlled, event-driven) and had the same overall objective to evaluate the CV safety and hematologic efficacy of vadadustat, as compared with darbepoetin alfa, for the treatment of anemia in HD and PD patients [47].

6.1.2.1 Comparability of patients across studies

A summary of key baseline demographic and disease characteristics is shown in Table 11. The demographic, clinical, and laboratory characteristics of the two treatment groups were generally well balanced.

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	INNO$_2$VATE Correction/Conversion (Incident DD-CKD)		INNO$_2$VATE Conversion (Prevalent DD-CKD)	
	Vadadustat	**Darbepoetin alfa**	**Vadadustat**	**Darbepoetin alfa**
Age, years	56.5	55.6	57.9	58.4
Gender – male, n (%)	107 (59.1%)	113 (60.1%)	990 (55.7%)	1,004 (56.5%)
BMI (kg/m2), mean (SD)	27.6 (6.1)	27.5 (6.0)	28.6 (7.2)	28.6 (7.2)
Duration of dialysis (years), mean (SD)	0.14 (0.09)	0.15 (0.28)	4.0 (4.0)	3.9 (4.0)
Baseline Hb (g/dL), mean (SD)	9.4 (1.1)	9.2 (1.1)	10.2 (0.9)	10.2 (0.8)
History of CVD, n (%)	69 (38.1%)	73 (38.8%)	868 (48.8%)	932 (52.4%)
History of diabetes, n (%)	105 (58.0%)	96 (51.1%)	971 (54.6%)	998 (56.2%)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Data on Danish patients comparable with the study populations from INNO$_2$VATE trials was sourced from the annual report for the year 2022 by the DNSL [26]. The report includes information on all patients receiving kidney replacement therapy (KRT) in a form of either kidney transplant, PD or HD. Table 12 presents characteristics of DD-CKD patients, many of which would be deemed appropriate for the treatment with vadadustat due to the high prevalence of anemia in this patient population.

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population; prevalent / incident [26]	Value used in health economic model (reference if relevant)
Age, years	67 / 66	N/A
Gender – male, n (%)	1,671 (62.9%) / 399 (64.4%)	N/A
Patient weight (kg) – male	86.4	N/A
Patient weight (kg) – female	71.4	N/A
BMI (kg/m2) – male*	26.6	N/A
BMI (kg/m2) – female*	25.7	N/A
History of CVD, n (%)	376 (14.2%) / 88 (14.2%)	N/A
History of diabetes, n (%)	620 (23.4%) / 174 (28.1%)	N/A

*BMI was calculated based on the general Danish population values from 2021 [48] using an online BMI calculator [49].

Overall, both prevalent and incident DD-CKD patients from the INNO$_2$VATE trials and Danish population are comparable. Most of them are male (over 60%) and a clear trend of older individuals being treated with dialysis (50 years of age and older). Even though history of diabetes and CVD are lower in the Danish DD-CKD patients compared to the population included in the INNO$_2$VATE trials, they are most prominent underlying diseases of DD-CKD patients in Denmark.

6.1.4 Efficacy – results per INNO$_2$VATE Correction/Conversion (Incident DD-CKD)

A total of 369 subjects were enrolled and randomized to vadadustat (N=181) or darbepoetin alfa (N=188). Of the subjects randomized, 179 and 186 subjects were treated with vadadustat and darbepoetin alfa, respectively.

The proportion of subjects who completed the studies was similar for vadadustat-treated subjects (N=160; 88.4%) and darbepoetin alfa-treated subjects (N=165; 87.8%). The most frequent reason for discontinuation from the studies was death in both the vadadustat (N=15; 8.3%) and darbepoetin alfa group (N=19; 10.1%).

The total number of discontinuations of study drug treatment was higher in the vadadustat group (60 [33.1%] subjects) compared with the darbepoetin alfa group (49 [26.1%] subjects). The most frequent primary reason for discontinuation of study drug was that the subject no longer wanted to receive study drug (11.0% and 5.3% in vadadustat and darbepoetin alfa group, respectively), which might be due to the open-label study design.

Of subjects randomized, 365 subjects were included in the safety population and 364 subjects were included in the FAS population.

Vadadustat was non-inferior to darbepoetin alfa as measured by a mean change in Hb between baseline and the primary evaluation period (Weeks 24–36) and secondary evaluation period (Weeks 40–52). The primary and key secondary efficacy endpoints met the prespecified non-inferiority margin of −0.75 g/dL (Table 13).

Table 13 Primary and Key Secondary Efficacy Endpoint Results – Incident Trial (AKB-6548-CI-0016) – Randomized Population

	Vadadustat (N=181)	Darbepoetin alfa (N=188)
Baseline Hb, g/dL, mean (SD)	9.37 (1.07)	9.19 (1.14)
Primary endpoint		
Weeks 24–36 Hb, g/dL, mean (SD)	10.36 (1.13)	10.61 (0.94)
Adjusted mean change from baseline, LS mean (95% CI)[a]	1.26 (1.05, 1.48)	1.58 (1.37, 1.79)
Difference, LS mean (95% CI)	−0.31 (−0.53, −0.10)	
Key secondary endpoint		
Weeks 40–52 Hb, g/dL, mean (SD)	10.51 (1.19)	10.55 (1.14)
Adjusted mean change from baseline, LS mean (95% CI)[a]	1.42 (1.17, 1.68)	1.50 (1.23, 1.76)
Difference, LS mean (95% CI)	−0.07 (−0.34, 0.19)	

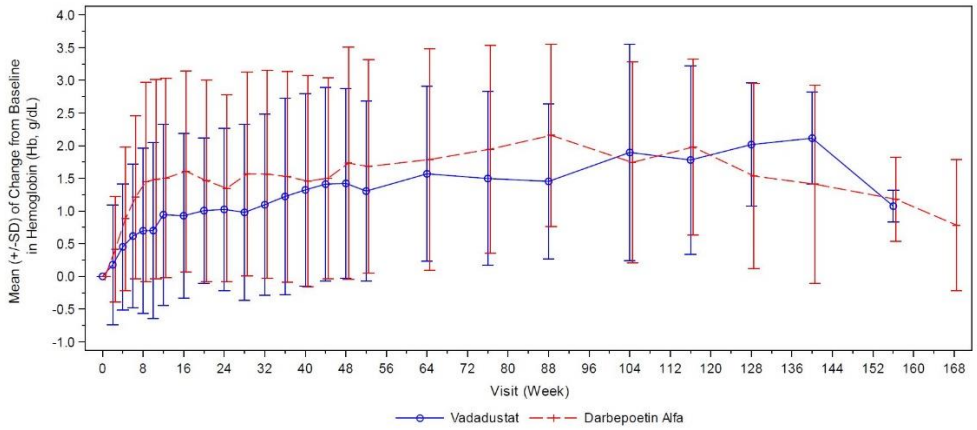
a Adjusted mean change from baseline is reported as observed + imputed.
CI, confidence interval; DD-CKD, dialysis-dependent chronic kidney disease; Hb, haemoglobin; LS, least squares; SD, standard deviation. Source: Clinical Study Report AKB-6548-CI-0016 [45]

A 2-sided 95% CI was calculated for both the primary and the secondary efficacy endpoints; this corresponded to 2-sided significance levels of 0.05. The formal testing procedure for the secondary efficacy endpoint would be stopped if the analysis failed to confirm non-inferiority of the primary efficacy endpoint in question using a 1-sided significance level of 2.5%.

The approach to primary analysis was ANCOVA with multiple imputation for missing data and mixed models for repeated measurements (MMRM) on observed data for sensitivity analysis. The general approach to analysis of the other continuous outcomes was ANCOVA with or without multiple imputation.

Furthermore, the mean change from baseline Hb over time is shown in Figure 1. The mean Hb level gradually increased during the initial correction/conversion period and stabilized by the start of the primary efficacy period.

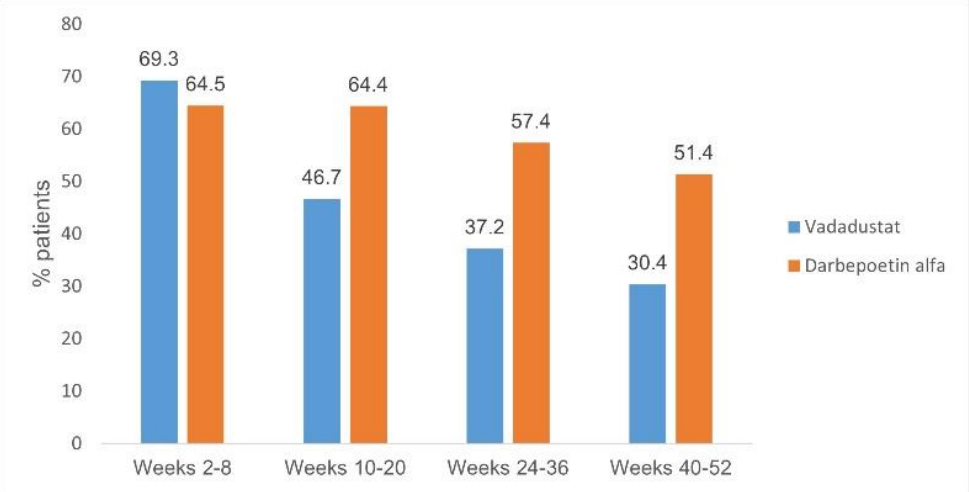
Figure 1 Mean (SD) of Change from Baseline in Hb (g/dL) – Incident Trial (AKB-6548-CI-0016) – Randomized Population



Note: Week 0 is Baseline. DD-CKD, dialysis-dependent chronic kidney disease; SD, standard deviation. Source: Clinical Study Report AKB-6548-CI-0016 [45]

In general, dose adjustments and dose interruptions to maintain subjects within target range were less frequent in the vadadustat group compared with the darbepoetin alfa group. The percentage of subjects that had dose increases or decreases based on Hb assessment during Weeks 24–36 were 37.2% and 57.4% and during Weeks 40–52 were 30.4% and 51.4% in the vadadustat and darbepoetin alfa groups, respectively (Figure 2).

Figure 2 Proportion of Patients with Dose Increased or Decreased Based on Hb Assessment – Incident Trial (AKB-6548-CI-0016) – Safety Population



DD-CKD, dialysis-dependent chronic kidney disease. Source: Clinical Study Report AKB-6548-CI-0016 [45]

6.1.5 Efficacy – results per INNO$_2$VATE Conversion (Prevalent DD-CKD)

A total of 3,554 subjects were enrolled and randomized to vadadustat (N=1,777) or darbepoetin alfa (N=1,777). Of subjects randomized, 1,768 and 1,769 subjects were treated with vadadustat and darbepoetin alfa, respectively.

The proportion of subjects who completed the study was similar for vadadustat-treated subjects (N=1,425; 1,425; 80.2%) and darbepoetin alfa-treated subjects (N=1,421; 80.0%).

