Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from MEDICE:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Kidney Research UK
   b. UK Kidney Association

4. **Expert personal perspectives** from:
   a. Sunil Bhandari– clinical expert, nominated by MEDICE
   b. Karen Jenkins – clinical expert nominated by MEDICE
   c. Faizan Awan – patient expert, nominated by Kidney Research UK
   d. [redacted] – patient expert, nominated by Kidney Care UK

5. **External Assessment Report** prepared by PenTAG

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Document B

Company evidence submission

April 2024

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ID3821_Vadadustat_Document B.docx	2.0	Yes	5th June 2024

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B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission is aligned with the granted marketing authorisation and the final National Institute for Health and Care Excellence (NICE) scope, as outlined in Table 1.

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Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis	Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis	Population is aligned with the NICE scope
Intervention	Vadadustat	Vadadustat	N/A
Comparator(s)	Erythropoiesis stimulating agents (ESAs)	Erythropoiesis stimulating agents (ESAs)	N/A
Outcomes	The outcome measures to be considered include: • Haemoglobin (Hb) response • Maintenance of haemoglobin levels • Use of additional therapy (including blood transfusion and intravenous iron) • Hospitalisation • Mortality • Adverse effects of treatment including major adverse cardiovascular events • Health-related quality of life (HRQoL)	The outcome measures include: • Haemoglobin (Hb) response • Maintenance of haemoglobin levels • Use of additional therapy (including blood transfusion and intravenous iron) • Hospitalisation • Mortality • Adverse effects of treatment including major adverse cardiovascular events	The clinical trial programme of vadadustat did not collect health-related quality of life (HRQoL) data. However, published literature has been used to support the input of EQ-5D data into the economic model. MEDICE assumes that the HRQoL associated with the use of vadadustat is at least the same as observed for ESAs, with potential additional benefits expected for vadadustat due to oral administration route.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account	As per NICE scope	N/A
Subgroups to be considered	If the evidence allows subgroups according to previous exposure to erythropoiesis stimulating agents will be considered	The following subgroups are presented: • Hb stratification level at baseline • Geographical region • New York Heart Association (NYHA) Congestive Heart	The pivotal trial programme for vadadustat was designed as two separate non-inferiority open-label randomised controlled trials (RCTs) to support the broader target

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		Failure (CHF) stratification level • Target Hb level • Demographics and medical history (age, sex, race, presence of diabetes mellitus and hypertension) • Baseline laboratory measurements (C-reactive protein, baseline TSAT and baseline ferritin)	population approved in its label for dialysis-dependent patients requiring correction and maintenance of Hb levels (limited exposure to ESAs) as well as maintenance of Hb levels (already receiving ESAs). Based on data available from the pivotal trials, no clinically meaningful differences between ESA and vadadustat are anticipated and MEDICE do not expect the available evidence to substantiate subgroup analyses
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	MEDICE believe that access to an oral option could reduce inequalities in access to care for dialysis-dependent (DD) CKD patients given that: • This disease is multi-comorbid in nature and its severity may vary among patients, thereby limiting their ability to access optimal anaemia care required for ESA administration. Although home haemodialysis (in possible cases) offers many advantages to patients in terms of convenience, self-administration of an injectable ESA may pose as an additional challenge for many patients. • Patients opting for peritoneal dialysis can be anxious and have a great deal of information and equipment to manage. An oral option would be preferable to many patients. Patient choice, patient empowerment and treatment delivery are crucial for equity and equality. • NHS is currently experiencing a severe shortage of medical staff (1, 2), including qualified nurses required to administer ESAs. • Vadadustat may also be an important treatment option for patients resistant to ESAs. The new UKKA Guidelines 2024[1] recommend starting a HIF-PHI in patients with inadequate response to high, escalating doses of ESAs (3). • Despite NICE recommending that all patients who are suitable for home therapies are offered the choice (4), less than 10% of the UK's Kidney Replacement Therapy patient population are on home therapies (5), and there is a lack of equity in which patients are offered them (6).	MEDICE believes NHS patient access to vadadustat is of reasonable urgency as it will offer benefits to both patients and the NHS that are tangible in nature in terms of convenience and cost-savings via averted resource use

Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin stimulating agent; Hb, haemoglobin; NA, not applicable; NHS, National Health Services; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; RCT, randomised controlled trial; TSAT, transferrin saturation; UK, United Kingdom

[1] The information taken from the UKKA guidelines 2024 is from a proposed update which is yet to be finalised and published.

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B.1.2 Description of the technology being evaluated

A description of the technology being evaluated is presented in Table 2. The current summary of product characteristics (SmPC) for vadadustat is available in Appendix C.

Table 2. Technology being evaluated

<table>
<tr><td>UK approved name and brand name</td><td>Vadadustat (Vafseo®)</td></tr>
<tr><td>Mechanism of action</td><td>Vadadustat is a hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) inhibitor. By inhibiting HIF-PH, vadadustat stimulates endogenous erythropoietin (EPO) production, increasing iron mobilisation and red blood cell production, resulting in a gradual rise in Hb (7-9).</td></tr>
<tr><td>Marketing authorisation/CE mark status</td><td>An application for UK MHRA marketing authorisation in adults with anaemia in CKD was made in February 2022. MHRA marketing authorisation was received on 19 May 2023. The MHRA granted the transfer of the marketing authorisation from Akebia to MEDICE GmbH on 15 March 2024.
An application for EMA marketing authorisation for the same indication was made in October 2021. The Committee for Medicinal Products for Human Use (CHMP) positive opinion was received on 23 February 2023. EU regulatory approval was received 24 April 2023.</td></tr>
<tr><td>Indications and any restriction(s) as described in the SmPC</td><td>Vadadustat is indicated for the treatment of symptomatic anaemia associated with CKD in adults on chronic maintenance dialysis (7-9).</td></tr>
<tr><td>Method of administration and dosage</td><td>Vadadustat will be available as 150 mg, 300 mg and 450 mg film-coated tablets for oral administration (7-9).
The recommended starting dose is 300 mg once daily. Dose increases of 150 mg are permitted once every four weeks up to a maximum of 600 mg; dose decreases of 150 mg can occur more frequently (7-9).</td></tr>
<tr><td>Additional tests or investigations</td><td>None</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The list price of a pack of 28 tablets of 300 mg vadadustat is £297.19. This equates to a cost of £10.61 per tablet per day for each patient.
<table>
<tr><th>Product</th><th>Quantity</th><th>NHS list price</th><th>Cost per unit</th></tr>
<tr><td rowspan="2">Vafseo® 150 mg</td><td>28 tablets</td><td>£148.59</td><td rowspan="2">£5.31</td></tr>
<tr><td>98 tablets</td><td>£520.08</td></tr>
<tr><td rowspan="2">Vafseo® 300 mg</td><td>28 tablets</td><td>£297.19</td><td rowspan="2">£10.61</td></tr>
<tr><td>98 tablets</td><td>£1,040.16</td></tr>
<tr><td rowspan="2">Vafseo® 450 mg</td><td>28 tablets</td><td>£445.78</td><td rowspan="2">£15.92</td></tr>
<tr><td>98 tablets</td><td>£1,560.23</td></tr>
</table></td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>MEDICE do not consider vadadustat a candidate for managed access because the evidence available to support the clinical and economic benefits is sufficiently robust for decision making. MEDICE are also not aware of any additional clinical data that would be available to inform a management access reassessment. Therefore, MEDICE do not expect data collection in NHS practice would be required to reduce decision making uncertainty.</td></tr>
</table>

Abbreviations: CKD, chronic kidney disease; CHMP, E Committee for Medicinal Products for Human Use; MA, European Medicines Agency; EPO, erythropoietin; Hb, haemoglobin; HIF-PH, hypoxia-inducible factor prolyl-hydroxylase; MHRA, Medicines and Healthcare Products Regulatory Agency; SmPC, summary of product characteristics; UK, United Kingdom

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B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Overview of anaemia in CKD

CKD is characterised by a progressive and irreversible loss of kidney function. Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as abnormalities of kidney structure or function, present for more than three months, with implications for health. CKD is classified based on cause, glomerular filtration rate (GFR) category (G1-G5), and albuminuria category (Figure 1). Patients with stage 5 CKD (the most severe) are classified as having kidney failure or end stage renal disease (ESRD) (10, 11).

Figure 1. Prognosis of CKD by GFR and Albuminuria Category (KDIGO 2013)

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate
Source: KDIGO, 2013 (10)

Risk factors for CKD include diabetes, hypertension, smoking, obesity, ethnicity, age, family history, socioeconomic status and long-term use of nephrotoxic medications (12, 13).

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CKD can be described as either non-dialysis-dependent (NDD) or dialysis-dependent (DD). In general, patients with Stage 1 to 4 CKD have NDD-CKD, whereas those with Stage 5 disease (ESRD) typically have DD-CKD and require renal replacement therapy (RRT) to perform the function of the kidney and to sustain life. The two main treatment options for stage 5 CKD/ESRD are dialysis and transplantation (14). Dialysis filters and purifies the blood. There are two main types of dialysis: haemodialysis (HD) and peritoneal dialysis (PD). HD directly filters the blood using a semi-permeable membrane in an external dialysis machine, whereas PD uses fluid exchange in the peritoneal cavity (often termed continuous ambulatory PD). HD predominantly takes place in hospital and dialysis clinics, with most patients requiring dialysis three times a week for about four hours at a time (14). PD uses the peritoneal membrane in a patient's abdomen as the filter. PD can be done at home, with fluid being exchanged several times a day or overnight (15).

Anaemia, the most common complication of CKD, is a condition that is characterised by a reduction in the quality and quantity of red blood cells (RBCs), and haemoglobin (Hb), such that the oxygen-carrying capacity in the blood is insufficient to meet physiologic demands (10, 16, 17). Anaemia associated with CKD is a serious and debilitating condition that often leads to cardiovascular (CV) comorbidities, reduced QoL, and higher mortality regardless of a patient's dependence on dialysis (18).

Diagnosis is based on blood tests, with European guidelines recommending a confirmed diagnosis of anaemia in CKD patients when Hb levels are <13.5 g/dL in adult males and <12.0 g/dL in adult females (19). NICE and the UK Kidney Association (UKKA) recommend investigating and managing anaemia in CKD patients with Hb levels <11 g/dL (16, 17).

The main cause of anaemia 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 (20-22). 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 (21). In CKD, the feedback loop is affected due to damage to the renal tissue, and the developing anaemia is not adequately compensated by a sufficient increase in the EPO production (22).

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Another important cause of anaemia in CKD is iron deficiency (meaning that not enough iron is available for RBC production) (22-25). Absolute iron deficiency is defined by severely reduced or absent iron stores, while functional iron deficiency is defined by adequate iron stores but insufficient iron availability for incorporation into erythroid precursors(26). Iron deficiency can result from blood loss caused by platelet dysfunction, low-grade gastrointestinal (GI) bleeding, frequent blood sampling or malabsorption, and elevated levels of hepcidin (23, 27, 28). In late-stage CKD patients, HD is the major cause of blood loss, as significant amounts of blood remain in the equipment after each dialysis (22, 23, 27). DD-CKD patients also lose blood through anticoagulation and post-dialysis bleeding at vascular access sites (29). Other causes of anaemia in CKD include resistance to EPO and shortened RBC life span (22-25, 29).

B.1.3.1.2 Epidemiology

CKD (all stages) is estimated to affect 11% to 13% of the population globally (30). Publications reporting CKD prevalence estimated the mean prevalence of CKD to be 18.4% in the general population (30). The prevalence of CKD is higher in developed regions than in regions where economies are growing (30). Rising rates of diabetes, hypertension and obesity are all contributing to an increase in the prevalence of CKD (31). It is estimated that as of 2023, 3.25 million people are living with CKD stages 3-5 in the UK (32). The prevalence of CKD stages 3-5 is expected to increase to 3.85 million over the next 10 years. This increase is primarily driven by an ageing population. The ageing population also captures a majority of CKD risk factors that include diabetes and hypertension (32).

In 2020, there were 29,354 adults receiving dialysis for ESRD in the UK, estimated to increase to 33,845 by 2033. As of 2020, in-centre dialysis was the most common form of dialysis delivered in the UK (24,155 adults), followed by PD (3,822 adults) and HD (1,377 adults) (32).

Anaemia is a common consequence of CKD. About half of CKD patients may experience anaemia, and the prevalence of renal anaemia increases to nearly 90% in DD patients (33-35). In England, the prevalence of anaemia is increased in the later CKD stages (36).

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B.1.3.1.3 Clinical burden

The clinical presentation of anaemia in CKD does not differ from anaemia due to other causes. Common symptoms include shortness of breath, fatigue, weakness, headaches, and dizziness (37). Common signs of anaemia are pale skin, respiratory distress, tachycardia, chest pain, and heart failure (HF). The pathophysiological response to anaemia is increased cardiac output, the development of left ventricular hypertrophy, angina, and congestive HF, and the progression of CKD. The pathophysiological response is one of the factors that contributes to the high morbidity and mortality in patients with chronic renal failure and their reduced survival (22).

Anaemia also has an impact on mental health and QoL, including depression, anxiety, impaired activity levels, loss of libido, and decline in cognitive function (38-42).

Anaemia in CKD is associated with an increased CV risk. Large observational studies in Germany and the United States (US) have shown that anaemia is associated with a higher risk of HF among patients with CKD (43, 44). A multinational prospective cohort study of 16,560 DD-CKD patients with anaemia found high rates of major adverse CV events (MACE) (MACE rates per 100 patient-years: North America, 17.2; 95% confidence interval [CI] 16.1–18.4; Europe, 15.6; 95% CI 14.9–16.3; Japan, 6.8; 95% CI 6.2–7.4) and MACE plus HF and thromboembolic events (TEE; MACE+) (MACE+ rates per 100 patient-years: North America, 19.4; 95% CI 18.2–20.7; Europe, 17.4; 95% CI 16.6–18.1; Japan, 7.5; 95% CI 6.9–8.1) (45). The risk of MACE increases with the severity of anaemia (46).

Anaemia in CKD is also associated with an increased risk of death. In an analysis of anaemia management and outcomes data from 4,591 HD patients in the EU-5 (France, Germany, Italy, Spain, and the UK), higher Hb concentrations were associated with a decreased relative risk (RR) for mortality (RR=0.95 for every 1 g/dL higher Hb, p=0.03) and hospitalisation (RR=0.96, p=0.02). Patients with Hb <10 g/dL were 29% more likely to be hospitalised than those with Hb levels between 11 and 12 g/dL (p<0.001) (47). The risk of acute hospitalisation and all-cause death increases with the severity of anaemia (46).

A survey of 5,276 adult patients with anaemia in CKD revealed a number of common comorbidities, including hypertension (reported by 78% of patients), type 2 diabetes (reported by 40%) and dyslipidaemia (reported by 29%) (48).

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B.1.3.1.4 Humanistic burden

CKD itself places a substantial burden on patients, particularly those with ESRD; this burden is exacerbated by the presence of anaemia (48). The impact of anaemia in CKD patients is multifaceted, affecting various aspects of health and well-being.

Anaemia in CKD can have a substantial impact on patients' HRQoL. This is exacerbated by reduced physical capacity and energy levels, which affect patients' ability to engage in activities of daily living, social interactions, and recreational pursuits (38). The impact on patients' HRQoL may be similar to other chronic conditions, such as diabetes, epilepsy and certain forms of cancer (38).

A review of the literature on HRQoL in CKD patients with anaemia (including review papers and pivotal trials of ESAs) concluded that anaemia primarily affects energy/vitality and physical function, as measured by the SF-36, the FACT-Fatigue questionnaire, and the KDQ questionnaire (49).

Data from a large, international cross-sectional survey of physicians and their CKD patients showed that anaemia affects patients' ability to work (48). In total, 1,923 patients with DD-CKD were included in the analysis. As measured by the Work Productivity and Activity Impairment questionnaire, those with anaemia had greater productivity losses (absenteeism and presenteeism) and greater total activity impairment than those with normal Hb levels.

Caregivers of patients with CKD experience a substantial burden. Patients undergoing dialysis for ESRD are often elderly and may have poor physical and/or cognitive function (50). Caregivers may therefore have a number of responsibilities, including taking patients to appointments, administering treatment, supporting dietary management, helping with everyday tasks and providing psychological support (50, 51). Their role is becoming increasingly important, given the increased complexity in communicative and therapeutic options including expansion of telemedicine during the COVID-19 pandemic, and given the goal to increase life expectancy in CKD patients (51).

Caregivers of HD patients have reported limitations to their personal and social activities owing to the frequency and duration of treatment (50). Their working life gets affected, as

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they need to rearrange their working hours or take time off to accompany patients to their appointments. Some caregivers also need to give up work or take early retirement (50).

Caregivers also report feeling tired, angry, depressed, helpless and guilty. They may neglect their own health owing to the demanding nature of caregiving (50).

A systematic review of studies reporting on caregiver burden in ESRD found that the burden is increased in the presence of the following factors: female sex of carer; carer anxiety, depression, and ill-health; caring for patients on HD and with poorer health; spending longer time giving care; lower socio-economic status; and living a significant distance from the dialysis centre (52).

B.1.3.1.5 Economic burden

The economic burden of anaemia in CKD is substantial and includes various direct and indirect costs. In DD-CKD patients, economic burden is increased by serious complications associated with increased CV morbidity, and other sources of increased healthcare resource utilisation (HCRU) and medical expenditures (53).

The current standard of care for anaemia in CKD includes oral or IV iron supplementation, ESAs, and RBC transfusion. However, each of these therapies is associated with its own set of patient concerns. High doses of ESAs, in particular, have been associated with increased rates of hospitalisation, CV events, and mortality (54).

Anaemia in CKD, especially in dialysis patients, is correlated with increased mortality and morbidity, impacting various aspects of health. Complications such as CV events contribute to hospitalisations, escalating the economic burden related to inpatient care, diagnostic tests, and procedures. Observational studies consistently associate anaemia with heightened risks of CV events and all-cause mortality (46, 55, 56). Hospitalisation costs, including those related to inpatient care, diagnostic tests, and procedures, contribute to the economic burden.

Management of anaemia in CKD involves various healthcare resources, including nephrologists, cardiologists, anaemia nurses, specialist renal nurses, general practitioners, dieticians, home care, blood tests, ESAs, blood transfusions, and facilities for diagnostic and intensive care (57). Other resources required include cold storage and cold chain

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delivery for ESAs, consumables, sharps bins and the necessary specialist disposal of sharps and bins.

The utilisation of these healthcare resources is tailored to the individual needs and circumstances of each patient with anaemia in CKD. A multidisciplinary approach involving collaboration among various healthcare professionals is often employed to optimise patient outcomes. Studies showed that, in spite of the related acquisition costs of ESAs, non-treatment of CKD-related anaemia entailed higher medical costs and HRU that outweighed ESA costs, highlighting the importance of treating this condition given its economic burden (53, 58, 59). For example, using data from 34 Spanish HD centres, Moreno et al. (2000) found that increasing epoetin dosage by 51% to normalise Hb levels at a mean of 12.5 g/dL led to a 58% reduction in hospitalisations and a 69% reduction in length of hospital stays (60).

Patients with moderate CKD and severe anaemia (Hb ≤9 g/dL) generally require more frequent hospitalisation compared with those without severe anaemia (61). Because patients with CKD and anaemia use more overall healthcare resources, their care incurs more costs than that of patients without anaemia (62).

Hepcidin secretion resulting from CKD-related inflammation can interfere with iron absorption and mobilisation, resulting in functional iron deficiency and ultimately leading to patients being resistant to ESAs. Such resistance to ESAs caused by inflammation (comorbidities) may in turn translate into higher costs and HRU as these patients have higher mortality and CV hospitalisation rates (63), and need substantially higher doses and more frequent administration of ESAs, or even transfusions, to manage their anaemia. Between 4.5% and 20% of patients on dialysis are resistant to ESAs (64). The need to control the delicate balance of iron regulation to obtain an optimal erythropoietic response with ESAs explains the importance of iron as a concomitant treatment (65).

Vadadustat offers the potential for a reduction in resource use specific to anaemia management (e.g., ESA rescue, blood transfusions, iron supplementation) compared with ESAs. The use of vadadustat could enable cost savings through reduced administration costs with oral administration, reduced costs of medical supplies (i.e., syringes, which are not required with oral administration), reduced logistics and storage costs (cold storage not required unlike ESAs), reduced drug wastage due to logistics and cold storage (cold

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storage not required unlike ESAs), and reduced costs associated with clinical waste disposal (e.g., sharps bins, needles).

The use of vadadustat could also enable cost savings through reduced nursing time. Vadadustat is an oral formulation which, unlike ESAs, does not require a qualified nurse to administer or support self-administration. Furthermore, vadadustat may also reduce systemic costs by helping to increase uptake of PD and/or HD, which is less resource intensive for the National Health Services (NHS) and patients than treatment in dialysis centres (6, 32). In 2019, cost estimates for in-centre HD were approximately £30,000 per patient per year, representing a huge cost burden to the NHS (66). PD and HD were significantly cheaper, with estimates of approximately £16,000 and £20,000 per patient per year for PD (ambulatory PD and automated PD, respectively), and £23,000 for HD (66). Increasing uptake of PD and/or HD could help free up resources at a time when the NHS is experiencing a severe shortage of medical staff (1, 2), including qualified nurses required to administer ESAs, and with dialysis centres reaching or at capacity in many units (67-71).

In the home dialysis setting, the use of vadadustat would also reduce the need for cold-chain storage (e.g., storage for several weeks in narrow temperature range of 2 to 8ºC, especially transport during periods of travel), which can be difficult for the patient and risks wastage/quality degradation of ESA products. For patients on PD, who are generally more mobile than those on HD, the use of vadadustat would also help make travelling easier, due to cold-chain storage not being required.

Avoiding the dependence on cold chains with high energy requirements and a lower drug wastage also contributes to the sustainability goals of the NHS to reduce the CO_2 footprint in the medium and long term (72-75).

Indirect costs associated with anaemia in CDK can also be substantial. These costs are often associated with the consequences of anaemia, including its effects on patients' ability to work and productivity. Anaemia can lead to fatigue, reduced energy levels, and decreased physical and cognitive function (76, 77). As a result, CKD patients on dialysis may experience challenges in maintaining employment or fulfilling work responsibilities. This can lead to absenteeism, reduced work hours, and decreased productivity, which in turn has an overall economic impact (48, 78).

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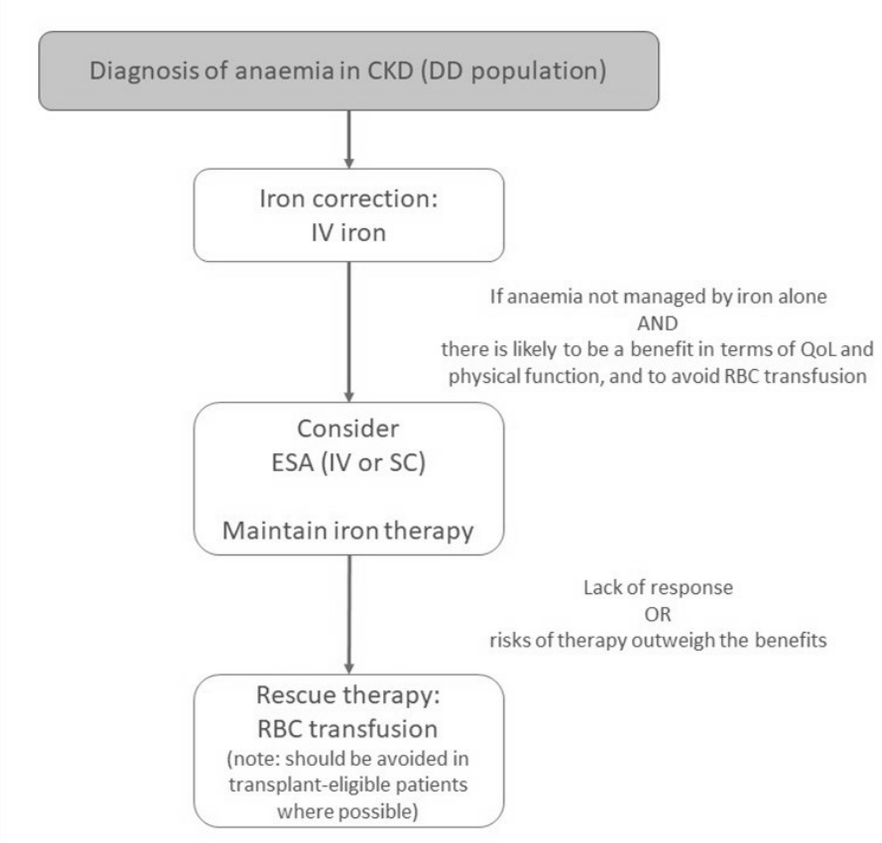
B.1.3.2 Current clinical pathway of care

Current treatment guidelines recommend a step-wise approach to treating anaemia in CKD (3, 16, 17, 79) (Figure 2).

Figure 2. Current treatment pathway for anaemia in DD-CKD



Abbreviations: CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; IV, intravenous; QoL, quality of life; RBC, red blood cell; SC, subcutaneous

As a first line, any correctable causes of anaemia, such as iron deficiency, should be addressed. Iron deficiency is generally treated with iron therapy; in patients with DD-CKD, this is usually administered via intravenous (IV) route during dialysis (10, 19).

If iron therapy alone does not correct Hb levels, guidelines recommend that ESAs should be offered to patients who are likely to benefit in terms of quality of life and physical function, and to avoid blood transfusion (16, 17). KDIGO guidelines recommend that ESAs be initiated in DD-CKD patients when Hb levels are 9-10 g/dL to avoid Hb levels falling below 9 g/dL (79). NICE and the UKKA recommend a target Hb level of 10 to 12 g/dL with ESA therapy (16, 17). The UK MHRA advises against over-correction of Hb levels (i.e. to higher than 12 g/dL), as this may increase the risk of death and serious CV events in patients with CKD (80). Most recently, the UKKA 2024 Clinical Practice Guideline (currently

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in consultation phase) suggests that treatment with HIF-PHI should be considered, after iron repletion, in people with DD-CKD and symptomatic anaemia (Hb <105 g/L) who are likely to benefit in terms of quality of life and physical function and to avoid blood transfusion; especially in people considered suitable for transplantation (3).

ESAs can be administered either IV or subcutaneous (SC) route for patients undergoing HD; patients undergoing PD can receive ESAs SC (79).

For ESAs to work effectively, iron levels must be adequate. NICE therefore recommends that all patients are offered iron therapy alongside ESAs to correct and maintain iron levels (17). For patients undergoing in-centre HD who are receiving ESAs and are iron deficient, NICE recommends a high-dose IV iron regimen. Once iron levels are corrected, maintenance iron should be offered; patients on HD will need the equivalent of 50-60 mg IV iron per week.

There is uncertainty regarding how patients with DD-CKD who do not respond to ESAs should be treated and these patients have a particularly high unmet need. Dose escalation does not ameliorate anaemia in patients who are resistant to ESAs, and the use of high doses of ESAs may contribute to the adverse clinical outcomes as shown in the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial (81, 82). Guidelines recommend that RBC transfusions are avoided where possible in patients with CKD, particularly in those eligible for kidney transplant (i.e. patients with ESRD), to avoid the risk of allosensitisation (sensitisation to foreign tissue) (16, 79). Allosensitisation can reduce the pool of eligible donors (thereby increasing the waiting time for transplantation) and is associated with increased organ rejection and graft loss (83). However, KDIGO does suggest that the benefits of RBC transfusions may outweigh the risks in patients in whom ESA therapy is not effective or in whom the risks of ESA therapy outweigh its benefits (e.g. in patients with previous or current cancer or who have had a stroke) (79). Recently, the UKKA 2024 Clinical Practice Guideline (currently in consultation phase) suggests that HIF-PHI treatment should be considered, after iron repletion, in people who are intolerant to ESA therapy (3).

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B.1.3.3 The need for alternative treatment options

The current standard of care for anaemia in CKD is the use of recombinant ESAs and/or iron supplementation. Limitations of these treatment options often lead to sub-optimal treatment (including both undertreated and untreated renal anaemia) as outlined below.

Both oral and IV iron supplementation are associated with potential complications. Furthermore, iron overload promotes endothelial dysfunction, CV disease (CVD), and immune dysfunction.

- Oral iron supplements are commonly associated with gastrointestinal (GI) adverse effects (e.g., constipation, stomach pain, nausea), which may negatively impact adherence (17, 79), and require large doses for long periods of time. Less than 10% of oral iron is absorbed, and this is further reduced in the presence of inflammation which raises levels of hepcidin, which blocks absorption of oral iron (84-86).
- Iron overload causes CVD, immune and endothelial dysfunction, which are the leading causes of death in CKD and ESRD patients on maintenance HD (87, 88).
- A prospective observational study in Japan measured serum ferritin every 3 months for 2 years in 1086 patients on maintenance HD. The risk for cerebrovascular disease and CVD (hazard ratio [HR]: 6.02; p=0.038), infection (HR: 5.22; p=0.001), and hospitalisation (HR: 2.77; p=0.015) was significantly higher in patients treated with high-dose IV iron compared to those not treated with iron (87, 88).

A treatment option is needed that can treat anaemia in DD-CKD patients while minimising the incidence of Hb fluctuations, maintaining target Hb levels and avoiding a rapid Hb increase.

- Hb excursions and the resulting Hb fluctuations due to ESAs are associated with an adverse impact on patient outcomes by disrupting homeostasis (47, 89-91).
- Kuragano *et al* found a high risk of death and/or adverse events (AEs) in patients with Hb levels outside the target range and with high-amplitude Hb fluctuations. The risk of cerebrovascular disease, CVD, infection, and hospitalisation was higher among patients outside target Hb range and who exhibited high-amplitude Hb fluctuations compared with patients who maintained target Hb range (87, 88).
- An analysis of 9,220 CKD patients who initiated ESA therapy investigated the association between “fast” and “slow” rising Hb concentrations over time and CV outcomes (composite of hospital admissions and deaths due to myocardial

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infarction [MI] and stroke). The study investigated the HR for different predefined trajectories of Hb increase. Rapid Hb rise was associated with adverse CV outcomes, with markedly lower risk for rates below a threshold trajectory of 0.125 g/dL/month (92).

The treatment of patients resistant to ESAs is a key area of unmet need in the management of anaemia in CKD. Currently, there is no standardised global definition to define resistance to ESAs.

- KDIGO defines initial resistance to ESAs as having no increase in Hb concentration after the first month of appropriate weight-based dosing, and acquired resistance to ESAs as requiring two increases in ESA doses up to 50% beyond the dose at which the patient had originally been stable (79).
- The NICE guidelines state that people with anaemia in CKD should be considered resistant to ESAs when aspirational Hb is not achieved despite treatment with 300 IU/kg/week or more of SC epoetin, 450 IU/kg/week or more of IV epoetin, 1.5 µg/kg/week of darbepoetin, or there is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range (17).
- Resistance to ESAs occurs in a small but important minority of patients with DD-CKD (93). As there is no agreed definition, the reported prevalence of resistance to ESAs varies according to the definition applied. Reported incidences of resistance to ESAs range from 2.4% to 15% of patients (64, 94-96).
- Compared to ESA responders, on average, patients with chronic resistance to ESAs had an approximately 7-fold higher monthly burden of transfusion (range of 0.19%–0.30% vs. 1.20%–2.17%, respectively). Patients with acute resistance to ESAs had a 5-fold greater transfusion burden than responders initially (0.97% vs. 0.19%) that appeared to decrease with recovery of ESA responsiveness (0.56% vs. 0.27%) in later months (96). Resistance to ESAs is also associated with increased morbidity, mortality, and healthcare resource utilisation (63, 97-100). These patients have very low levels of Hb despite high ESA doses and have extremely poor quality of life.
- There is uncertainty about the management of patients who are resistant to ESAs; it is unclear whether high-dose ESAs should be continued in people with resistance in an attempt to limit the number of blood transfusions, or whether people should stop ESA treatment and be treated with transfusions alone. Patients resistant to

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ESAs show evidence of increased morbidity and mortality compared with those who respond well to ESA therapy (17, 101).