The most frequent reason for discontinuation from the study was death in both the vadadustat (N=262; 14.7%) and darbepoetin alfa group (N=278; 15.6%).

The total number of discontinuations of study drug treatment was higher (899 [50.6%] subjects) in the vadadustat group compared with the darbepoetin alfa group (653 [36.7%] subjects). The primary reason for discontinuation of study drug was that the subject no longer wanted to receive study drug (12.0% and 5.8% in the vadadustat and darbepoetin alfa groups, respectively), which might be due to the open-label study design. There were more subjects who discontinued study drug treatment due to unacceptable toxicity, drug intolerability, or AE, or due to the investigator's decision, in the vadadustat group compared to the darbepoetin alfa group.

Of subjects randomized, 3,537 subjects were included in the safety population, and 3,514 subjects were included in the FAS population.

Vadadustat was non-inferior to darbepoetin alfa as measured by a mean change in Hb between baseline and the primary evaluation period (Weeks 24–36) and secondary evaluation period (Weeks 40–52). The primary and key secondary efficacy endpoints met the prespecified non-inferiority margin of −0.75 g/dL (Table 14).

Table 14 Primary and Key Secondary Efficacy Endpoint Results – Prevalent Trial (AKB-6548-Cl-0017) – Randomized Population

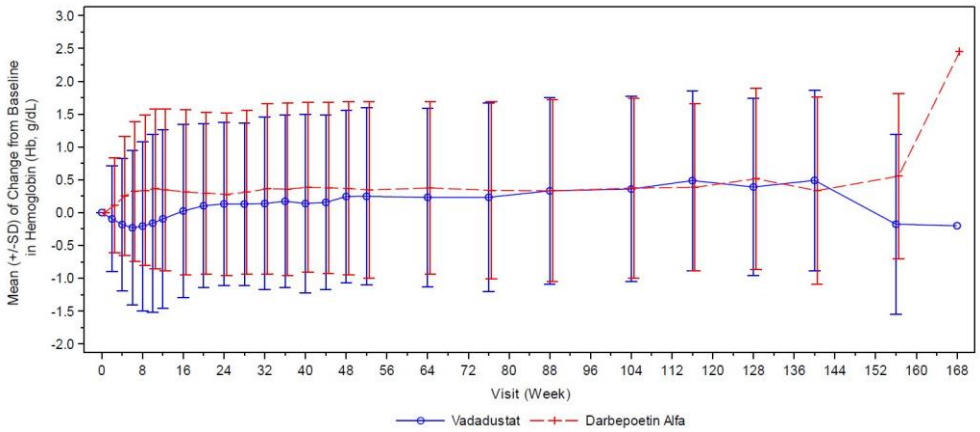
	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)
Baseline Hb, g/dL, mean (SD)	10.25 (0.85)	10.23 (0.83)
Primary endpoint		
Weeks 24–36 Hb, g/dL, mean (SD)	10.36 (1.01)	10.53 (0.96)
Adjusted mean change from baseline, LS mean (95% CI)[a]	0.19 (0.12, 0.25)	0.36 (0.29, 0.42)
Difference, LS mean (95% CI)	−0.17 (−0.23, −0.10)	
Key secondary endpoint		
Weeks 40–52 Hb, g/dL, mean (SD)	10.40 (1.04)	10.58 (0.98)
Adjusted mean change from baseline, LS mean (95% CI)[a]	0.23 (0.16, 0.29)	0.41 (0.34, 0.48)
Difference, LS mean (95% CI)	−0.18 (−0.25, −0.12)	

a Adjusted mean change from baseline is reported as observed + imputed.
CI, confidence interval; DD-CKD, dialysis-dependent chronic kidney disease; Hb, haemoglobin; LS, least squares; SD, standard deviation. Source: Clinical Study Report AKB-6548-Cl-0017 [46]

For a description of the statistical analysis and handling of missing data, please refer to section 6.1.4.

Furthermore, the mean change from baseline Hb over time is shown in Figure 3. The Hb level initially decreased in the vadadustat 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.

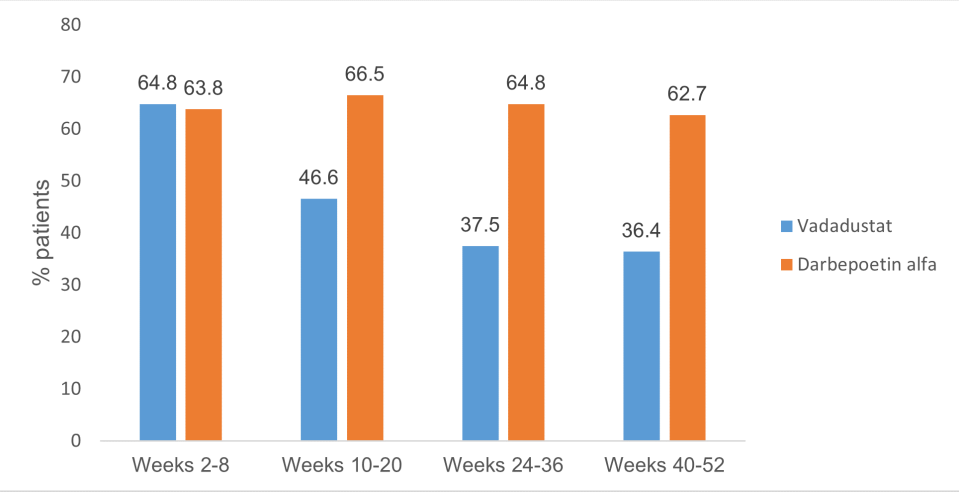
Figure 3 Mean (SD) of Change from Baseline in Hb (g/dL) – Prevalent Trial (AKB-6548-Cl-0017) – Randomized Population



Note: Week 0 is Baseline. DD-CKD, dialysis-dependent chronic kidney disease; SD, standard deviation. Source: Clinical Study Report AKB-6548-Cl-0017 [46]

In general, dose adjustments and dose interruptions to maintain subjects within target range were less frequent in the vadadustat group compared to the darbepoetin alfa group. The percentage of subjects that had dose increases or decreases based on Hb assessment during Weeks 24–36 were 37.5% and 64.8% and during Weeks 40–52 were 36.4% and 62.7% in the vadadustat and darbepoetin alfa groups, respectively (Figure 4).

Figure 4 Proportion of Patients with Dose Increased or Decreased Based on Hb Assessment – Prevalent Trial (AKB-6548-Cl-0017) – Safety Population



DD-CKD, dialysis-dependent chronic kidney disease. Source: Clinical Study Report AKB-6548-Cl-0017 [46]

7. Comparative analyses of efficacy

Since vadadustat was compared directly to darbepoetin alfa in head-to-head trials, which is included as efficacy evidence in this reimbursement application, this section is N/A. Primary and key secondary efficacy outcomes from the head-to-head trials are presented in Table 15 and Table 16.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

Table 15 Results from the comparative analysis of vadadustat vs. darbepoetin alfa for DD-CKD anemic patients (Randomized Population - AKB-6548-Cl-0016)

Outcome measure	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Result
Adjusted mean Hb, g/dL change from baseline, LS mean (95% CI), weeks 24-36	1.26 (1.05, 1.48)	1.58 (1.37, 1.79)	−0.31 (−0.53, −0.10)
Adjusted mean Hb, g/dL change from baseline, LS mean (95% CI), weeks 40-52	1.42 (1.17, 1.68)	1.50 (1.23, 1.76)	−0.07 (−0.34, 0.19)

Source: [45]

Table 16 Results from the comparative analysis of vadadustat vs. darbepoetin alfa for DD-CKD anemic patients (Randomized Population - AKB-6548-Cl-0017)

Outcome measure	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)	Result
Adjusted mean Hb, g/dL change from baseline, LS mean (95% CI), weeks 24-36	0.19 (0.12, 0.25)	0.36 (0.29, 0.42)	−0.17 (−0.23, −0.10)
Adjusted mean Hb, g/dL change from baseline, LS mean (95% CI), weeks 40-52	0.23 (0.16, 0.29)	0.41 (0.34, 0.48)	−0.18 (−0.25, −0.12)

Source: [46]

For more information on efficacy and study outcomes of INNO$_2$VATE trials, please refer to chapter 6 and Appendix B.

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

This chapter is N/A since a CMA was conducted.

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

N/A

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 17 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/Assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A

Method/approach	Description/Assumption
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A.

8.1.2 Calculation of transition probabilities

N/A.

Table 18 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	N/A	
	Death	N/A	
Recurrence	Death	N/A	
Health state/Transition		N/A	

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

N/A

Table 19 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A

Table 20 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
[Intervention]	N/A	N/A	N/A
[Comparator]	N/A	N/A	N/A

9. Safety

9.1 Safety data from the clinical documentation

The safety population is defined as all subjects in the randomized population who received at least 1 dose of study drug.

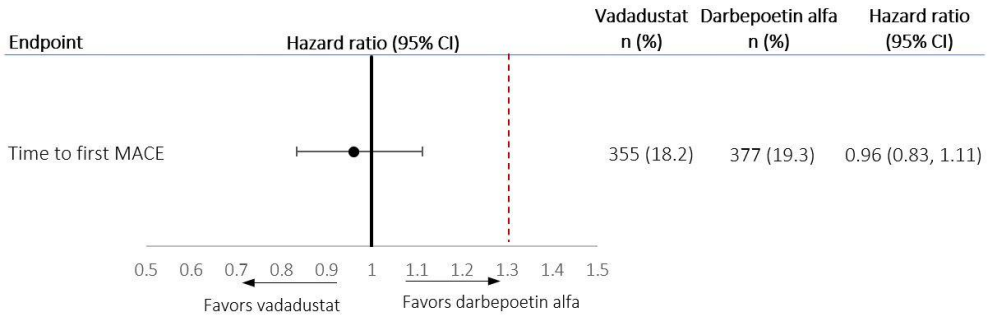
9.1.1 Primary safety endpoint

Results of the primary safety endpoint (time to first MACE) are presented based on the pooled safety population for both INNO$_2$VATE trials. The proportion of subjects who completed the studies was similar for vadadustat-treated subjects (N=1,583; 81.3%) and darbepoetin alfa-treated subjects (N=1,582; 80.9%).

The HR (95% CI) for the time to first adjudicated MACE for vadadustat compared to darbepoetin alfa was 0.96 (0.833, 1.113). The upper bound of the 95% CI of the HR was below the prespecified non-inferiority margin of 1.30, thereby establishing non-inferiority of vadadustat to darbepoetin alfa (Figure 5, Figure 6).

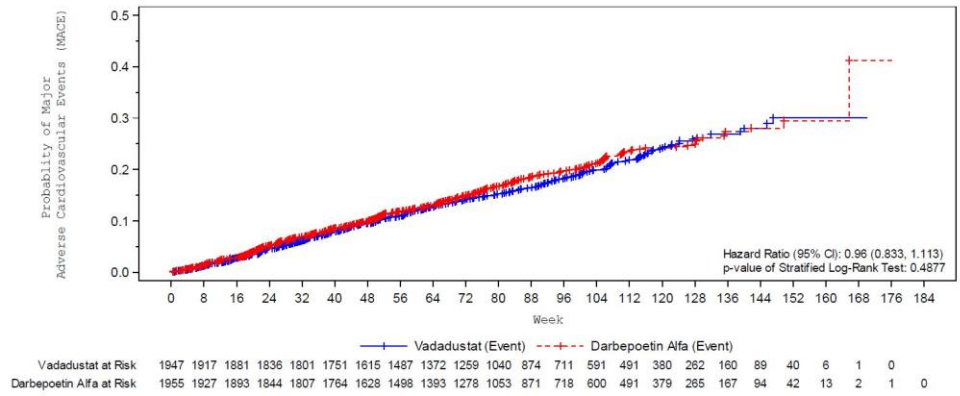
The numbers and percentages of patients in whom the first MACE was death from any cause, a non-fatal MI, or a non-fatal stroke were 253 (13.0%), 76 (3.9%), and 26 (1.3%), respectively, in the vadadustat group and 253 (12.9%), 87 (4.5%), and 37 (1.9%), respectively, in the darbepoetin alfa group.

Figure 5 Primary Safety Endpoint: Time to first MACE – Pooled DD-CKD (Safety Population)



CI, confidence interval; DD-CKD, dialysis-dependent chronic kidney disease; MACE, major adverse cardiovascular events. Source: INNO$_2$VATE MACE Report [50]

Figure 6 Kaplan-Meier Curve of Time to First MACE – Pooled DD-CKD (Safety Population)



CI, confidence interval; DD-CKD, dialysis-dependent chronic kidney disease; MACE, major adverse cardiovascular events. Source: INNO$_2$VATE MACE Report [50]

The safety profile of vadadustat was comparable to that of darbepoetin alfa and demonstrated non-inferiority to darbepoetin alfa in time to first MACE (primary safety endpoint), regardless of geographic region. Vadadustat was well-tolerated in the treatment of anemia secondary to DD-CKD and had an acceptable safety profile.

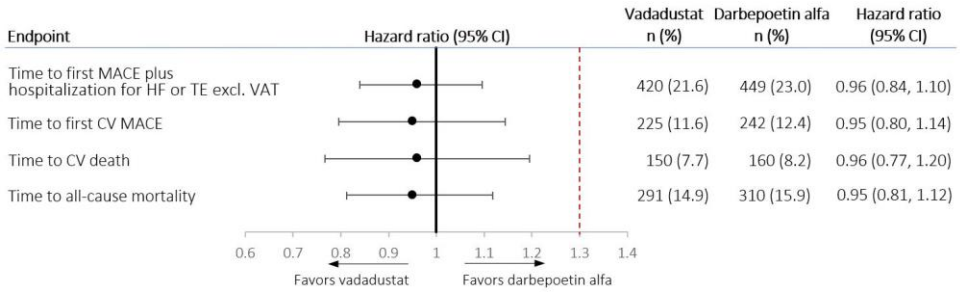
The most frequent reason for discontinuation from both studies was death in both the vadadustat and darbepoetin alfa groups (14.2% and 15.1% of subjects, respectively).

For more information on serious adverse events safety, please refer to Appendix E.

9.1.2 Key Secondary Safety Endpoints

The results for the primary MACE endpoint were supported by the results from the key secondary endpoints. Vadadustat was non-inferior to darbepoetin alfa with regards to time to first MACE plus hospitalisation for heart failure or thromboembolic events excluding vascular access thrombosis, time to first CV MACE, time to CV death, and time to all-cause mortality (Figure 7).

Figure 7 Key Secondary Safety Endpoints – Pooled DD-CKD (Safety Population)

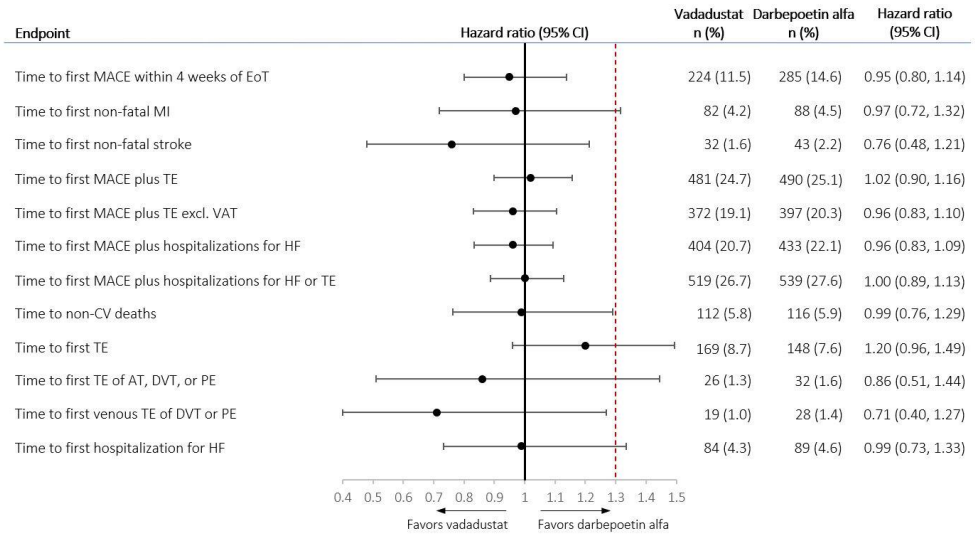


CI, confidence interval; CV, cardiovascular; DD-CKD, dialysis-dependent chronic kidney disease; excl., excluding; HF, heart failure; MACE, major adverse cardiovascular events; TE, thromboembolic event; VAT, vascular access thrombosis. Source: INNO$_2$VATE MACE Report [50]

9.1.3 Other Safety Analyses

The results of the primary safety endpoint were also demonstrated for other safety endpoints (Figure 8).

Figure 8 Other Safety Endpoints – Pooled DD-CKD (Safety Population)



AT, arterial thrombosis; CI, confidence interval; CV, cardiovascular; DD-CKD, dialysis-dependent chronic kidney disease; DVT, deep vein thrombosis; EoT, end of treatment; excl., excluding; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; PE, pulmonary embolism; TE, thromboembolic event; VAT, vascular access thrombosis. Source: $INNO_2VATE$ MACE Report [50]

When deaths within 30 days of the myocardial infarction were reviewed, event rates were similar in the vadadustat and darbepoetin alfa groups (19 [23.2%] vs. 22 [25.0%]). This was also true for deaths occurring within 30 days of the stroke (9 [28.1%] vs. 13 [30.2%]).

9.1.4 Treatment-Emergent Adverse Events

Pooled safety population included all patients who received at least one dose of the trial treatment. TEAE was defined as an AE that begins (or a preexisting AE that worsens) on or after the first dose. A total of 1,047 (53.8%) subjects were exposed to vadadustat, and 1,317 (67.3%) subjects were exposed to darbepoetin alfa for ≥52 weeks. A total of 275 (14.1%) subjects were exposed to vadadustat and 403 (20.6%) subjects were exposed to darbepoetin alfa for ≥104 weeks. The mean (standard deviation [SD]) duration of exposure was 59.5 (37.6) weeks in the vadadustat group and 71.3 (36.7) weeks in the darbepoetin alfa group. The most frequent drug-related TEAEs reported for subjects in the vadadustat group were in the system organ class gastrointestinal disorders, which may be related to the oral route of vadadustat administration.

Table 21 and Table 22 present overviews of events in safety populations of the incident and prevalent DD-CKD $INNO_2VATE$ trials respectively.

Table 21 Overview of safety events in $INNO_2VATE$ Incident Trial (52 weeks)

	Vadadustat (N=179) [45, 47]	Darbepoetin alfa (N=186) [45, 47]	Difference,% (95 % CI)
Number of adverse events, n	1,074	1,199	N/A

	Vadadustat (N=179) [45, 47]	Darbepoetin alfa (N=186) [45, 47]	Difference,% (95 % CI)
Number and proportion of patients with ≥1 adverse events, n (%)	150 (83.3%)	159 (85.5%)	-2.2% (N/A)
Number of serious adverse events*, n	270	284	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	89 (49.7%)	105 (56.5%)	-6.8% (N/A)
Number of CTCAE grade ≥ 3 events, n	186**	188**	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	60 (33.5%)**	64 (34.4%)**	-0.9% (N/A)
Number of adverse reactions (drug-related TEAE), n	13	7	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	7 (3.9%)	5 (2.7%)	1.2% (N/A)
Number and proportion of patients who had a dose reduction, n (%)	N/A However, 58 (37.2%) and 38 (30.4%) had a dose increase or decrease during study week 24-36 and week 40-52, respectively.	N/A However, 97 (57.4%) and 72 (51.4%) had a dose increase or decrease during study week 24-36 and week 40-52, respectively.	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	60 (33.5%)	49 (26.3%)	7.2% (N/A)

	Vadadustat (N=179) [45, 47]	Darbepoetin alfa (N=186) [45, 47]	Difference,% (95 % CI)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	5 (2.8%)	2 (1.1%)	1.7% (N/A)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

**Listed as severe treatment emergent adverse event in the CSR.

§ CTCAE v. 5.0 must be used if available.

Table 22 Overview of safety events in INNO$_2$VATE Prevalent Trial (52 weeks)

	Vadadustat (N=1,768) [46, 47]	Darbepoetin alfa (N=1,769) [46, 47]	Difference,% (95 % CI)
Number of adverse events (TEAEs), n	13,404	14,048	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	1,562 (88.3%)	1,580 (89.3%)	-1.0% (N/A)
Number of serious adverse events* (treatment-emergent SAE), n	3,448	3,707	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	973 (55.0%)	1,032 (58.3%)	-3.3% (N/A)
Number of CTCAE grade ≥ 3 events, n	2,171**	2,454**	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	707 (40.0%)	749 (42.3%)	-2.3% (N/A)
Number of adverse reactions (drug-related TEAE), n	262	82	N/A

	Vadadustat (N=1,768) [46, 47]	Darbepoetin alfa (N=1,769) [46, 47]	Difference,% (95 % CI)
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	169 (9.6%)	68 (3.8%)	5.8% (N/A)
Number and proportion of patients who had a dose reduction, n (%)	N/A However, 553 (37.5%) and 476 (36.4%) had a dose increase or decrease during study week 24-36 and week 40-56, respectively.	N/A However, 1,045 (64,8%) and 932 (62.7%) had a dose increase or decrease during study week 24-36 and week 40-56, respectively.	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	899 (50.8%)	653 (37.0%)	13.8% (N/A)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	91 (5.1%)	20 (1.1%)	4.0 % (N/A)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

**Listed as severe treatment emergent adverse event in the CSR.

§ CTCAE v. 5.0 must be used if available.

The median (Q1, Q3) duration of study drug exposure to vadadustat and darbepoetin alfa in INNO$_2$VATE Incident trial were 56.14 (28.86, 85.43) and 72.14 (44.86, 98.71) weeks, respectively. Serious adverse events (SAEs) incurred during that time are presented in Table 23.