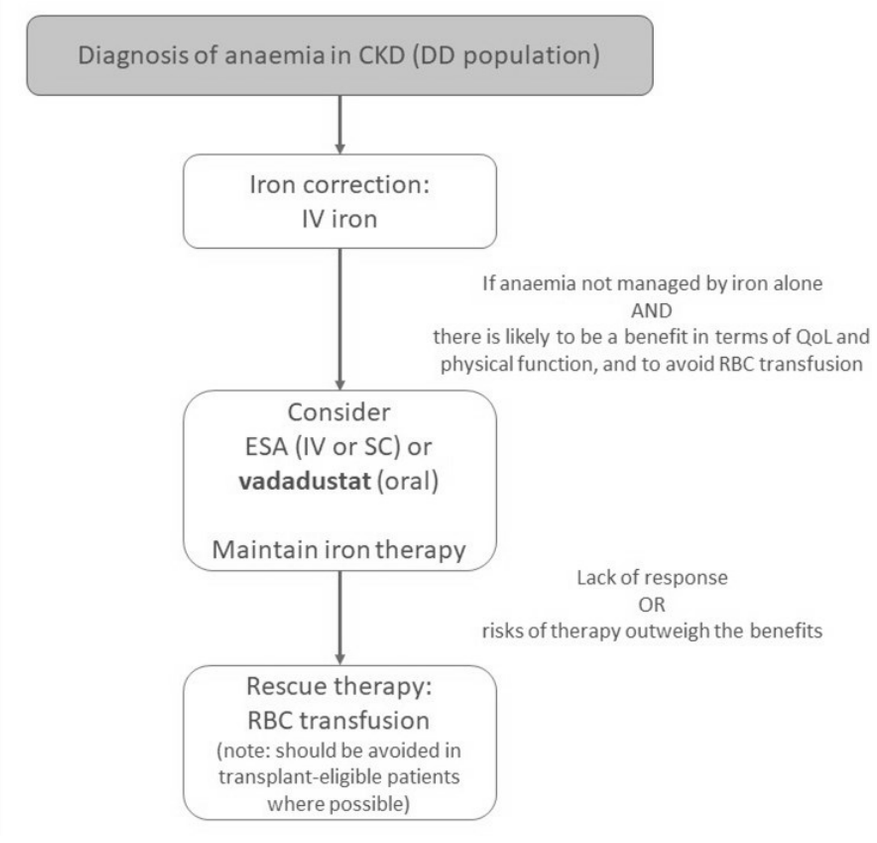
Not all patients are suitable for ESA treatment. ESAs are also contraindicated in the following patients (67, 102, 103):

- Patients who develop pure red cell aplasia (PRCA) following treatment with any ESA should not receive any other ESA. However, PRCA is very rare: average annual incidence of 1.06 (95% confidence internal [CI], 0.83-1.28) per million (104).
- Uncontrolled (or poorly controlled; epoetin beta) hypertension.

B.1.3.4 Proposed positioning of vadadustat

It is anticipated that vadadustat will be positioned as an alternative option to ESAs in PD and HD regardless of setting (Figure 3). This positioning is aligned the upcoming UKKA 2024 Clinical Practice Guideline (currently in consultation phase) which suggests that treatment with HIF-PHI should be considered, after iron repletion, in people with DD-CKD and symptomatic anaemia (Hb <105 g/L), and for those who are intolerant to ESAs (3).

Figure 3. Proposed position of vadadustat in the treatment pathway for DD-CKD



CKD, chronic kidney disease; DD, dialysis-dependent; IV, intravenous; QoL, quality of life; RBC, red blood cell; SC, subcutaneous

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B.1.4 Equality considerations

If recommended by NICE, vadadustat will be the only HIF-PHI recommended for the treatment of anaemia in DD-CKD patients. MEDICE believe that access to an oral option to treat anaemia could reduce inequalities in access to care for DD-CKD patients given the severity and multi-comorbid nature of their disease, which may limit their ability to access outpatient care required for ESA administration. As an oral formulation, which does not require a qualified nurse for administration or to support self-administration, vadadustat facilitates PD and/or home HD, and shared care HD, thereby providing choice for patients and healthcare professionals (6, 105), which has been lacking to date. Despite NICE recommending that all patients who are suitable for home HD should be offered the choice (4), only 2% of the UK's kidney replacement therapy patient population are on home HD (5), and there is a lack of equity in which patients are offered home HD (6). In addition, only 5.6% patients among all patients registered for kidney transplant wait-list in 2021 were on PD (including automated and continuous ambulatory PD) in England (106). Furthermore, a discrete choice study amongst patients in the NDD-CKD population found that 83% of patients with CKD-related anaemia preferred an oral mode of administration over existing treatments (typically SC injection) (107). Vadadustat will provide an alternate treatment option, with a new oral administration route.

Vadadustat may also be an important treatment option for individuals who are resistant to ESAs, which has an incidence of 12.5–30% for CKD patients, depending on the definition (81, 108). Current treatment for these patients is a continual increase in ESA dose, which increases their risk of AEs and is associated with higher cost (e.g., cost of higher doses of ESAs, increased cost of AE management). In principle, patients who are resistant to ESAs remain suitable for ESA therapy. However, when ESAs are required at very high doses, as in the case of a lack of haematological response, ESA treatment would be stopped, and blood transfusions typically performed; blood transfusions are associated with significant cost, and also risk of developing antibodies which impact their suitability to receive a transplant. These patients have very low levels of Hb despite high ESA doses and have extremely poor quality of life.

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B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify evidence investigating the clinical efficacy and safety of vadadustat versus the potential comparators in scope for this submission, namely ESAs, for the treatment of anaemia in adults with CKD who are DD. The methods used to identify the relevant clinical evidence are described in Appendix D.

The SLR included two pivotal phase III trials of vadadustat (INNO$_2$VATE – incident and INNO$_2$VATE – prevalent). Both these trials compared oral vadadustat once daily (OD) versus darbepoetin alfa in adult patients with anaemia in CKD and were considered relevant for this submission. These trials are also the primary source of clinical evidence for the economic model.

The SLR also identified two other phase III clinical trials of vadadustat (FO$_2$CUS [NCT04707768] and MT-6548-J03 [NCT03439137]) which were not considered relevant to this submission due to the geographies in which they were conducted (namely the US and Japan, respectively). FO$_2$CUS was a non-inferiority phase III clinical trial which evaluated the clinical efficacy and safety of vadadustat versus a long-acting ESA (methoxy polyethylene glycol-epoetin beta [Mircera®]) for the maintenance treatment of anaemia in patients undergoing HD for CKD in the US, using non-approved dosage regimens of vadadustat (600mg or 900mg three times weekly) (109). MT-6548-J03 was a phase III clinical trial which evaluated the clinical efficacy and safety of vadadustat versus darbepoetin alfa for the treatment of anaemia in patients undergoing HD for CKD in Japan (110).

Two phase II trials of vadadustat (FO2RWARD-2 [NCT03799627] and AKB-6548-CI-0018 [NCT03140722]) which compared the clinical efficacy and safety of vadadustat versus epoetin alfa were also identified from the SLR. However, these trials are not included in this submission as the phase III trials (INNO$_2$VATE studies) used for regulatory approval are considered a more robust source of evidence.

A full list of studies that were included and excluded during the SLR is provided in Appendix D.

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B.2.2. List of relevant clinical effectiveness evidence

As discussed in Section B.2.1, the SLR included INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials for investigating the efficacy and safety of vadadustat for treating anaemia in CKD (Table 3). Both these trials were designed to test whether vadadustat was non-inferior to ESAs in the treatment of anaemia in CKD.

INNO$_2$VATE – incident was a phase III, randomised, open-label, active-controlled, global, multicentre, non-inferiority clinical trial that compared vadadustat OD (n=181) to darbepoetin alfa (n=188) for the correction or maintenance treatment of anaemia after correction of Hb or conversion from current ESA in adult patients with CKD with incident dialysis (initiation of chronic maintenance PD or HD within 16 weeks prior to screening) (111).

INNO$_2$VATE – prevalent was a phase III, randomised, open-label, active-controlled, global, multicentre, non-inferiority clinical trial that compared vadadustat OD (n=1,777) to darbepoetin alfa (n=1,777) for the maintenance treatment of anaemia in patients with DD-CKD (either PD or HD) after conversion from ESA therapy (112).

These trials are described in full detail in section B.2.3.

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Table 3. Clinical effectiveness evidence

Study name (number)	INNO$_2$VATE – incident (NCT02865850)	INNO$_2$VATE – prevalent (NCT02892149)
Study design	Phase III, randomised, open-label, sponsor-blinded, active-controlled, global, multicentre, non-inferiority study	Phase III, randomised, open-label, sponsor-blinded, active-controlled, global, multicentre, non-inferiority study
Population	Patients with anaemia who have recently initiated dialysis treatment for DD-CKD	Patients with anaemia who have dialysis treatment for DD-CKD
Intervention(s)	Vadadustat	Vadadustat
Comparator(s)	Darbepoetin alfa	Darbepoetin alfa
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Reported outcomes specified in the decision problem	• Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36). • Change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52). • Receipt of any RBC transfusion, the time to first RBC transfusion (for entire study), the total number of RBC transfusion episodes received, and **the rate of RBC transfusions, calculated as the number of episodes divided by the duration of at-risk follow-up in person-years.** • **Time to the first adjudicated MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke.** • AEs, SAEs, **TEAEs**, treatment-emergent SAEs, vital signs, and laboratory results, the following was included: o Hb excursions ▪ Hb >12.0 g/dL, >13.0 g/dL, >14.0 g/dL, <9.0 g/dL, or <8.0 g/dL ▪ Hb increase >1.0 g/dL within any two-week interval or >2.0 g/dL within any four-week interval	• Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36). • Change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52). • Receipt of any RBC transfusion, the time to first RBC transfusion (for entire study), the total number of RBC transfusion episodes received, and **the rate of RBC transfusions, calculated as the number of episodes divided by the duration of at-risk follow-up in person-years.** • **Time to the first adjudicated MACE, defined as all-cause mortality, non-fatal MI, or non-fatal stroke.** • AEs, SAEs, **TEAEs**, treatment-emergent SAEs, vital signs, and laboratory results, the following was included: o Hb excursions ▪ Hb >12.0 g/dL, >13.0 g/dL, >14.0 g/dL, <9.0, or <8.0 g/dL ▪ Hb increase >1.0 g/dL within any two-week interval or >2.0 g/dL within any four-week interval

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Study name (number)	INNO$_2$VATE – incident (NCT02865850)	INNO$_2$VATE – prevalent (NCT02892149)
All other reported outcomes	• 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, having at least one Hb value in the geography-specific target range in the primary and secondary efficacy periods, having Hb values in the geography-specific target range for at least one-half of the observations in the primary and secondary efficacy periods, Hb increase of >1.0 g/dL from baseline to week 52, and time to achieve Hb increase of >1.0 g/dL from baseline Hb (censored at week 52). • 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), and the total number and maximum duration of ESA episodes. • Dose adjustments from baseline to week 52. • Changes in iron-related parameters from baseline to the primary efficacy period (weeks 24 to 36) and secondary efficacy period (weeks 40 to 52), the mean weekly dose of elemental iron administered from baseline to week 52 in patients who had received IV and/or oral iron, and the receipt of at least one administration of elemental iron (IV or oral). • Changes in serum glucose and lipid parameters between baseline and the primary efficacy period (weeks 24 to 36) and secondary efficacy period (weeks 40 to 52).	• 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, having at least one Hb value in the geography-specific target range in the primary and secondary efficacy periods, and having Hb values in the geography-specific target range for at least one-half of the observations in the primary and secondary efficacy. • 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), and the total number and maximum duration of ESA episodes. • Dose adjustments from baseline to week 52. • Changes in iron-related parameters from baseline to the primary efficacy period (weeks 24 to 36) and secondary efficacy period (weeks 40 to 52), the mean weekly dose of elemental iron administered from baseline to week 52 in patients who had received IV and/or oral iron, and the receipt of at least one administration of elemental iron (IV or oral). • Changes in serum glucose and lipid parameters between baseline and the primary efficacy period (weeks 24 to 36) and secondary efficacy period (weeks 40 to 52).

Abbreviations: AE, adverse events; CKD, chronic kidney disease; DD, dialysis dependent; ESA, erythropoietin stimulating agent; Hb, haemoglobin; IV, intravenous; MACE, major adverse cardiovascular events; MI, myocardial infarction; OD, once daily; RBC, red blood cell; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events
Source: CSR INNO$_2$VATE – incident (111); CSR INNO$_2$VATE – prevalent (112); Eckardt et al 2021 (113)

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B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

INNO$_2$VATE – incident and INNO$_2$VATE – prevalent investigated the clinical efficacy and safety of vadadustat for treating anaemia in CKD. These trials are described in detail in the following subsections below.

B.2.3.1 INNO$_2$VATE – incident

B.2.3.1.1 Trial design

INNO$_2$VATE – incident was a phase III, randomised, open-label, sponsor-blinded, active-controlled, global, multicentre, non-inferiority study of vadadustat versus darbepoetin alfa for the correction or maintenance treatment of anaemia after correction of Hb or conversion from current ESA in adult patients with incident dialysis (initiation of chronic maintenance PD or HD within 16 weeks prior to screening). The initial study design allowed the restricted use of ESA prior to randomisation. The initial restriction which disallowed ESA use in the four weeks prior to and during the initial screening period was first relaxed and subsequently removed, as finding patients with such restricted ESA use was not possible, as almost all dialysis patients started on ESAs at the initiation of dialysis (111, 113). Patients were randomised to vadadustat or darbepoetin alfa in a 1:1 ratio, stratified by:

- Geographic region (United States [US] versus Europe versus Rest of World [ROW]);
- New York Heart Association (NYHA) HF Class 0 (no HF) or I versus II or III;
- Study entry Hb (<9.5 versus ≥9.5 g/dL).

Following randomisation, there were three periods during the study:

- *Incident 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.

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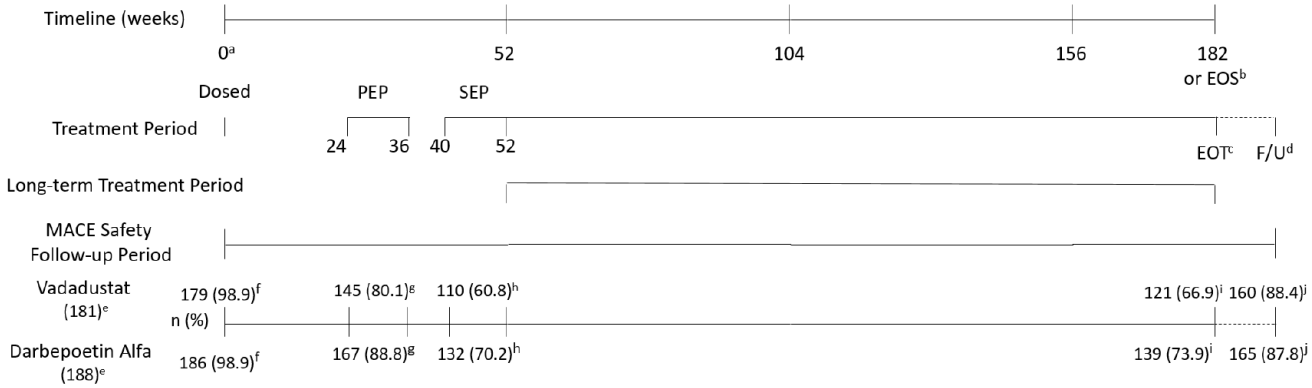
- *Follow-up period (EOT + four weeks):* post-treatment visit for safety (either in person or via telephone).

Patients who discontinued study drug were followed to the end of study (EOS) to assess MACE (111). An outline of study periods is displayed in Figure 4.

Figure 4. INNO$_2$VATE – incident trial design



Abbreviations: EOS: end of study; EOT: end of treatment; F/U: follow-up; MACE: major adverse cardiovascular events; PEP: primary efficacy period; SEP: secondary efficacy period

Note: MACE information was collected beginning after week 0 until EOS, regardless of patient treatment status.

[a.] Randomisation occurred at week 0

[b.] EOS occurred once 631 MACE events were recorded

[c.] EOT occurred once patient permanently discontinued study drug, or upon announcement of global EOS

[d.] F/U occurred four weeks after EOT

[e.] Number of patients randomised

[f.] Number of patients dosed

[g.] Number of patients who completed PEP

[h.] Number of patients who completed SEP

[i.] Number of patients on treatment at EOS

[j.] Number of patients who completed study (including MACE Safety Follow-up)

Source: CSR INNO$_2$VATE – incident (111)

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B.2.3.1.2 Eligibility criteria for study patients

The eligibility criteria for study patients are presented in Table 4.

Table 4. Inclusion/exclusion criteria for INNO$_2$VATE – incident trial

Inclusion criteria	Exclusion criteria
• ≥18 years of age. • Initiated chronic maintenance dialysis (either peritoneal or haemodialysis) for end-stage kidney disease within 16 weeks prior to screening. • Mean screening Hb between 8.0 and 11.0 g/dL (inclusive), as determined by the average of two Hb values measured by the central laboratory during screening. • Serum ferritin ≥100 ng/mL and TSAT ≥20% during screening. • Folate and vitamin B12 measurements ≥ lower limit of normal during screening. • Understood the procedures and requirements of the study and provided written informed consent and authorisation for protected health information disclosure.	• Patient presented with anaemia due to a cause other than CKD or patients with active bleeding or recent blood loss. • Patients with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, haematologic malignancy, myeloma, haemolytic anaemia, thalassaemia, or pure red cell aplasia. • RBC transfusion within eight weeks prior to randomisation. • Anticipated to recover adequate kidney function to no longer require dialysis. • AST/SGOT, ALT/SGPT, or total bilirubin >2.0 × ULN during screening. Patients with a history of Gilbert's syndrome were not excluded. • Uncontrolled hypertension (defined as confirmed predialysis SBP >190 mmHg or DBP >110 mmHg at rest) at or during screening. Note: Eligibility was based on BP at screening visit 1 and screening visit 2 only. • Severe HF during screening (NYHA Class IV). • Acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for HF, or stroke within 12 weeks prior to or during screening. • History of active malignancy within two years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ. • History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to randomisation. • History of haemosiderosis or haemochromatosis. • History of prior organ transplantation or scheduled organ transplant (patients on the kidney transplant wait-list or with a history of failed kidney transplant

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	were not excluded), or prior haematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis were not excluded). • Hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients. • Use of an investigational medication or participation in an investigational study within 30 days or five half-lives of the investigational medication (whichever was longer), prior to or during screening. • Previous participation in this study or previous participation in a study with another HIF prolyl-hydroxylase inhibitor other than vadadustat. • Females who were pregnant or breastfeeding. Women of childbearing potential who were unable or unwilling to use an acceptable method of contraception. • Non-vasectomised male patients who were unable or unwilling to use an acceptable method of contraception. • Any other reason, which in the opinion of the investigator made the patient not suitable for participation in the study. • Patients that met criteria of ESA resistance within eight weeks prior to or during screening defined as follows: o epoetin >7,700 units/dose three times per week or >23,000 units per week; o darbepoetin alfa >100 µg/week; o methoxy polyethylene glycol-epoetin beta >100 µg every other week or >200 µg every month.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESA, erythropoietin stimulating agent; HF, heart failure; HIF, hypoxia-inducible factor; MI, myocardial infarction; NYHA; New York Health Association; RBC, red blood cells; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TSAT, transferrin saturation; ULN, upper limit of normal
Source: CSR INNO$_2$VATE – incident (111); Eckardt et al 2021 (113)

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B.2.3.1.3 Settings and locations where data were collected

INNO$_2$VATE – incident was a multicentre study which enrolled patients from 83 centres in 10 countries. Of those, the United States had 43 centres. Since most centres had small sample sizes, no centre-specific analyses was planned (111).

B.2.3.1.4 Trial drugs and concomitant medications

Vadadustat was provided as film coated tablets for oral administration and darbepoetin alfa was provided in pre-filled syringes as an injectable solution for IV or SC administration. Both vadadustat and darbepoetin alfa were supplied as open-label supplies.

Any medication, prescribed and non-prescribed (including vitamins, herbals, topicals, inhaled, and intranasal), taken before the date of the first dose of study drug was considered prior medication. Any medication taken at any time from the date of the first dose of study drug through the date of the last dose of the study drug was considered concomitant medication.

Patients were instructed to take any oral iron supplements (including multivitamins containing iron), iron containing phosphate binders, or any medication containing iron at least two hours before or two hours after the dose of vadadustat (111, 113).

B.2.3.1.5 Prespecified primary and secondary outcomes

The primary and secondary outcomes of the INNO$_2$VATE – incident trial are shown in Table 5 below (111).

Table 5. Prespecified primary and secondary outcomes

Primary efficacy outcome	Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)
Secondary efficacy outcome	Change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52)
Other efficacy outcomes	
Endpoints related to haemoglobin	• Change in average Hb value between baseline and the combined primary efficacy period and secondary efficacy period (weeks 24 to 52) • Having average Hb value in the geography-specific target range in weeks 24 to 36 (yes/no variable)

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	• Having average Hb value in the geography-specific target range in weeks 40 to 52 (yes/no variable) • Having at least one Hb value in the geography-specific target range in weeks 24 to 36 (yes/no variable) • Having at least one Hb value in the geography-specific target range in weeks 40 to 52 (yes/no variable) • Having Hb values in the geography-specific target range for at least one-half of the observations in weeks 24 to 36 (yes/no variable) • Having Hb values in the geography-specific target range for at least one-half of the observations in weeks 40 to 52 (yes/no variable) • Hb increase of >1.0 g/dL from baseline to Week 52 (yes/no variable) • Time to achieve Hb increase of >1.0 g/dL from baseline Hb (censored at week 52)
Endpoints related to red blood cell transfusion	• Receipt of any 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 erythropoiesis-stimulating agent rescue	• Receipt of any ESA medication (in the darbepoetin alfa treatment group, use only included an ESA other than darbepoetin alfa as well as increases in darbepoetin alfa which the investigator specifically designates as rescue) • Time to first ESA medication (for entire study) • Total number and maximum duration of ESA episodes

Abbreviations: ESA, erythropoietin stimulating agent; Hb, haemoglobin; RBC, red blood cell
Source: CSR INNO$_2$VATE – incident (111)

B.2.3.1.6 Prespecified subgroup analyses

The subgroups of key interest were (111):

- Hb stratification level at baseline (<9.5 g/dL, ≥9.5 g/dL)
- Geographical region (US, EU, ROW)
- NYHA congestive HF stratification level (0 and 1, 2 and 3)
- Target Hb level (10 to 11 g/dL, 10 to 12 g/dL)
- Demographics and medical history (age: <65 years, ≥65 years; sex: male, female; race: white, all others; diabetes mellitus: yes, no; hypertension: yes, no)
- Baseline laboratory measurements (C-reactive protein: ≤0.6 mg/dL, >0.6 mg/dL; baseline transferrin saturation (TSAT): <median of baseline TSAT [%], ≥median of baseline TSAT [%]; baseline ferritin: <median of baseline ferritin [ng/mL], ≥median of baseline ferritin [ng/mL])

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B.2.3.1.7 Demographics and baseline characteristics

A summary of patient demographic characteristics is provided in Table 6. The two treatment groups were well balanced with respect to mean age, sex, height, weight, and body mass index for the randomised population (111).

Table 6. Demographic and baseline characteristics of randomised patients in the INNO$_2$VATE – incident trial

Baseline characteristic	Vadadustat N=181	Darbepoetin alfa N=188	Total N=369
Age (years), mean (SD)[a]	56.5 (14.8)	55.6 (14.6)	56.0 (14.7)
Age category, n (%)			
<65 years	122 (67.4)	137 (72.9)	259 (70.2)
≥65 years	59 (32.6)	51 (27.1)	110 (29.8)
Sex, n (%)			
Male	107 (59.1)	113 (60.1)	220 (59.6)
Female	74 (40.9)	75 (39.9)	149 (40.4)
Ethnicity, n (%)			
Hispanic or Latino	71 (39.2)	66 (35.1)	137 (37.1)
Not Hispanic or Latino	104 (57.5)	118 (62.8)	222 (60.2)
Not reported	5 (2.8)	3 (1.6)	8 (2.2)
Unknown	1 (0.6)	1 (0.5)	2 (0.5)
Race, n (%)			
American Indian or Alaska Native	1 (0.6)	0	1 (0.3)
Asian	12 (6.6)	8 (4.3)	20 (5.4)
Black or African American	38 (21.0)	35 (18.6)	73 (19.8)
Native Hawaiian or Other Pacific Islander	0	0	0
White	129 (71.3)	143 (76.1)	272 (73.7)
Not reported	0	1 (0.5)	1 (0.3)
Other	0	1 (0.5)	1 (0.3)
Multiple	1 (0.6)	0	1 (0.3)
Region, n (%)			
United States	97 (53.6)	102 (54.3)	199 (53.9)
Europe[b]	26 (14.4)	16 (8.5)	42 (11.4)
Rest of World	58 (32.0)	70 (37.2)	128 (34.7)
Body mass index (kg/m^2)			
N	174	181	355
Mean (SD)	27.64 (6.09)	27.49 (6.00)	27.56 (6.04)
Blood pressure (mm Hg), mean (SD)			
Systolic	142.7 (21.5)	142.8 (20.2)	142.7 (20.9)
Diastolic	76.8 (13.2)	78.8 (12.7)	77.9 (13.0)
History of diabetes, n (%)	105 (58.0)	96 (51.1)	201 (54.5)
History of CV disease, n (%)[c]	69 (38.1)	73 (38.8)	142 (38.5)
Baseline Hb (g/dL), mean (SD)	9.369 (1.070)	9.190 (1.138)	9.278 (1.107)
New York Heart Association HF class, n (%)			
Class 0 (no HF) or I	162 (89.5)	162 (86.2)	324 (87.8)
II or III	19 (10.5)	26 (13.8)	45 (12.2)
IV iron and transfusion history, n (%)			

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Baseline characteristic	Vadadustat N=181	Darbepoetin alfa N=188	Total N=369
IV iron use prior to first dose of study drug	119 (65.7)	140 (74.5)	259 (70.2)
Receive a transfusion within the four-week screening period prior to randomisation through to the first dose of study drug	6 (3.3)	9 (4.8)	15 (4.1)
Baseline ferritin (ng/mL)			
n	181	188	369
Mean (SD)	469.72 (316.92)	527.76 (401.10)	499.29 (362.94)
<median (418) of baseline ferritin (ng/mL), n (%)	91 (50.3)	93 (49.5)	184 (49.9)
≥median (418) of baseline ferritin (ng/mL), n (%)	90 (49.7)	95 (50.5)	185 (50.1)
Baseline TSAT (%)			
Mean (SD)	31.32 (9.45)	34.21 (12.68)	32.79 (11.29)
<median (30) of baseline TSAT, n (%)	96 (53.0)	85 (45.2)	181 (49.1)
≥median (30) of baseline TSAT, n (%)	85 (47.0)	103 (54.8)	188 (50.9)
Baseline C-reactive protein (mg/dL)			
n	177	187	364
Mean (SD)	0.91 (1.71)	0.97 (1.46)	0.94 (1.59)
<0.6 mg/dL, n (%)	116 (65.5)	119 (63.6)	235 (64.6)
>0.6 mg/dL, n (%)	61 (34.5)	68 (36.4)	129 (35.4)
Baseline ESA dose use (U/kg/week)[d]			
n	92	85	177
Epoetin	54 (58.7)	44 (51.8)	98 (55.4)
Darbepoetin alfa	18 (19.6)	21 (24.7)	39 (22.0)
Methoxy polyethylene glycol-epoetin beta	20 (21.7)	20 (23.5)	40 (22.6)
n	90	83	173
Mean (SD)	154.70 (113.28)	147.53 (115.02)	151.26 (113.84)
≤90 U/kg/week	36 (40.0)	30 (36.1)	66 (38.2)
>90 and <300 U/kg/week	45 (50.0)	47 (56.6)	92 (53.2)
≥300 U/kg/week	9 (10.0)	6 (7.2)	15 (8.7)
Baseline iron dose use (mg/week)			
0 – patients not receiving any iron	52 (28.7)	56 (29.8)	108 (29.3)
I – patients receiving oral iron only	19 (10.5)	9 (4.8)	28 (7.6)
II – patients receiving IV iron only	92 (50.8)	110 (58.5)	202 (54.7)
III – patients receiving IV and oral iron	18 (9.9)	13 (6.9)	31 (8.4)
IV iron			
n	68	75	143
Mean (SD)	567.33 (3379.68)	402.52 (1018.41)	480.89 (2436.53)
Oral iron			
n	29	20	49

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Baseline characteristic	Vadadustat N=181	Darbepoetin alfa N=188	Total N=369
Mean (SD)	3766.55 (7606.59)	2196.85 (1812.64)	3125.86 (5971.60)
Aetiology of CKD, n (%)			
Diabetes	81 (44.8)	82 (43.6)	163 (44.2)
Hypertension	79 (43.6)	85 (45.2)	164 (44.4)
Autoimmune/glomerulonephritis/vasculitis	24 (13.3)	29 (15.4)	53 (14.4)
Interstitial nephritis/pyelonephritis	11 (6.1)	11 (5.9)	22 (6.0)
Cystic/hereditary/congenital disease	7 (3.9)	8 (4.3)	15 (4.1)
Neoplasms/tumours	0	1 (0.5)	1 (0.3)
Other	16 (8.8)	24 (12.8)	40 (10.8)
Years since CKD diagnosis[e]			
N	177	183	360
Mean (SD)	4.84 (7.80)	4.14 (5.95)	4.48 (6.92)

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; SD, standard deviation; TSAT, transferrin saturation

[a.] reported age on the electronic case report forms

[b.] United Kingdom was included in Europe for analysis

[c.] Cardiovascular disease included coronary artery disease, myocardial infarction, stroke, and heart failure

[d.] ESA doses were converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin alfa to IV epoetin was 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin was 1:220; subcutaneous epoetin to IV epoetin was 1:1.25.

[e.] The handling of the partial date of CKD diagnosis: If day was missing, day was set to 15th of the month. If month was missing, month and day were set to July 1. If year was missing, date was missing. Years since CKD diagnosis was calculated based on date of CKD diagnosis and date of informed consent.

Source: CSR INNO$_2$VATE – incident (111)

B.2.3.2 INNO$_2$VATE – prevalent

B.2.3.1.1 Trial design

INNO$_2$VATE – prevalent was a phase III, randomised, open-label, sponsor-blinded, active-controlled, global, multicentre, non-inferiority study of vadadustat versus darbepoetin alfa for the maintenance treatment of anaemia in patients with DD-CKD (either PD or HD) after conversion from ESA therapy (112, 113). Patients were randomised to vadadustat or darbepoetin alfa in a 1:1 ratio, stratified by:

- Geographic region (US versus Europe versus Rest of World [ROW])
- New York Heart Association (NYHA) HF Class 0 (no HF) or I versus II or III
- Study entry Hb (<10.0 versus ≥10.0g/dL)

Following randomisation, there were three periods during the study (Figure 5):

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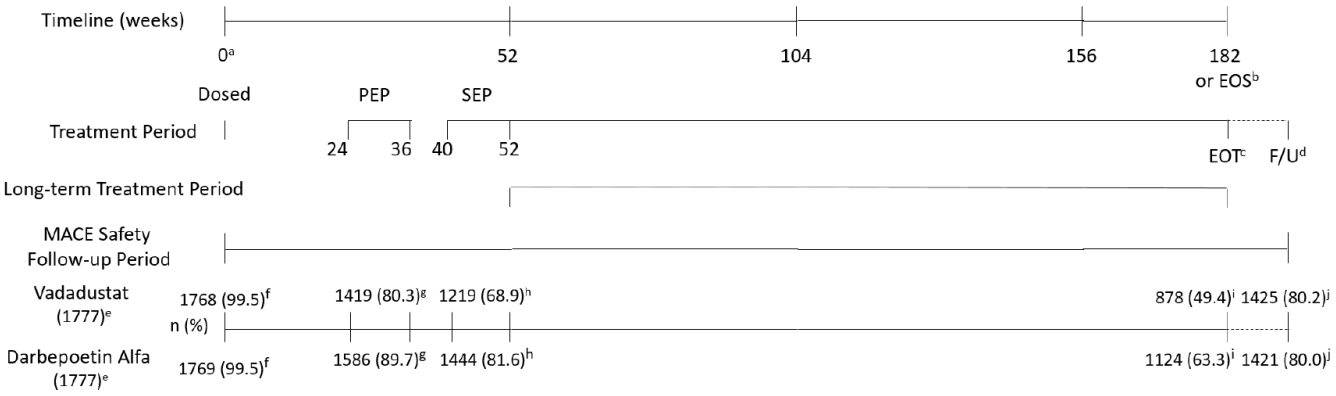
- Conversion and maintenance period (weeks 0 to 52): conversion to study drug for maintaining Hb (weeks 0 to 23), primary efficacy period (weeks 24 to 36), and secondary efficacy period (weeks 40 to 52);
- Long-term treatment period (week 53 to end of treatment [EOT]): continued study drug to assess long-term safety;
- Follow-up period (EOT + four weeks): post-treatment visits for safety (either in person or via telephone).