Table 23 Serious adverse events in INNO$_2$VATE Incident Trial (52 weeks)

Adverse events	Vadadustat (N=179)		Darbepoetin alfa (N=186)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events

Adverse events	Vadadustat (N=179)		Darbepoetin alfa (N=186)	
Infections and infestations, n (%)	41 (22.9%)	74	46 (24.7%)	73
Cardiac disorders, n (%)	23 (12.8%)	34	25 (13.4%)	44
Injury, poisoning, and procedural complications, n (%)	18 (10.1%)	24	18 (9.7%)	20
Vascular disorders, n (%)	16 (8.9%)	28	18 (9.7%)	19
Gastrointestinal disorders, n (%)	11 (6.1%)	12	22 (11.8%)	40
Metabolism and nutrition disorders, n (%)	14 (7.8%)	36	11 (5.9%)	17
Respiratory, thoracic, and mediastinal disorders, n (%)	15 (8.4%)	18	10 (5.4%)	14

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

The median (Q1, Q3) duration of study drug exposure per patient to vadadustat and darbepoetin alfa in INNO$_2$VATE Prevalent trial was 45.00 (28.00, 73.14) and 50.14 (36.00, 80.14) weeks, respectively. SAEs incurred during that time are presented in Table 24.

Table 24 Serious adverse events in INNO$_2$VATE Prevalent Trial (52 weeks)

Adverse events	Vadadustat (N=1,768)		Darbepoetin alfa (N=1,769)	
	Number of patients with adverse events	**Number of adverse events**	**Number of patients with adverse events**	**Number of adverse events**
Infections and infestations, n (%)	491 (27.8%)	835	499 (28.2%)	904
Cardiac disorders, n (%)	296 (16.7%)	512	353 (20.0%)	578
Injury, poisoning and procedural complications, n (%)	232 (13.1%)	319	240 (11.8%)	354

Adverse events	Vadadustat (N=1,768)		Darbepoetin alfa (N=1,769)	
Metabolism and nutrition disorders, n (%)	195 (11.0%)	272	208 (11.8%)	284
Respiratory, thoracic, and mediastinal disorders, n (%)	179 (10.1%)	263	191 (10.8%)	281
Gastrointestinal disorders, n (%)	187 (10.6%)	283	181 (10.2%)	269
Vascular disorders, n (%)	178 (10.1%)	234	178 (10.1%)	250
Nervous system disorders, n (%)	140 (7.9%)	186	157 (8.9%)	216
General disorders and administration site conditions, n (%)	119 (6.7%)	136	103 (5.8)	111

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Since safety of vadadustat was acknowledged to be comparable and non-inferior to darbepoetin alfa, no safety data was included in the CMA.

Table 25 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	N/A	N/A	N/A	N/A

9.2 Safety data from external literature applied in the health economic model

N/A since safety was not included in the CMA.

Table 26 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

N/A. HRQoL was not studied in the INNO$_2$VATE trial program and due to the nature of the health economic analysis (CMA), HRQoL is not included.

The INNO$_2$VATE trials showed that vadadustat is non-inferior in efficacy compared to ESAs in treating anemia in DD-CKD adult patients as well as being non-inferior in terms of safety. Therefore, it can be expected that the health-related benefits of vadadustat will be at least similar to, and may be higher than, ESAs for DD-CKD patients with anemia. Because vadadustat is to be taken orally, compared to ESAs administered by subcutaneous injection, vadadustat offers the convenience of being taken at home, with minimal disruption of patients' daily routine.

Table 27 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
N/A	N/A	N/A

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

N/A

10.1.1 Study design and measuring instrument

N/A

10.1.2 Data collection

N/A

Table 28 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	N/A	N/A	N/A	N/A

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Time point 1	N/A	N/A	N/A	N/A

10.1.3 HRQoL results

N/A

Example of figure displaying the mean change from baseline through the different data collection time points for both the intervention and comparator:

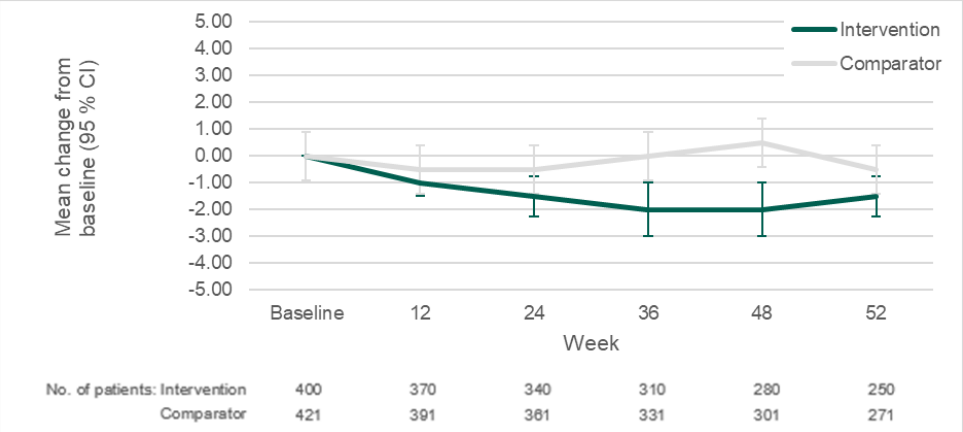


Table 29 HRQoL [instrument 1] summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	N/A	N/A	N/A	N/A	N/A
Time point 1	N/A	N/A	N/A	N/A	N/A

10.2 Health state utility values (HSUVs) used in the health economic model

N/A

10.2.1 HSUV calculation

N/A

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A

10.2.3 HSUV results

N/A

Table 30 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A
…				
[Disutilities]	N/A	N/A	N/A	N/A
…				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 31 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A
HSUV B	N/A	N/A	N/A	N/A
…				
[Disutilities]	N/A	N/A	N/A	N/A
…				

Table 32 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	N/A	N/A	N/A	N/A
[Disutility A]				
…	N/A	N/A	N/A	N/A

11. Resource use and associated costs

The costs included in the base case of this CMA were drug acquisition costs, drug administration costs, IV iron rescue therapy costs, and patient time and transport costs. The inclusion of drug wastage costs was tested in scenario analysis.

All costs were calculated on a quarterly basis, based on the dosage, drug administration, and IV iron rescue therapy data from the clinical trials [45, 46] (see the tab 'Model_Inputs'). The in-detail calculations are presented in the "Calculations" sheet of the CMA.

11.1 Medicine costs - intervention and comparator

The average weekly dose of vadadustat and darbepoetin alfa was informed by the dosing from the INNO$_2$VATE trials, [redacted]

The prices of vadadustat and darbepoetin alfa are presented in pharmacy purchase price (AIP) in Table 33. In the CMA, the prices are presented in AIP/unit which were calculated based on the cheapest AIP of the medicines (for vadadustat the unit is mg and for darbepoetin alfa it is mcg). Vafseo is available in the following strengths: 150 mg and 300 mg (both strengths come in pack sizes of 28 or 98). In the CMA, it was used the AIP for the strength of 150 mg and pack size of 98 ([redacted]). Regarding darbepoetin alfa (comparator), the following pack sizes are available in Medicinpriser (in mcg): 10, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300, and 500. The price used in the CMA for darbepoetin alfa was the average AIP per mcg based on all the strengths available (darbepoetin alfa is sold at a flat price per mcg).

The cost of drug wastage was only implemented in the darbepoetin alfa arm as using vadadustat was assumed to not have drug wastage since it is administered orally. The cost of wastage was calculated as a proportion of the darbepoetin alfa acquisition cost and added on top of the acquisition cost. The proportion of drug wastage is user editable. In the base case, it was assumed drug wastage for darbepoetin alfa was 0%, which is a conservative assumption (since a cost/mg was implemented in the CMA, as opposed to a cost/pack). Different wastage proportions were tested in scenario analyses.

Treatment with vadadustat and darbepoetin alfa is assumed to be continuous in the CMA, as these are chronic patients and it is in line with the respective summary of product characteristics (SmPC).

Table 33 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	AIP [DKK]
Vadadustat	[redacted]	100% (assumption)	Once daily	N/A (oral)	AIP: [redacted] AIP/mg (used in the CMA): [redacted]

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	AIP [DKK]
	[redacted]				
Darbepoetin alfa	[redacted]	100% (assumption)	Once every week	No	[redacted]

¥ The presented AIP price is for Vafseo with strength 150 mg with a pack size of 98. [redacted] *Average AIP per mcg for darbepoetin alfa (based on all the strengths available in Medicinpriser, in mcg: 10, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300, and 500). Abbreviations: AIP, Pharmacy purchase price (*Apotekernes indkøbspris*); CMA, Cost-minimisation analysis; N/A, Not applicable. Source for vadadustat price: Medice Arzneimittel Pütter GmbH & Co. KG; Source for darbepoetin alfa price: Medicinpriser [51].

11.2 Medicine costs – co-administration

N/A.

11.3 Administration costs

Vadadustat can be orally administered by the patient. Therefore, the model assumed no administration costs for Vadadustat (DKK 0). In general, darbepoetin alfa is expected to be administered in conjunction to dialysis treatment thus do not incur administration cost for the majority of patients. However, patients managing their dialysis treatment outside of a hospital or dialysis center, i.e. through HHD or PD, may require help for the administration of darbepoetin alfa [52]. [redacted]. These patients were assumed to require one nurse visit per week for the administration of darbepoetin alfa. The

remaining patients on HHD or PD were assumed to not incur administration costs (DKK 0).

The cost of a nurse visit is presented in Table 34. The unit cost of a nurse visit (DKK 455) was applied to [redacted], yielding a weekly cost of DKK [redacted].

Table 34 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
District nurse visit (nurse helps with drug administration)	Once a week	455	”Sygeplejersker”	DMC [54]

Abbreviations: DRG, Diagnosis-related group.

11.4 Disease management costs

N/A as it is not used in the CMA.

Table 35 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
N/A				

11.5 Costs associated with management of adverse events

N/A.

Table 36 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
N/A		

11.6 Subsequent treatment costs

The percentage of patients requiring at least one IV iron administration per week, and the average dose of IV iron, were informed by the INNO$_2$VATE trials.

The unit cost of IV iron rescue was calculated by summing the acquisition cost of Cosmofer (sourced from Medicinpriser [51]) and an IV administration cost (sourced from the Sundhedsdatastyrelsen DRG 2024 list [55]). The drug acquisition cost for IV iron rescue was applied to the proportion of patients receiving at least one IV iron administration per week (from INNO$_2$VATE trials) whereas the IV administration cost was applied to [redacted]

[redacted]. This was a similar approach to the one used in the quantification of administration costs, described in Section 11.3.

The price of IV iron rescue therapy is presented in AIP in Table 37. In the CMA, the price is presented in AIP/unit which were calculated based on the [redacted].

Table 37 Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Cosmofer*	[redacted]	[redacted]	[redacted]	100%	N/A

*[redacted]

Abbreviations: AIP, Pharmacy purchase price (*Apotekernes indkøbspris*); CMA, cost-minimisation analysis.
Source for IV iron rescue: Medicinpriser [51].

11.7 Patient costs

Transport costs were assumed to occur among patients who receive HHD or PD and require IV iron rescue therapy. This was calculated by applying a mean proportion of patients who require IV iron rescue therapy informed by the INNO$_2$VATE trials to [redacted].

Transport costs were not calculated for the remaining patients as these patients are nonetheless traveling to hospital/center for the dialysis treatment. The round trip cost (DKK 140) and the average hourly rate for patient time (203 DKK/h) used in the CMA were sourced from DMC's Værdisætning af enhedsomkostninger [54].

Table 38 Patient costs used in the model

Activity	Time spent [hours]
Patient time	[redacted]

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

12.1 Base case overview

The base case of the present CMA is summarized in Table 39.

Table 39 Base case overview

Feature	Description
Comparator	Darbepoetin alfa
Type of model	Cost-minimization model
Time horizon	3 years
Treatment line	N/A. Subsequent treatment with IV iron rescue therapy is included.
Measurement and valuation of health effects	N/A. Health effects were not explored in the model due to the chosen model type.
Costs included	Drug acquisition costs Drug administration costs IV iron rescue costs Patient time and transport costs
Dosage of medicine	Based on average dosing from the INNO$_2$VATE trial [redacted] See more on Section 11.1.
Average time on treatment	N/A
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	No. No waste is expected for vadadustat as it is administered orally. The acquisition cost calculation is considered conservative for darbepoetin alfa since a cost/mg was implemented in the CMA. Wastage is explored in scenario analyses.
Average time in model health state Health state 1	N/A

Feature	Description
Health state 2	
Health state 3	
Death	

12.1.1 Base case results

The base case results from the CMA are presented in Table 40. Vadadustat resulted in a total of DKK [redacted] costs saved compared to the treatment with darbepoetin alfa, after 3 years of use.

Table 40 Base case results, discounted estimates (3-year period)

	Vadadustat	Darbepoetin alfa	Difference
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs (IV iron rescue)	[redacted]	[redacted]	[redacted]
Patient time and transport costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Total life years	**N/A**	**N/A**	**N/A**
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs per life year gained		**N/A**	
Incremental cost per QALY gained (ICER)		**N/A**	

12.2 Sensitivity analyses

Both deterministic sensitivity analyses and probabilistic sensitivity analyses were considered not applicable, but scenario analyses on wastage and price discount are presented.

12.2.1 Deterministic sensitivity analyses

N/A

Table 41 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
N/A					

Scenario analyses

A range of scenarios were tested and results are presented in Table 42. The results show the scenario generating highest price decrease for the three years of the analysis was [redacted]

Table 42. Scenario analyses

Scenario	Description	Total costs (3 years) for vadadustat [DKK]	Total costs (3 years) for darbepoetin alfa [DKK]	Incremental costs [DKK]
Base case	-	[redacted]	[redacted]	[redacted]
Inclusion of wastage in the darbepoetin alfa arm	Inclusion of 5% wastage	[redacted]	[redacted]	[redacted]
	Inclusion of 10% wastage	[redacted]	[redacted]	[redacted]
Price discount to AIP for Vafseo 150 mg with a pack size of 98 tablets	10% discount [redacted]	[redacted]	[redacted]	[redacted]
	25% discount [redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIP, Pharmacy purchase price (*Apotekernes indkøbspris*).

12.2.2 Probabilistic sensitivity analyses

N/A, as this CMA was undertaken because of clinical non-inferiority, with very little uncertainty about the cost implications.

13. Budget impact analysis

This budget impact analysis describes how budgets will be affected over a five-year period if vadadustat is introduced in Denmark.

Number of patients (including assumptions of market share)

The expected number of patients eligible for treatment with vadadustat has been described in detail in Section 3.2. In this budget impact analysis, the prevalent population was estimated to be approximately 1,695 and 429 patients (for hemodialysis and peritoneal dialysis, respectively), resulting in a total of 2,124 patients (which is equivalent to 80% of the prevalent population on dialysis in Denmark) [26, 27]. As mentioned previously in Section 3.2, using 2022 numbers was considered an appropriate approach. This is because the trend from the last 5 years shows quite constant number of prevalent and incident patients, hence it is assumed that the eligible population for treatment with vadadustat in the next five years would also remain constant. For this reason, only the prevalent population numbers were included in the budget impact analysis.

If vadadustat is recommended, it was assumed that vadadustat would have a market share [redacted]. Contrarily, if vadadustat is not recommended, it was assumed that ESAs (i.e., darbepoetin alfa) would have a market share of 100% during the entire five-year period. In this BIM, every new year, the patient population that did not start treatment with vadadustat in the previous year was eligible to receive treatment with vadadustat (i.e., catch-up population was included). The patient numbers adjusted for market share in both scenarios (vadadustat is recommended vs is NOT recommended) are presented in Table 43.

The price per pack (in AIP) for vadadustat used in the model was DKK [redacted], and the AIP per mcg for darbepoetin alfa was DKK [redacted] (see Section 11.1). Furthermore, the AIP per pack for IV iron rescue used in the CMA was DKK [redacted] (see Section 11.6). Prices presented in the BIM are undiscounted.

In the analysis, it was estimated that [redacted] of the patients would receive treatment at home, with the remaining patients receiving treatment at the hospital. This impacted the calculation of administration and IV iron rescue costs. The calculation of administration costs is described in Section 11.3, and the calculation of IV iron rescue costs is described in Section 11.6.

Table 43 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	2025	2026	2027	2028	2029
			Recommendation		
Vadadustat (cumulative)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	2025	2026	2027	2028	2029
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Vadadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

The obtained budget impact is presented in Table 44. In 2029 (year 5), the introduction of vadadustat is expected to have a budget impact of about DKK [redacted].

Table 44 Expected budget impact of recommending the medicine for the indication

	2025	2026	2027	2028	2029
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

N/A – no clinicians were consulted during this application submission.

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Appendix A. Main characteristics of studies included

Table 45 Main characteristic of studies included - AKB-6548-CI-0016

Trial name:" INNO$_2$VATE – Correction/Conversion"	NCT number: AKB-6548-CI-0016
Objective	To demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia after the correction of Hb or conversion from current ESA therapy, in subjects who have recently initiated dialysis treatment for DD-CKD.
Publications – title, author, journal, year	Eckardt et al., 2021 - *Global Phase 3 programme of vadadustat for treatment of anaemia of chronic kidney disease: rationale, study design and baseline characteristics of dialysis-dependent patients in the INNO2VATE trials. Nephrol Dial Transplant* [56] Eckardt et al., 2021 - *Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis. N Engl J Med* [47] Sarnak et al., 2023 - *Vadadustat for treatment of anemia in patients with dialysis-dependent chronic kidney disease receiving peritoneal dialysis. Nephrol Dial Transplant* [57] Koury et al., 2022 - *Erythropoietic effects of vadadustat in patients with anemia associated with chronic kidney disease. Am J Hematol* [58] Agarwal et al., 2022 - *Overall Adverse Event Profile of Vadadustat versus Darbepoetin Alfa for the Treatment of Anemia Associated with Chronic Kidney Disease in Phase 3 Trials. Am J Nephrol* [59]
Study type and design	Randomized phase III, open-label, active comparator-control, sponsor-blinded, global multi-center study; subjects randomized to vadadustat or darbepoetin alfa in a 1:1 ratio.
Sample size (n)	369
Main inclusion criteria	Subjects who: • are DD-CKD and have anemia • are ≥18 years old, had understood the procedures and requirements of the study and provided written informed consent and authorization for protected health information disclosure • initiated chronic maintenance dialysis (either PD or HD) for ESRD within 16 weeks prior to screening • have mean screening Hb between 8.0 and 11.0 g/dL (inclusive), as determined by the average of 2 Hb values during screening • have serum ferritin ≥100 ng/mL and TSAT ≥20% during Screening

Trial name:" $INNO_2VATE$ – Correction/Conversion"	NCT number: AKB-6548-CI-0016
Main exclusion criteria	Subjects who: • have anemia due to other cause than CKD or subjects with active bleeding or recent blood loss • have sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia • had RBC transfusion within 8 weeks prior to randomization • anticipated to recover adequate kidney function to no longer require dialysis
Intervention	**Vadadustat** (179 subjects); The initial dose was 300 mg/day taken orally. Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on Hb level measurements every 4 weeks to maintain target Hb levels of 10-12 g/dL. During the study, vadadustat was dosed according to the Dose Adjustment Algorithms.
Comparator	**Darbepoetin alfa** (186 subjects); The initial dose was based on the current PI for investigational sites in the US, and the SmPC for all other investigational sites (non-US) for adult subjects with CKD on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen. Darbepoetin alfa dosing was independent of the study visit schedule, and the dosing schedule could be shifted per local standard of care, the subject's dialysis schedule, and per investigator discretion. In general, darbepoetin alfa was dosed IV for subjects on chronic hemodialysis and SC for subjects receiving peritoneal dialysis and in accordance with the approved product label. Darbepoetin alfa was dosed IV or SC following dose conversion, with dose adjustments based on the Dose Adjustment Algorithm.
Follow-up time	Following randomization, there were 3 periods during the study: • Correction/Conversion and Maintenance Period (Weeks 0 to 52): initial period on study drug for maintaining Hb (Weeks 0 to 23), primary efficacy period (Weeks 24 to 36), and secondary efficacy period (Week 40 to 52). • Long-term Treatment Period (Week 53 to end of treatment [EOT]): continued study drug to assess long-term safety. • Follow-up Period (EOT + 4 weeks): post-treatment visit for safety (either in person or via telephone). Approximately 60% of vadadustat treated subjects and approximately 70% of darbepoetin alfa treated subjects remained on treatment at Weeks 40 to 52.
Is the study used in the health economic model?	Yes, to inform dosing of vadadustat and darbepoetin alfa.

Trial name:" INNO$_2$VATE – Correction/Conversion"	NCT number: AKB-6548-CI-0016

Primary, secondary and exploratory endpoints

Endpoints included in this application:

• Primary efficacy endpoint: change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)

• Key secondary efficacy endpoint: change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52)

• Mean weekly dose of elemental iron administered from Baseline to week 52 in subjects who had received IV and/or oral iron

• receipt of at least 1 administration of elemental iron (IV or oral).

• Primary safety endpoint: Time to first adjudicated MACE, defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke.

Other endpoints:

Endpoints related to Hb:

• Change in average Hb value between Baseline and the combined primary efficacy period and secondary efficacy period (weeks 24 to 52).