Patients who discontinued study drug were followed to the end of study (EOS) to assess major adverse cardiovascular events (MACE) (112). An outline of study periods is displayed in Figure 5.

Figure 5. INNO$_2$VATE – prevalent trial design



Abbreviations: EOS: end of study; EOT: end of treatment; F/U: follow-up; MACE: major adverse cardiovascular events; PEP: primary efficacy period; SEP: secondary efficacy period
Note: MACE information was collected beginning after week 0 until EOS, regardless of patient treatment status.
[a.] Randomisation occurred at week 0
[b.] EOS occurred once 631 MACE events were recorded
[c.] EOT occurred once patient permanently discontinued study medication, or up on announcement of global EOS
[d.] F/U occurred four weeks after EOT
[e.] Number of patients randomised
[f.] Number of patients dosed
[g.] Number of patients who completed PEP
[h.] Number of patients who completed SEP
[i.] Number of patients on treatment at EOS
[j.] Number of patients who completed study (including MACE Safety Follow-up)
Source: CSR INNO$_2$VATE – prevalent (112)

B.2.3.1.2 Eligibility criteria for study patients

The eligibility criteria for study patients are presented in Table 7.

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Table 7. Inclusion/exclusion criteria for INNO$_2$VATE – prevalent trial

Inclusion criteria	Exclusion criteria
• ≥18 years of age. • Had received chronic maintenance dialysis (either peritoneal or haemodialysis) for end-stage kidney disease for at least 12 weeks prior to screening. • Was currently maintained on ESA therapy, with a dose received within six 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 two Hb values measured by the central laboratory during screening. • Serum ferritin ≥100 ng/mL and TSAT ≥20% during screening. • Folate and vitamin B12 measurements ≥ lower limit of normal during screening. • Understood the procedures and requirements of the study and provided written informed consent and authorisation for protected health information disclosure.	• Patient presented with anaemia due to a cause other than CKD or patients with active bleeding or recent blood loss. • History of sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, haematologic malignancy, myeloma, haemolytic anaemia, thalassemia, or pure red cell aplasia. • RBC transfusion within eight weeks prior to randomisation. • Anticipated to recover adequate kidney function to no longer require dialysis. • AST/SGOT, ALT/SGPT, or total bilirubin >2.0 × ULN during screening. Patients with a history of Gilbert's syndrome were not excluded. • Uncontrolled hypertension (defined as confirmed pre-dialysis SBP >190 mmHg or DBP >110 mmHg at rest) during screening. • Severe HF during screening (NYHA Class IV). • Acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for HF, or stroke within 12 weeks prior to or during screening. • History of active malignancy within two years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ. • History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to randomisation. • History of haemosiderosis or haemochromatosis. • History of prior organ transplantation or scheduled organ transplant (patients on the kidney transplant wait-list or with a history of failed kidney transplant were not excluded), or prior haematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis were not excluded). • Hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients. • Use of an investigational medication or participation in an investigational study within 30 days or five half-lives of the investigational medication (whichever was longer), prior to screening.

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	• Previous participation in this study or previous participation in a study with another HIF prolyl-hydroxylase inhibitor other than vadadustat. • Females who were pregnant or breastfeeding. Women of childbearing potential who were unable or unwilling to use an acceptable method of contraception. • Non-vasectomised male patients who were unable or unwilling to use an acceptable method of contraception. • Any other reason, which in the opinion of the investigator made the patient not suitable for participation in the study.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; ESA, erythropoietin stimulating agent; HF, heart failure; HIF, hypoxia-inducible factor; MI, myocardial infarction; NYHA; New York Health Association; RBC, red blood cells; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TSAT, transferrin saturation; ULN, upper limit of normal
Source: CSR INNO$_2$VATE – prevalent (112); Eckardt et al. 2021 (113).

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B.2.3.1.3 Settings and locations where data were collected

$INNO_2VATE$ – prevalent enrolled patients from 275 centres in 18 countries. The majority of the centres were located in the US (128 centres). Since most centres had small sample sizes, no centre-specific analyses were planned (112).

B.2.3.1.4 Trial drugs and concomitant medications

Vadadustat was provided as film-coated tablets for oral administration and darbepoetin alfa was provided in pre-filled syringes as an injectable solution for IV or SC administration. Both vadadustat and darbepoetin alfa were supplied as open-label supplies.

Any medication prescribed and non-prescribed (including vitamins, herbals, topicals, inhaled, and intranasal), taken before the date of the first dose of study drug was considered prior medication. Any medication taken at any time from the date of the first dose of study drug through the date of the last dose of the study drug was considered concomitant medication. Patients were instructed to take any oral iron supplements (including multivitamins containing iron), iron containing phosphate binders, or any medication containing iron at least two hours before or two hours after the dose of vadadustat (112, 113).

B.2.3.1.5 Prespecified primary and secondary outcomes

The primary and secondary outcomes of the $INNO_2VATE$ – incident trial are shown in Table 8 below.

Table 8. Prespecified primary and secondary outcomes

Primary efficacy outcome	Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)
Secondary efficacy outcome	Change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52)
Other efficacy outcomes	
Endpoints related to haemoglobin	• Change in average Hb value between baseline and the combined primary efficacy period and secondary efficacy period (weeks 24 to 52) • Having average Hb value in the geography-specific target range in weeks 24 to 36 (yes/no variable) • Having average Hb value in the geography-specific target range in weeks 40 to 52 (yes/no variable)

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	• Having at least one Hb value in the geography-specific target range in weeks 24 to 36 (yes/no variable) • Having at least one Hb value in the geography-specific target range in weeks 40 to 52 (yes/no variable) • Having Hb values in the geography-specific target range for at least one-half of the observations in weeks 24 to 36 (yes/no variable) • Having Hb values in the geography-specific target range for at least one-half of the observations in weeks 40 to 52 (yes/no variable)
Endpoints related to red blood cell transfusion	• Receipt of any 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 erythropoiesis-stimulating agent rescue	• Receipt of any ESA medication (in the darbepoetin alfa treatment group, use only included an ESA other than darbepoetin alfa as well as increases in darbepoetin alfa which the investigator specifically designates as rescue) • Time to first ESA medication (for entire study) • Total number and maximum duration of ESA episodes.

Abbreviations: ESA, erythropoietin stimulating agent; Hb, haemoglobin; RBC, red blood cell
Source: CSR INNO$_2$VATE – prevalent (112)

B.2.3.1.6 Prespecified subgroup analyses

The subgroups of key interest were:

- Hb stratification level at baseline (<10.0 g/dL, ≥10.0 g/dL)
- Geographical region (US, EU, ROW)
- NYHA CHF stratification level (0 and 1, 2 and 3)
- Target Hb level (10 to 11 g/dL, 10 to 12 g/dL)
- Demographics and medical history (age: <65 years, ≥65 years; sex: male, female; race: white, all others; diabetes mellitus: yes, no; hypertension: yes, no)
- Medications (baseline ESA dose: ≤90 U/kg/week, >90 and <300 U/kg/week, ≥300 U/kg/week)
- Baseline laboratory measurements (C-reactive protein: ≤0.6 mg/dL, >0.6 mg/dL; baseline TSAT: <median of baseline TSAT [%], ≥median of baseline TSAT [%]; baseline ferritin: <median of baseline ferritin [ng/mL], ≥median of baseline ferritin [ng/mL]) (112).

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B.2.3.1.7 Demographics and baseline characteristics

A summary of patient demographic characteristics is provided in Table 9. The two treatment groups were well balanced with respect to mean age, sex, height, weight, and body mass index for the randomised population (112).

Table 9. Demographic and baseline characteristics of randomised patients in the INNO$_2$VATE – prevalent trial

Baseline characteristic	Vadadustat N=1,777	Darbepoetin alfa N=1,777	Total N=3,554
Age (years), mean (SD)[a]	57.9 (13.9)	58.4 (13.8)	58.1 (13.9)
Age category, n (%)			
<65 years	1,167 (65.7)	1,161 (65.3)	2,328 (65.5)
≥65 years	610 (34.3)	616 (34.7)	1,226 (34.5)
Sex, n (%)			
Male	990 (55.7)	1,004 (56.5)	1,994 (56.1)
Female	787 (44.3)	773 (43.5)	1,560 (43.9)
Ethnicity, n (%)			
Hispanic or Latino	682 (38.4)	674 (37.9)	1,356 (38.2)
Not Hispanic or Latino	1,043 (58.7)	1,040 (58.5)	2,083 (58.6)
Not reported	36 (2.0)	47 (2.6)	83 (2.3)
Unknown	16 (0.9)	16 (0.9)	32 (0.9)
Race, n (%)			
American Indian or Alaska Native	19 (1.1)	30 (1.7)	49 (1.4)
Asian	76 (4.3)	99 (5.6)	175 (4.9)
Black or African American	432 (24.3)	444 (25.0)	876 (24.6)
Native Hawaiian or Other Pacific Islander	13 (0.7)	6 (0.3)	19 (0.5)
White	1,135 (63.9)	1,096 (61.7)	2,231 (62.8)
Not reported	52 (2.9)	52 (2.9)	104 (2.9)
Other	42 (2.4)	45 (2.5)	87 (2.4)
Multiple	8 (0.5)	5 (0.3)	13 (0.4)
Region, n (%)			
United States	1,090 (61.3)	1,086 (61.1)	2,176 (61.2)
Europe[b]	254 (14.3)	281 (15.8)	535 (15.1)
Rest of World	433 (24.4)	410 (23.1)	843 (23.7)
Body mass index (kg/m^2)			
N	1749	1749	3498
Mean (SD)	28.58 (7.2)	28.56 (7.2)	28.57 (7.2)
Blood pressure (mm Hg), mean (SD)			
Systolic	142.9 (23.1)	143.3 (22.3)	143.1 (22.7)
Diastolic	76.3 (13.2)	76.4 (13.2)	76.3 (13.2)
History of diabetes, n (%)	971 (54.6)	998 (56.2)	1969 (55.4)
History of CV disease, n (%)[c]	868 (48.8)	932 (52.4)	1800 (50.6)
Baseline Hb (g/dL), mean (SD)	10.249 (0.850)	10.229 (0.825)	10.239 (0.837)
New York Heart Association HF class, n (%)			
Class 0 (no HF) or I	1,545 (86.9)	1,547 (87.1)	3,092 (87.0)

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Baseline characteristic	Vadadustat N=1,777	Darbepoetin alfa N=1,777	Total N=3,554
II or III	232 (13.1)	230 (12.9)	462 (13.0)
IV iron and transfusion history, n (%)			
IV iron use prior to first dose of study drug	1,372 (77.3)	1,326 (74.7)	2,698 (76.0)
Receive a transfusion within the four-week screening period prior to randomisation through to the first dose of study drug	31 (1.7)	29 (1.6)	60 (1.7)
Baseline ferritin (ng/mL)			
n	1,776	1,777	3,553
Mean (SD)	846.78 (562.65)	840.65 (538.49)	843.72 (550.63)
<median (754) of baseline ferritin (ng/mL), n (%)	879 (49.5)	896 (50.4)	1,775 (50.0)
≥median (754) of baseline ferritin (ng/mL), n (%)	897 (50.5)	881 (49.6)	1,778 (50.0)
Baseline TSAT (%)			
n	1,774	1,777	3,551
Mean (SD)	38.06 (13.45)	37.63 (13.17)	37.85 (13.31)
<median (35) of baseline TSAT, n (%)	880 (49.6)	889 (50.0)	1769 (49.8)
≥median (35) of baseline TSAT, n (%)	894 (50.4)	888 (50.0)	1782 (50.2)
Baseline C-reactive protein (mg/dL)			
n	1,755	1,738	3,493
Mean (SD)	1.02 (2.01)	0.97 (1.74)	0.99 (1.88)
<0.6 mg/dL, n (%)	1,109 (63.2)	1,083 (62.3)	2,192 (62.8)
>0.6 mg/dL, n (%)	646 (36.8)	655 (37.7)	1301 (37.2)
Baseline ESA dose use (U/kg/week)[d]			
n	1,765	1,774	3,539
Epoetin	970 (55.0)	967 (54.5)	1,937 (54.7)
Darbepoetin alfa	484 (27.4)	521 (29.4)	1,005 (28.4)
Methoxy polyethylene glycol-epoetin beta	311 (17.6)	286 (16.1)	597 (16.9)
n	1,742	1,759	3,501
Mean (SD)	116.61 (109.37)	111.89 (109.67)	114.24 (109.53)
≤90 U/kg/week	916 (52.6)	968 (55.0)	1,884 (53.8)
>90 and <300 U/kg/week	724 (41.6)	693 (39.4)	1,417 (40.5)
≥300 U/kg/week	102 (5.9)	98 (5.6)	200 (5.7)
Baseline iron dose use (mg/week)			
0 – patients not receiving any iron	660 (37.1)	721 (40.6)	1,381 (38.9)
I – patients receiving oral iron only	123 (6.9)	118 (6.6)	241 (6.8)
II – patients receiving IV iron only	911 (51.3)	853 (48.0)	1,764 (49.6)
III – patients receiving IV and oral iron	83 (4.7)	85 (4.8)	168 (4.7)
IV iron			
n	610	560	1,170
Mean (SD)	114.12 (257.40)	144.54 (474.97)	128.68 (377.65)
Oral iron			

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Baseline characteristic	Vadadustat N=1,777	Darbepoetin alfa N=1,777	Total N=3,554
n	156	159	315
Mean (SD)	3,684.40 (10,025.91)	2,711.47 (3,648.53)	3,193.30 (7,520.30)
Aetiology of CKD, n (%)			
Diabetes	794 (44.7)	820 (46.1)	1,614 (45.4)
Hypertension	892 (50.2)	908 (51.1)	1,800 (50.6)
Autoimmune/glomerulonephritis/vasculitis	175 (9.8)	185 (10.4)	360 (10.1)
Interstitial nephritis/pyelonephritis	85 (4.8)	71 (4.0)	156 (4.4)
Cystic/hereditary/congenital disease	69 (3.9)	63 (3.5)	132 (3.7)
Neoplasms/tumours	7 (0.4)	7 (0.4)	14 (0.4)
Other	195 (11.0)	205 (11.5)	400 (11.3)
Years since CKD diagnosis[e]			
N	1719	1715	3434
Mean (SD)	6.73 (6.253)	6.93 (6.697)	6.83 (6.478)

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; IV, intravenous; SD, standard deviation; TSAT, transferrin saturation

[a.] Reported age on the electronic case report forms

[b.] United Kingdom was included in Europe for analysis

[c.] Cardiovascular disease included coronary artery disease, myocardial infarction, stroke, and heart failure

[d.] ESA doses were converted to IV epoetin equivalent unit per kilogram per week (U/kg/week): Darbepoetin alfa to IV epoetin was 1:200; Methoxy polyethylene glycol-epoetin beta to IV epoetin was 1:220; subcutaneous epoetin to IV epoetin was 1:1.25.

[e.] The handling of the partial date of CKD diagnosis: If day was missing, day was set to 15th of the month. If month was missing, month and day were set to Jul 1. If year was missing, date was missing. Years since CKD diagnosis was calculated based on date of CKD diagnosis and date of informed consent.

Source: CSR INNO$_2$VATE – prevalent (112)

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The statistical analysis methods and definitions of study groups used in the pivotal trials (INNO$_2$VATE – incident and INNO$_2$VATE – prevalent) are described in Table 10 (111, 112).

B.2.4.1 Statistical methods and analysis sets

Table 10. Summary of statistical analysis in the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials

Study name (number)	INNO$_2$VATE – incident (NCT02865850)	INNO$_2$VATE – prevalent (NCT02892149)
Analysis sets	The analysis populations were defined as follows: • *Randomised population:* all patients randomised. Analyses of this population was based on the randomised treatment. • *FAS population:* all patients in the randomised population who received at least one dose of study drug and had at least one post-	

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Study name (number)	INNO$_2$VATE – incident (NCT02865850)	INNO$_2$VATE – prevalent (NCT02892149)
	dose Hb. Analyses of this population was based on the randomised treatment. • *Safety population:* all patients in the randomised population who received at least one dose of study drug. Analysis of this population was based on the actual treatment received. Patients who received in error both vadadustat and darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received study drug. • *Per Protocol (PP) population:* all randomised patients who received study drug during the primary efficacy period (weeks 24 to 36), had at least one Hb assessment during the primary efficacy period (weeks 24 to 36), and had no critical or major protocol deviation affecting the primary endpoint analyses, i.e., prior to week 36. Analyses of this population was based on actual treatment received, as described for the Safety population. Efficacy analyses utilised the randomised, FAS, and PP populations while safety analyses (including analyses of MACE) utilised the Safety population.	
	• Randomised population: n=369 • FAS population: n=364 • Safety population: n=365 • PP population: n=249	• Randomised population: n=3,554 • FAS population: n=3,514 • Safety population: n=3,537 • PP population: n=2,557
Statistical analysis for primary outcome	Assessment of the primary outcome involved analysis of covariance (ANCOVA) with multiple imputation for missing data. The randomised population was used for primary efficacy analyses. Establishment of non-inferiority was based on a margin of -0.75 g/dL applied to the difference in mean change: vadadustat minus darbepoetin alfa. Mixed models for repeated measurements (MMRM) on observed data was used for sensitivity analysis.	
Statistical analysis for key and other secondary outcomes	Secondary outcomes: Analysis of covariance (ANCOVA) with multiple imputation for missing data. This endpoint was analysed formally only if the primary analysis met the prespecified non-inferiority margin. Mixed models for repeated measurements (MMRM) on observed data was used for sensitivity analysis.	
Statistical analysis of further outcomes	ANCOVA with or without multiple imputation	
Statistical analysis of safety outcomes	Most of the analysis of safety data was descriptive without formal statistical testing. In some cases, 95% CIs for the change from baseline as well as for the difference in the mean changes or mean percent changes between the study treatment groups were reported. Formal statistical methodology was used for the MACE data.	

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Study name (number)	INNO$_2$VATE – incident (NCT02865850)	INNO$_2$VATE – prevalent (NCT02892149)
Sample size & power calculation	The sample sizes for this study were calculated using a 2-sample t-test with equal variance and the actual analyses used methods for analysis of covariance (ANCOVA). For the primary efficacy analysis power, the mean change from baseline in Hb for vadadustat and darbepoetin alfa was assumed to be identical with a common standard deviation (SD) of 1.5 g/dL. Non-inferiority was established if the lower limit of the 2-sided 95% confidence interval (CI) for the difference between the mean in the vadadustat treatment group and the mean in the darbepoetin alfa treatment group was -0.75 g/dL or higher.	
	A sample size of 200 patients per treatment group in this study would yield greater than 90% power to show non-inferiority.	A sample size of 1,650 patients per treatment group in this study would yield greater than 90% power to show non-inferiority.
Data management, patient withdrawals	**Handling of missing data** Standard multiple imputation, where imputation of missing values was based on the group to which the patient was randomised, was used for primary and secondary analyses, except the tipping point analysis. The tipping point analysis assessed the effect of potential deviations from MAR and explored the consequences of assuming that data in the vadadustat treatment group were MNAR. Missing data was handled using a procedure specific to each variable. **Premature discontinuation of trial medication** The patient's participation in this clinical study could have resulted in permanent discontinuation of study drug as a result of: • Unacceptable toxicity or drug intolerability • Investigator's discretion • Patient withdrawal of consent • Patient became pregnant • Receipt of a kidney transplant • Lack of efficacy (defined as inadequate response to vadadustat or darbepoetin alfa in the investigator's opinion) • Adverse events (AEs) • Other reasons Study drug was permanently discontinued if a patient met one of the following criterion: • ALT or AST >3 × ULN and total bilirubin >2 × ULN • ALT or AST >3 × ULN and international normalised ratio >1.5 • ALT or AST >8 × ULN • ALT or AST remains >5 × ULN over two weeks (re-challenge generally should have been avoided with ALT or AST >5 × ULN unless there were no other good therapeutic options) • ALT or AST >3 × ULN with symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, and rash) or eosinophilia **Withdrawal of informed consent** Patients were free to withdraw consent for some or all aspects of the trial at any time.	

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Abbreviations: AE, adverse event; ALT, alanine transaminase; ANCOVA, analysis of covariance; FAS, full analysis set; AST, aspartate aminotransferase; CI, confidence interval; MACE, major adverse cardiovascular events; MAR, missing at random; MMRM, mixed models for repeated measurements; MNAR, missing not at random; PP, per protocol; SD, standard deviation; ULN, upper limit of normal
Source: CSR INNO$_2$VATE – incident (111); CSR INNO$_2$VATE – prevalent (112)

B.2.4.2 Patient flow in the relevant randomised controlled trials

B.2.4.2.1 INNO$_2$VATE – incident

In INNO$_2$VATE – incident, 652 patients were screened at entry level. Of these, 283 patients failed screening and 369 patients were enrolled and randomised into the study. Among randomised patients, 179 and 186 were treated with vadadustat and darbepoetin alfa, respectively. Of these, 160 (88.4%) patients from the vadadustat group and 165 (87.8%) from the darbepoetin alfa group completed the study (111).

Among randomised patients, 365 were included in the safety population and 364 were included in the full analysis set (FAS) population (111).

The total number of discontinuations of study drug treatment was higher in the vadadustat treatment group compared with the darbepoetin alfa treatment group (60 [33.1%] vs. 49 [26.1%], respectively). The most frequent primary reason for discontinuation of study drug was that the patient no longer wanted to receive study drug (11.0% and 5.3% in vadadustat and darbepoetin alfa treatment groups, respectively) (111).

Patient flow in the INNO$_2$VATE – incident trial is shown in Appendix D, section D.2.

B.2.4.2.2 INNO$_2$VATE – prevalent

In INNO$_2$VATE – prevalent, 4,944 patients were screened at entry level. Of these, 1,390 patients failed screening and 3,554 patients were enrolled and randomised in the study. Among randomised patients, 1,768 and 1,769 patients were treated with vadadustat and darbepoetin alfa, respectively. Of these, 1,425 (80.2%) patients from the vadadustat group and 1,421 (80.0%) from the darbepoetin alfa group completed the study (112).

Among randomised patients, 3,537 were included in the safety population and 3,514 were included in the FAS population (112).

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The total number of discontinuations of study drug treatment was higher in the vadadustat treatment group compared with the darbepoetin alfa treatment group (899 [50.6%] vs. 653 [36.7%], respectively). The primary reason for discontinuation of study drug was that the patient no longer wanted to receive study drug (12.0% and 5.8% in the vadadustat and darbepoetin alfa treatment groups, respectively) (112).

Patient flow in the INNO$_2$VATE – prevalent trial is shown in Appendix D, section D.2.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

The critical appraisal of INNO$_2$VATE trials is provided in Appendix D. Overall, the trials were found to be adequately randomised. The outcomes' assessors were blinded. Valid explanation was provided for any discontinuation that occurred in either treatment arm. All outcomes were adequately reported. However, there were some concerns regarding adequate concealment of treatment allocation. The participants and investigators were not found to be blinded to the intervention and comparator. Apart from this, the study was found to be free from any other kind of bias.

B.2.6. Clinical effectiveness results of the relevant studies

B.2.6.1. INNO$_2$VATE – incident

All results presented in the following subsections are for the randomised population.

B.2.6.1.1. Primary outcome: Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)

The primary endpoint was analysed using analysis of covariance (ANCOVA) with multiple imputation for the randomised population and demonstrated a least squares (LS) mean (standard error of mean [SEM]) change from baseline of 1.26 (0.109) and 1.58 (0.108) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (standard error of mean [SEM]) treatment group difference was -0.31 (0.110) g/dL (95% CI: -0.53, -0.10). The lower bound of the 95% CI (-0.53) was above -0.75 g/dL. Thus, the non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the lower bound of the 95% CI was above the prespecified non-inferiority margin of -0.75 g/dL.

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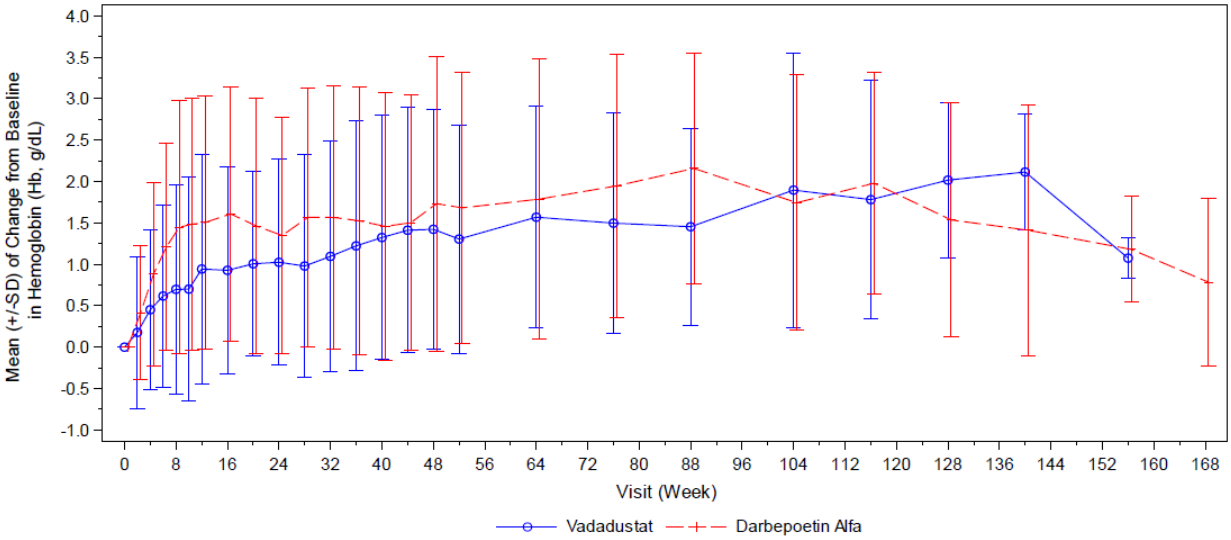
The change from baseline in Hb to the average over weeks 24 to 36 is provided in Table 11. A display of the mean change from baseline in Hb is shown in Figure 6.

Table 11. Change from baseline in Hb (g/dL) to the average over weeks 24 to 36 (ANCOVA with multiple imputations) (randomised population)

Visit Statistics	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Treatment comparison vadadustat – darbepoetin alfa
Change from baseline			
Mean (SD)	0.99 (1.276)	1.42 (1.414)	-
Least squared mean (SEM)	1.26 (0.109)	1.58 (0.108)	-0.31 (0.110)
95% CI	1.05, 1.48	1.37, 1.79	-0.53, -0.10

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; Hb, haemoglobin; N: number of patients; SD: standard deviation; SEM: standard error of mean
Source: CSR INNO2VATE – incident (111)

Figure 6. Mean (SD) of change from baseline in Hb (g/dL) (randomised population)



Abbreviations: Hb, haemoglobin; SD, standard deviation
Notes: Week 0 denotes baseline
Source: CSR INNO2VATE – incident (111)

B.2.6.1.2. Secondary outcome: Change in average Hb between baseline and the secondary efficacy period (weeks 40 to 52)

As the primary endpoint met the non-inferiority margin, the key secondary endpoint for this study of mean change in Hb from baseline to average Hb over weeks 40 to 52 was analysed formally.

The secondary endpoint, analysed using ANCOVA with multiple imputation, demonstrated a LS mean (SEM) change from baseline of 1.42 (0.132) and 1.50

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(0.136) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (SEM) treatment difference between treatment groups was -0.07 (0.134) g/dL (95% CI: -0.34, 0.19). The lower bound of the 95% CI was 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.

The change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52) is shown in Table 12.

Table 12. Change from baseline in Hb (g/dL) to the average over weeks 40 to 52 (ANCOVA with multiple imputations) (randomised population)

Visit Statistics	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Treatment comparison vadadustat – darbepoetin alfa
Change from baseline			
Mean (SD)	1.15 (1.345)	1.36 (1.568)	-
Least squared mean (SEM)	1.42 (0.132)	1.50 (0.136)	-0.07 (0.134)
95% CI	1.17, 1.68	1.23, 1.76	-0.34, 0.19

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; Hb, haemoglobin; N: number of patients; SD: standard deviation; SEM: standard error of mean
Source: CSR INNO$_2$VATE – incident (111)

Other clinical outcomes reported from the trial are presented in Appendix M.

B.2.6.2. INNO$_2$VATE – prevalent

All results presented in the following subsections are for the randomised population.

B.2.6.2.1. Primary outcome: Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)

The primary efficacy endpoint for this study was the mean change in average Hb between baseline and the primary efficacy period (weeks 24 to 36). The primary endpoint, analysed using ANCOVA with multiple imputation, demonstrated LS mean (SEM) change from baseline of 0.19 (0.032) and 0.36 (0.032) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (SEM) treatment group difference was -0.17 (0.033) g/dL (95% CI: -0.23, -0.10). Non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the lower bound of the 95% CI was above the prespecified non-inferiority margin of -0.75 g/dL.

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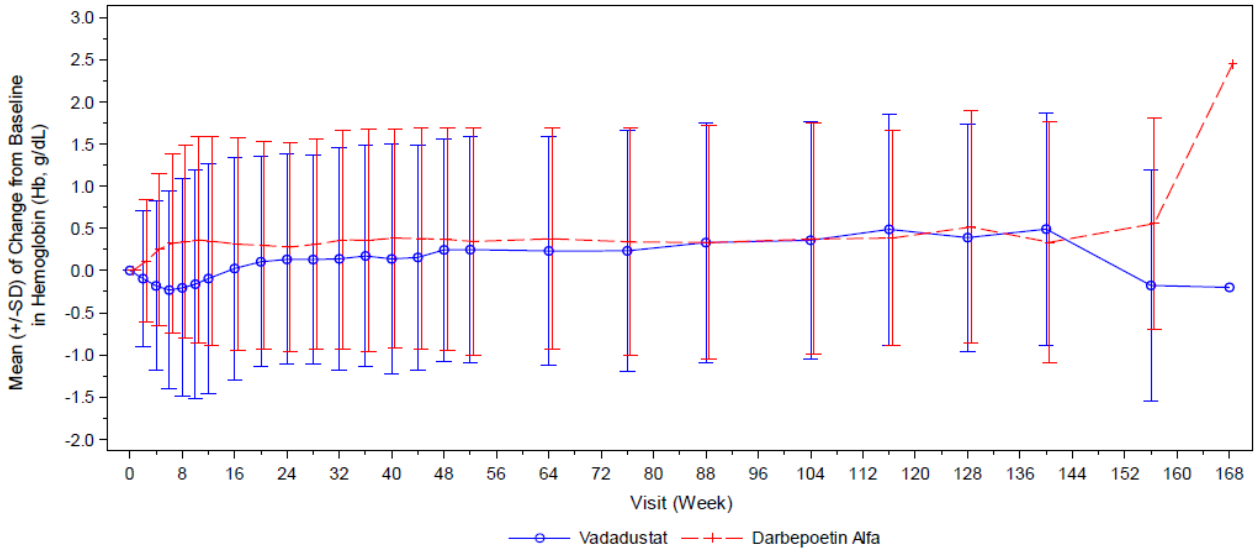
The change from baseline in Hb to the average over weeks 24 to 36 is displayed in Table 13. A display of the mean change from baseline in Hb is shown in Figure 7.

Table 13. Change from baseline in Hb (g/dL) to the average over weeks 24 to 36 (ANCOVA with multiple imputations) (randomised population)

Visit Statistics	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)	Treatment comparison vadadustat – darbepoetin alfa
Change from baseline			
Mean (SD)	0.11 (1.108)	0.30 (1.103)	-
Least squared mean (SEM)	0.19 (0.032)	0.36 (0.032)	-0.17 (0.033)
95% CI	0.12, 0.25	0.29, 0.42	-0.23, -0.10

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; Hb, haemoglobin; N: number of patients; SD: standard deviation; SEM: standard error of mean
Source: CSR INNO$_2$VATE – prevalent (112)

Figure 7. Mean (SD) of change from baseline in Hb (g/dL) (randomised population)



Abbreviations: Hb, haemoglobin; SD, standard deviation
Notes: Week 0 denotes baseline
Source: CSR INNO$_2$VATE – prevalent (112)

B.2.6.2.2. Secondary outcome: Change in average Hb between baseline and the secondary efficacy period (weeks 40 to 52)

As the primary endpoint met the non-inferiority margin, the key secondary endpoint for this study of mean change in Hb from baseline to average Hb over weeks 40 to 52 was analysed formally.

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The secondary endpoint was analysed using ANCOVA with multiple imputation for the randomised population and demonstrated a LS mean (SEM) change from baseline of 0.23 (0.035) and 0.41 (0.033) g/dL in the vadadustat and darbepoetin alfa treatment groups, respectively. The LS mean (SEM) treatment difference between treatment groups was -0.18 (0.035) g/dL (95% CI: -0.25, -0.12). The lower bound of the 95% CI was 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. The change in average Hb value between baseline and the secondary efficacy period (weeks 40 to 52) is displayed in Table 14.

Table 14. Change from baseline in Hb (g/dL) to the average over weeks 40 to 52 (ANCOVA with multiple imputations) (randomised population)

Visit Statistics	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)	Treatment comparison vadadustat – darbepoetin alfa
Change from baseline			
Mean (SD)	0.15 (1.178)	0.35 (1.131)	-
Least squared mean (SEM)	0.23 (0.035)	0.41 (0.033)	-0.18 (0.035)
95% CI	0.16, 0.29	0.34, 0.48	-0.25, -0.12

Abbreviations: ANCOVA: analysis of covariance; CI: confidence interval; Hb, haemoglobin; N: number of patients; SD: standard deviation; SEM: standard error of mean
Source: CSR INNO$_2$VATE – prevalent (112)

Other clinical outcomes reported from the trial are presented in Appendix M.

B.2.7. Subgroup analysis

The prespecified subgroup analyses consistently supported the primary and key secondary efficacy endpoint results and met the non-inferiority criterion. A summary of the results for the subgroups is provided in Appendix E.

B.2.8. Meta-analysis

Results from the clinical SLR (Appendix D) suggest that the pivotal trials described above provide the most robust source of evidence available to compare the efficacy and safety of vadadustat to the relevant comparator for this decision problem, i.e., ESAs, as reflected by the control arm receiving darbepoetin alfa in the INNO$_2$VATE trials. The effectiveness of vadadustat compared to darbepoetin alfa is generalisable to the broader ESA therapeutic class. NICE treatment guidelines for managing anaemia in CKD indicate that available evidence on efficacy suggest no difference

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between darbepoetin alfa and epoetin alfa, or between darbepoetin alfa and epoetin beta (17, 114). Generalisability is also supported by several studies which similarly conclude equivalent efficacy between ESAs (having similar duration of action) at equivalent doses (115-119).

A class effect for ESAs is well established and acknowledged within the clinical and research community. For example, a 2014 Cochrane review comparing the efficacy and safety of ESAs in the CKD setting concluded insufficient evidence to suggest the superiority of any ESA formulation, although scarcity of data was acknowledged (120). Based on this conclusion, Palmer et al. 2014 suggest that given similar comparative effectiveness, other considerations should be made when determining choice of ESA, such as drug cost, availability, and dosing frequency preferences (120). Furthermore, a 2023 update to the original Cochrane review, which included 62 additional studies, reported findings consistent with the 2014 review (121). Finally, an independent 2018 systematic review and meta-analysis similarly found no differences in efficacy and safety between ESAs (122).

The current appraisal is the first to allow NICE to assess the evidence for a HIF-PHI versus ESAs in the DD-CKD group; therefore, no precedent for a committee accepting an ESA class effect in the target DD-CKD population exists. However, the 2022 NICE appraisal for roxadustat (TA807) in the NDD-CKD population was supportive of the assumption of a class effect for ESAs in a NDD-CKD population (123). While acknowledging some differences in the frequency of administration, the TA807 committee concluded that the effectiveness of ESAs is similar, supporting a class effect.

Therefore, MEDICE also believes that the INNO$_2$VATE trials comparing vadadustat to a single ESA (i.e., darbepoetin alfa) serves as sufficient evidence to establish the benefits of vadadustat compared to the entire class of ESAs when administered as standard of care to DD-CKD patients in the NHS. This is supported by evidence from the FO$_2$CUS phase IIIb clinical trial (US geography) which demonstrated non-inferiority of vadadustat versus the long-acting ESA methoxy polyethylene glycol-epoetin beta (Mircera®) (109) and reported similar efficacy and safety results versus ESA treatment to that found in the INNO$_2$VATE trials.

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B.2.9. Indirect and mixed treatment comparisons

As per the rationale already described in section B.2.8, no indirect and mixed treatment comparisons were conducted given data from the INNO$_2$VATE studies provide a robust direct comparison of vadadustat versus ESA treatment (darbepoetin alfa).

B.2.10. Adverse reactions

The primary safety analyses (including MACE analyses) for the INNO$_2$VATE studies were performed on the safety population.

B.2.10.1 INNO$_2$VATE – incident

The median (Q1, Q3) duration of study drug exposure per patient to vadadustat and darbepoetin alfa was 45.00 (28.00, 73.14) and 50.14 (36.00, 80.14) weeks, respectively. There were 44.7% and 47.8% of vadadustat and darbepoetin alfa treated patients with at least 52 weeks of study drug exposure.

An overall summary of TEAEs is provided in Table 15. At least one TEAE was experienced in 83.8% and 85.5% of patients in the vadadustat and darbepoetin alfa treatment groups, respectively. The incidence of study drug discontinuation due to a TEAE was 2.8% and 1.1% in the vadadustat and darbepoetin alfa treatment groups, respectively. The incidence of TEAEs considered drug-related by the investigator was 3.9% and 2.7% in the vadadustat and darbepoetin alfa treatment groups, respectively. The incidence of any drug-related TEAEs leading to study drug discontinuation was 1.1% and 0% in the vadadustat and darbepoetin alfa treatment groups, respectively.

The incidence of treatment-emergent SAEs was lower in the vadadustat treatment group (49.7%) compared to the darbepoetin alfa treatment group (56.5%). Only 0.6% and 2.2% of patients had treatment-emergent SAEs considered to be drug-related in the vadadustat and darbepoetin alfa treatment groups, respectively.

Across the study, 8.4% and 10.8% of patients died in the vadadustat and darbepoetin alfa treatment groups, respectively. Deaths due to any TEAEs were 8.4% and 9.7% in the vadadustat and darbepoetin alfa treatment groups, respectively.

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Table 15. Overall summary of treatment-emergent adverse events (safety population)

Statistics	Vadadustat (N=179)	Darbepoetin alfa (N=186)	Total (N=365)
Any TEAEs	150 (83.8)	159 (85.5)	309 (84.7)
Any drug-related TEAEs	7 (3.9)	5 (2.7)	12 (3.3)
Any severe TEAEs	60 (33.5)	64 (34.4)	124 (34.0)
Any treatment-emergent SAEs	89 (49.7)	105 (56.5)	194 (53.2)
Any drug-related treatment-emergent SAEs	1 (0.6)	4 (2.2)	5 (1.4)
Any TEAEs leading to study treatment discontinuation	5 (2.8)	2 (1.1)	7 (1.9)
Any drug-related TEAEs leading to study treatment discontinuation	2 (1.1)	0	2 (0.5)
Any TEAEs leading to death	15 (8.4)	18 (9.7)	33 (9.0)
All deaths[a]	15 (8.4)	20 (10.8)	35 (9.6)

Abbreviations: N: number of patients; n (%): number (percent) of patients with events; SAEs: serious adverse events; TEAE: treatment-emergent adverse event

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

[a] Any deaths were reported during the study no matter whether deaths were caused by TEAEs or not.

Source: CSR INNO$_2$VATE – incident DD-CKD (111)

B.2.10.2 INNO$_2$VATE – prevalent

The median (Q1, Q3) duration of study drug exposure to vadadustat and darbepoetin alfa was 56.14 (28.86, 85.43) and 72.14 (44.86, 98.71) weeks, respectively. There were 54.7% and 69.4% of vadadustat and darbepoetin alfa treated patients with at least 52 weeks of study treatment exposure.

An overall summary of TEAEs is provided in Table 16. At least one TEAE was experienced by 88.3% and 89.3% of patients in the vadadustat and darbepoetin alfa treatment groups, respectively. The incidence of TEAEs considered drug-related by the investigator was 9.6% and 3.8%, and the incidence of TEAEs leading to study drug discontinuation was 5.1% and 1.1%, in the vadadustat and darbepoetin alfa treatment groups, respectively.

The incidence of treatment-emergent SAEs was 55.0% and 58.3% in the vadadustat and darbepoetin alfa treatment groups, respectively. Only 1.6% and 1.5% of patients had treatment-emergent SAEs considered to be drug-related by the investigator in the vadadustat and darbepoetin alfa treatment groups, respectively.

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The incidence of drug-related TEAEs leading to study drug discontinuation was 2.4% and 0.3% in the vadadustat and darbepoetin alfa treatment groups, respectively.

Overall, 15.6% and 16.4% of patients died in the vadadustat and darbepoetin alfa treatment groups, respectively. Deaths due to any TEAEs were 15.0% and 15.6% in the vadadustat and darbepoetin alfa treatment groups, respectively.

Table 16. Overall summary of treatment-emergent adverse events (safety population)

Statistics	Vadadustat (N=1,768)	Darbepoetin alfa (N=1,769)	Total (N=3,537)
Any TEAEs	1,562 (88.3)	1,580 (89.3)	3,142 (88.8)
Any drug-related TEAEs	169 (9.6)	68 (3.8)	237 (6.7)
Any severe TEAEs	707 (40.0)	749 (42.3)	1,456 (41.2)
Any treatment-emergent SAEs	973 (55.0)	1,032 (58.3)	2,005 (56.7)
Any drug-related treatment-emergent SAEs	29 (1.6)	27 (1.5)	56 (1.6)
Any TEAEs leading to study treatment discontinuation	91 (5.1)	20 (1.1)	111 (3.1)
Any drug-related TEAEs leading to study treatment discontinuation	42 (2.4)	5 (0.3)	47 (1.3)
Any TEAEs leading to death	266 (15.0)	276 (15.6)	542 (15.3)
All deaths[a]	276 (15.6)	290 (16.4)	566 (16.0)

Abbreviations: N: number of patients; n (%): number (percent) of patients with events; SAEs: serious adverse events; TEAE: treatment-emergent adverse event

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

[a] Any deaths were reported during the study no matter whether deaths were caused by TEAEs or not.

Source: CSR INNO$_2$VATE – prevalent DD-CKD (112)

More details on AEs and a detailed account of the MACE analysis are provided in Appendix F.

B.2.11. Ongoing studies

There are no ongoing studies of vadadustat relevant for this appraisal.

B.2.12. Interpretation of clinical effectiveness and safety evidence

Evidence investigating the clinical effectiveness and safety of vadadustat versus ESAs for the treatment of anaemia in adults with DD-CKD was identified by an SLR. Two pivotal phase III trials comparing vadadustat versus darbepoetin alfa were included: INNO$_2$VATE – incident and INNO$_2$VATE – prevalent. These two trials comparing

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vadadustat to a single ESA (i.e., darbepoetin alfa) serve as sufficient evidence to establish vadadustat's clinical effectiveness and safety compared to the entire class of ESAs, based on the well-established and acknowledged class effect (120-122).

The goals of the phase III, randomised, open-label, active-controlled INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials were to evaluate the efficacy, safety and CV risk associated with vadadustat treatment in DD-CKD patients with anaemia, as compared to darbepoetin alfa. The INNO$_2$VATE – incident trial was a study of vadadustat versus darbepoetin alfa for the correction or maintenance treatment of anaemia after correction of Hb or conversion from current ESA in adult patients with incident dialysis. The INNO$_2$VATE – prevalent trial was a study of vadadustat versus darbepoetin alfa for the maintenance treatment of anaemia in patients with DD-CKD after conversion from ESA therapy. In both trials, treatment with vadadustat OD demonstrated non-inferiority compared to darbepoetin alfa for the primary and secondary outcomes; change in average Hb between baseline and primary efficacy period (weeks 24 to 36), and between baseline and the secondary efficacy period (weeks 40 to 52), respectively. Prespecified subgroup analyses for the primary and key secondary efficacy endpoints yielded consistent and supportive results.

In the INNO$_2$VATE – incident trial, post-hoc analysis showed that the incidence of ESA rescue was less or similar with vadadustat treatment compared to darbepoetin alfa treatment. The incidence of RBC transfusion was slightly higher with vadadustat in Weeks 2 to 8, and thereafter similar between the 2 treatment groups. Therapeutic phlebotomy was required at similar low incidence in both treatment groups. In the INNO$_2$VATE – prevalent trial, there was more frequent use of RBC transfusions and ESA rescue therapy early on after vadadustat initiation compared with darbepoetin alfa using the protocol-specified definitions for narrow and broad-on-treatment rescue therapy. Additional post-hoc analyses were performed that included evaluating increases of ≥50% or ≤100% of darbepoetin alfa doses as rescue for the darbepoetin alfa treatment group. These analyses demonstrated greater or similar proportions of patients on darbepoetin alfa treatment received ESA rescue therapy.

Overall, vadadustat was well tolerated in patients with anaemia in DD-CKD. In the INNO$_2$VATE – incident trial, an evaluation of safety findings demonstrated comparable

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distribution of TEAEs and treatment-related AE rates between the two treatment groups. Furthermore, the distribution of TEAEs among the vadadustat treated patients did not differ when evaluated across subgroups including age, sex, race, and history of diabetes and hypertension. The overall incidence of TEAEs that lead to study drug discontinuation was minimal in both treatment groups. The incidence of treatment-emergent SAEs was lower in the vadadustat treatment group compared with the darbepoetin alfa treatment group, and the overall incidence was low in both groups. All AESIs were more frequently observed among patients treated with darbepoetin alfa compared to those treated with vadadustat. Furthermore, hepatic AEs were more frequent with darbepoetin alfa treatment compared to vadadustat. Overall, the incidence of events under monitoring (HF, malignancies, retinal effects due to VEGF expression) was comparable across the vadadustat and darbepoetin alfa treatment groups, with very few events reported. Vadadustat did not appear to influence vital signs or body weight. No clinically significant changes were noted for clinical safety laboratory parameters with either treatment.

A similar distribution of TEAEs between the treatment groups was also reported in the INNO$_2$VATE – prevalent trial, although there were more drug-related TEAEs and TEAEs leading to discontinuation of study drug with vadadustat compared with darbepoetin alfa (primarily driven by gastrointestinal disorders). However, vadadustat treatment was associated with similar SAE rates to that seen with darbepoetin alfa treatment during the overall treatment period. This included fewer overall deaths with vadadustat treatment compared with darbepoetin alfa treatment. No clinically meaningful changes were noted for haematology and clinical safety laboratory findings with either treatment.

For both trials, the number of patients with any MACE, the number of MACE, and MACE events per 100 patient-years for the individual MACE components (death, non-fatal MI, and non-fatal stroke) were similar in the vadadustat and the darbepoetin alfa treatment groups. In addition, the number of patients with CV MACE events, number of CV MACE events, and CV MACE events per 100 patient-years (including individual components of CV death, non-fatal MI, and non-fatal stroke), any TEEs (including vascular access thrombosis (VAT), arterial thrombosis, deep vein thrombosis, and

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pulmonary embolism, as well as any hospitalisation for HF were similar between the vadadustat and darbepoetin alfa treatment groups.

For both trials, discontinuation from study drug treatment was higher in the vadadustat treatment group compared to patients in the darbepoetin alfa treatment group. The key driver for vadadustat study drug discontinuation was patients no longer wanting to receive study drug, which was not unexpected given the open-label design comparing an investigational new oral agent to a known parenteral comparator.

In conclusion, robust clinical trial data demonstrates that vadadustat is non-inferior to darbepoetin alfa with respect to Hb response and maintenance of Hb levels in patients with anaemia in DD-CKD. Overall, the safety and tolerability profile of vadadustat was comparable to that of darbepoetin alfa. Furthermore, acknowledging the strength and high quality of this evidence, the UKKA's updated clinical guidelines have recently recommended the use of HIF-PHIs for the treatment of adult patients with anaemia in DD-CKD (3).

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B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

An SLR was conducted in November 2021 and updated in January 2024 to obtain all published economic evidence for the treatment of anaemia in CKD in the population under consideration (patients with anaemia in DD-CKD). Full details of the SLR are provided in Appendix G.

The SLR identified 26 economic evaluations, none of which applied a UK perspective. The studies identified included seven cost-minimisation studies (124-131), which were not deemed appropriate to inform cost-utility model structure of vadadustat as cost-minimisations studies were not likely to capture the full extent of efficacy, costs, and quality of life difference required for an incremental analysis. Also, five studies (132-136) were based on budget-impact models which could not be considered to inform the cost-effectiveness model. The remaining 14 studies identified included ten cost-utility analyses (i.e., reporting cost per quality-adjusted life-years [QALY]) (124-131), three cost-effectiveness analyses (i.e., reporting cost per life-years gained [LYG]) (137-139), and one cost consequence analysis. The majority of the identified cost-effectiveness or cost-utility studies were based on a cohort Markov model approach (125, 128, 131, 139-141), with one being a decision-tree model (127). Three studies used a combined approach with a decision tree for stratifying a cohort of patients among different Hb levels who then enter a cohort Markov model to simulate each Hb level where CVD occurrence was modelled for patients on HD (124, 129, 130).

The models concepts applied in the identified cost-utility or cost-effectiveness studies employed a variety of structural approaches and definitions of health states. Some studies modelled transitions between health states defined by different Hb level cut-offs to reflect the clinically important outcomes associated with improved Hb levels (125, 129), while other studies modelled transitions between health states that were defined according to type of RRT received (128, 130, 131, 140). Three studies modelled health states defined by cardiovascular events that occur in patients with anaemia (124, 129, 135). The remaining studies employed a combination of health states defined by anaemia and/or cardiovascular and renal events. Al Kharboush 2020

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used a Markov model to simulate anaemia and MACE occurrence in HD patients (124). Wong 2013 developed a Markov model with health states defined by meeting Hb level target and associated ESA treatment modification including related side-effects (141). Powe 1993 defined the health states modelled a decision tree approach by the presence of treatment response and side effects (135).

No previous NICE appraisals exist for the comparators in scope of the decision problem addressed in this submission (i.e., ESAs). For this reason, the economic model submitted to NICE for the appraisal of roxadustat in a similar indication [TA807] (123) was considered while developing the vadadustat model as it reflects a related disease area (i.e., anaemia in NDD-CKD). The roxadustat model previously submitted to NICE employed a structure based on stratification of patients among Hb level cut-offs. It modelled transitions between eight health states (seven based on different Hb levels and death), a choice which was critiqued by the NICE external review group (ERG) as the rationale behind the use of seven health states linked to Hb levels was not clear. Furthermore, the ERG concluded that use of seven distinct health states to model improvement in Hb levels was overly complex and increased uncertainty of the model results (123).

The findings from the SLR and the ERG and committee's critique of the roxadustat model were considered in the conceptualisation of the vadadustat model. To avoid similar criticism of the model developed for vadadustat, the approach was designed to address the limitations of the roxadustat model, where possible. More details on the structure of the vadadustat model and the rationale for the approach taken is provided in section B.3.2.2.

B.3.2. Economic analysis

A de novo model was developed in Microsoft Excel® 2016 macro-enabled workbook (.xlsm) to assess the cost-effectiveness of vadadustat in patients with anaemia in DD-CKD. The model was designed to be flexible and easily customised for use in any country-specific population and setting of interest.

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B.3.2.1. Patient population

The modelled patient population reflects DD-CKD patients with anaemia. This is in line with the scope of this NICE appraisal as well as the enrolment criteria of the INNO$_2$VATE – incident (111) and INNO$_2$VATE – prevalent (112) trials (hereafter referred to as INNO$_2$VATE trials) which form the evidence base for this submission. The patient populations from both INNO$_2$VATE trials (i.e., patients who recently initiated dialysis [incident] as well as patients who were already on dialysis [prevalent]) were used in the model. The demographics and baseline characteristics of the patients were sourced from the INNO$_2$VATE trials. All analyses were performed on the randomised population of the INNO$_2$VATE trials, except for the analyses for AEs and MACE outcomes (which were performed on the safety population). The INNO$_2$VATE program was designed so that the pooled analyses included enough independently adjudicated endpoints to allow a meaningful comparison of vadadustat and darbepoetin alfa with respect to MACE (113). For non-MACE related outcomes (where pooling of data was not performed), weighted average of the sample taken from both the trials was used.

B.3.2.2. Model structure

The model employs a Markov cohort design and is comprised of three mutually exclusive and exhaustive health states reflective of the clinical course of DD-CKD, including DD, transplant, and death (Figure 8). The model accommodates Hb level cut-offs for patients initiating vadadustat or ESAs of <10 g/dL, 10 - <12 g/dL, and ≥12 g/dL as they are the most commonly reported values in the UK (confirmed by KOLs). The distribution of patients across the three Hb levels changes at each cycle according to the Hb outcomes reported in the INNO$_2$VATE trial. Different Hb levels were associated with different levels of anaemia-related disutilities which affect the quality of life of patients as the anaemia-related disutility is larger for patients with lower Hb level (108).

The DD and transplant health states are further subdivided into three sub-states, namely no history of MACE (denoted as ‘No MACE’), history of MACE (denoted as ‘Hx MACE’) and new non-fatal MACE (denoted as ‘New MACE’). The death health state is further subdivided into two sub-states, namely deaths due to MACE-related

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causes and deaths due to non-MACE-related causes. Compared to the roxadustat model, the Markov model developed for vadadustat offers a simpler modelling approach as it defines health states according to the renal care received (dialysis, transplant), with sub-health states based on the history and occurrence of MACE, all of which are associated with relevant differences in costs, HRQoL and survival. The novel vadadustat model structure also offers advantages compared to currently published models identified from the SLR as it reflects the clinical course of CKD patients with anaemia through distinct clinically meaningful health states that can be modelled directly using the INNO$_2$VATE trial results.

At the start of the modelled time horizon, all patients enter the model through either the 'No MACE' DD health state or 'Hx MACE' DD health state and may subsequently transit to either transplant or death health states. Patients in the DD or transplant health states with no prior history of MACE who experience any non-fatal MACE event during a modelling cycle transit into the 'New MACE' sub-state of the respective health state. Similarly, patients in the DD or transplant health states with a prior history of MACE who experience a non-fatal MACE event during a modelling cycle transit into 'Hx MACE' sub-state of that respective health state. The model also allows a choice between two MACE definitions as defined in the INNO$_2$VATE trials: 1) MACE (comprised of all-cause mortality, non-fatal MI and non-fatal stroke), and 2) expanded MACE (comprised of MACE plus hospitalisation for HF or TEE excluding VAT). For the base case of the cost-effectiveness model, health states defined by MACE was used as it was the primary safety endpoint in the INNO$_2$VATE trial; the impact of modelling transitions between health states defined by expanded MACE was assessed as a scenario analysis.

Patients transition from the DD to transplant health states; however, a proportion of patients may also transition from transplant back to the DD health state as the transplant may fail. When patients experience a new MACE event (regardless of prior MACE history), they enter the 'New MACE' health-state only for one cycle, and then they transfer to 'Hx MACE'. It is possible for the same patient to experience a new MACE event several times during model horizon. Patients who die during the

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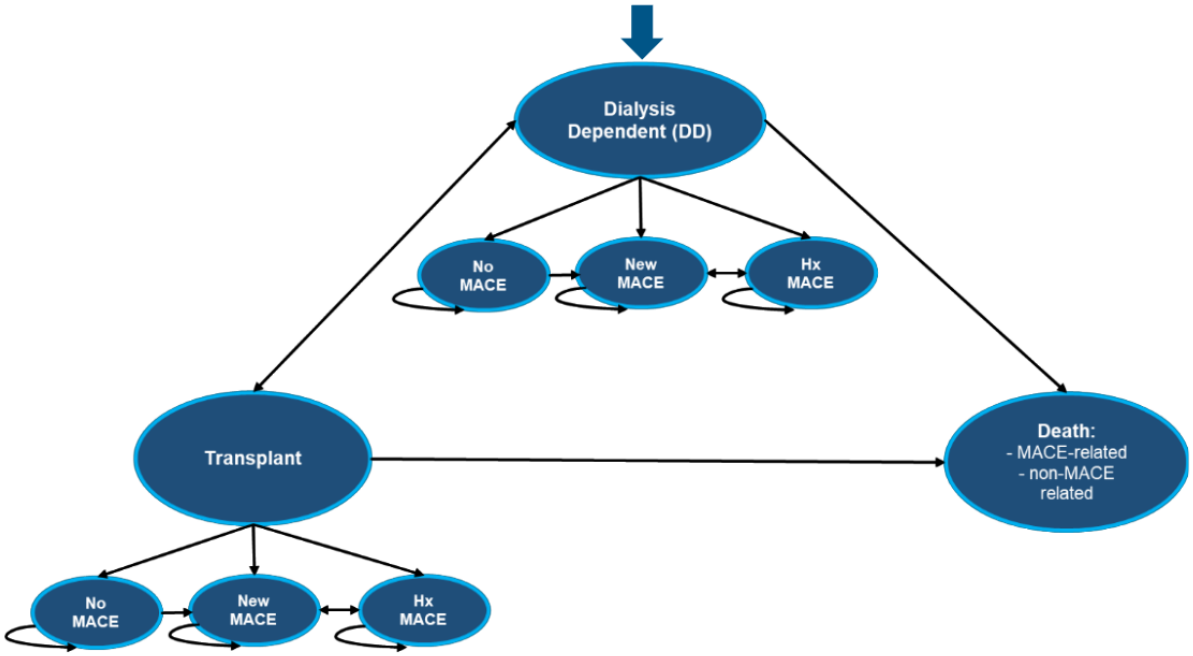
modelling cycle transit to the death health state (MACE or non-MACE) where they remain for the remaining duration of modelling horizon.

A schematic representation of the transition health states included in the model is provided in Figure 8. The key features of the cost-effectiveness analysis used in the model are summarised in Table 17.

Figure 8: Schematic representation diagram of vadadustat cost-effectiveness model



Abbreviations: DD, dialysis-dependent; MACE, major adverse cardiovascular event

Table 17: Features of the economic analysis

	Current evaluation	
Factor	**Chosen values**	**Justification**
Time horizon	42 years	Time horizon of 42 years represents a lifetime horizon as in the current model, 100% patients die at year 41 (cycle 52, month 156). Hence this covers more than the expected life span of all patients.
Perspective	Payer (NHS and PSS)	As per NICE Methods Guide
Cycle length	Three months	In line with the NICE guideline on management of CKD, it is the recommended frequency of monitoring iron deficiency. A three-month cycle was considered appropriate to monitor the changes in Hb levels alongside results of the therapy used.
Treatment waning effect	Yes	INNO$_2$VATE trials lasted for 52 weeks. Given the long time horizon which models treatment effects based on 52 week data, an assumption was made that the treatment

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	Current evaluation	
Factor	**Chosen values**	**Justification**
		effect of vadadustat on the risk of MACE reduction persisted for only five years. After five years, the risk of reduction was assumed to be equal for both vadadustat and darbepoetin alfa arms.
Treatment stopping rule	Yes	In line with the SmPC, a treatment stopping rule was applied at 24 weeks if clinically meaningful Hb increase did not occur.
Half cycle correction	Yes	As per NICE Methods Guide
Source of clinical data	INNO$_2$VATE trials	The pivotal phase III clinical trials provide a robust source of clinical evidence as they were the source of positive regulatory approval in the UK.
Source of utilities	HRQoL SLR (Appendix H)	As per NICE Methods Guide
Source of costs	NHS and PSS price sources	As per NICE Methods Guide
Discounting	3.5% per annum for costs and effects	As per NICE Methods Guide

Abbreviations: HRQoL, health-related quality of life; LY, life-years; NHS, National Health Services; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality-adjusted life-years; SLR, systematic literature review

B.3.2.3. Intervention technology and comparators

In the INNO$_2$VATE trials, vadadustat (300 mg with titration to 150-600 mg once daily) was dosed to achieve a target Hb level of 10-12 g/dL. However, the mean dose varied as treatment dose was adjusted over the course of the trial. Therefore, in the model, exact estimates of the doses used in INNO$_2$VATE trials for year 1 and 2 were used for the first and second year of model horizon, after which the estimate of year 3 was used until the end of the modelling horizon.

In line with the INNO$_2$VATE trials, the base case of the cost effectiveness model included darbepoetin alfa as the main comparator of the economic assessment. A scenario analysis was, however, conducted to compare vadadustat with other ESAs available in the UK market (namely epoetin alfa, epoetin beta, epoetin-zeta, and continuous erythropoiesis receptor activator [CERA]) as well as a mixture of ESAs to compare vadadustat with ESAs as a class. In the model, darbepoetin alfa was dosed in a similar manner to vadadustat based on the INNO$_2$VATE trial, as described above. For sourcing the doses for other ESAs, ESAs conversion factors from Aranesp®

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prescriber information/Choi 2013 conversion factor (142). The base case of the cost-effectiveness model sourced doses for other ESAs from the former (in line with the roxadustat submission).

B.3.3. Clinical parameters and variables

B.3.3.1. Baseline characteristics

The baseline characteristics of the patients entering the model were derived from the INNO$_2$VATE trials and are presented in Table 18.

Table 18: Baseline characteristics of the modelled cohort

Parameter	Incident and prevalent CKD patients with anaemia	
Age (years, mean)	57.9	
Females (%)	43.6	
Baseline history of MACE (%)	49.5	
Dialysis type (%)		
Haemodialysis	92.1	
Peritoneal dialysis	7.9	
Median time since dialysis initiation (years)	2.4	
Hb levels (%)	Vadadustat	ESA
<10 g/dL	39.2	39.2
≥10-<12 g/dL	59.0	59.8
≥12 g/dL	1.8	0.9

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; ESA, erythropoietin stimulating agent; Hb, haemoglobin; HF, heart failure; MI, myocardial infarction
Source: Pooled data from the INNO$_2$VATE trials (143)

B.3.3.2. Transition probabilities

The transition probabilities for patients to move from the DD to transplant, transplant to DD, DD to death, and transplant to death states were based on data from the 25th UKRR annual report (144). Cumulative probabilities of transitioning between RRT modalities (dialysis, transplant) and death since kidney replacement therapy start at 90-day, 1-year, 3-years and 5-years, based on the 25th UKRR annual report (144), were used to estimate baseline transition probabilities in DD patients. To estimate year-on-year transition probabilities from cumulative probabilities, a linear trend between above mentioned data points was assumed. Annual transition probabilities which were used to inform probability of travelling between health states are presented in Table 19.

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Table 19: Baseline transition probabilities per cycle of transitioning between renal replacement therapy modality and mortality

Time	DD to DD	DD to Transplant	DD to Death	Transplant to DD	Transplant to Transplant	Transplant to death
90 days	0.9404	0.0159	0.0438	0.0050	0.9930	0.0020
1 year	0.9326	0.0274	0.0399	0.0020	0.9946	0.0034
3 years	0.9172	0.0307	0.0521	0.0005	0.9962	0.0033
5 years	0.9068	0.0138	0.0794	0.0005	0.9935	0.0059

Abbreviations: DD, dialysis dependent
Source: 25th UKRR annual report (144)

B.3.3.2.1. Occurrence of MACE

To determine MACE and inputs according to their definition in the INNO$_2$VATE trials, the distribution of MACE and expanded MACE events was sourced from pooled INNO$_2$VATE data (Table 20). MACE comprised non-fatal MI and non-fatal stroke in line with the definition of the primary MACE safety endpoint. Expanded MACE comprised non-fatal MI, non-fatal stroke, hospitalisation for HF and TEEs excluding VAT, in line with the definition of the secondary MACE safety endpoint. The distribution of individual MACE events was used to inform disutility and cost estimates for MACE sub-states by weighting disutility and cost estimates for individual MACE events with the distribution of individual MACE events.