• Having the average Hb value in the geography-specific target range in the primary and secondary efficacy periods, respectively

• Having at least 1 Hb value in the geography-specific target range in the primary and secondary efficacy periods, respectively

• Having Hb values in the geography-specific target range for at least one-half of the observations in the primary and secondary efficacy periods, respectively

• Hb increase of >1.0 g/dL from Baseline to week 52

• Time to achieve Hb increase of >1.0 g/dL from Baseline Hb (censored at week 52).

Endpoints related to RBC transfusion:

• Receipt of any red blood cell (RBC) transfusion

• Time to first RBC transfusion (for entire study)

• Total number of RBC transfusion episodes received

• Rate of RBC transfusions, calculated as the number of episodes divided by the duration of at risk follow-up in person-years.

Endpoints related to ESA rescue

•Receipt of any ESA medication (in the darbepoetin alfa group, use only included an ESA other than darbepoetin alfa as well as increases in darbepoetin alfa which the investigator specifically designated as rescue),

• Time to first ESA medication (for entire study)

• Total number and maximum duration of ESA episodes.

Endpoints related to iron:

Trial name:" INNO$_2$VATE – Correction/Conversion"	NCT number: AKB-6548-CI-0016

	• Changes in iron-related parameters from Baseline to the primary efficacy period (weeks 24 to 36) and secondary efficacy period (weeks 40 to 52), Other: • Dose adjustments from Baseline to week 52. • Changes in serum glucose and lipid parameters between Baseline and the primary (weeks 24 to 36) and secondary (weeks 40 to 52) efficacy period. Key secondary safety endpoints: • Time to first MACE plus hospitalisation for heart failure or thromboembolic event excluding vascular access thrombosis • Time to first CV MACE (CV death, non-fatal myocardial infarction or non-fatal stroke) • Time to CV death • Time to all-cause mortality
Method of analysis	The primary analysis were performed on the randomized population. Efficacy analyses utilized the Randomized, FAS, and PP populations, while safety analyses (including analyses of MACE) utilized the Safety population. The approach to primary and key secondary endpoint analysis was analysis of covariance (ANCOVA) with multiple imputation for missing data. Mixed models for repeated measurements (MMRM) on observed data was used for sensitivity analysis. The general approach to analysis of the other continuous outcomes was ANCOVA with or without multiple imputation. **Safety analyses were performed using the Safety population** (all subjects in the Randomized population who received at least 1 dose of study drug). All MACE analyses were conducted on the pooled safety population from both INNO$_2$VATE trials combined. Most of the analysis of safety data was descriptive without formal statistical testing. Formal statistical methodology was used for the MACE data.
Subgroup analyses	Vadadustat was effective in maintaining Hb across all subgroups including demographic and baseline characteristics, baseline laboratory assessments (Hb, iron-related parameters, and CRP), regions (US, Europe, ROW), diabetes mellitus status, CV history, and NYHA functional class
Other relevant information	*N/A*

Table 46 Main characteristic of studies included - AKB-6548-CI-0017

Trial name: "INNO$_2$VATE – Conversion"	NCT number: AKB-6548-CI-0017
Objective	The primary objective of this study was to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with DD-CKD.
Publications – title, author, journal, year	Eckardt et al., 2021 - *Global Phase 3 programme of vadadustat for treatment of anaemia of chronic kidney disease: rationale, study design and baseline characteristics of dialysis-dependent patients in the INNO2VATE trials. Nephrol Dial Transplant* [56] Eckardt et al., 2021 - *Safety and Efficacy of Vadadustat for Anemia in Patients Undergoing Dialysis. N Engl J Med* [47] Sarnak et al., 2023 - *Vadadustat for treatment of anemia in patients with dialysis-dependent chronic kidney disease receiving peritoneal dialysis. Nephrol Dial Transplant* [57] Koury et al., 2022 - *Erythropoietic effects of vadadustat in patients with anemia associated with chronic kidney disease. Am J Hematol* [58] Agarwal et al., 2022 - *Overall Adverse Event Profile of Vadadustat versus Darbepoetin Alfa for the Treatment of Anemia Associated with Chronic Kidney Disease in Phase 3 Trials. Am J Nephrol* [59]
Study type and design	Randomized phase III, open-label, active comparator-control, sponsor-blinded, global multicenter study; subjects randomized to vadadustat or darbepoetin alfa in a 1:1 ratio.
Sample size (n)	3,554
Main inclusion criteria	Subjects who: • were ≥18 years of age. • had received chronic maintenance dialysis (either peritoneal or hemodialysis) for end-stage kidney disease for at least 12 weeks prior to Screening. • was currently maintained on ESA therapy, with a dose received within 6 weeks prior to or during Screening. • mean screening Hb between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) outside of the US, as determined by the average of 2 Hb values measured screening. • serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during screening.
Main exclusion criteria	Subjects who: • presented with anemia due to a cause other than CKD or subjects with active bleeding or recent blood loss • had history of sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia

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	• had RBC transfusion within 8 weeks prior to randomization • anticipated to recover adequate kidney function to no longer require dialysis
Intervention	**Vadadustat** (1,768 subjects); The initial dose was 300 mg/day taken orally. Thereafter, vadadustat was taken once daily on an outpatient basis. Up-and-down titration to 150, 300, 450, and 600 mg (available tablet strength was administered as the appropriate number of 150 mg tablets) was allowed during the study based on Hb level measurements every 4 weeks to maintain target Hb levels of 10-12 g/dL. During the study, vadadustat was dosed according to the Dose Adjustment Algorithms.
Comparator	**Darbepoetin alfa** (1,769 subjects); The initial dose was based on the current PI for investigational sites in the US, and the SmPC for all other investigational sites (non-US) for adult subjects with CKD on dialysis. For subjects already on darbepoetin alfa, the initial dosing regimen in the study was based on the prior dosing regimen. Darbepoetin alfa dosing was independent of the study visit schedule, and the dosing schedule could be shifted per local standard of care, the subject's dialysis schedule, and per investigator discretion. In general, darbepoetin alfa was dosed IV for subjects on chronic hemodialysis and SC for subjects receiving peritoneal dialysis and in accordance with the approved product label. Darbepoetin alfa was dosed IV or SC following dose conversion, with dose adjustments based on Dose Adjustment Algorithm.
Follow-up time	Following randomization, there were 3 periods during the study: Correction /conversion: week 0-23; Maintenance: 24-52; Long-term treatment: week 53 – end of treatment; Follow-up: 4 weeks Approximately 70% of vadadustat treated subjects and approximately 80% of darbepoetin alfa treated subjects remained on treatment at Weeks 40 to 52.
Is the study used in the health economic model?	Yes, to inform dosing of vadadustat and darbepoetin alfa.
Primary, secondary and exploratory endpoints	See Table 45
Method of analysis	See Table 45
Subgroup analyses	Vadadustat was effective in maintaining Hb across all subgroups including demographic and baseline characteristics, baseline laboratory assessments (Hb, iron-related parameters, and C-reactive protein [CRP]), regions (US,

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	Europe, rest of world [ROW]), diabetes mellitus status, CV history, and NYHA functional class.
Other relevant information	*N/A*

Appendix B. Efficacy results per study

Results per study

Results for primary and key secondary endpoint, and iron-related endpoints used in the cost-minimization analysis are presented in this appendix.

Table 47 Results per study INNO$_2$VATE – Incident, Correction/Conversion (NCT02865850)

Results of INNO$_2$VATE – Incident, Correction/Conversion (NCT02865850)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Adjusted mean change in average Hb between baseline and primary efficacy period (w 24-36)	Vadadustat	181	1.26 (1.05, 1.48)	-0.31	(−0.53, -0.10)	N/A	N/A	N/A	N/A	The primary endpoint was analyzed using ANCOVA with multiple imputation for the randomized population. The lower bound of the 95% CI (-0.53) is above -0.75 g/dL. Thus, the non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the lower bound of the 95% CI is above the prespecified non-inferiority margin of -0.75 g/dL.	[45, 47]
	Darbepoetin alfa	188	1.58 (1.37, 1.79)								
	Vadadustat	181	1.42 (1.17, 1.68)	-0.07	(−0.34, 0.19)	N/A	N/A	N/A	N/A		[45, 47]

Results of INNO$_2$VATE – Incident, Correction/Conversion (NCT02865850)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Adjusted mean change in average Hb between baseline and secondary primary efficacy period (w 40-52)	Darbepoetin alfa	188	1.50 (1.23, 1.76)							The secondary endpoint was analyzed using ANCOVA with multiple imputation for the randomized population. The lower bound of the 95% CI is above -0.75 g/dL. Thus, the non-inferiority of vadadustat to darbepoetin alfa was demonstrated at the prespecified non-inferiority margin of -0.75.	
Proportion of patients with ≥1 administration of IV iron (week 2-8)	Vadadustat	[redacted]	[redacted]	0.029	(-0.0715, 0.1289)	N/A	OR: 1.1	(0.74, 1.72)	N/A	From Mantel Haenszel method stratified by the 3 randomization stratification factors. Within any stratum, if there are no subjects in any treatment group or there are no responders in both treatment groups, unstratified Mantel Haenszel method is used instead for analysis.	[45]
	Darbepoetin alfa	[redacted]	[redacted]								

Results of INNO$_2$VATE – Incident, Correction/Conversion (NCT02865850)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with ≥ 1 administration of IV iron (week 10-20)	Vadadustat	[redacted]	[redacted]	0.048	(-0.0508, 0.1473)	N/A	OR: 1.2	(0.79, 1.95)	N/A	See above	[45]
	Darbepoetin alfa	[redacted]	[redacted]								
Proportion of patients with ≥1 administration of IV iron (week 24-36)	Vadadustat	[redacted]	[redacted]	0.054	(-0.0482, 0.1557)	N/A	OR: 1.3	(0.80, 2.03)	N/A	See above	[45]
	Darbepoetin alfa	[redacted]	[redacted]								
Proportion of patients with ≥1 administration of IV iron (week 40-52)	Vadadustat	[redacted]	[redacted]	0.011	(-0.1061, 0.1272)	N/A	OR: 1.0	(0.64, 1.72)	N/A	See above	[45]
	Darbepoetin alfa	[redacted]	[redacted]								

Results of INNO$_2$VATE – Incident, Correction/Conversion (NCT02865850)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
LSM weekly dose (mg) of elemental Iron (week 2-8)	Vadadustat	[redacted]	[redacted]	-65.05	(-284.03, 153.92)	0.5604	N/A	N/A	N/A	Treatment comparison was made using an ANCOVA model with treatment and the 3 randomization stratification factors as fixed effects.	[45]
	Darbepoetin alfa	[redacted]	[redacted]								
LSM weekly dose (mg) of elemental Iron (week 10-20)	Vadadustat	[redacted]	[redacted]	-72.85	(-254.56, 108.86)	0.4320				See above	[45]
	Darbepoetin alfa	[redacted]	[redacted]								
LSM weekly dose (mg) of elemental Iron (week 24-36)	Vadadustat	[redacted]	[redacted]	-21.55	(-160.88, 117.78)	0.7617	N/A	N/A	N/A	See above	[45]
	Darbepoetin alfa	[redacted]	[redacted]								