Table 20: Percentage of patients experiencing MACE events

MACE event	Vadadustat	Darbepoetin alfa
MACE		
MI, non-fatal	77%	76%
Stroke, non-fatal	23%	24%
Thromboembolic event¸ excluding vascular access throm	0%	0%
Hospitalisation for HF	0%	0%
Expanded MACE		
MI, non-fatal	37%	37%
Stroke, non-fatal	11%	15%
Thromboembolic event¸ excluding vascular access throm	12%	11%
Hospitalisation for HF	40%	37%

Abbreviations: HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction
Source: Pooled data from the INNO$_2$VATE trials (143)

To correct baseline transition probabilities for the risk of MACE and death, the probability of occurrence of a MACE event was estimated quarterly for each sub-state (i.e., 'No MACE', 'Hx MACE', and 'New MACE') using one year of patient-level data

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for the darbepoetin alfa arm from the INNO$_2$VATE trials (Table 21). IPD on the number of MACE/expanded MACE events from the INNO$_2$VATE trials captured all events (first and subsequent) occurring in the trials. The probability of death was derived from the INNO$_2$VATE trials. Probability of death was re-weighted into MACE-related and non-MACE-related death based on the distribution of patients between death causes based on the 25th UKRR annual report (144). To distinguish between MACE and non-MACE deaths, the transition probabilities to the death state were re-weighted using the percentage of patients that die from cardiac and cerebrovascular diseases and those that die from other causes. Re-weighting was based on the 25th UKRR annual report which reported that 20.3% and 79.7% of patients on kidney replacement therapy died from cardiac/cerebrovascular diseases and other causes, respectively (144). It was assumed that the split between MACE-related and non-MACE related death stayed constant through the modelling time horizon. MACE risks derived from quarter 1 of the INNO$_2$VATE trials were applied to cycle 1, while averaged MACE risks from quarter 2 to 4 were applied to cycles 2 to 20. The probability of transitioning to other states/substates was adjusted proportionally. The risk of MACE was allocated proportionally across transition probabilities for DD and transplant.

Table 21: Probabilities of MACE occurrence by cycle

		Cycle 1	Cycle 2-4
Vadadustat			
Non-fatal MACE	No HX	[redacted]	[redacted]
Non-fatal MACE	HX	[redacted]	[redacted]
Death only	No HX	[redacted]	[redacted]
Death only	HX	[redacted]	[redacted]
ESA			
Non-fatal MACE	No HX	[redacted]	[redacted]
Non-fatal MACE	HX	[redacted]	[redacted]
Death only	No HX	[redacted]	[redacted]
Death only	HX	[redacted]	[redacted]

Abbreviations: ESA, erythropoietin stimulating agent; MACE, major adverse cardiovascular event
Source: INNO$_2$VATE trials; 25th UKRR annual report (144)

For vadadustat, the probability of occurrence of a new fatal/non-fatal MACE event was estimated based on the relative risks versus ESA from the INNO$_2$VATE trials (Table 22). The relative risk of MACE was based on the hazard ratio for time to first MACE/ first expanded MACE event (primary and secondary safety endpoints in INNO$_2$VATE, respectively) and was assumed to be the same for those with and without a history of

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MACE. Since the INNO$_2$VATE trials reported hazard ratios of time to first MACE/expanded MACE, while IPD was only available for all MACE/expanded MACE events, an assumption was made that hazard ratios of time to first MACE/expanded MACE reflect the risk reduction associated with vadadustat for first as well as subsequent events.

Table 22: Relative risks used for estimating the probability of occurrence of a new MACE

Endpoint	Estimate (95% CI)
Hazard ratio of time to first MACE	0.96 (0.833; 1.113)
Hazard ratio of time to first MACE plus hospitalizations for HF or thromboembolic events excluding vascular access thrombosis	0.96 (0.840; 1.096)

Abbreviations: CI, confidence interval; HF, heart failure; MACE, major adverse cardiovascular event
Source: Pooled data from the INNO$_2$VATE trials

To account for potential reduction in vadadustat impact on long-term risk of MACE beyond the INNO$_2$VATE trials period, treatment waning was incorporated into the model by specifying the timepoint beyond which the improved risk of MACE associated with vadadustat (represented by the hazard ratios above) is negated. In the base case analysis, vadadustat is associated with a lower risk of MACE up to cycle 20 (5 years), after which the risk of MACE between arms is equal, which was validated with a clinical expert (Appendix N). In the scenario analyses, a scenario which assumes a lower risk of MACE with vadadustat across the whole modelling horizon is presented.

Transition probabilities for cycle 1 to 20 for vadadustat and darbepoetin alfa are presented below (Table 23).

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Table 23: Health state transition probabilities

Health state		Sub-state	Vadadustat								ESAs							
			DD			Transplant			Death		DD			Transplant			Death	
			No MACE	Hx MACE	New MACE	No MACE	Hx MACE	New MACE	MACE	Non-MACE	No MACE	Hx MACE	New MACE	No MACE	Hx MACE	New MACE	MACE	Non-MACE
Cycle 1	DD	No MACE																
		Hx MACE																
		New MACE																
	Transplant	No MACE																
		Hx MACE																
		New MACE																
	Death	MACE																
		Non-MACE																
Cycle 2-4	DD	No MACE																
		Hx MACE																
		New MACE																
	Transplant	No MACE																
		Hx MACE																
		New MACE																
	Death	MACE																
		Non-MACE																
Cycle 5-12	DD	No MACE																
		Hx MACE																
		New MACE																
	Transplant	No MACE																
		Hx MACE																
		New MACE																
	Death	MACE																
		Non-MACE																
Cycle 13-20+	DD	No MACE																
		Hx MACE																
		New MACE																
	Transplant	No MACE																
		Hx MACE																
		New MACE																
	Death	MACE																
		Non-MACE																

Abbreviations: DD, dialysis dependent; ESA, erythropoietin stimulating agent; Hx, history of; MACE, major adverse cardiovascular event
Source: 25th UKRR annual report (144)

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Transition probabilities from cycle 20 adjusted for the probability of death beyond 5-years were applied until the end of the modelling horizon. Long-term survival data was sourced from the 25th UKRR annual report, which provided survival data based on years since the start of kidney replacement therapy, to estimate long-term mortality. To do this, data reporting survival for 10 years after the start of kidney replacement therapy in the age group 55-64 years, in line with the average INNO$_2$VATE baseline cohort age, were digitized using WebPlotDigitizer software (145). The percentage of patients surviving at each point was subtracted from 100% to calculate mortality. Mortality data was then extrapolated into the future using a regression model to determine the relationship between time since kidney replacement therapy start and mortality. Several regression models were tested including linear and logarithmic regressions. Both regression types explained more than 95% of variation in mortality data. The clinical expert contacted for model validation expressed an opinion that linear regression is not representative, as after 10-years on KRT a plateau in mortality is expected. Therefore, logarithmic regression was chosen for the mortality extrapolation method in the current model. Logarithmic regression yielded a coefficient of 0.2572 and an intercept of 0.0338 (Figure 9). Using the parameters above, death probability per cycle was calculated for the darbepoetin alfa arm. For the vadadustat arm, the above-mentioned transition probabilities were corrected using the hazard ratios of time to MACE. For implementing death probabilities into the model, time since KRT was tracked based on patients having had a median of 2.4 years on dialysis at baseline in the INNO$_2$VATE trials.

Probability of mortality elicited using regression analysis was compared to death probabilities of the general population mortality based on Office of National Statistics data. If general population mortality estimates exceeded KRT mortality estimates at any model cycle, the larger probability of death was applied.

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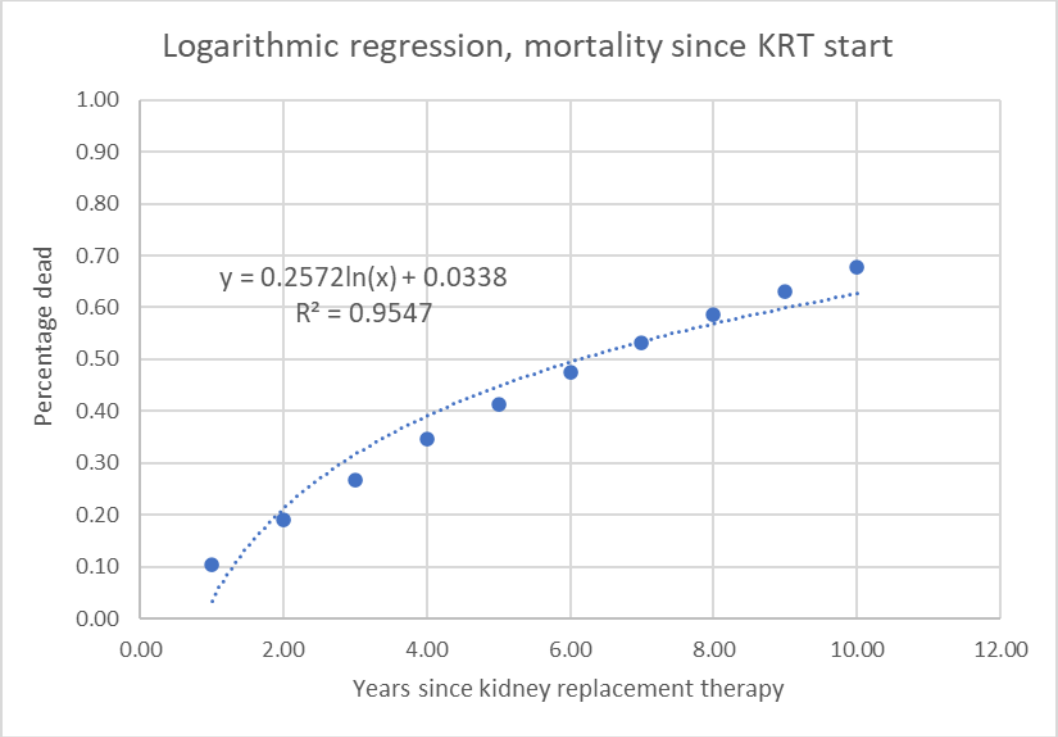
Figure 9: Estimation of long-term mortality (logarithmic regression)



Abbreviations: KRT, kidney replacement therapy
Source: 25th UKRR annual report (144)

B.3.3.3. Haemoglobin levels

Different Hb levels were considered in the model to reflect the quality of life impact of lower Hb levels through anaemia-related disutilities, which increase as the Hb level decreases. To estimate disutility associated with Hb levels, the weighted average of disutilities associated with each Hb level threshold and distribution of patients among Hb level thresholds was estimated. The Hb levels are also used in the model to incorporate the stopping rule specified in the vadadustat SmPC which advises treatment should stop beyond week 24 if a clinically meaningful increase in Hb levels is not achieved. The stopping rule was applied to the vadadustat arm using the proportion of patients falling under a <10 g/dL cut-off at week 24. All patients who stopped taking vadadustat due to the stopping rule, as per discontinuation policy in the INNO$_2$VATE trials, transitioned to receiving darbepoetin alfa. It was assumed that patients discontinuing vadadustat will switch to transition probabilities of ESA arm as the INNO$_2$VATE trials did not capture efficacy in vadadustat responders and non-responder in line with the stopping rule. In cycle 2 of the model, subset of vadadustat patients discontinuing vadadustat will progress in the model in line with ESA arm

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transition probabilities and darbepoetin alfa costs were applied to patients stopping vadadustat treatment in line with the stopping rule. As the proportion of patients with Hb level <10 g/dL was higher than discontinuation rate in vadadustat arm in cycle 2, to avoid potential double-counting general discontinuation of vadadustat was not applied in cycle 2 of the model. Other parameters inclusion rates of rescue therapy and rescue therapy doses were prescribed to patients who discontinued vadadustat in line with vadadustat arm estimates. Beyond 52 weeks, the stratification of patients between Hb levels remains the same until the end of modelling horizon.

The distributions of patients in the vadadustat and ESA treatment groups by Hb level were estimated using patient-level data from the INNO$_2$VATE trials (Table 24). For the first year of the modelling time horizon, the Hb levels were based on the quarterly data derived from the INNO$_2$VATE trials. For the second year and onwards, Hb levels were based on data from the fourth quarter of the trial and were assumed to remain constant until the end of modelling horizon. Distributions were estimated considering the safety population of the INNO$_2$VATE trials, including those who discontinued treatment during trial.

Table 24: Cohort distribution by Hb level

	Week 1 Cycle 0	Week 12 Cycle 1	Week 24 Cycle 2	Week 36 Cycle 3	Week 52 Cycle 4
Vadadustat					
<10 g/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10-<12 g/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 g/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESA					
<10 g/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10-<12 g/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 g/dL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESA, erythropoietin stimulating agent
Source: Estimated using INNO$_2$VATE trials (111, 112)

B.3.3.4. Treatment discontinuation

The proportion of patients remaining on treatment at a particular time interval was sourced from the INNO$_2$VATE trials. The majority of the INNO$_2$VATE trial sites were in the US, where a narrower limit of 10-11 g/dL for Hb levels was applied. For the first year of the modelling horizon, the proportion of patients remaining on treatment was

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based on the quarterly data obtained from the trials (Table 25). For the second year and onwards, no additional treatment discontinuation was assumed to occur (i.e., all patients remaining on treatment after first year were assumed to continue treatment for the remaining time horizon).

Table 25: Proportion of patients remaining on treatment

Week	Cycle	Vadadustat	ESA
Weeks 2-8	1	100%	100%
Weeks 10-20	2	93%	97%
Weeks 24-36	3	84%	91%
Weeks 40-52	4+	74%	83%

Abbreviations: ESA, erythropoietin stimulating agent
Source: INNO$_2$VATE trials (111, 112)

B.3.3.5. Rescue therapy

The frequency of rescue therapy (in the form of IV iron, blood transfusion or ESA) use was derived from the INNO$_2$VATE trials. The use of rescue therapy was estimated considering all randomised patients.

The frequency of IV iron administration was not recorded in the course of the INNO$_2$VATE trials. Instead, a proportion of patients using IV iron was reported, therefore, one administration per week was assumed due to the chronic nature of the treatment. For the first year of the modelling horizon, the use of rescue therapy was based on the quarterly data obtained from the INNO$_2$VATE trials. For the second year and onwards, the use of rescue therapy was based on data from the fourth quarter of the trials and was assumed to remain constant for the remaining modelling horizon (Table 26).

Table 26: Proportion of patients receiving IV iron rescue therapy

Type of rescue therapy	Week	Cycle	Vadadustat	ESA
IV iron rescue therapy (%)	Week 2-8	1	50.8	53.0
	Week 10-20	2	55.6	55.6
	Week 24-36	3	57.3	56.8
	Week 40-52	4	58.9	59.2
	Week 64+	5+	63.0	65.0

Abbreviations: ESA, erythropoietin stimulating agent; IV, intravenous
Source: INNO$_2$VATE trials (111, 112)

Blood transfusion and ESAs were characterised in terms of the mean number of administrations of any rescue therapy. For RBC and ESAs rescue therapies, the rates

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per 100 patient-years (PY) were sourced from the INNO$_2$VATE trials and were transformed to probabilities per cycle to be used in the model (Table 27). The cost-effectiveness model used the definitions of narrow rescue treatment (as defined in the INNO$_2$VATE trials) for RBC and ESAs rescue therapies.

Table 27: Rates of receiving RBC and ESA rescue therapy

Type of rescue therapy	Vadadustat	ESA
RBC transfusion (rate per 100 PY)	9.43	6.84
ESA (rate per 100 PY)	30.47	8.29
RBC transfusion (probability per cycle)	0.023	0.017
ESA rescue (probability per cycle)	0.073	0.021

Abbreviations: ESA, erythropoietin stimulating agent; PY, patient-year; RBC, red blood cell
Source: INNO$_2$VATE trials (111, 112)

B.3.3.6. Adverse events (other than MACE)

For the economic analysis, the occurrence of AEs in patients entering the model was sourced from the INNO$_2$VATE trials (Table 28). In the model, it was assumed that the AEs occur shortly after the treatment initiation during cycle 1.

From the INNO$_2$VATE trials, severe TEAEs whose occurrence in patients exceed at least 2% in any treatment arm were included in the model. This criterion was fulfilled by pneumonia, sepsis, fluid overload and hyperkalaemia.

Other non-MACE AEs were infrequent and similar across vadadustat and darbepoetin alfa treatment arms, and hence were not considered relevant for the analysis as their inclusion was not expected to have any impact on the model results.

Table 28: Proportion of patients experiencing severe TEAEs excluding MACE

	Vadadustat		ESA	
	Percentage of patients (%)	SE	Percentage of patients (%)	SE
Pneumonia	4.4%	0.4%	3.9%	0.4%
Sepsis	3.2%	0.3%	3.3%	0.3%
Fluid overload	3.6%	0.4%	2.3%	0.2%
Hyperkalaemia	0.2%*	0.0%	0.2%*	0.0%

Abbreviations: ESA, erythropoietin stimulating agent; SE, standard error; TEAE, treatment-emergent adverse event
Note: *The percentage of patients experiencing hyperkalaemia was >2% in INNO$_2$VATE – incident. However, when a weighted average of the percentage of patients experiencing hyperkalaemia in INNO$_2$VATE – incident and INNO$_2$VATE – prevalent was calculated, it was 0.2% for both the treatment arms, as the sample size of INNO$_2$VATE – incident is much lower than the sample size of INNO$_2$VATE – prevalent.
Source: INNO$_2$VATE trials (111, 112)

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B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

The INNO$_2$VATE trials did not collect HRQoL data. Therefore, published evidence served as the source of the utility values within the model.

B.3.4.2. Mapping

Not applicable.

B.3.4.3. Health-related quality-of-life studies

An SLR was conducted in November 2021 and updated in January 2024 to identify and collate the utility and disutility inputs for the health states and AEs associated with anaemia in CKD. Full details of the search strategy, study selection process and results are presented in Appendix H. However, none of the studies captured in the SLR were conducted in a UK setting and hence were not used to inform the vadadustat cost-effectiveness model.

In the base-case, health state utilities were sourced from Liem et al. 2008 (146), which provides a meta-analysis of utility estimates. This study was not identified in the SLR because it did not include a population with anaemia and CKD, however it was selected for use in the model as this study reported utilities per kidney replacement therapy type (HD, PD and transplant) in patients with CKD. Furthermore, the same source was also used and accepted for the appraisal of roxadustat in CKD (TA807) (123). All other health state utilities were based on those applied in the roxadustat submission in NDD-CKD.

B.3.4.4. Adverse reactions

The vadadustat cost-effectiveness model also incorporated the disutility inputs associated with AEs occurring in patients entering the model. These disutility inputs were sourced from Sullivan 2011 (for pneumonia and sepsis) (147), NICE TA599 (for fluid overload) (148), and NICE TA877 (for hyperkalaemia) (149), as these AEs are not CKD-specific and are assumed to be managed in a similar manner as in patients with any other condition. The details of the disutilities applied in the cost-effectiveness model are presented in section B.3.4.5.

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B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

The utility/disutility values used in the base-case of the cost-effectiveness analysis are presented in Table 29.

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Table 29: Summary of utility/disutility values for cost-effectiveness analysis

Parameter		Vadadustat		ESAs		Source	Reference in submission	Justification for choice of utility value
		Utility value, mean	SE	Utility value, mean	SE			
Annual health state utilities								
Haemodialysis (HD)	No MACE	0.56	0.06	0.56	0.06	Liem 2008* (146)	B.3.4.3	Relevant literature for health-states specified in the model; HRQoL was not evaluated as part of vadadustat clinical trial programme
	Hx MACE*	0.52	0.05	0.52	0.05			
	New MACE*	0.48	0.05	0.48	0.05			
Peritoneal dialysis (PD)	No MACE	0.58	0.06	0.58	0.06			
	Hx MACE*	0.54	0.05	0.54	0.05			
	New MACE*	0.50	0.05	0.50	0.05			
Dialysis (total)	No MACE	0.56	0.06	0.56	0.06			
	Hx MACE*	0.53	0.05	0.53	0.05			
	New MACE*	0.49	0.05	0.49	0.05			
Transplant	No MACE	0.81	0.08	0.81	0.08			
	Hx MACE*	0.77	0.08	0.77	0.08			
	New MACE*	0.73	0.07	0.73	0.04			
Disutilities due to adverse events								
MACE-related disutilities	Acute MI	-0.06	0.01	-0.06	0.01	Sullivan 2011 (147)	B.3.4.4	Relevant catalogue of utility scores for the UK
	History of MI	-0.04	0.03	-0.04	0.03			
	Acute stroke	-0.12	0.01	-0.12	0.01			
	History of stroke	-0.03	0.02	-0.03	0.02			
	Acute TEE	-0.06	0.01	-0.06	0.01			
	History of TEE	0.00	0.00	0.00	0.00			
	Acute HF (sustained)	-0.12	0.01	-0.12	0.01			
	History of HF	0.00	0.00	0.00	0.00			
Non-MACE AEs disutilities	Pneumonia	-0.08	0.02	-0.08	0.02	Sullivan 2011 (147)		
	Sepsis	-0.06	0.03	-0.06	0.03			
	Fluid overload	-0.0029	0.00	-0.0029	0.00	NICE TA599 (148)		Relevant based on values used in previous appraisal; assumed disutility for oedema

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Parameter		Vadadustat		ESAs		Source	Reference in submission	Justification for choice of utility value
		Utility value, mean	SE	Utility value, mean	SE			
								is equal to disutility for fluid overload
	Hyperkalaemia	-0.03	0.00	-0.03	0.00	NICE TA877 (149)		Relevant based on values used in previous appraisal
Utility adjustment to Hb level								
Hb-related utility loss (reference Hb≥13 g/dL)	Utility loss per 1 g/dL decrease in Hb	-0.0114	0.00	-0.0114	0.00	Yarnoff 2016 (108)	-	Relevant based on values used in previous appraisal (TA 807); HRQoL was not evaluated as part of vadadustat clinical trial programme
Hb level and related utility	<10 g/dL	-0.0627	0.01	-0.0627	0.01	Calculated from Yarnoff 2016 (108)		
	≥10-<12 g/dL	-0.0285	0.003	-0.0285	0.003			
	≥12 g/dL	-0.0057	0.001	-0.0057	0.001			
Utility adjustment to mode of administration								
Mode of administration utility increment	Utility increment per cycle	0.0103	0.00	0.0015	0.00	Lorenzo 2023 (150)	-	Relevant based on published cost-effectiveness study identified in economic SLR

Abbreviations: ESA, erythropoietin stimulating agent; Hb, haemoglobin; HRQoL, health-related quality of life; Hx, History of; MACE, major adverse cardiovascular event; SE, Standard error; TEE; thromboembolic event

Note: *Liem 2008 was used as a source only for No MACE substate. For Hx MACE and New MACE, disutilities for MACE were applied given MACE events occurrence in INN$_2$OVATE trials (which differ depending on MACE endpoint chosen: MACE or expanded MACE)

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B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify cost and resource use associated with the treatment of anaemia in patients with CKD. Full details of the search strategy, study selection process and results are presented in Appendix I. Most of the studies identified were conducted outside of the UK and deemed irrelevant for sourcing the costs, while some studies were conference abstracts that did not provide the necessary level of details required for this submission. Hence, most of the inputs for costs and resource use were sourced from the roxadustat appraisal (TA807) (123) and NHS Reference Costs 2020/21 (151).

B.3.5.1. Intervention and comparators' costs and resource use

Average weekly doses for vadadustat and darbepoetin alfa were sourced from INNO$_2$VATE trials from years 1,2 and 3. Doses from year 3 were assumed to be equal to long term doses for both treatment and were applied through modelling horizon beyond year 3. To calculate respective weekly dose of other ESAs, conversion factors were applied as in Table 30.

The treatment cost values used in the model are presented in Table 31. The list prices of the treatments were sourced from the British National Formulary (BNF).

Table 30: Dose conversion factors for ESAs

ESA	Conversion	Dose conversion factor	Source
Darbepoetin alfa	N/A	1	Aranesp® (darbepoetin alfa) US FDA label* (152)
Epoetin-A	mcg to IU	362.5	
Epoetin-B	mcg to IU	362.5	
Epoetin-Z	mcg to IU	362.5	
CERA	mcg to mcg	1.21	Choi 2013 conversion factor (142)

Abbreviations: CERA, Continuous erythropoiesis receptor activator; FDA, Food and Drug Administration; IU, International Unit; mcg, microgram; N/A, not applicable; US, United States
Note: *US FDA labels were used because the EMA SmPCs did not provide dose conversion factors. Same conversion factor was used for darbepoetin alfa, epoetin-A, epoetin-B and epoetin-Z

In the base case, the cost per cycle of vadadustat was calculated by applying the average mg cost of drug across formulation and weekly average dose from the INNO$_2$VATE trials (Table 31). To estimate the cost of treatment per cycle, the weekly

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dose of the drug was multiplied by the number of weeks in a cycle and the average cost of the treatment. Treatment wastage was applied to this calculation in one of the scenario analyses. For darbepoetin alfa, the average weekly dose was calculated by applying the cost of a pack containing one administration of weekly dose rounded up (40 mg pack). For other ESA agents, average weekly doses derived from darbepoetin alfa trial dose corrected for conversion factors was multiplied by the number of weeks in a cycle and the average unit cost of the treatment. For vadadustat, the cost of one weekly treatment was estimating by combining packs with the least residual content. For year 1, one pack of 300 mg 98 tablets and one pack of 150 mg 28 tablets per cycle were considered; while for years 2 and 3, one pack of 300 mg 98 tablets and one pack of 300 mg 28 tablets per cycle were considered.

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Table 31: Cost of treatment with vadadustat and ESAs

Treatment	Time period	Dose per week without treatment wastage	Dose per week with treatment wastage	Cost per unit (£)	Cost per cycle without treatment wastage (£)	Cost per cycle with treatment wastage (£)	Source
Vadadustat	Year 1	[redacted]	-	0.035	[redacted]	[redacted]	MEDICE data on file
	Year 2		-				
	Year 3+		-				
Darbepoetin alfa	Year 1	32 mcg	40 mcg	1.47	621.15	765.98	BNF (darbepoetin alfa) (153)
	Year 2	37 mcg	40 mcg		713.56	765.98	
	Year 3+	40 mcg	40 mcg		761.85	765.98	
Epoetin alfa	Year 1	11,758 IU	12,000 IU	0.0058	882.21	900.40	BNF (epoetin alfa) (154)
	Year 2	13,507 IU	14,000 IU		1,013.46	1,050.47	
	Year 3+	14,421 IU	15,000 IU		1,082.04	1,125.50	
Epoetin beta	Year 1	11,758 IU	12,000 IU	0.0070	1,075.82	1,098.00	BNF (epoetin beta) (155)
	Year 2	13,507 IU	14,000 IU		1,235.88	1,281.00	
	Year 3+	14,421 IU	15,000 IU		1,319.50	1,372.50	
Epoetin zeta	Year 1	12,000 IU	12,000 IU	0.0048	737.80	753.01	BNF (epoetin zeta) (156)
	Year 2	14,000 IU	14,000 IU		847.57	878.51	
	Year 3+	15,000 IU	15,000 IU		904.92	941.26	
CERA	Year 1	39 mcg	40 mcg	1.468	751.63	766.07	BNF (methoxy polyethylene glycol-epoetin beta) (157)
	Year 2	45 mcg	50 mcg		863.45	957.59	
	Year 3+	48 mcg	50 mcg		921.88	957.59	

Abbreviations: BNF, British National Formulary

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B.3.5.2. Health-state unit costs and resource use

B.3.5.2.1. Administration cost

Given vadadustat is an oral treatment, its administration cost was assumed to be zero. The administration cost of darbepoetin alfa was calculated using the distribution of patients based on their preferred route of administration and the cost associated with that route. In line with NICE TA807 (123), it was assumed that 15% patients on PD will have assisted SC administration (nurse visit) as PD patients are not routinely in medical facilities. According to Michalopoulos 2022, 81% of DD patients receive IV ESAs. In line with this, it was assumed that 81% of HD patients in the model will receive IV ESAs in hospital. Remaining patients on HD and PD were assumed to have administered SC ESAs independently. A clinical expert has confirmed that the preferred mode of administration is representative for the UK population of DD-CKD patients with anaemia. These assumptions were then used to recalculate the type of administration according to the distribution of patients between PD and HD in the INNO$_2$VATE trials. After performing the recalculation, it was estimated that 75%, 24% and 1% patients would receive darbepoetin alfa via the IV, SC (independent) and SC (assisted) routes, respectively. IV, SC (independent) and SC (assisted) routes were associated with a unit cost of £30.88 (based on per hour patient-related nurse work in hospital setting), £0 and £22.95 (based on per hour patient-related home district nurse appointment), respectively[2]. The overall administration costs associated with vadadustat and ESAs are presented in Table 32.

Table 32: Cost of administration with vadadustat and ESAs

Treatment	Frequency of administration per week	Frequency of administration per cycle	Cost per cycle (£)	Source
Vadadustat	7	91.3	0	Vadadustat SmPC (7-9)
Darbepoetin alfa	1	13.0	304.01	Calculated as per assumption based on TA807 (158) Administration frequencies based on relevant SmPCs (159-
Epoetin alfa	2	26.1	608.0	
Epoetin beta	2	26.1	608.0	
Epoetin zeta	2	26.1	608.0	
CERA	1	13.0	304.01	

[2] Costs were sourced from Personal Social Services Research Unit (PSSRU) Unit cost, 2018/19 and inflated to 2023. More information on inflation indices can be found in Appendix O.

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				163) and were confirmed by clinical expert

Abbreviations: SmPC, summary of product characteristics

B.3.5.2.2. Monitoring cost

The monitoring cost was calculated using the unit cost of a consultant visit in a hospital setting (assuming a 15-minute appointment; £30.76) and the number of visits per quarter. These costs are presented in Table 33.

Table 33: Cost of monitoring with vadadustat and darbepoetin alfa

Treatment	Year	Number of visits per quarter	Cost per cycle (£)
Vadadustat	Year 1	4.0	123.03
	Year 2+	1.5	46.14
Darbepoetin alfa, other ESAs	Year 1	4.0	123.03
	Year 2+	1.5	46.14

Abbreviations: PSSRU, Personal Social Services Research Unit
Source: NICE TA807 (123); PSSRU 2021 (164)

B.3.5.2.3. Disease management cost

Management of CKD involves either dialysis or transplant. The costs associated with dialysis (HD and PD), one-time dialysis insertion procedure, and transplant were sourced from NHS reference costs 2021/2022 (151) (Table 34). The management of CKD involves either dialysis or transplant. The costs associated with dialysis (HD and PD), one-time dialysis insertion procedure, and transplant were sourced from NHS reference costs 2021/2022 (151).

Table 34: Cost associated with dialysis and transplant health states

Model input	Reference	HRG code	Annual cost	Cost per cycle
Insertion procedure				
Access insertion procedure for HD*	NHS reference costs 2021/2022 (151)	YR41A	£1,013	-
Access insertion procedure for PD*		LA05Z	£1,202	-
Dialysis				
HD	NHS reference costs 2021/2022 (151)	LD01A-LD10A	£21,585	£5,396
PD		LD11A-LD13A	£27,682	£6,921
Transplantation				

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Acute event	NHS reference costs 2021/2022 (151) Organ Donation and Transplant: Activity Report 2022/23 (165)	Recipient costs • Procedure: LA01A-LA03A • Pre-screening & follow-up: LA12A, LA13A Donor costs • Pre-screening & follow-up: LA10Z, LA11Z	£18,899	-
Long-term (annual)	Kerr 2012 (166), inflated to 2022**	-	£9,135	£2,284

Abbreviations: HD, haemodialysis; PD, peritoneal dialysis
Note: *One-off costs incurred by incidence DD patients only
**Cost was inflated to 2022 since the 2022-23 price index was not published at the time of informing costs to the model (more details on the inflation indices can be found in Appendix O)

B.3.5.3. Adverse reaction unit costs and resource use

The costs associated with MACE events and resultant hospitalisations were sourced from NHS Reference Costs 2021–22 (151). The cost associated with AEs (non-MACE) were sourced from NHS National Cost Collection 2021/22 (151) and NHS trust and NHS foundation trusts 2023 (75). These costs are presented in Table 35.

Table 35: Adverse event costs

		Cost per event (£)	SE	Source
MACE costs				
Acute events	MI (non-fatal) and rehabilitation (HRG code: EB10A-EB10E, VC38Z)	2,567.9	256.8	NHS Reference Costs 2021–22 (151)
	MI, fatal	2,083.9	208.4	
	Stroke (non-fatal) and rehabilitation (HRG code: A35A-A35F, VC04Z)	4,941.8	494.2	
	Stroke, fatal	4,408.6	440.9	
	Non-MACE death	0.0	0.0	
	TEEs (HRG codes: YQ51A-E, YQ50A-F, DZ09J-Q)	1,094.7	109.5	
	Hospitalisation for HF (HRG code: EB03-E)	2,542.4	254.2	
Long-term maintenance	MI, non-fatal	733.5	73.4	NICE TA 317 (167)
	Stroke, non-fatal	5,160.4	516.0	Xu et al., 2017 (168)
	Thromboembolic events	0.0	0.0	Assumed
	Hospitalisation for HF	1,019.4	101.9	NICE TA 679 (169)
Non-MACE costs				
Pneumonia		385.2	38.5	NHS National Cost Collection 2021/22 (151) and NHS trust and NHS foundation trusts 2023 (75)
Sepsis		456.6	45.7	
Fluid overload		640.5	64.1	

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	Cost per event (£)	SE	Source
Hyperkalaemia	85.7	8.6	TA877 (149); NHS National Cost Collection 2021/22 (151) and NHS trust and NHS foundation trusts 2023 (75)

Abbreviations: HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; NHS, National Health Services; TEE; thromboembolic event

Hospitalisation costs (Table 36) were quantified using the MACE events distribution in Table 19. The INNO$_2$VATE trials did not assess rates or frequencies of hospitalisation associated with MACE events. It was assumed all MACE events and hospitalisation for HF (both fatal and non-fatal) resulted in hospitalisation.