Results of INNO$_2$VATE – Incident, Correction/Conversion (NCT02865850)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
LSM weekly dose (mg) of elemental Iron (week 40-52)	Vadadustat	[redacted]	[redacted]	16.09	(-58.07, 90.25)	0.6706	N/A	N/A	N/A	See above	[45]
	Darbepoetin alfa	[redacted]	[redacted]								

a) Only subjects taking at least one dose are included in the analysis

LSM: Least square mean, OR: odds ratio, SD: Standard deviation

Table 48 Results per study INNO$_2$VATE – Prevalent, Conversion (NCT02892149)

Results of INNO$_2$VATE – Conversion (NCT02892149)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Adjusted mean	Vadadustat	1,777	0.19 (0.12, 0.25)	-0.17	(−0.23, −0.10)	N/A				The primary endpoint, analyzed using ANCOVA with	[46, 47]

Results of INNO$_2$VATE – Conversion (NCT02892149)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
change from baseline and primary efficacy period (w 24-36)	Darbepoetin alfa	1,777	0.36 (SD: 0.29, 0.42)							multiple imputation for the randomized population. Non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the lower bound of the 95% CI is above the prespecified non-inferiority margin of -0.75 g/dL.	
Adjusted mean change in average Hb between baseline and secondary efficacy period (w 40-52)	Vadadustat	1,777	0.23 (0.16, 0.29)	−0.18	(−0.25, −0.12)	N/A	N/A	N/A	N/A	The secondary endpoint was analyzed using ANCOVA with multiple imputation for the randomized population. The lower bound of the 95% CI is above -0.75 g/dL. Thus, the non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the prespecified non-inferiority margin was -0.75 g/dL.	[46, 47]
	Darbepoetin alfa	1,777	0.41 (0.34, 0.48)								
Proportion of patients	Vadadustat	[redacted]	[redacted]	-0.024	(-0.0569, 0.0079)	N/A	OR: 0.9	(0.79, 1.03)	N/A	From Mantel Haenszel method stratified by the 3	[46]

Results of INNO$_2$VATE – Conversion (NCT02892149)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
with >1 administration of IV iron (week 2-8)	Darbepoetin alfa	[redacted]	[redacted]							randomization stratification factors. Within any stratum, if there are no subjects in any treatment group or there are no responders in both treatment groups, unstratified Mantel Haenszel method is used instead for analysis.	
Proportion of patients with > 1 administration of IV iron (week 10-20)	Vadadustat	[redacted]	[redacted]	-0.003	(-0.0364, 0.0302)	N/A	OR: 1.0	(0.86, 1.13)	N/A	See above	[46]
	Darbepoetin alfa	[redacted]	[redacted]								
Proportion of patients with >1 administration of IV iron (week 24-36)	Vadadustat	[redacted]	[redacted]	0.003	(-0.0318, 0.0376)	N/A	OR: 1.0	(0.88, 1.17)	N/A	See above	[46]
	Darbepoetin alfa	[redacted]	[redacted]								

Results of INNO$_2$VATE – Conversion (NCT02892149)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients with >1 administration of IV iron (week 40-52)	Vadadustat	[redacted]	[redacted]	-0.001	(-0.0371, 0.0354)		OR: 1.0	(0.86, 1.16)	N/A		[46]
	Darbepoetin alfa	[redacted]	[redacted]								
LSM weekly dose (mg) of elemental Iron (week 2-8)	Vadadustat	[redacted]	[redacted]	-10.64	(-31.56, 10.29)	0.3193	N/A	N/A	N/A		[46]
	Darbepoetin alfa	[redacted]	[redacted]								
LSM weekly dose (mg) of elemental Iron (week 10-20)	Vadadustat	[redacted]	[redacted]	-3.68	(-22.34, 14.99)	0.6995	N/A	N/A	N/A		[46]
	Darbepoetin alfa	[redacted]	[redacted]								

Results of INNO$_2$VATE – Conversion (NCT02892149)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
LSM weekly dose (mg) of elemental Iron (week 24-36)	Vadadustat	[redacted]	[redacted]	1.51	(-22.04, 25.05)	0.9002	N/A	N/A	N/A		[46]
	Darbepoetin alfa	[redacted]	[redacted]								
LSM weekly dose (mg) of elemental Iron (week 40-52)	Vadadustat	[redacted]	[redacted]	-6.21	(-36.39, 23.97)	0.6867	N/A	N/A	N/A		[46]
	Darbepoetin alfa	[redacted]	[redacted]								

a) Only subjects taking at least one dose are included in the analysis

LSM: Least square mean, OR: odds ratio, SD: Standard deviation

Appendix C. Comparative analysis of efficacy

N/A Submission is based on direct head-to-head studies.

Table 49 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

N/A as the model does not include (nor extrapolates) efficacy measures. The following heading in this appendix are not applicable.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

Appendix E. Serious adverse events

Tables below present serious adverse events (SAEs) observed in patients during the duration of both clinical trials of vadadustat (INCIDENT [AKB-6548-CI-0016] and PREVALENT [AKB-6548-CI-0017]). SAEs presented in this section include any TEAEs resulting in death as well as any treatment emergent SAEs.

Table 50 Treatment-emergent AEs resulting in death in either treatment group (Safety Population) INNO$_2$VATE INCIDENT DD-CKD

	Vadadustat N=179		Darbepoetin Alfa N=186		Total N=365	
System Organ Class		PY = 241.3		PY = 258.0		PY = 499.3
Preferred Term	n (%)	E (E·100/PY)	n (%)	E (E·100/PY)	n (%)	E (E·100/PY)
Any TEAEs resulting in death	15 (8.4)	15 (6.2)	18 (9.7)	18 (7.0)	33 (9.0)	33 (6.6)
Cardiac disorders	6 (3.4)	6 (2.5)	6 (3.2)	6 (2.3)	12 (3.3)	12 (2.4)
Cardiac arrest	1 (0.6)	1 (0.4)	2 (1.1)	2 (0.8)	3 (0.8)	3 (0.6)
Acute myocardial infarction	1 (0.6)	1 (0.4)	1 (0.5)	1 (0.4)	2 (0.5)	2 (0.4)
Cardiac failure	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)
Cardiac failure acute	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)
Cardiac failure chronic	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)
Cardiac valve disease	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Cardio-respiratory arrest	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Cardiogenic shock	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Myocardial infarction	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Infections and infestations	3 (1.7)	3 (1.2)	4 (2.2)	4 (1.6)	7 (1.9)	7 (1.4)
Septic shock	1 (0.6)	1 (0.4)	2 (1.1)	2 (0.8)	3 (0.8)	3 (0.6)
Pneumonia	2 (1.1)	2 (0.8)	0	0	2 (0.5)	2 (0.4)
Sepsis	0	0	2 (1.1)	2 (0.8)	2 (0.5)	2 (0.4)
General disorders and administration site conditions	2 (1.1)	2 (0.8)	2 (1.1)	2 (0.8)	4 (1.1)	4 (0.8)
Death	1 (0.6)	1 (0.4)	1 (0.5)	1 (0.4)	2 (0.5)	2 (0.4)
Cardiac death	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)
Sudden cardiac death	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Vascular disorders	1 (0.6)	1 (0.4)	2 (1.1)	2 (0.8)	3 (0.8)	3 (0.6)
Arteriosclerosis	0	0	2 (1.1)	2 (0.8)	2 (0.5)	2 (0.4)
Peripheral arterial occlusive disease	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Renal and urinary disorders	0	0	2 (1.1)	2 (0.8)	2 (0.5)	2 (0.4)
End stage renal disease	0	0	2 (1.1)	2 (0.8)	2 (0.5)	2 (0.4)
Gastrointestinal disorders	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Large intestine perforation	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Injury, poisoning, and procedural complications	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Subdural haemorrhage	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Metabolism and nutrition disorders	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)
Cachexia	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Metastases to spine	1 (0.6)	1 (0.4)	0	0	1 (0.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)
Acute pulmonary oedema	0	0	1 (0.5)	1 (0.4)	1 (0.3)	1 (0.2)

E: number of events; E (E·100/PY): number of events (event rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects within specific category; PY: patient-year; TEAE: treatment-emergent adverse event
Note: A TEAE was an adverse event (AE) that begins (or a preexisting AE that worsens) on or after the first dose. TEAEs were coded using MedDRA version 22.1.

Source: Table 37 in CSR AKB-6548-CI-0016 [45]

Table 51 Treatment-emergent SAEs in >2% of subjects (by SOC or PT) in either treatment group (Safety Population) INNO$_2$VATE INCIDENT DD-CKD

	Vadadustat N=179		Darbepoetin Alfa N=186		Total N=365	
System Organ Class Preferred Term	n (%)	PY = 241.3 E (E·100/PY)	n (%)	PY = 258.0 E (E·100/PY)	n (%)	PY = 499.3 E (E·100/PY)
Any treatment-emergent SAE	89 (49.7)	270 (111.9)	105 (56.5)	284 (110.1)	194 (53.2)	554 (111.0)
Infections and infestations	41 (22.9)	74 (30.7)	46 (24.7)	73 (28.3)	87 (23.8)	147 (29.4)
Pneumonia	8 (4.5)	15 (6.2)	7 (3.8)	8 (3.1)	15 (4.1)	23 (4.6)
Sepsis	3 (1.7)	3 (1.2)	6 (3.2)	6 (2.3)	9 (2.5)	9 (1.8)
Osteomyelitis	4 (2.2)	4 (1.7)	4 (2.2)	4 (1.6)	8 (2.2)	8 (1.6)
Cellulitis	4 (2.2)	5 (2.1)	2 (1.1)	3 (1.2)	6 (1.6)	8 (1.6)
Staphylococcal sepsis	4 (2.2)	5 (2.1)	2 (1.1)	2 (0.8)	6 (1.6)	7 (1.4)
Cardiac disorders	23 (12.8)	34 (14.1)	25 (13.4)	44 (17.1)	48 (13.2)	78 (15.6)
Coronary artery disease	4 (2.2)	5 (2.1)	4 (2.2)	4 (1.6)	8 (2.2)	9 (1.8)
Acute myocardial infarction	3 (1.7)	4 (1.7)	4 (2.2)	4 (1.6)	7 (1.9)	8 (1.6)
Atrial fibrillation	3 (1.7)	3 (1.2)	4 (2.2)	5 (1.9)	7 (1.9)	8 (1.6)
Cardiac failure congestive	3 (1.7)	4 (1.7)	4 (2.2)	6 (2.3)	7 (1.9)	10 (2.0)
Injury, poisoning, and procedural complications	18 (10.1)	24 (9.9)	18 (9.7)	20 (7.8)	36 (9.9)	44 (8.8)
Arteriovenous fistula thrombosis	3 (1.7)	3 (1.2)	6 (3.2)	6 (2.3)	9 (2.5)	9 (1.8)
Vascular disorders	16 (8.9)	28 (11.6)	18 (9.7)	19 (7.4)	34 (9.3)	47 (9.4)
Hypertensive urgency	7 (3.9)	12 (5.0)	3 (1.6)	3 (1.2)	10 (2.7)	15 (3.0)
Gastrointestinal disorders	11 (6.1)	12 (5.0)	22 (11.8)	40 (15.5)	33 (9.0)	52 (10.4)
Pancreatitis acute	0	0	4 (2.2)	4 (1.6)	4 (1.1)	4 (0.8)
Metabolism and nutrition disorders	14 (7.8)	36 (14.9)	11 (5.9)	17 (6.6)	25 (6.8)	53 (10.6)
Fluid overload	10 (5.6)	16 (6.6)	2 (1.1)	5 (1.9)	12 (3.3)	21 (4.2)
Hyperkalaemia	5 (2.8)	8 (3.3)	4 (2.2)	4 (1.6)	9 (2.5)	12 (2.4)
Respiratory, thoracic, and mediastinal disorders	15 (8.4)	18 (7.5)	10 (5.4)	14 (5.4)	25 (6.8)	32 (6.4)
Acute respiratory failure	5 (2.8)	5 (2.1)	4 (2.2)	4 (1.6)	9 (2.5)	9 (1.8)
Pulmonary oedema	4 (2.2)	4 (1.7)	2 (1.1)	2 (0.8)	6 (1.6)	6 (1.2)
Nervous System Disorders	8 (4.5)	12 (5.0)	9 (4.8)	9 (3.5)	17 (4.7)	21 (4.2)
General disorders and administration site conditions	8 (4.5)	9 (3.7)	7 (3.8)	8 (3.1)	15 (4.1)	17 (3.4)
Investigations	5 (2.8)	6 (2.5)	5 (2.7)	5 (1.9)	10 (2.7)	11 (2.2)
Blood and lymphatic system disorders	3 (1.7)	3 (1.2)	5 (2.7)	7 (2.7)	8 (2.2)	10 (2.0)
Hepatobiliary disorder	2 (1.1)	2 (0.8)	4 (2.2)	7 (2.7)	6 (1.6)	9 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.1)	2 (0.8)	4 (2.2)	4 (1.6)	6 (1.6)	6 (1.2)
Pychiatric disorders	0	0	4 (2.2)	4 (1.6)	4 (1.1)	4 (0.8)