Table 36: Hospitalisation costs for MACE events

		Vadadustat	ESA
		Cost (£)	Cost (£)
MACE endpoint			
Acute costs	MACE (non-fatal)	3,118.65	3,133.12
	MACE death	2,623.24	2,637.41
	Non-MACE death	0.00	0.00
Long-term costs	MACE (non-fatal)	1,760.55	1,787.53
Expanded MACE endpoint			
Acute costs	MACE (non-fatal)	2,647.22	2,750.65
	MACE death	2,408.12	2,493.55
	Non-MACE death	0.00	0.00
Long-term costs	MACE (non-fatal)	1,255.10	1,421.10

Abbreviations: ESA, erythropoietin stimulating agent; MACE, major adverse cardiovascular event; SE, standard error

Source: NHS Reference Costs 2021–22 (151)

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Rescue therapy cost

The cost associated with IV iron rescue therapy was calculated using the average weekly dose, unit cost of IV iron, administration cost and percentage of patients requiring rescue therapy (sourced from INNO$_2$VATE trials; Table 37). IV iron was assumed to be a chronic treatment which is used once weekly. To calculate IV iron cost, the weighted average cost of 1 mg of IV iron medications presented in the BNF was multiplied by the IV iron dose reported in INNO$_2$VATE trials (3, 4). IV iron market shares from the NHS PCA database for 2022 were used to weight the cost per mg.

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Table 37: Average doses of IV iron

Week from trial	Cycle	Average IV iron dose per cycle (mg)	
		Vadadustat	Darbepoetin alfa
2-8	1	85.56	100.57
10-20	2	79.74	88.70
24-36	3	82.20	81.90
40-52	4	78.44	82.29
64+	5+	72.47	68.03

Abbreviations: IV, intravenous; mg, milligrams
Source: INNO$_2$VATE trials (111, 112)

RBC and ESA rescue was applied only to patients requiring this type of rescue and was calculated by applying transition probabilities to rescue therapy (Table 38). The cost associated with RBC transfusion rescue therapy was calculated using the unit cost of RBC transfusion, and administration cost. The cost associated with ESA rescue therapy was calculated using, unit cost of ESA together with administration costs the average dose per episode. Average ESA rescue dose was assumed to be equal to the average trial darbepoetin dose increased by 75%.

Table 38: Rescue therapy costs

	Cycle	Vadadustat	ESA
		Cost (£)	Cost (£)
IV iron, cost per cycle	1	2,410.44	2,526.07
	2	2,632.94	2,642.17
	3	2,718.60	2,694.05
	4	2,790.73	2,805.32
	5+	2,982.21	3,069.56
IV iron administration cost		356.38	356.38
IV iron cost per mg		0.09	0.09
RBC transfusions, per episode		695	695
ESAs rescue, per episode		94	94

Abbreviations: ESA, erythropoietin stimulating agent; IV, intravenous; Q, quarter; RBC, red blood cell; SE, standard error
Source: INNO$_2$VATE trials (111, 112)

B.3.6. Severity

It is not anticipated that vadadustat would qualify for a severity modifier in this indication.

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B.3.7. Uncertainty

The company believes there is no aspect of the condition or technology presented in this submission that would impact the ability to generate high-quality evidence.

B.3.8. Managed access proposal

MEDICE do not consider vadadustat a candidate for managed access because the evidence available to support the clinical and economic benefits is sufficiently robust for decision making. MEDICE are also not aware of any additional clinical data that would be available to inform a management access reassessment. Therefore, MEDICE do not expect data collection in NHS practice would be required to reduce decision making uncertainty.

B.3.9. Summary of base-case analysis inputs and assumptions

B.3.9.1. Summary of base-case analysis inputs

The base-case cost-effectiveness analysis settings and variables are provided in Table 39 and Table 40, respectively.

Table 39: Base-case model settings

Parameter	Base case	Alternative
Model settings		
Modelling perspective	Payer (NHS and PSS)	-
Time horizon	42 years	• 5 years • 10 years • 20 years
WTP threshold	£20,000	£30,000
Discounting	Costs and effects at 3.5%	0%
Half-cycle correction	Yes	No
Disease-specific settings		
Patient population	Incident and prevalent CKD population with anaemia	-
Comparator	Darbepoetin alfa 100%	• Birnie 2017 (ESA mix) • ESAs sales volumes as per IQVIA market share analysis (2022) (ESA mix) • NHS PCA database 2022 (ESA mix) • Equal ESAs market shares (ESA mix)

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Parameter	Base case	Alternative
		• Epoetin alfa 100% • Epoetin beta 100% • Epoetin zeta 100% • CERA 100%
Anaemia Hb level definition	• <10 g/dL • 10 - <12 g/dL • ≥12 g/dL	-
Key safety cardiovascular endpoint	MACE	Expanded MACE
HD/PD share	INNO$_2$VATE trials	-
Efficacy		
Efficacy source	INNO$_2$VATE trials	-
Vadadustat efficacy stop timepoint for treatment waning	Cycle 20 (5 years)	According to clinical KOL advice
Stopping rule applied at week 24	Yes	-
Arm-specific MACE rates?	Yes	No
Safety		
Arm-specific TEAEs rates?	Yes	No
Rescue therapy		
RBC transfusion rescue therapy definition	Narrow	-
ESAs rescue therapy definition	Narrow	-
Dosing		
Source of dosing for other than darbepoetin alfa ESAs	ESAs conversion factors	-
Treatment wastage		
Treatment wastage applied to darbepoetin alfa and vadadustat?	No	Yes
Utilities		
Age-related adjustment for utilities?	Yes	No
MoA utility increment for PD patients applied?	No	Yes
Correct utility for Hb level?	Yes	No
Arm-specific MACE distribution applied to utilities?	Yes	No

Abbreviations: CERA, continuous erythropoiesis receptor activator; ESA, erythropoietin stimulating agent; Hb, haemoglobin; HD, haemodialysis; KOL, key opinion leader; MoA, mode of administration; MACE, major adverse cardiovascular events; PCS, prescription cost analysis; PD, peritoneal dialysis; NHS, National Health Services; TEAE, treatment-emergent adverse event; UKRR, United Kingdom renal registry; WTP, willingness to pay

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Table 40: Variables applied in the economic model

Variable	Value	SE	Distribution	Section
Discount rate - Costs	0.04	0.00	-	B.3.2.2
Discount rate - Outcomes	0.035	0.00	-	
Willingness to pay (£) per QALY	20000	0.00	-	
Starting age (years, mean)	57.90	5.79	-	B.3.3.1
Percentage of females	0.44	0.04	-	
History of CVD, %	0.49	0.05	-	
History of MI, %	0.49	0.05	-	
History of Stroke, %	0.51	0.05	-	
History of Thromboembolic Events, %	0	0.00	-	
History of Hospitalization for HF, %	0	0.00	-	
Patients on haemodialysis, %	0.92	0.09	-	
Patients on peritoneal dialysis, %	0.08	0.01	-	
Time since chronic dialysis initiation (years, median)	2.40	0.24	-	
Assumed uncertainty if unknown - Costs/resource	0.1	-	-	B.3.11
Assumed uncertainty if unknown - Effects	0.1	-	-	
Assumed uncertainty if unknown - Utilities	0.1	-	-	
Assumed uncertainty if unknown - Other	0.1	-	-	
Proportion of MACE-related death in CKD population, %	0.20	0.02	Dirichlet	B.3.3.2
Proportion of non-MACE related death in CKD population, %	0.80	0.08	Dirichlet	
Transition probabilities ESA, DD No MACE to DD No MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD New MACE to DD No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx No MACE to DD No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx New MACE to DD No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death MACE to DD No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death nonMACE to DD No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD No MACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD New MACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx No MACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx New MACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death MACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death nonMACE to DD Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD No MACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD New MACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx No MACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx New MACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death MACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death nonMACE to DD New MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD No MACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD New MACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death MACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx No MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD No MACE to Tx Hx MACE, cycle 1			Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx Hx MACE, cycle 1			Dirichlet	

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Variable	Value	SE	Distribution	Section
Transition probabilities ESA, DD New MACE to Tx Hx MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx Hx MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx Hx MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx Hx MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx Hx MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx Hx MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx New MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death MACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death nonMACE, cycle 1	[redacted]	[redacted]	Dirichlet	
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Transition probabilities ESA, DD Hx MACE to DD No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	

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Variable	Value	SE	Distribution	Section
Transition probabilities ESA, DD No MACE to Tx No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
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Transition probabilities ESA, Tx Hx MACE to Tx No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx No MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx Hx MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
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Transition probabilities ESA, DD Hx MACE to Tx New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
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Transition probabilities ESA, Tx Hx MACE to Tx New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
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Transition probabilities ESA, Death nonMACE to Tx New MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
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Transition probabilities ESA, DD New MACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death MACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
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Transition probabilities ESA, DD Hx MACE to Death nonMACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death nonMACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death nonMACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death nonMACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death nonMACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death nonMACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death nonMACE, cycles 2 to 4	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	

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Variable	Value	SE	Distribution	Section
Transition probabilities ESA, Death MACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx No MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx Hx MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx New MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death MACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death nonMACE, cycles 5 to 12	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	

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Variable	Value	SE	Distribution	Section
Transition probabilities ESA, Tx Hx MACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to DD New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx No MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Tx New MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD No MACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death MACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	

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Variable	Value	SE	Distribution	Section
Transition probabilities ESA, DD No MACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD Hx MACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, DD New MACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx No MACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx Hx MACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Tx New MACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death MACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Transition probabilities ESA, Death nonMACE to Death nonMACE, cycle 13 and beyond	[redacted]	[redacted]	Dirichlet	
Vadadustat efficacy, HR of MACE, no history of MACE	0.96	1.08	Lognormal	B.3.3.2.1
Vadadustat efficacy, HR of MACE, history of MACE	0.96	1.08	Lognormal	
MACE HR not applied beyond timepoint, in cycles	20	-	-	B.3.3.2
Transition probabilities Vadadustat, DD No MACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to DD No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to DD Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to DD New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx No MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx Hx MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx Hx MACE, cycle 1	[redacted]	-	-	

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Variable	Value	SE	Distribution	Section
Transition probabilities Vadadustat, DD No MACE to Tx New MACE, cycle 1	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx New MACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD New MACE to Tx New MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx New MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx New MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx New MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Death MACE to Tx New MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx New MACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD No MACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD New MACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx No MACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx New MACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Death MACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, Death nonMACE to Death MACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD No MACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD New MACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx No MACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, Tx New MACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, Death MACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, Death nonMACE to Death nonMACE, cycle 1		-	-	
Transition probabilities Vadadustat, DD No MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death MACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death nonMACE to DD No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death MACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death nonMACE to DD Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death MACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death nonMACE to DD New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to Tx No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to Tx No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx No MACE, cycles 2 to 4		-	-	

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Variable	Value	SE	Distribution	Section
Transition probabilities Vadadustat, Death MACE to Tx No MACE, cycles 2 to 4	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx No MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death MACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx Hx MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death MACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx New MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death MACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death nonMACE to Death MACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD New MACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx No MACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Tx New MACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death MACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, Death nonMACE to Death nonMACE, cycles 2 to 4		-	-	
Transition probabilities Vadadustat, DD No MACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD New MACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Tx No MACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Tx New MACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Death MACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Death nonMACE to DD No MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD No MACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD New MACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Tx No MACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Tx New MACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Death MACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, Death nonMACE to DD Hx MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD No MACE to DD New MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD New MACE, cycles 5 to 12		-	-	
Transition probabilities Vadadustat, DD New MACE to DD New MACE, cycles 5 to 12		-	-	

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Variable	Value	SE	Distribution	Section
Transition probabilities Vadadustat, Tx No MACE to DD New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to DD New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to DD New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx No MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx Hx MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx New MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Death MACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Death nonMACE, cycles 5 to 12	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	

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Variable	Value	SE	Distribution	Section
Transition probabilities Vadadustat, DD New MACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to DD No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to DD Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to DD New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	

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Variable	Value	SE	Distribution	Section
Transition probabilities Vadadustat, Tx New MACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx No MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx Hx MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Tx New MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD No MACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Death MACE, cycle 13 and beyond	[redacted]	-	-	

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Variable	Value	SE	Distribution	Section
Transition probabilities Vadadustat, DD No MACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD Hx MACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, DD New MACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx No MACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx Hx MACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Tx New MACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death MACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Transition probabilities Vadadustat, Death nonMACE to Death nonMACE, cycle 13 and beyond	[redacted]	-	-	
Time on treatment				
Patients on treatment, vadadustat, cycle 1	1.00	0.10	Beta	B.3.3.4
Patients on treatment, vadadustat, cycle 2	0.93	0.09	Beta	
Patients on treatment, vadadustat, cycle 3	0.84	0.08	Beta	
Patients on treatment, vadadustat, cycle 4+	0.74	0.07	Beta	
Patients on treatment, ESA, cycle 1	1.00	0.10	Beta	
Patients on treatment, ESA, cycle 2	0.97	0.10	Beta	
Patients on treatment, ESA, cycle 3	0.91	0.09	Beta	
Patients on treatment, ESA, cycle 4+	0.83	0.08	Beta	
Safety				
Vadadustat - Pneumonia	0.04	0.00	Beta	B.3.3.6
Vadadustat - Sepsis	0.03	0.00	Beta	
Vadadustat - Fluid overload	0.04	0.00	Beta	
Vadadustat - Hyperkalaemia	0.00	0.00	Beta	
Darbepoetin alfa - Pneumonia	0.04	0.00	Beta	
Darbepoetin alfa - Sepsis	0.03	0.00	Beta	
Darbepoetin alfa - Fluid overload	0.02	0.00	Beta	
Darbepoetin alfa - Hyperkalaemia	0.00	0.00	Beta	
Hb level distribution				
Hb level distribution, vadadustat, <10 g/dL; c0	[redacted]	[redacted]	Dirichlet	B.3.3.3
Hb level distribution, vadadustat, 10-12 g/dL; c0	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, >12 g/dL; c0	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat,<10 g/dL; c1	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, 10-12 g/dL; c1	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, >12 g/dL; c1	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, <10 g/dL; c2	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, 10-12 g/dL; c2	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, >12 g/dL; c2	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, <10 g/dL; c3	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, 10-12 g/dL; c3	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, >12 g/dL; c3	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, <10 g/dL; c4	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, 10-12 g/dL; c4	[redacted]	[redacted]	Dirichlet	
Hb level distribution, vadadustat, >12 g/dL; c4	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, <10 g/dL; c0	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, 10-12 g/dL; c0	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, >12 g/dL; c0	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, <10 g/dL; c1	[redacted]	[redacted]	Dirichlet	

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Variable	Value	SE	Distribution	Section
Hb level distribution, ESA, 10-12 g/dL; c1	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, >12 g/dL; c1	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, <10 g/dL; c2	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, 10-12 g/dL; c2	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, >12 g/dL; c2	[redacted]	[redacted]	Dirichlet	
Hb level distribution, ESA, <10 g/dL; c3	[redacted]	[redacted]	Dirichlet	
Rescue therapy				
IV iron weekly dose, vadadustat, c1	85.56	-	-	B.3.3.5
IV iron weekly dose, vadadustat, c2	79.74	-	-	
IV iron weekly dose, vadadustat, c3	82.20	-	-	
IV iron weekly dose, vadadustat, c4	78.44	-	-	
IV iron weekly dose, vadadustat, c5+	72.47	-	-	
IV iron weekly dose, ESA, c1	100.57	-	-	
IV iron weekly dose, ESA, c2	88.70	-	-	
IV iron weekly dose, ESA, c3	81.90	-	-	
IV iron weekly dose, ESA, c4	82.29	-	-	
IV iron weekly dose, ESA, c5+	68.03	-	-	
IV iron use, vadadustat, c1	0.51	0.05	Beta	
IV iron use, vadadustat, c2	0.56	0.06	Beta	
IV iron use, vadadustat, c3	0.57	0.06	Beta	
IV iron use, vadadustat, c4	0.59	0.06	Beta	
IV iron use, vadadustat, c5+	0.63	0.06	Beta	
IV iron use, ESA, c1	0.53	0.05	Beta	
IV iron use, ESA, c2	0.56	0.06	Beta	
IV iron use, ESA, c3	0.57	0.06	Beta	
IV iron use, ESA, c4	0.59	0.06	Beta	
IV iron use, ESA, c5+	0.65	0.06	Beta	
RBC transfusion rescue therapy probability, vadadustat	0.02	0.00	Beta	
RBC transfusion rescue therapy probability, ESA	0.02	0.00	Beta	
ESAs rescue therapy probability, vadadustat	0.07	0.01	Beta	
ESAs rescue therapy probability, ESA	0.02	0.00	Beta	
ESAs use for rescue, darbepoetin alfa	1	-	-	
ESAs use for rescue, epoetin alfa	0	-	-	
ESAs use for rescue, epoetin beta	0	-	-	
ESAs use for rescue, epoetin zeta	0	-	-	
ESAs use for rescue, CERA	0	-	-	
Number of IV administration episodes per cycle	13.04	-	-	
ESAs rescue dose, vada	63.86	-	-	
ESAs rescue dose, ESA	0.00	-	-	
Quality of life				
Utility, DD, No MACE, vadadustat	0.56	0.06	Beta	B.3.4
Utility, DD, Hx MACE, vadadustat	0.53	-	-	
Utility, DD, New MACE, vadadustat	0.49	-	-	
Utility, Transplant, No MACE, vadadustat	0.81	0.08	Beta	
Utility, Transplant, Hx MACE, vadadustat	0.77	-	-	
Utility, Transplant, New MACE, vadadustat	0.73	-	-	
Utility, DD, No MACE, ESA	0.56	0.06	Beta	
Utility, DD, Hx MACE, ESA	0.53	-	-	
Utility, DD, New MACE, ESA	0.49	-	-	
Utility, Transplant, No MACE, ESA	0.81	0.08	Beta	
Utility, Transplant, Hx MACE, ESA	0.77	-	-	
Utility, Transplant, New MACE, ESA	0.73	-	-	
Disutility MI acute	-0.06	-0.01	Gamma (negative)	

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Variable	Value	SE	Distribution	Section
Disutility stroke acute	-0.12	-0.01	Gamma (negative)	
Disutility TEE acute	-0.06	-0.01	Gamma (negative)	
Disutility HF acute	-0.12	-0.01	Gamma (negative)	
Disutility of history of MI	-0.04	0.00	Gamma (negative)	
Disutility of history of stroke	-0.03	0.00	Gamma (negative)	
Disutility of history of TEE	0.00	0.00	Gamma (negative)	
Disutility of history of HF	0.00	0.00	Gamma (negative)	
Disutility - Pneumonia	-0.08	0.02	Gamma (negative)	
Disutility - Sepsis	-0.06	0.03	Gamma (negative)	
Disutility - Fluid overload	0.00	0.00	Gamma (negative)	
Disutility - Hyperkalaemia	-0.03	0.00	Gamma (negative)	
Disutility duration - Pneumonia	0.15	0.02	Gamma	
Disutility duration - Sepsis	0.15	0.02	Gamma	
Disutility duration - Fluid overload	0.15	0.02	Gamma	
Disutility duration - Hyperkalaemia	0.15	0.02	Gamma	
Disutility, Hb level, <10 g/dL	-0.063	0.01	Gamma (negative)	
Disutility, Hb level, 10-12 g/dL	-0.029	0.00	Gamma (negative)	
Disutility, Hb level, >12 g/dL	-0.006	0.00	Gamma (negative)	
MoA utility increment, vadadustat	0.0008	0.00	Beta	
MoA utility increment, ESAs	0.0001	0.00	Beta	
Drug acquisition and administration costs				
Drug costs, vadadustat, y1	[redacted]	-	-	B.3.5.1
Drug costs, vadadustat, y2	[redacted]	-	-	
Drug costs, vadadustat, y3	[redacted]	-	-	
Drug costs, ESA, y1	621	-	-	
Drug costs, ESA, y2	714	-	-	
Drug costs, ESA, y3	762	-	-	
Dose per week of vadadustat, year 1	[redacted]	-	-	
Dose per week of darbepoetin alfa, year 1	32	-	-	
Dose per week of epoetin alfa, year 1	11758	-	-	
Dose per week of epoetin beta, year 1	11758	-	-	
Dose per week of epoetin zeta, year 1	11758	-	-	
Dose per week of CERA, year 1	39	-	-	
Dose per week of vadadustat, year 2	[redacted]	-	-	
Dose per week of darbepoetin alfa, year 2	37	-	-	
Dose per week of epoetin alfa, year 2	13507	-	-	
Dose per week of epoetin beta, year 2	13507	-	-	
Dose per week of epoetin zeta, year 2	13507	-	-	
Dose per week of CERA, year 2	45	-	-	
Dose per week of vadadustat, year 3	[redacted]	-	-	
Dose per week of darbepoetin alfa, year 3	40	-	-	

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Variable	Value	SE	Distribution	Section
Dose per week of epoetin alfa, year 3	14421	-	-	
Dose per week of epoetin beta, year 3	14421	-	-	
Dose per week of epoetin zeta, year 3	14421	-	-	
Dose per week of CERA, year 3	48	-	-	
Cost per unit, vadadustat	[redacted]	-	-	
Cost per unit, darbepoetin alfa	1.47	-	-	
Cost per unit, epoetin alfa	0.01	-	-	
Cost per unit, epoetin beta	0.01	-	-	
Cost per unit, epoetin zeta	0.00	-	-	
Cost per unit, CERA	1.47	-	-	
Discount, vadadustat	[redacted]	-	-	
Discount, darbepoetin alfa	1	-	-	
Discount, epoetin alfa	1	-	-	
Discount, epoetin beta	1	-	-	
Discount, epoetin zeta	1	-	-	
Discount, CERA	1	-	-	
Drug administration costs, vada	0	-	-	
Drug administration costs, ESA	304	-	-	
Drug administration costs, darbepoetin alfa	23	-	-	
Drug administration costs, epoetin alfa	23	-	-	
Drug administration costs, epoetin beta	23	-	-	
Drug administration costs, epoetin zeta	23	-	-	
Drug administration costs, CERA	23	-	-	
ESA drug administration frequency, vadadustat	7	0.70	Gamma	
ESA drug administration frequency, darbepoetin alfa	1	0.10	Gamma	
ESA drug administration frequency, epoetin alfa	2	0.20	Gamma	
ESA drug administration frequency, epoetin beta	2	0.20	Gamma	
ESA drug administration frequency, epoetin zeta	2	0.20	Gamma	
ESA drug administration frequency, CERA	1	0.10	Gamma	
Cost of hospital ESA administration	31	3.09	Gamma	
Cost of unassisted ESA administration	0	0.00	Gamma	
Cost of ESA administration assisted by a nurse	23	2.30	Gamma	
Cost of vadadustat administration	0	0.00	Gamma	
Mode of administration, oral, vadadustat	1	-	-	
Mode of administration, hospital, darbepoetin alfa	0.75	0.07	Dirichlet	
Mode of administration, unassisted, darbepoetin alfa	0.24	0.02	Dirichlet	
Mode of administration, nurse, darbepoetin alfa	0.01	0.00	Dirichlet	
Mode of administration, hospital, epoetin alfa	0.75	0.07	Dirichlet	
Mode of administration, unassisted, epoetin alfa	0.24	0.02	Dirichlet	
Mode of administration, nurse, epoetin alfa	0.01	0.00	Dirichlet	
Mode of administration, hospital, epoetin beta	0.75	0.07	Dirichlet	
Mode of administration, unassisted, epoetin beta	0.24	0.02	Dirichlet	
Mode of administration, nurse, epoetin beta	0.01	0.00	Dirichlet	
Mode of administration, hospital, epoetin zeta	0.75	0.07	Dirichlet	
Mode of administration, unassisted, epoetin zeta	0.24	0.02	Dirichlet	
Mode of administration, nurse, epoetin zeta	0.01	0.00	Dirichlet	
Mode of administration, hospital, epoetin CERA	0.75	0.07	Dirichlet	
Mode of administration, unassisted, epoetin CERA	0.24	0.02	Dirichlet	
Mode of administration, nurse, epoetin CERA	0.01	0.00	Dirichlet	
Rescue therapy costs				
IV iron rescue cost, vadadustat, c1	2410	-	-	B.3.5.4.1
IV iron rescue cost, vadadustat, c2	2633	-	-	
IV iron rescue cost, vadadustat, c3	2719	-	-	
IV iron rescue cost, vadadustat, c4	2791	-	-	

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Variable	Value	SE	Distribution	Section
IV iron rescue cost, vadadustat, c5	2982	-	-	
IV iron rescue cost, ESA, c1	2526	-	-	
IV iron rescue cost, ESA, c2	2642	-	-	
IV iron rescue cost, ESA, c3	2694	-	-	
IV iron rescue cost, ESA, c4	2805	-	-	
IV iron rescue cost, ESA, c5	3070	-	-	
RBC rescue cost	695	-	-	
ESAs rescue cost	94	-	-	
ESA rescue dose, darbepoetin alfa	64	-	-	
ESA rescue dose, epoetin alfa	23150	-	-	
ESA rescue dose, epoetin beta	23150	-	-	
ESA rescue dose, epoetin zeta	23150	-	-	
ESA rescue dose, CERA	77	-	-	
Cost of IV iron, per mg	0.09	0.01	Gamma	
Cost of IV iron administration, per episode	356	35.64	Gamma	
Disease management costs				
Disease monitoring cost, vadadustat, cycle 1	123	-	-	B.3.5.2.3
Disease monitoring cost, vadadustat, cycle 2+	46	-	-	
Disease monitoring cost, ESA, cycle 1	123	-	-	
Disease monitoring cost, ESA, cycle 2+	46	-	-	
Number of monitoring visits, vadadustat, cycle 1	4	0.40	Beta	
Number of monitoring visits, vadadustat, cycle 2+	1.5	0.15	Beta	
Number of monitoring visits, ESA, cycle 1	4	0.40	Beta	
Number of monitoring visits, ESA, cycle 2+	1.5	0.15	Beta	
Cost of monitoring visit	31	3.08	Gamma	
Dialysis and transplantation costs				
Dialysis service cost	5517	551.67	Gamma	B.3.5.2.3
Dialysis insertion procedure cost	1028	-	-	
Transplant cost, acute	18899	-	-	
Long-term transplant cost	2284	228.38	Gamma	
MACE-related costs				
Non-fatal MACE cost, vadadustat	3119	-	-	B.3.5.3
Non-fatal MACE cost, ESA	3133	-	-	
Fatal MACE cost, vadadustat	2623.239307	-	-	
Fatal MACE cost, ESA	2637.408695	-	-	
Non-MACE death cost, vadadustat	0	-	-	
Non-MACE death cost, ESA	0	-	-	
Non-fatal MACE, long term costs, vadadustat	1761	-	-	
Non-fatal MACE, long term costs, ESA	1788	-	-	
Cost MI, non-fatal, acute	2568	256.79	Gamma	
Cost MI, fatal, acute	2084	208.39	Gamma	
Cost stroke, non-fatal, acute	4942	494.18	Gamma	
Cost stroke, fatal, acute	4409	440.86	Gamma	
Cost of non-MACE death	0	0.00	Gamma	
Cost of thromboembolic events, acute	1095	109.47	Gamma	
Cost of hospitalisation for HF, acute	2542	254.24	Gamma	
Cost of MI, non-fatal, long term	734	73.35	Gamma	
Cost of stroke, non-fatal, long term	5160	516.04	Gamma	
Cost of thromboembolic events, non-fatal, long term	0	0.00	Gamma	
Cost of hospitalisation for HF, non-fatal, long term	1019	101.94	Gamma	
Event frequency MI, vadadustat	0.768	0.08	Dirichlet	
Event frequency stroke, vadadustat	0.232	0.02	Dirichlet	
Event frequency TEE, vadadustat	0	0.00	Dirichlet	
Event frequency HF, vadadustat	0	0.00	Dirichlet	

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Variable	Value	SE	Distribution	Section
Event frequency MI, ESA	0.762	0.08	Dirichlet	
Event frequency stroke, ESA	0.238	0.02	Dirichlet	
Event frequency TEE, ESA	0	0.00	Dirichlet	
Event frequency HF, ESA	0	0.00	Dirichlet	
Hospitalisation frequency, MI, non-fatal, vadadustat	1	-	-	
Hospitalisation frequency, MI, fatal, vadadustat	1	-	-	
Hospitalisation frequency, stroke, non-fatal, vadadustat	1	-	-	
Hospitalisation frequency, stroke, fatal, vadadustat	1	-	-	
Hospitalisation frequency, nonMACE death, vadadustat	0	-	-	
Hospitalisation frequency, TEE, vadadustat	0	-	-	
Hospitalisation frequency, HF, vadadustat	0	-	-	
Hospitalisation frequency, MI, non-fatal, ESA	1	-	-	
Hospitalisation frequency, MI, fatal, ESA	1	-	-	
Hospitalisation frequency, stroke, non-fatal, ESA	1	-	-	
Hospitalisation frequency, stroke, fatal, ESA	1	-	-	
Hospitalisation frequency, nonMACE death, ESA	0	-	-	
Hospitalisation frequency, TEE, ESA	0	-	-	
Hospitalisation frequency, HF, ESA	0	-	-	
Cost of adverse events				
Costs - Pneumonia	385	38.52	Gamma	B.3.5.3
Costs - Sepsis	457	45.66	Gamma	
Costs - Fluid overload	641	64.05	Gamma	
Costs - Hyperkalaemia	86	8.57	Gamma	
Regression coefficient for mortality estimates				
Mortality regression intercept	0.0338	-	-	B.3.3.2.1
Mortality regression coefficient	0.2572	-	-	

Abbreviations: CERA, continuous erythropoiesis receptor activator; CKD, chronic kidney disease; CVD, cardiovascular diseases; DD, dialysis-dependent; ESA, erythropoietin stimulating agent; Hb, haemoglobin; HF, heart failure; HR, hazard ratio; IV, intravenous; MACE, major adverse cardiovascular event; MI, myocardial infarction; QALY, quality-adjusted life-years; TEE, thromboembolic events; Tx, transplant.

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B.3.9.2. Assumptions

The following assumptions were made in the vadadustat cost-effectiveness model, which were validated with economic model experts.

Assumption detailed	Justification
The uncertainty associated with costs/resources, effects, utilities and other inputs was assumed to be 10%	10% uncertainty was considered an appropriate estimate to substitute for standard error when measure of variation was not reported in the parameter source
The Hb levels of patients entering the model and the use of rescue therapy were assumed to remain constant after the second year of the modelling horizon	As the INNO$_2$VATE trials duration was 52 weeks, data on long-term Hb levels is not available
It was assumed that there were no treatment discontinuations after the first year of modelling horizon	Given vadadustat SmPC outlined a stopping rule at week 24, it is expected patients not benefiting from therapy will discontinue at week 24. Patients receiving vadadustat were not expected to experience new AEs beyond 1 year after treatment initiation
The relative risk of MACE event occurrence was based on the hazard ratio of first MACE event, and was assumed to be same for patients with or without history of MACE	As the INNO$_2$VATE trials recruited both patients with and without prior CVD history, applying the HR of MACE occurrence to both groups was considered relevant
The annual costs of vadadustat and ESAs were calculated in the model assuming 100% patient compliance	No real-world data on compliance rates for vadadustat exists therefore it was assumed 100%
One mcg of darbepoetin was assumed equal to 200 IU of epoetin-A/B and 1.21 mcg CERA (Choi 2013) (142)	Conversion factors were considered appropriate for approximating equivalent dose to match observed dose of darbepoetin alfa in the trial with equivalent doses of other ESA agents
ESAs dose was assumed to be increased by 75% of an average ESA trial dose when used for rescue therapy	In consultation with clinical KOL, 75% increase in ESAs dose was considered appropriate to represent a rescue therapy dose
The cost associated with non-MACE-related deaths assumed to be £0 (NICE TA 393) (170)	As vadadustat is not expected to influence occurrence of non-MACE deaths, non-MACE related death costs were not included
Non-MACE AEs were assumed to last 2 weeks	It is expected that AEs associated with vadadustat will arise shortly after treatment initiation
Patients on peritoneal dialysis were assumed to experience quality of life gain associated with oral mode of administration for vadadustat in line with Lorenzo 2023 (150)	In consultation with clinical KOL, it is expected peritoneal dialysis patients will experience quality of life gain similar to those in non-dialysis patients due to non-invasive oral administration of vadadustat
Long-term mortality of patients on kidney replacement therapy from 25th	Logarithmic regression was considered appropriate to extrapolate mortality data onto a longer time horizon as 95.5% of data was explained with it as

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Assumption detailed	Justification
UKRR report was extrapolated using logarithmic regression	indicated by R squared and was representative of patient's survival as per clinical expert opinion

Abbreviations: AEs, adverse events; CERA, continuous erythropoiesis receptor activator; ESA, erythropoietin stimulating agent; Hb, haemoglobin; IU, International Unit; MACE, major adverse cardiovascular event; NICE, National Institute for Health and Care Excellence

B.3.10. Base-case results

B.3.10.1. Base-case incremental cost-effectiveness analysis results

B.3.10.1.1. List price analyses

Table 41 shows the base-case probabilistic cost-effectiveness results for vadadustat compared to darbepoetin alfa over a lifetime (42 years) horizon at list prices. Darbepoetin alfa resulted in per-patient costs, life-years and QALYs of £313,518, 8.81 and 4.91, respectively. Vadadustat resulted in an incremental gain in life-years (0.07) and QALYs (0.03), compared with darbepoetin alfa, while increasing the cost by £801 per person. Vadadustat demonstrated an ICER of £31,666/QALY compared to darbepoetin alfa. Incremental net health benefit (NHB) at £20,000 and £30,000 per QALY was -0.015 and -0.001, respectively. At the list price, the ICER exceeded the £20,000 and £30,000 thresholds per QALY gained. At the list price, the incremental net health benefit (INHB) at the £20,000 and £30,000 thresholds is slightly negative (Table 42) indicating that the net health benefits of vadadustat are not sufficient to outweigh the health losses that arise from the healthcare that ceases to be funded in order to fund vadadustat.

Table 43 shows the base-case deterministic cost-effectiveness results for vadadustat compared to darbepoetin alfa over a lifetime (42 years) horizon at list prices. Vadadustat demonstrated an ICER of £51,254/QALY compared to darbepoetin alfa. At the list price, the INHB for deterministic results at the £20,000 and £30,000 thresholds is slightly negative (Table 44) indicating that the net health benefits of vadadustat are not sufficient to outweigh the health losses that arise from the healthcare that ceases to be funded in order to fund vadadustat.

The clinical outcomes of the model and disaggregated results of the base-case analysis are presented in Appendix J.

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Table 41: Base-case probabilistic results (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	314,319	8.89	4.94	801	0.07	0.03	31,666
Darbepoetin alfa	313,518	8.81	4.91	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Table 42: Net health benefit for probabilistic results (at list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	INHB at £20,000	INHB at £30,000
Vadadustat	314,319	4.94	801	0.03	-0.015	-0.001
Darbepoetin alfa	313,518	4.91	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; INHB, incremental net health benefit

Table 43: Base-case deterministic results (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	314,694	8.892	4.935	1,184	0.08	0.02	51,254
Darbepoetin alfa	313,510	8.815	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Table 44: Net health benefit for deterministic results (at list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	INHB at £20,000	INHB at £30,000
Vadadustat	314,174	4.935	971	0.02	-0.025	-0.009
Darbepoetin alfa	313,203	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; INHB, incremental net health benefit

B.3.10.1.2. Discounted price analyses

At the discounted price, incremental health benefits remained the same with an overall saving of [redacted] per patient with vadadustat compared to darbepoetin alfa in the probabilistic analysis. At this price, the ICER is dominant with vadadustat offering incremental life-years and QALYs at a lower overall cost per patient compared to darbepoetin alfa (Table 45). A summary of the INHB at the discounted price is presented in Table 46, which demonstrates vadadustat offers net health benefits that are sufficient to outweigh the health losses that arise from the healthcare that ceases

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to be funded in order to fund vadadustat. Results from deterministic analyses are shown in Table 47 and Table 48 and are aligned with the probabilistic results.

Table 45: Base-case probabilistic results (at discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	[redacted]	8.89	4.94	[redacted]	0.07	0.03	Dominant
Darbepoetin alfa	313,391	8.81	4.91	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Table 46: Net health benefit for probabilistic results (at discounted price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	INHB at £20,000	INHB at £30,000
Vadadustat	[redacted]	4.94	[redacted]	0.03	0.056	0.046
Darbepoetin alfa	313,391	4.91	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; INHB, incremental net health benefit

Table 47: Base-case deterministic results (at discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	[redacted]	8.892	4.935	[redacted]	0.08	0.02	Dominant
Darbepoetin alfa	313,203	8.815	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Table 48: Net health benefit for deterministic results (at discounted price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	INHB at £20,000	INHB at £30,000
Vadadustat	[redacted]	4.935	[redacted]	0.02	0.048	0.040
Darbepoetin alfa	313,203	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; INHB, incremental net health benefit

B.3.11. Exploring uncertainty

B.3.11.1. Overall assessment of uncertainty

The current analysis presented here should be considered a conservative base case analysis as it relies on conservative assumptions and estimates; for example, incorporating a treatment waning assumption despite no evidence that benefits would wane over time and by applying the costs of the least costly ESA agent as a

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comparator. Furthermore, the current economic analysis has not incorporated all of vadadustat's potential savings to the NHS compared with ESAs.

There is a low-level of uncertainty within the base-case analyses, for example short term trial results were necessarily extrapolated over the model time horizon, however these assumptions were validated with external experts and a conservative approach taken in the base-case. In addition, while quality of life data were not available from the clinical trials suitable inputs were identified from the literature. The availability of head-to-head efficacy and safety data for vadadustat compared to darbepoetin alfa treatment also reduces uncertainty in the model outcomes. Finally, a comprehensive set of sensitivity and scenario analyses, presented in the sections below, was conducted to explore uncertainty. The assessment of uncertainty demonstrated that results are associated with little to no uncertainty as all scenario analyses were consistent with the base case, with no scenarios above the WTP threshold of £20,000 per QALY.

B.3.11.2. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken, through simultaneous sampling of critical parameters from their respective distributions, to investigate parameter uncertainty and inform decision-making. Ten thousand PSA iterations utilising the full cohort over a lifetime horizon were utilised to ensure that reliable estimates of the mean model outputs were obtained.

The PSA assessed risk relevant to baseline population parameters, transition probabilities, efficacy parameters of vadadustat, patient stratification among Hb levels, mortality estimates, probability and distribution of events, distribution of preferred mode of darbepoetin alfa administration, proportion of patients with AEs, as well as cost and utilities including utility decrement and increments. When available, observed standard error (SE) was used to determine the probabilistic distribution of all parameters. When SE was not directly available, SE was assumed equal to 10% of the mean. Transition probabilities, as well as stratification of patients between several categories, were assigned a Dirichlet distribution to assure relevant parameters added up to 1. Risk factors were assigned a lognormal distribution while probabilities and proportion of patients with AEs were assigned a beta distribution. All cost parameters

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were assigned a gamma distribution. Health state utilities were assigned a beta distribution whilst AE disutilities were assigned a negative gamma distribution. Details on the parameters, SEs, and assumptions are provided in section B.3.9.

Convergence plots, showing the rolling average for the incremental costs, incremental QALYs, incremental net monetary benefit (INMB), and the ICER are shown in Figure 10. At approximately 2,500 iterations, the incremental costs and incremental QALYs converged showing a small but positive gain in QALYs for vadadustat. The resulting probabilistic ICER had less interpretability due to the ratio nature of the statistic combined with small incremental costs and incremental QALYs, however, the INMB converged showing stability in the cost-effectiveness conclusions above 2,500 iterations. To ensure adequate convergence, it was decided that the base case analysis should be conducted using 10,000 iterations to increase the stability of the probabilistic results.

The PSA scatterplot in Figure 11 and Figure 12 demonstrated that points are symmetrically distributed at list price and discounted price, respectively. Incremental costs were also symmetrically distributed suggesting that in a proportion of cases vadadustat is cost saving treatment. The cost-effectiveness acceptability curves in Figure 13 and Figure 14 reflect a 48.69% probability of vadadustat being cost-effectiveness with a WTP threshold of £20,000, and a 49.45% probability with a WTP threshold of £30,000, at list price and discounted price, respectively.

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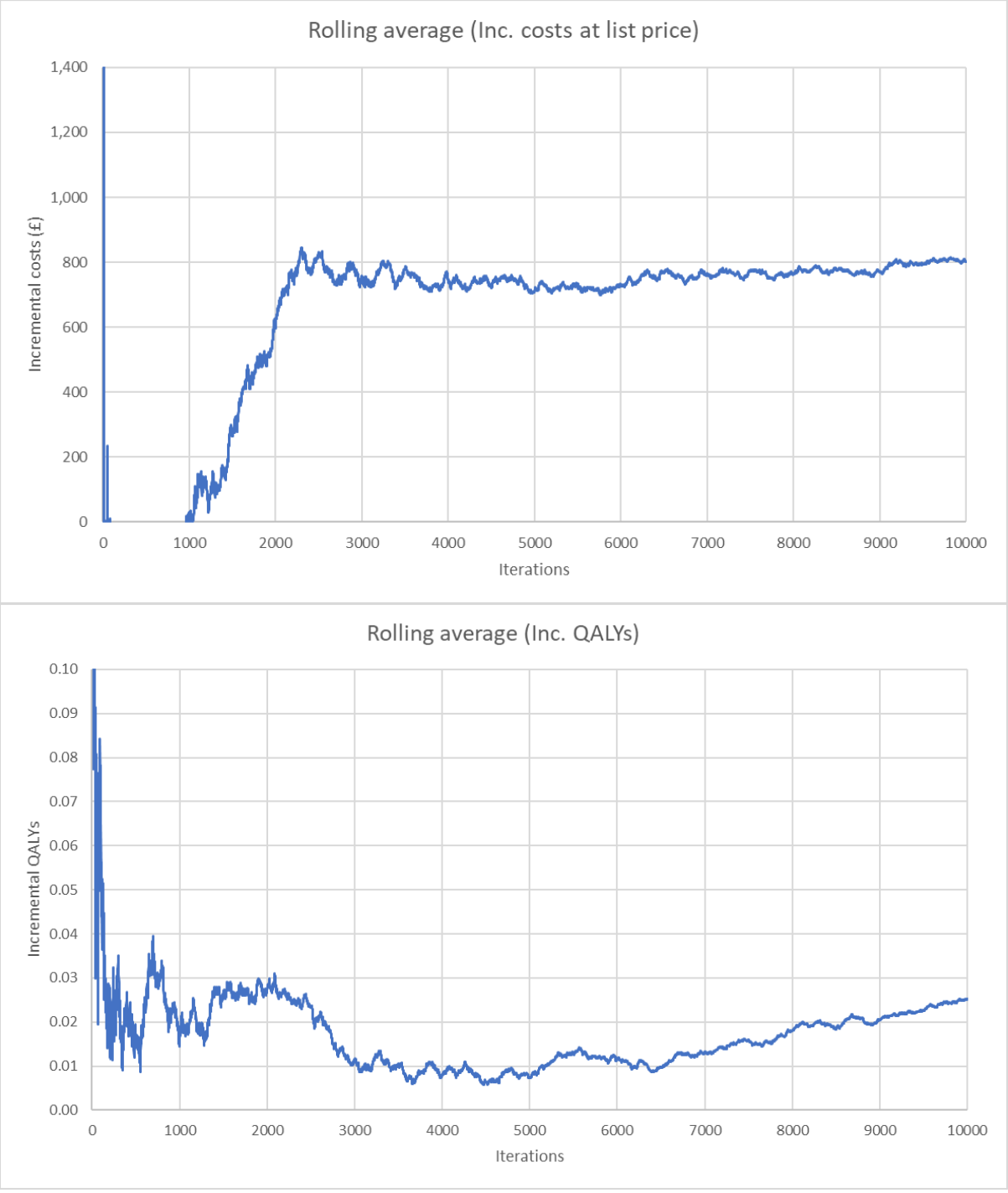
Figure 10. Convergence plots for PSA for vadadustat compared to darbepoetin alfa (at list price)



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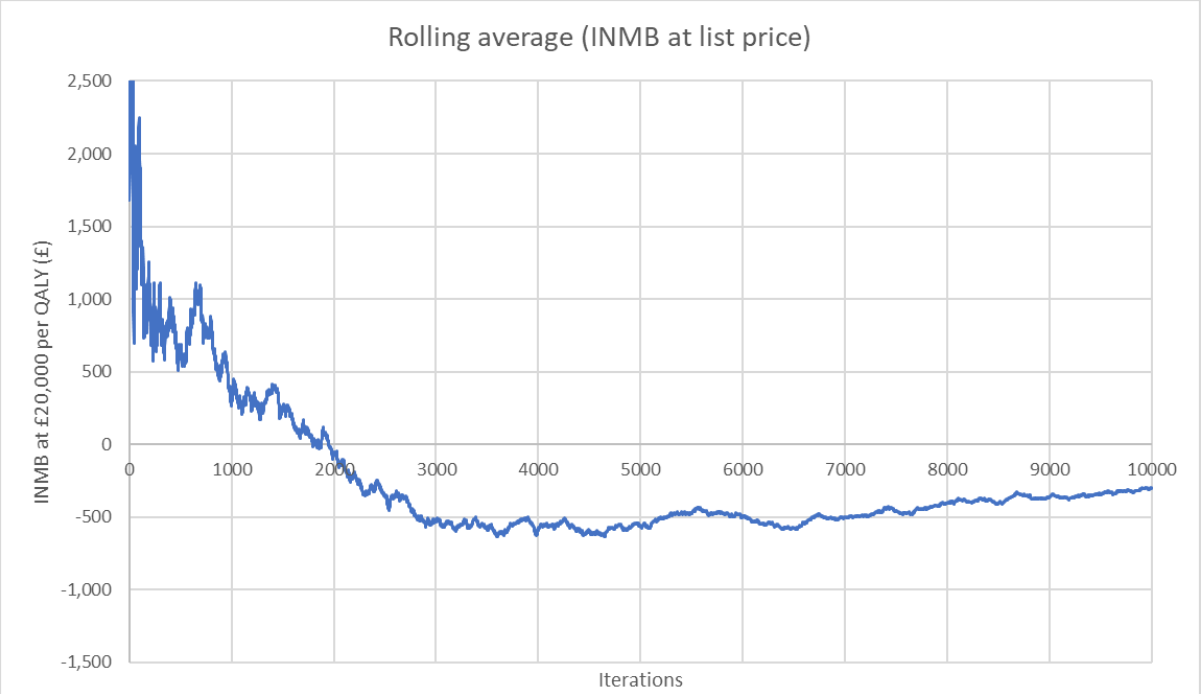

Abbreviations: Inc., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; INHB, incremental net monetary benefit

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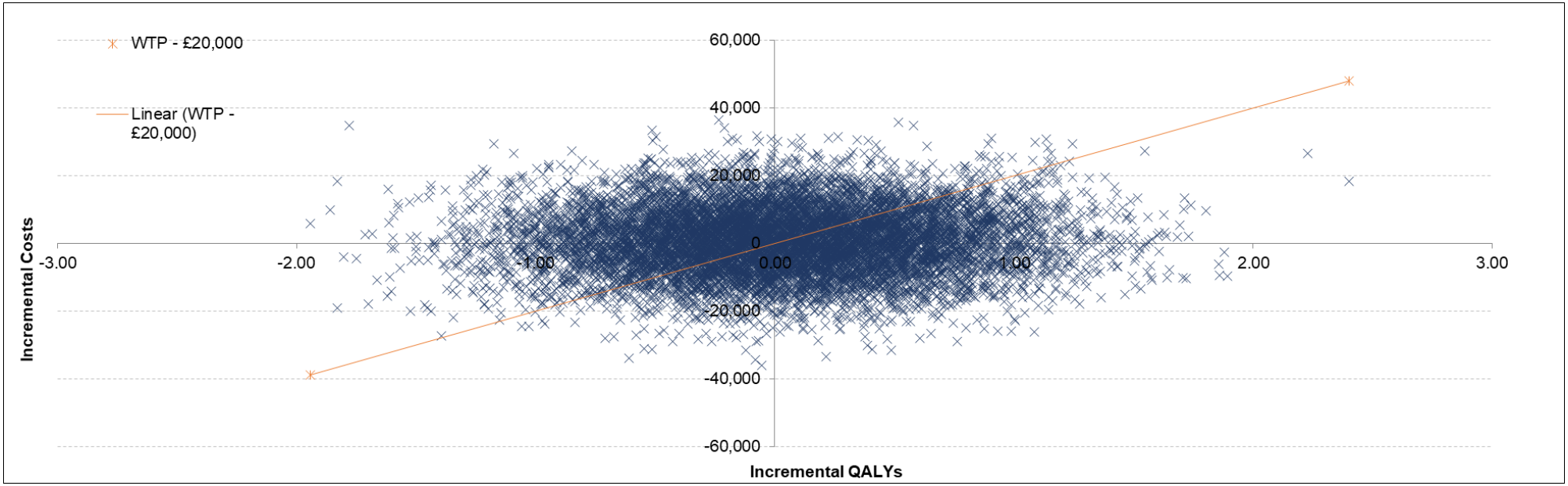
Figure 11. PSA cost-effectiveness plane for vadadustat compared to darbepoetin alfa (at list price)



Abbreviations: QALYs, quality-adjusted life-years; WTP, willingness to pay

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Figure 12: PSA cost-effectiveness plane for vadadustat compared to darbepoetin alfa (at discount price)

Abbreviations: QALYs, quality-adjusted life-years; WTP, willingness to pay

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Figure 13. PSA cost-effectiveness acceptability curve for vadadustat compared to darbepoetin alfa (at list price)

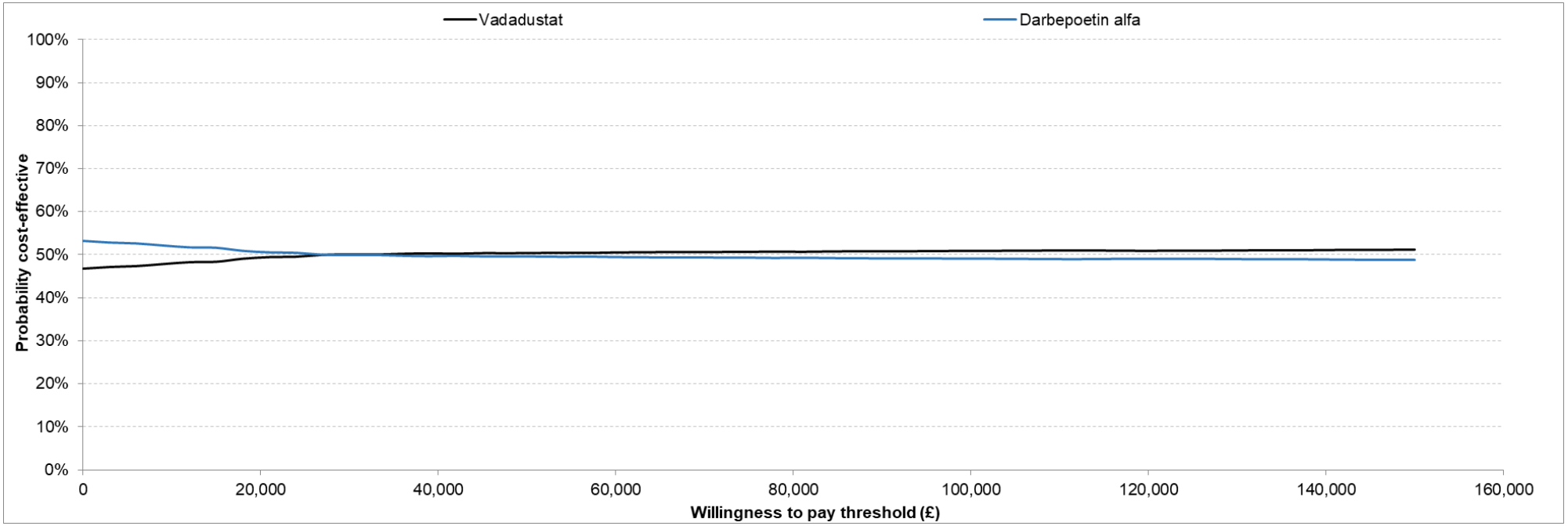

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Figure 14: PSA cost-effectiveness acceptability curve for vadadustat compared to darbepoetin alfa (at discounted price)

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B.3.11.3. Deterministic sensitivity analysis

Deterministic OWSA was performed to assess how varying individual parameters sequentially, whilst holding all other parameters constant, impacted the predicted cost and outcomes of vadadustat compared to ESAs. Analyses were performed on an exhaustive list of parameters (clinical data, costs, utilities and disutilities, response to treatment) with the upper and lower values defined by the observed 95% confidence interval, if available. If this was not available, a percent change of 10% from the point estimate was assumed for all parameters. Table 49 and Table 50 presents the OWSA results for the top 10 most influential parameters in the model at list price and discounted price, respectively. Figure 15 and Figure 16 show the tornado diagrams for these results at list price and discounted price, respectively. The model is highly sensitive to changes in cost parameters. As incremental QALY gain with vadadustat versus ESAs is limited, small changes in costs subsequently influence the ICER significantly. INMB is reported as an outcome of OWSA as ICER/QALY falls into south-west quadrant (less costly, less effective) with some parameter variation.

Table 49: Deterministic one-way sensitivity analysis inputs and results (at list price)

Parameter	Input -Low	INMB (£) Input-Low	Input -High	INMB (£) Input-High
Utility, DD, No MACE, vadadustat	0.45	-12,592	0.67	11,574
Utility, DD, No MACE, ESA	0.45	11,482	0.67	-12,500
Utility, Transplant, No MACE, vadadustat	0.65	-10,188	0.97	9,170
Utility, Transplant, No MACE, ESA	0.65	9,070	0.97	-10,088
Vadadustat efficacy, HR of MACE, no history of MACE	0.83	-3,462	1.11	2,880
Vadadustat efficacy, HR of MACE, history of MACE	1	-1,763	1	970
Cost of hospital ESA administration	24.82	-1,267	36.93	249
Discount rate - Outcomes	0	-97	0	-681
Cost of IV iron administration, per episode	287	-756	426	-262
Discount rate – Costs	0.00	-826	0.06	-335

Abbreviations: Hb, haemoglobin; INMB, incremental net monetary benefit; IV, intravenous; QALY, quality-adjusted life years

Note: INMB reported (vs ICER/QALY gained) due to ICER results being less effective-less costly for some parameter variation

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Table 50: Deterministic one-way sensitivity analysis inputs and results (at discounted price)

Parameter	Input-Low	INMB (£) Input-Low	Input - High	INMB (£) Input-High
Utility, DD, No MACE, vadadustat	[redacted]	[redacted]	[redacted]	[redacted]
Utility, DD, No MACE, ESA	[redacted]	[redacted]	[redacted]	[redacted]
Utility, Transplant, No MACE, vadadustat	[redacted]	[redacted]	[redacted]	[redacted]
Utility, Transplant, No MACE, ESA	[redacted]	[redacted]	[redacted]	[redacted]
Vadadustat efficacy, HR of MACE, no history of MACE	[redacted]	[redacted]	[redacted]	[redacted]
Vadadustat efficacy, HR of MACE, history of MACE	[redacted]	[redacted]	[redacted]	[redacted]
Cost of hospital ESA administration	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate - Outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Cost of IV iron administration, per episode	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis service cost	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DD, dialysis dependent; ESA, erythropoietin stimulating agent; HR, hazard ratio; INMB, incremental net monetary benefit; IV, intravenous; MACE, major adverse cardiovascular event.
Note: INMB reported (vs ICER/QALY gained) due to dominant and dominated ICER results at discounted vadadustat price

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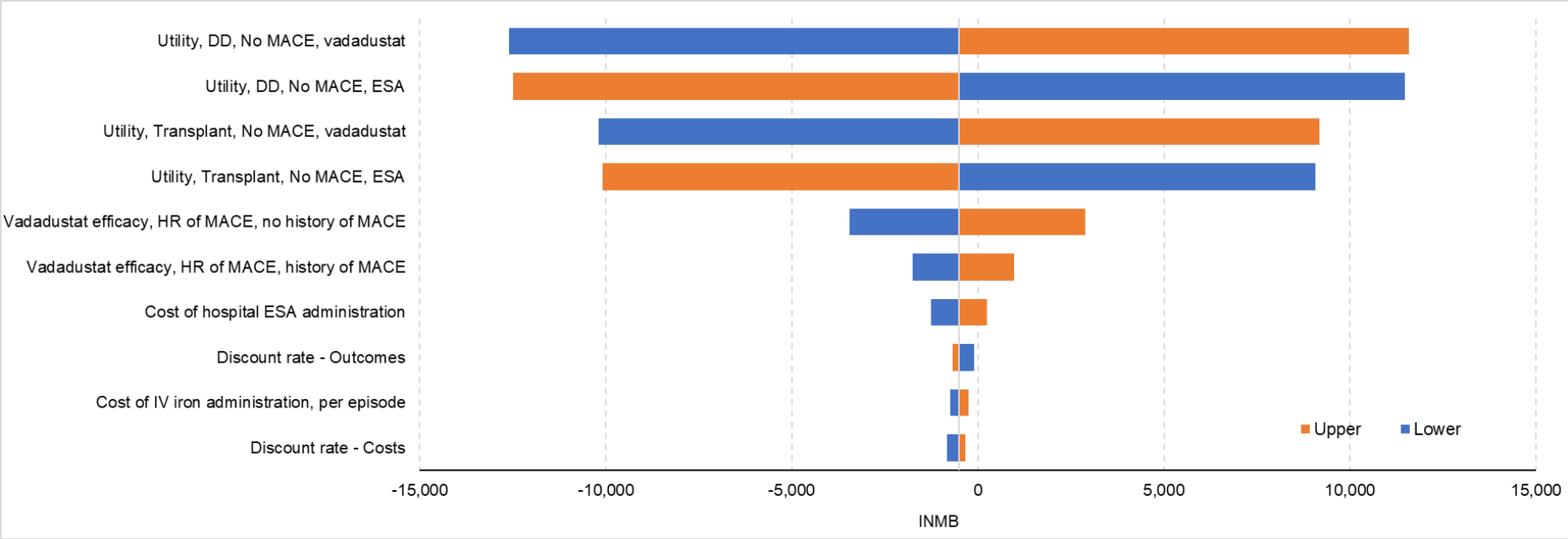
Figure 15. Deterministic OWSA tornado diagram for INMB results (at list price)



Abbreviations: DD, dialysis dependent; HR, hazard ratio; ESA, erythropoietin stimulating agent; INMB, incremental net monetary benefit; IV, intravenous; MACE, major adverse cardiovascular event; OWSA, one-way sensitivity analysis

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Figure 16. Deterministic OWSA tornado diagram for INMB results (at discount price)

Abbreviations: DD, dialysis dependent; HR, hazard ratio; ESA, erythropoietin stimulating agent; INMB, incremental net monetary benefit; IV, intravenous; MACE, major adverse cardiovascular event; OWSA, one-way sensitivity analysis

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B.3.11.4. Scenario analysis

Scenario analyses were performed to test the robustness of conclusions on cost-effectiveness to the choice of risk equations, parameters and assumptions applied in the model as compared to the base-case. The results of these scenario analyses at list price and discounted price are presented in Table 51 and Table 52. Results of the scenario analysis using the discounted price demonstrates that the results remain consistent with the base case despite variations to the analytical specifications and assumptions.

Table 51. Scenario analyses: ICERs for vadadustat compared to darbepoetin alfa (list price, deterministic analysis results)

Scenario	Description	ICER (£/QALY)	% change relative to base-case ICER
Base case	**-**	**51,254**	**0%**
Modelling horizon 5 years	Modelling horizon set to 5 years	Dominated	**-**
Modelling horizon 10 years	Modelling horizon set to 10 years	198,655	**373%**
Modelling horizon 20 years	Modelling horizon set to 20 years	55,704	**33%**
Discounting for costs and effects at 0%	Discount rates for costs and effects are set to 0%	29,486	**-30%**
Half-cycle correction not applied	Half-cycle correction not performed	43,838	**4%**
Birnie 2017 (ESA mix)	ESA mix as a comparator with distribution in line with Birnie 2017	Dominant	**-**
ESAs sales volumes as per IQVIA market share analysis (2022) (ESA mix)	ESA mix as a comparator with distribution in line with IQVIA market share analysis	Dominant	**-**
NHS PCA database 2022 (ESA mix)	ESA mix as a comparator with distribution in line with NHS PCA database analysis	Dominant	**-**
Equal ESAs market shares (ESA mix)	ESA mix as a comparator with equal distribution of ESAs according to assumption	Dominant	**-**
Epoetin alfa 100%	Epoetin alfa as comparator	Dominant	**-**
Epoetin beta 100%	Epoetin beta as comparator	Dominant	**-**
Epoetin zeta 100%	Epoetin zeta as comparator	Dominant	**-**
CERA 100%	CERA as comparator	Dominant	**-**

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Scenario	Description	ICER (£/QALY)	% change relative to base-case ICER
Key cardiovascular endpoint: Expanded MACE excluding VAT	Model uses secondary safety cardiovascular endpoint – Expanded MACE excluding VAT	Dominant	-
Vadadustat treatment waning, efficacy stop at cycle 5 (beyond 1 year)	Vadadustat reduced risk of MACE is applied for 1 year in line with $INNO_2VATE$ trial length	Less costly, less effective	-
Vadadustat treatment waning not applied, indefinite efficacy of vadadustat	Vadadustat reduced risk of MACE is applied through modelling horizon	36,872	**-12%**
Treatment wastage applied	Treatment wastage is applied to vadadustat and ESA treatment	39,401	**-6%**
Mode of administration utility increment applied to PD patients	Utility increment associated with oral mode of administration of vadadustat is applied to PD patients as suggested by clinical expert	20,761	**-51%**
Higher ESA costs due to cold chain storage and disposal (+5%)	Increased drug acquisition costs of ESAs to reflect cold chain storage and disposal costs associated with ESA treatment	21,765	**-48%**
Higher ESA costs due to cold chain storage and disposal (+10%)		1,500	**-96%**

Abbreviations: CERA, continuous erythropoietin stimulating agent; ESA, erythropoietin stimulating agent; Hb, haemoglobin; HD, haemodialysis; ICER, incremental cost effectiveness ratio; MACE, major adverse cardiovascular events; NICE, National Institute for Health and Care Excellence; PCA, prescription cost analysis; PD, peritoneal dialysis; QALY, quality adjusted life year; RBC, red blood cell; VAT, vascular access thrombosis

Table 52: Scenario analyses: ICERs for vadadustat compared to darbepoetin alfa (discounted price, deterministic analysis results)

Scenario	Description	ICER (£/QALY)	% change relative to base-case ICER
Base case	**-**	**Dominant**	**0%**
Modelling horizon 5 years	Modelling horizon set to 5 years	Less costly, less effective	-
Modelling horizon 10 years	Modelling horizon set to 10 years	Dominant	-
Modelling horizon 20 years	Modelling horizon set to 20 years	Dominant	-
Discounting for costs and effects at 0%	Discount rates for costs and effects are set to 0%	Dominant	-
Half-cycle correction not applied	Half-cycle correction not performed	Dominant	-

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Scenario	Description	ICER (£/QALY)	% change relative to base-case ICER
Birnie 2017 (ESA mix)	ESA mix as a comparator with distribution in line with Birnie 2017	Dominant	-
ESAs sales volumes as per IQVIA market share analysis (2022) (ESA mix)	ESA mix as a comparator with distribution in line with IQVIA market share analysis	Dominant	-
NHS PCA database 2022 (ESA mix)	ESA mix as a comparator with distribution in line with NHS PCA database analysis	Dominant	-
Equal ESAs market shares (ESA mix)	ESA mix as a comparator with equal distribution of ESAs according to assumption	Dominant	-
Epoetin alfa 100%	Epoetin alfa as comparator	Dominant	-
Epoetin beta 100%	Epoetin beta as comparator	Dominant	-
Epoetin zeta 100%	Epoetin zeta as comparator	Dominant	-
CERA 100%	CERA as comparator	Dominant	-
Key cardiovascular endpoint: Expanded MACE excluding VAT	Model uses secondary safety cardiovascular endpoint – Expanded MACE excluding VAT	Dominant	-
Vadadustat treatment waning, efficacy stop at cycle 5 (beyond 1 year)	Vadadustat reduced risk of MACE is applied for 1 year in line with INNO$_2$VATE trial length	Less costly, less effective	-
Vadadustat treatment waning not applied, indefinite efficacy of vadadustat	Vadadustat reduced risk of MACE is applied through modelling horizon	16,099	-
Treatment wastage applied	Treatment wastage is applied to vadadustat and ESA treatment	Dominant	-
Mode of administration utility increment applied to PD patients	Utility increment associated with oral mode of administration of vadadustat is applied to PD patients as suggested by clinical expert	Dominant	-
Higher ESA costs due to cold chain storage and disposal (+5%)	Increased drug acquisition costs of ESAs to reflect cold chain storage and disposal costs associated with ESA treatment	Dominant	-
Higher ESA costs due to cold chain storage and disposal (+10%)		Dominant	-

Abbreviations: CERA, continuous erythropoietin stimulating agent; ESA, erythropoietin stimulating agent; Hb, haemoglobin; HD, haemodialysis; ICER, incremental cost effectiveness ratio; MACE, major adverse cardiovascular

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B.3.12 Subgroup analysis

Not applicable.