E: number of events; E (E·100/PY): number of events (event rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects within specific category; PT: preferred term; PY: patient-year; SAE: serious adverse event; SOC: System Organ Class; TEAE: treatment-emergent adverse event

Note: A TEAE was an adverse events (AE) that begins (or a preexisting AE that worsens) on or after the first dose. TEAEs were coded using MedDRA version 22.1.

Source: Table 38 in AKB-6548-CI-0016 [45]

Table 52 Treatment-emergent AEs resulting in death reported by >1% of subjects (by SOC or PT) in either treatment group (Safety Population) INNO$_2$VATE PREVALENT DD-CKD

	Vadadustat N=1768		Darbepoetin Alfa N=1769		Total N=3537	
System Organ Class Preferred Term	n (%)	PY = 2980.7 E (E·100/PY)	n (%)	PY = 2987.7 E (E·100/PY)	n (%)	PY = 5968.5 E (E·100/PY)
Any TEAEs	266 (15.0)	266 (8.9)	276 (15.6)	277 (9.3)	542 (15.3)	543 (9.1)
Cardiac disorders	103 (5.8)	103 (3.5)	105 (5.9)	105 (3.5)	208 (5.9)	208 (3.5)
Cardiac arrest	35 (2.0)	35 (1.2)	37 (2.1)	37 (1.2)	72 (2.0)	72 (1.2)
Cardio-respiratory arrest	22 (1.2)	22 (0.7)	23 (1.3)	23 (0.8)	45 (1.3)	45 (0.8)
Infections and infestations	47 (2.7)	47 (1.6)	57 (3.2)	57 (1.9)	104 (2.9)	104 (1.7)
Septic shock	23 (1.3)	23 (0.8)	21 (1.2)	21 (0.7)	44 (1.2)	44 (0.7)
General disorders and administration site conditions	34 (1.9)	34 (1.1)	30 (1.7)	30 (1.0)	64 (1.8)	64 (1.1)
Death	24 (1.4)	24 (0.8)	14 (0.8)	14 (0.5)	38 (1.1)	38 (0.6)
Respiratory, thoracic and mediastinal disorders	13 (0.7)	13 (0.4)	19 (1.1)	19 (0.6)	32 (0.9)	32 (0.5)
Renal and urinary disorders	19 (1.1)	19 (0.6)	10 (0.6)	10 (0.3)	29 (0.8)	29 (0.5)

E: number of events; E (E·100/PY): number of events (event rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects within specific category; PT: preferred term; PY: patient-year; SOC: System Organ Class; TEAEs: treatment-emergent adverse events

Note: A TEAE is an adverse event (AE) that begins (or a pre-existing AE that worsens) on or after the first dose. TEAEs were coded using MedDRA version 22.1.

Source: Table 38 in CSR AKB-6548-CI-0017 [46]

Table 53 Treatment-emergent SAEs in reported in >2% of subjects (by SOC or PT) in either treatment group (Safety Population) INNO$_2$VATE PREVALENT DD-CKD

	Vadadustat N=1768		Darbepoetin Alfa N=1769		Total N=3537	
System Organ Class Preferred Term	n (%)[a]	PY = 2980.7 E (E·100/PY)	n (%)a	PY = 2987.7 E (E·100/PY)	n (%)a	PY = 5968.5 E (E·100/PY)
Any treatment-emergent SAE	973 (55.0)	3448 (115.7)	1032 (58.3)	3707 (124.1)	2005 (56.7)	7155 (119.9)
Infections and infestations	491 (27.8)	835 (28.0)	499 (28.2)	904 (30.3)	990 (28.0)	1739 (29.1)
Pneumonia	140 (7.9)	180 (6.0)	119 (6.7)	142 (4.8)	259 (7.3)	322 (5.4)
Sepsis	76 (4.3)	83 (2.8)	88 (5.0)	96 (3.2)	164 (4.6)	179 (3.0)
Septic shock	44 (2.5)	46 (1.5)	45 (2.5)	47 (1.6)	89 (2.5)	93 (1.6)
Cellulitis	43 (2.4)	47 (1.6)	38 (2.1)	41 (1.4)	81 (2.3)	88 (1.5)
Osteomyelitis	31 (1.8)	35 (1.2)	39 (2.2)	47 (1.6)	70 (2.0)	82 (1.4)
Cardiac disorders	296 (16.7)	512 (17.2)	353 (20.0)	578 (19.3)	649 (18.3)	1090 (18.3)
Acute myocardial infarction	81 (4.6)	97 (3.3)	78 (4.4)	89 (3.0)	159 (4.5)	186 (3.1)
Cardiac arrest	49 (2.8)	52 (1.7)	60 (3.4)	61 (2.0)	109 (3.1)	113 (1.9)
Cardiac failure congestive	45 (2.5)	54 (1.8)	50 (2.8)	57 (1.9)	95 (2.7)	111 (1.9)
Atrial fibrillation	44 (2.5)	49 (1.6)	37 (2.1)	43 (1.4)	81 (2.3)	92 (1.5)
Injury, poisoning and procedural complications	232 (13.1)	319 (10.7)	240 (13.6)	354 (11.8)	472 (13.3)	673 (11.3)
Arteriovenous fistula thrombosis	56 (3.2)	66 (2.2)	38 (2.1)	46 (1.5)	94 (2.7)	112 (1.9)
Metabolism and nutrition disorders	195 (11.0)	272 (9.1)	208 (11.8)	284 (9.5)	403 (11.4)	556 (9.3)
Fluid overload	98 (5.5)	138 (4.6)	98 (5.5)	132 (4.4)	196 (5.5)	270 (4.5)
Hyperkalaemia	55 (3.1)	60 (2.0)	76 (4.3)	89 (3.0)	131 (3.7)	149 (2.5)
Respiratory, thoracic and mediastinal disorders	179 (10.1)	263 (8.8)	191 (10.8)	281 (9.4)	370 (10.5)	544 (9.1)
Acute respiratory failure	44 (2.5)	49 (1.6)	50 (2.8)	55 (1.8)	94 (2.7)	104 (1.7)
Respiratory failure	27 (1.5)	32 (1.1)	42 (2.4)	42 (1.4)	69 (2.0)	74 (1.2)
Gastrointestinal disorders	187 (10.6)	283 (9.5)	181 (10.2)	269 (9.0)	368 (10.4)	552 (9.2)
Vascular disorders	178 (10.1)	234 (7.9)	178 (10.1)	250 (8.4)	356 (10.1)	484 (8.1)
Nervous system disorders	140 (7.9)	186 (6.2)	157 (8.9)	216 (7.2)	297 (8.4)	402 (6.7)
General disorders and administration site conditions	119 (6.7)	136 (4.6)	103 (5.8)	111 (3.7)	222 (6.3)	247 (4.1)
Blood and lymphatic system disorders	70 (4.0)	80 (2.7)	71 (4.0)	87 (2.9)	141 (4.0)	167 (2.8)
Anaemia	35 (2.0)	38 (1.3)	37 (2.1)	40 (1.3)	72 (2.0)	78 (1.3)
Musculoskeletal and connective tissue disorders	47 (2.7)	54 (1.8)	54 (3.1)	58 (1.9)	101 (2.9)	112 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38 (2.1)	38 (1.3)	58 (3.3)	64 (2.1)	96 (2.7)	102 (1.7)
Renal and urinary disorders	48 (2.7)	51 (1.7)	30 (1.7)	30 (1.0)	78 (2.2)	81 (1.4)
Investigations	40 (2.3)	44 (1.5)	27 (1.5)	33 (1.1)	67 (1.9)	77 (1.3)
Hepatobiliary disorders	30 (1.7)	36 (1.2)	35 (2.0)	41 (1.4)	65 (1.8)	77 (1.3)
Skin and subcutaneous tissue disorders	20 (1.1)	21 (0.7)	35 (2.0)	40 (1.3)	55 (1.6)	61 (1.0)

E: number of events; E (E·100/PY): number of events (event rate per 100 patient-years); MedDRA: Medical Dictionary for Regulatory Activities; N: number of subjects; n: number of subjects within specific category; PT: preferred term; PY: patient-year; SAE: serious adverse events; SOC: System Organ Class; TEAE: treatment-emergent adverse event

Note: A TEAE is an adverse event (AE) that begins (or a pre-existing AE that worsens) on or after the first dose. TEAEs were coded using MedDRA version 22.1.

Source: Table 39 in CSR AKB-6548-CI-0017 [46]

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

N/A

Table 54. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
N/A				
HSUV				
N/A				
Costs				
N/A				

Appendix H. Literature searches for the clinical assessment

N/A

Appendix I. Literature searches for health-related quality of life

N/A

Appendix J. Literature searches for input to the health economic model

N/A

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