B.3.13 Benefits not captured in the QALY calculation

The health economic impact reflected in this submission is limited to the NHS perspective as required by the reference case. For anaemia in CKD, however, a broader, societal perspective that reflects the spill-over effects such a progressively debilitating disease can have on patients, their caregivers and society would be relevant. Most notably, the impact of anaemia in CKD on the patient and caregiver productivity is not negligible and, if included, would further increase the potential for vadadustat to offer cost-savings to not only the NHS but also to individuals and other sectors of society (171).

Shifting to an oral treatment would also reduce the footfall in the kidney care centres of UK which would further help the NHS to achieve sustainable nephrology care by reducing the use of single-use plastics, saving energy/fuel, and reducing carbon footprint (by avoiding transportation). This would help in significantly minimising environmental damage by setting ambitious goals for decarbonisation and reducing other environmental impacts of kidney care in the UK.

B.3.14 Validation

B.3.14.1 Technical quality control of the cost-effectiveness model

The model developers performed a check of internal validity in accordance with a quality control process, including checks on the selection and results of different modelling options, calculation spot checks, cross checks against source data and extreme value testing.

The following general aspects of the model were explored:

- Top-down tests, including systematic variation of the model input parameters to establish whether changes in inputs result in predictable changes in the

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model outputs. The tests were designed to identify failures in model logic or material computation errors.

- Model internal functionality (e.g., testing of all key model parameters, extreme value testing). The following aspects of the spreadsheet were identified as key areas for detailed checking: Markov traces, translation of drug prices, complications and resource use into state costs.

- Internal consistency and accuracy of input data were checked by comparing the model inputs in Excel against the data sources referenced.

B.3.14.2 External validation of cost-effectiveness analysis

The model approach and assumption was validated by clinical and health economic experts during a series of meetings carried out during the first and second quarter of 2024 (172). During these meetings, no structural or major modelling aspects were highlighted, and all other insights were incorporated into the clinical positioning and modelling approach.

B.3.15 Interpretation and conclusions of economic evidence

A de novo Markov model comparing vadadustat with ESA treatment in DD-CKD with anaemia was developed to generate health economic evidence supporting a recommendation for its use by the NHS. Results from the probabilistic base-case cost-effectiveness analysis of this model when using the discounted price demonstrated that vadadustat is a cost-effective use of NHS resources as it was shown to dominate darbepoetin alfa. In other words, vadadustat treatment leads to less costs and more QALYs gained compared to darbepoetin alfa.

Vadadustat's cost-effectiveness was shown to be consistent across the probabilistic and deterministic analysis and to be of high certainty with [redacted] of all discounted price iterations falling below the WTP of £20,000 per QALY gained. The assessment of uncertainty demonstrated that results are associated with little to no uncertainty as all scenario analyses were consistent with the base case, with no scenarios above the WTP threshold of £20,000 per QALY. Nonetheless, the model is sensitive to the unit price of vadadustat and the efficacy and utility inputs, with the former being influenced

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by the small difference in QALYs and the latter due to the nature of modelling longer term outcomes when extrapolating outcomes based on a 52-week trial duration. For this reason, assumptions for the long-term efficacy of vadadustat were made, which currently in the base case is assumed to wane over time. It is possible this assumption however is conservative, as there is equally no evidence that the treatment benefits wane over time with continued use of vadadustat. Another source of uncertainty originates from the lack of health-related quality of life data from the INNO$_2$VATE clinical trial programme. Due to this limitation, utilities were sourced from published literature, selected to represent as close as possible the quality of life of patients enrolled in the trial. Deterministic and scenarios analyses, however, show that this source of uncertainty does not meaningfully impact the results as the conclusion for cost-effectiveness remains despite variation in utility inputs. One additional source of uncertainty is in the comparative effectiveness to ESAs besides darbepoetin alfa. Currently available evidence suggests that there is no evidence supporting or refuting a class effect within the ESA therapy class. Nonetheless, the base case results showing cost-effectiveness compared to darbepoetin alfa remain the most relevant demonstration of vadadustat's added value compared to the NHS standard of care as it has been demonstrated through observational data sources as well elicitation of expert opinion that darbepoetin alfa is the most frequently administered ESA in this population. Finally, for centres where darbepoetin alfa may not be the dominant treatment option, vadadustat remains cost-effective nonetheless across a range of assumptions for ESA mix. Therefore, the results for vadadustat's cost-effectiveness should be considered representative of all patients eligible in the NHS clinical setting for the treatment of adult patients with symptomatic anaemia associated with DD-CKD.

The current analysis presented here should be considered a conservative base case analysis as it relies on conservative assumptions and estimates; for example, incorporating a treatment waning assumption despite no evidence that benefits would wane over time and by applying the costs of the least costly ESA agent as a comparator. Furthermore, the current economic analysis has not incorporated all of vadadustat's potential savings to the NHS compared with ESAs. Because vadadustat is given orally, it would reduce the costs of administration and the costs of medical supplies, such as syringes, which would not be needed (unlike for ESAs, which are

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given by injection). It would also reduce the costs to the NHS of the disposal of syringes (unlike for ESAs). ESAs also require cold storage, which is not needed for vadadustat, and therefore, the use of vadadustat could reduce storage costs. Because it is taken orally in tablet form, vadadustat does not require that a qualified nurse is present to support with administering the treatment. Therefore, the use of vadadustat could also save resources by reducing nursing time associated with administration. Vadadustat could further reduce costs to the NHS by allowing more patients to switch to undergo their dialysis at home, which is less resource intensive for the NHS (6, 32). Home dialysis could also reduce costs for patients, as they would not need to travel to dialysis centres for their treatment (32). Finally, the current analysis does not incorporate the impact of frequent dosing adjustments to manage Hb levels which occurs with ESA treatment. Dose adjustments do present a cost to the NHS in terms of time, and should this cost have been quantifiable, its incorporation would further increase the health economic benefits of vadadustat treatment.

In addition, the broader environmental sustainability benefits of vadadustat have not been captured within the current economic analysis. First, because vadadustat does not require cold storage, which requires high use of energy, the use of vadadustat would also help support the NHS in its objective to reducing its CO_2 footprint (while also reducing the fridge capacity for patients). Second, single use injections have implications for environmental sustainability; therefore, reliance on single use plastics is clearly not ideal. Third, and finally, cold storage delivery also has environmental impact, as does incineration of hazardous waste which costs the NHS a large amount of money annually. For these reasons combined, vadadustat would hence help NHS move towards a “green therapy” (173).

To conclude, the evidence presented in this submission supports a positive clinical and economic evidence assessment for vadadustat compared to the NHS standard of care for treatment of DD-CKD patients with symptomatic anaemia. A positive recommendation for vadadustat for this population would offer realisation of the very meaningful clinical benefits of anaemia control to NHS DD-CKD patients with symptomatic anaemia where an important unmet need currently exists, especially for patients not benefiting from currently available treatment options. Offering vadadustat

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as an additional treatment option also facilitates patient and healthcare practitioner choice to allow treatment decision making that considers individual patient needs for care, which is of utmost importance considering the high levels of comorbidity present in this patient population. Vadadustat further benefits the NHS by providing an alternative oral treatment option that can be taken at home as it will release NHS resources (i.e., costs and practitioner time) so they can be diverted to other areas of need within the healthcare system. In conclusion, the evidence presented in this submission demonstrates that vadadustat represents a clinically and cost-effective use of NHS resources for the treatment of adult DD-CKD patients with symptomatic anaemia and should receive a positive non-restricted recommendation for NHS use.

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B.5. Appendices

Clinical trial reports and protocols have been shared with NICE for the relevant clinical studies. The following appendices have been supplied as part of the submission package:

- Appendix C: Summary of product characteristics and UK public assessment report;
- Appendix D: Identification, selection and synthesis of clinical evidence (see section 2.1);
- Appendix E: Subgroup analysis (see section 2.7);
- Appendix F: Adverse reactions (see section 2.10);
- Appendix G: Published cost-effectiveness studies (see section 3.1);
- Appendix H: Health-related quality-of-life studies (see section 3.4.3);
- Appendix I: Cost and healthcare resource identification, measurement and valuation (see section 3.5);
- Appendix J: Clinical outcomes and disaggregated results from the model (see section 3.10.1);
- Appendix K: Price details of treatments included in the submission;
- Appendix L: Checklist of confidential information;
- Appendix M: Other clinical outcomes from the INNO$_2$VATE trials
- Appendix N: Clinical experts' opinion;
- Appendix O: Inflation indices.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
ID3821_Vadadustat_SIP	2.0	No	05th June 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Vadadustat (1-4) **Brand name:** Vafseo® (1-4)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

This appraisal focuses on patients who are aged 18 years and above who are undergoing ongoing dialysis with symptoms of anaemia in chronic kidney disease (CKD).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare Products Regulatory Agency (MHRA) is the government agency that is responsible for regulating medicines in the UK. Vadadustat received approval from the MHRA on 19th May 2023 for the treatment of patients aged 18 years and above who have anaemia in CKD and who are on dialysis (1-4). The marketing authorisation was first granted to Akebia Therapeutics, who developed the product, and was then transferred from Akebia to MEDICE Arzneimittel Pütter GmbH & Co. KG. on 15th March 2024.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

At the time of submitting this appraisal, MEDICE served as an industry partner to Kidney Research UK (KRUK) at a cost of £2,500 for the year.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is anaemia in CKD?

CKD is a long-term (chronic) condition in which kidney function is gradually reduced and eventually lost as the disease progresses. CKD is classified into five different stages, based on severity (5). Patients with the most severe stage of CKD (stage 5) experience kidney failure (also referred to as end stage renal disease) (5, 6). Patients with CKD can be categorised as either not dependent on dialysis or dependent on dialysis.

Anaemia is the most common complication of CKD. This is a condition in which the quality and quantity of red blood cells and of haemoglobin (Hb) is reduced. Hb is the iron-rich protein in the red blood cells that carries oxygen to tissues and organs in the body. When the amount of red blood cells or Hb is reduced, the oxygen-carrying capacity of the blood is also reduced and is insufficient to meet the body's needs (5, 7, 8). Anaemia in CKD is a serious condition that severely limits patients' ability to carry on with regular activities, and it often leads to cardiovascular complications, reduced quality of life and a higher risk of death (9). The causes of anaemia in CKD are multifaceted, but it primarily results from erythropoietin deficiency or iron deficiency. Iron is required to produce Hb in your bone marrow and disruptions in the iron balance can lead to iron-deficiency anaemia which is the most common form of anaemia (10, 11). Iron-deficiency anaemia in individuals with CKD may result from functional iron deficiency, absolute iron deficiency, or both. Functional iron deficiency occurs when there are sufficient iron stores in the body but your body is unable to access it to make Hb, while absolute iron deficiency is characterised by a significant decrease or complete absence of iron stores (11).

How many people get anaemia in CKD?

CKD (including all stages) is estimated to affect 11% to 13% of the population globally (12). Based on 2023 figures, it is estimated that approximately 3.25 million people are living with CKD (stages 3-5) in the UK (13). CKD (stages 3-5) is expected to increase to 3.85 million in the UK over the next 10 years, because of an ageing population (13). Anaemia is estimated to affect about half of patient with CKD, and in patients with later stages (3-5) of CKD who are dependent on dialysis, nearly 90% experience anaemia (14-16).

What is the impact of anaemia in CKD on patients' and families/caregivers' quality of life?

Patients with CKD, especially those with end stage renal disease, experience a high burden on their quality of life. This burden is made worse by the presence of anaemia (17). Anaemia in CKD affects many different aspects of health and well-being, such as reduced energy levels and reduced capacity for physical activity, which limits patients' ability to participate in activities of daily living, social interactions, and leisure activities (18). The impact of anaemia in CKD on patients' quality of life is similar to that of other serious chronic illnesses, such as diabetes, epilepsy and some cancers (18). Anaemia in CKD has also been found to limit patients' ability to work (17).

Caregivers of patients with CKD also experience a high burden on their quality of life. Patients with end stage renal disease who are on dialysis and elderly may need extra support from their caregivers. Caregivers may have many responsibilities, such as taking patients to medical appointments, administering medical treatment, support with managing nutrition and diet, help with everyday tasks, and providing psychological support (19, 20). Caregivers have reported limitations to their work life and personal and social activities as a result (20).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is anaemia in CKD diagnosed?

Anaemia in CKD is diagnosed based on blood tests that measure the level of Hb in the blood. In the UK, nephrologists prefer to keep your Hb within a range of 10-12 g/dL as an optimal target (21).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatment guidelines are available for patients with anaemia in CKD in the UK?

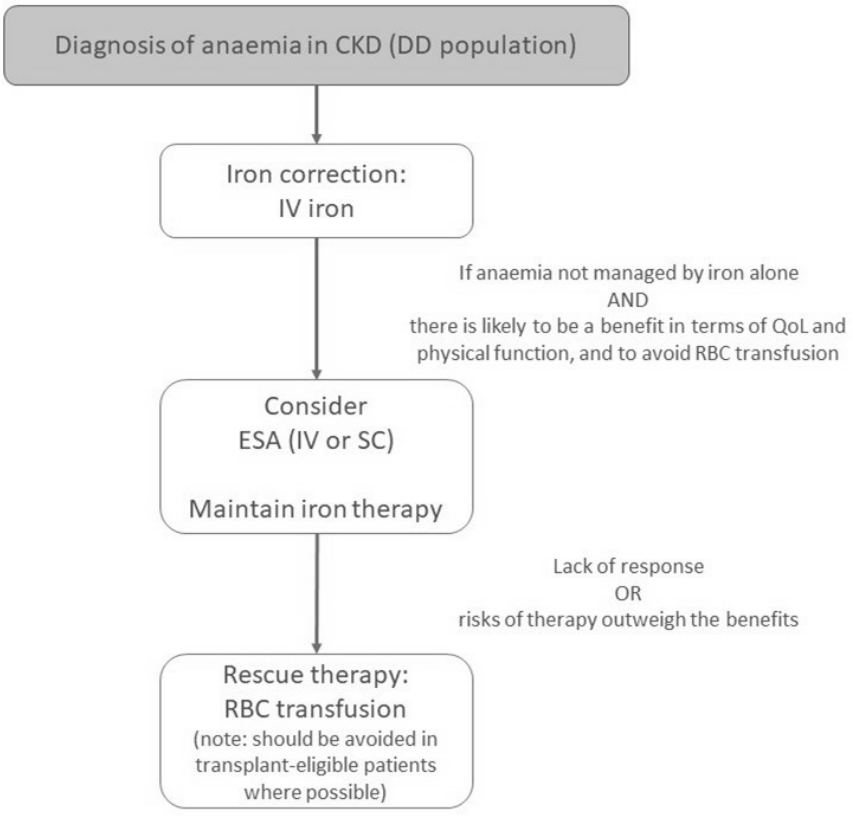
Guidelines for treating patients with anaemia in CKD are issued by the National Institute for Health and Care Excellence (NICE) (8) and the UK Kidney Association (UKKA) (21).

What are the current treatment options?
Current UK and global treatment guidelines (7, 8, 21, 22) recommend treating anaemia in CKD in a series of different steps.

As a first step, the causes of anaemia that can be corrected, such as low levels of iron in the blood, should be treated. Low levels of iron are treated with iron supplements, usually given intravenously (5, 23). If iron therapy does not increase levels of Hb in the blood, the next step recommended within the guidelines is to offer treatment with erythropoiesis-stimulating agents (ESAs) (7, 8). Where patients don't respond to ESA therapy, or where the risks of this treatment outweigh the benefits, red blood cell transfusions may be recommended (22). It is advised that patients with CKD, especially those who are candidates for a kidney transplant (that is, patients with End-Stage Renal Disease or ESRD), should minimise the use of RBC transfusions to prevent the risk of allosensitisation, which is an immune response to foreign tissue. Allosensitisation may decrease the number of suitable donors, leading to longer wait times for transplants, and is linked to a higher rate of organ rejection and loss of the transplanted organ.

The current treatment pathway for anaemia in CKD is shown in Figure 1 below.

Figure 1. Current treatment pathway for patients with anaemia in CKD who are dependent on dialysis (DD-CKD)



Abbreviations: CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; IV, intravenous; QoL, quality of life; RBC, red blood cell; SC, subcutaneous

What are the limitations of the current treatment options?
ESA treatment is not suitable for all patients with anaemia in CKD. Patients who develop pure red cell aplasia, a rare disease that prevents the bone marrow from producing red blood cells, should not receive ESA treatment (24-26). Patients who have uncontrolled or poorly controlled high blood pressure are also unsuitable for ESA treatment (24-26). Furthermore, a proportion of patients with anaemia in CKD do not respond well to treatment with ESAs (27). The estimated number of patients who are resistant to ESA treatment varies because of a lack of an agreed definition of resistance to ESAs. Depending on the definition used, resistance to ESAs affects 12.5-30% of CKD patients (28). It is uncertain how this group of patients should be treated, and this is a key area of unmet need in anaemia in CKD. In current clinical practice, this means that these patients are often given either increasingly larger doses of ESAs or no treatment at all. Patients who are resistant to ESAs have a higher risk of death, low levels of Hb despite high ESA doses, and a very poor quality of life (29).

Who is vadadustat recommended for?
Vadadustat will be positioned as an alternative option to treatment with ESAs for adult patients who have symptoms of anaemia in CKD and who are on ongoing dialysis.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A study conducted by interviewing key opinion leaders and patient advocates indicated the need for improved education on anaemia in chronic kidney disease (aCKD) for both physicians and patients (30). It highlighted the importance of understanding anaemia's clinical aspects and its impact on patients' quality of life (QoL). It also suggested that physicians should refresh their knowledge of aCKD guidelines and consider the humanistic burden of anaemia. Patients should be educated about anaemia symptoms and treatments to empower them for better self-care and decision-making. The role of patient organisations in providing support and hope is also emphasised. Education should be personalised, accessible, and delivered through various channels. Research suggests that both physicians and patients need to engage in open communication for effective disease management and improved patient QoL (30).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Anaemia in CKD is a condition that is commonly caused by iron deficiency and erythropoietin (EPO) deficiency, especially in those patients requiring kidney replacement therapy like dialysis (21). EPO is a hormone that regulates the production of red blood cells in the bone marrow, which in turn affects the blood's capacity to supply oxygen to the body (31-33). EPO is mainly produced in the kidney, and the production of EPO is regulated by a very sensitive feedback loop. In patients with CKD, the feedback loop is not working as it should because of damage to the kidneys (31). Therefore, not enough EPO is produced, which in turn affects the regulation and production of red blood cells in the body.

Vadadustat is a treatment that stimulates an endogenous (or more natural) production of EPO, and therefore increases the production of red blood cell and Hb in the body. This will increase the blood's capacity to carry oxygen around the body and may reduce the anaemia symptoms. Vadadustat stimulates the production of EPO by inhibiting a substance called hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) (1-4). HIF-PH inhibitors are a new class of drugs for the treatment of anaemia in CKD, to be taken orally.

The MHRA summary of product characteristics (SmPC) and patient information leaflet (PIL) can be downloaded from the below links:

- 150mg: link
- 300mg: link
- 450mg: link

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections

on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
Vadadustat is intended for adult patients who are undergoing ongoing dialysis with symptoms of anaemia in CKD. Vadadustat is not supposed to be taken in combination with any other therapy.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
How is vadadustat taken? Vadadustat is available in tablet form and should be taken orally once a day with or without food. Vadadustat can be taken at any time before, during or after dialysis. The recommended starting dose is 300 mg (1-3). The dose can be increased by 150 mg once every four weeks, up to a maximum of 600 mg (1-3). Reductions in the dose can happen more frequently than every four weeks. Your doctor would give you a detailed plan for taking vadadustat if it is prescribed to you. Vadadustat should be taken at least one hour before oral iron supplements, products whose primary component consists of iron or iron-containing phosphate binders. Vadadustat should be taken at least one hour before or two hours after non-iron-containing phosphate binders or other medicinal products whose primary component consists of elements such as calcium, magnesium, or aluminium. Vadadustat may also increase the effects of breast cancer resistant protein (BCRP) substances (such as fluvastatin, nelfinavir, pitavastatin, and topotecan) and some other medicines such as sulfasalazine, simvastatin, and rosuvastatin when co-administered. Dose adjustment of co-prescribed medications may be needed. For more information regarding drug interactions and most common side effects, please refer to the SmPCs (the links to which are provided in section 3a). An oral therapy offers a lot of advantages over other therapies such as those delivered by intravenous, or sub-cutaneous (under the skin) routes. Unlike ESAs, vadadustat does not require a qualified nurse to administer or support self-administration; use of an oral treatment over injectable may also reduce nursing time. Furthermore, vadadustat may also reduce costs to the healthcare system by making it more appealing to choose either peritoneal dialysis (PD) and/or home haemodialysis (HHD), which is less resource intensive for the National Health Services (NHS) and patients than treatment in dialysis centres (13, 34). Moreover, patients may also prefer a tablet taken orally due to the ease of administration, no training required, and reduced stress and anxiety about medication which results in higher treatment compliance. For patients, as an oral tablet treatment vadadustat (unlike ESAs) does not require storage in the fridge, which can be difficult for individuals when travelling for example. It also avoids concerns about potential needle hazards for other family members in the house. In a UK advisory board conducted by MEDICE, clinical experts also suggested that oral therapies

can be beneficial for patients who are homeless or have no fixed address, as storage in a fridge is not required.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Clinical studies of vadadustat in adults with anaemia in CKD

Vadadustat was studied in two global phase III clinical trials (which we refer to as INNO$_2$VATE – incident and INNO$_2$VATE – prevalent) (35, 36). These two trials compared vadadustat to a single ESA, called darbepoetin alfa. Darbepoetin alfa was chosen as the comparator because it is the most used ESA.

INNO$_2$VATE – incident and INNO$_2$VATE – prevalent

Participants in the two trials included over 3,900 adults over the age of 18, both male and female, with anaemia in CKD who were on dialysis. The INNO$_2$VATE – prevalent trial recruited patients who were already on dialysis from treatment centres in 10 different countries, and the INNO$_2$VATE – incident trial recruited patients who had recently initiated dialysis from treatment centres in 18 countries. Patients were randomly assigned to receive either vadadustat or darbepoetin alfa. The two treatment groups were well balanced across average age, sex, height, and weight. Both trials completed in 2020.

There are no ongoing trials for vadadustat.

Details about the INNO$_2$VATE – incident trial are available at: https://clinicaltrials.gov/study/NCT02865850. Details about the INNO$_2$VATE – prevalent trial are available at: https://clinicaltrials.gov/study/NCT02892149.

More information can be found in the following publications:

- Eckardt KU, Agarwal R, Aswad A, Awad A, Block GA, Bacci MR, Farag YM, Fishbane S, Hubert H, Jardine A, Khawaja Z. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. New England Journal of Medicine. 2021 Apr 29;384(17):1601-12.
- Koury MJ, Agarwal R, Chertow GM, Eckardt KU, Fishbane S, Ganz T, Haase VH, Hanudel MR, Parfrey PS, Pergola PE, Roy-Chaudhury P. Erythropoietic effects of vadadustat in patients with anemia associated with chronic kidney disease. American Journal of Hematology. 2022 Sep;97(9):1178-88.
- Sarnak MJ, Agarwal R, Boudville N, Chowdhury PC, Eckardt KU, Gonzalez CR, Kooienga LA, Koury MJ, Ntoso KA, Luo W, Parfrey PS. Vadadustat for treatment of anemia in patients with dialysis-dependent chronic kidney disease receiving peritoneal dialysis. Nephrology Dialysis Transplantation. 2023 Oct;38(10):2358-67.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The $INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent trials were designed to compare the efficacy and safety of vadadustat with darbepoetin alfa in the treatment of anaemia in CKD in patients undergoing dialysis. The trials were non-inferiority trials, which means that they were designed to test whether a new treatment (vadadustat) is not worse than the existing treatment (darbepoetin alfa) and provides at least the same benefits as the latter.

Change in average Hb levels

Both trials showed that vadadustat was no worse than darbepoetin alfa after the first (weeks 24 to 36) and second (weeks 40 to 52) treatment efficacy periods (35, 36). Doses of vadadustat and darbepoetin alfa were adjusted gradually in line with dose adjustment guidelines to maintain target Hb concentrations (37). Vadadustat maintained Hb in the target range while minimising variations in Hb concentrations outside of the target range, ensuring stable and predictable rises in Hb. In PD patients the mean Hb remained in range for 156 weeks of treatment. This means that patients were not subjected to increased risk of major adverse cardiovascular events (MACE), including myocardial infarction (heart attack), stroke and all-cause mortality (i.e., death due to any cause), because of variations in Hb concentrations (37). In addition, levels of hepcidin, the hormone that regulates iron in the body, decreased which allowed the patients in the study to access the iron in their stores more effectively which may mean fewer iron infusions required to ensure adequate iron stores for erythropoiesis (production of red blood cells) (37).

Need for red blood cell transfusion

In both trials, the proportion of patients who needed red blood cell transfusions was overall similar between the vadadustat and the darbepoetin alfa treatment groups.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The impact of vadadustat on the quality of life of patients

EuroQol 5 Dimension 5 Level (EQ-5D) is the tool that is preferred by NICE to measure the health-related quality of life (HRQoL) in adults. However, in the INNO$_2$VATE clinical trials, EQ-5D data was not collected. The INNO$_2$VATE trials showed that vadadustat was no worse than ESAs in terms of how well the treatment worked in treating anaemia in CKD in adults on dialysis, and that it was not inferior to ESAs in terms of how safe the treatment was for patients. 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 patients with anaemia in CKD who are on dialysis. Because vadadustat is to be taken orally, compared to ESAs which are administered by injection under the skin, vadadustat offers the convenience of being taken at home, with minimal disruption of patients' daily routine (38). A recent study that looked at patients' treatment preferences in a population of patients with CKD not on dialysis, found that 83% of patients with anaemia in CKD preferred a treatment in oral form over the existing injectable treatment options (39, 40). Patients who may be worried about their families or children being potentially exposed to needle stick injury may also potentially benefit from the vadadustat tablet.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, vadadustat can cause side effects. The most common side effects of vadadustat (experienced by more than 1 in 10 patients) are high blood pressure, blood clots and diarrhoea (1-4). One in 10 to one in 100 patients may experience headache, low blood pressure, cough, constipation, nausea, vomiting and elevated liver enzymes. (1-3). The occurrence of increased bilirubin in blood is very uncommon. For more details regarding the side effects, please refer to the SmPCs (the links to which are provided in section 3a).

Vadadustat was shown to be overall well-tolerated by patients in the two INNO$_2$VATE trials, and to have a safety and tolerability profile similar to that of darbepoetin alfa (35, 36). The level of side effects was similar between the vadadustat and the darbepoetin alfa treatment groups. The occurrence of side effects leading to study participants having to stop treatment was minimal in both study treatment groups, suggesting good tolerability. In both trials, the number of patients who experienced major cardiovascular events (such as stroke, heart attack or death) were similar in the vadadustat and the darbepoetin alfa treatment groups (35, 36).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

If vadadustat is recommended by NICE, it would be the only recommended treatment for anaemia in CKD for patients on ongoing dialysis that works through the HIF-PHI mechanism of action.

Vadadustat comes in tablet form to be taken orally once a day, without patients needing the support of a qualified nurse. Oral administration also has the advantages that the start dose is the same for all patients, with a simple titration algorithm to adjust dose as required, no cold chain storage needed at the patient's home, and less support needed from carers.

It has been demonstrated by robust clinical evidence that vadadustat is an effective treatment for anaemia in CKD for patients on dialysis, and that clinical results with vadadustat are not worse than the current standard of care (35, 36).

Vadadustat would provide a potentially effective treatment for those patients not responding to conventional ESA therapy, meeting an important unmet need (41), and could potentially prevent blood transfusions as the last treatment option.

Because it is taken orally, vadadustat reduces barriers for patients to undergo dialysis at home, providing greater choice for patients as well as more independence (e.g. for travelling).

Minimal training is required to take vadadustat, which reduces the time for eligible patients to access the treatment.

Because it is taken orally, vadadustat can potentially reduce costs to the health care services, through reducing the costs of treatment administration, medical supplies, cold storage, and nursing time. Taking your medication orally could free up more of your nurse's time to spend on other important activities, whether you take your medication at a centre or at home. It may make PD, which is less resource intensive for the NHS, more attractive for patients, as they won't have to self-inject an ESA. A simple dosing regimen resulting in a stable Hb helps control patients' symptoms with fewer dose changes than conventional therapy. Vadadustat can also benefit patients by achieving a gradual increase in Hb levels.

It was overall well tolerated by patients in two phase III clinical trials, with a similar safety profile to the current standard of care (35, 36).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Vadadustat has been shown to have a good safety and tolerability profile, similar to the current standard of care. There are no specific disadvantages of vadadustat compared with the existing treatment options.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to the existing treatments. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a health economic model (a theoretically constructed representation of a process in which the cost and benefits of a new treatment are compared with the existing treatments of that disease area). The pharmaceutical company uses the health economic model to perform an analysis which compares the costs and benefits of the new treatment (vadadustat) with the existing treatment (darbepoetin alfa).

The model reflects the experience of patients living with anaemia in CKD

Informed by a literature review of published cost-effectiveness models in anaemia in CKD, as well as several interviews with clinical experts in anaemia in CKD, a health economic model was developed to capture the costs and benefits of introducing vadadustat into the current care pathway. This model was developed to accurately reflect the experience of patients with anaemia in CKD in England and uses evidence from the clinical trials of vadadustat (i.e., INNO$_2$VATE – incident and INNO$_2$VATE – prevalent).

The cost-effectiveness model compares the costs and benefits of treatment with vadadustat versus darbepoetin alfa in the target population. Darbepoetin alfa, an ESA, was selected for the comparison as a representative of current standard of care. There are currently three different ESAs that are approved for use in England and Wales. The available evidence on how well these treatments work suggests that there are no differences between the three ESAs (42, 43). Available data indicates that darbepoetin alfa is the ESA most frequently used in the NHS (44).

The model for vadadustat included the following trial results to determine the benefit of vadadustat and to quantify the efficacy of vadadustat as compared to darbepoetin alfa: distribution of patients within Hb level cut-offs, risk of MACE outcomes (myocardial infarction, stroke and all-cause mortality), proportion of patients using intravenous iron, probability of using red blood cell transfusion or ESAs rescue therapies (i.e., additional therapy to help bring Hb into the correct range), and frequency of adverse events. The trial data was available for up to 52 weeks for the outcomes used in the model. Beyond 52 weeks, the latest observed trial parameter was carried out to the end of the modelling period, or other statistical methods were used to extend estimates for the longer term.

Costs in the model included the costs of vadadustat and darbepoetin alfa, administration costs associated with ESAs, anaemia monitoring costs, costs for managing adverse reactions, cost of intravenous iron use and administration, cost of red blood cell transfusions, costs of ESA therapy for rescue, renal care costs (dialysis, dialysis insertion procedure, transplant, and costs associated with pre-

and post-transplantation), and costs associated with MACE. Quality of life for patients who received vadadustat and darbepoetin alfa was not assessed during the INNO$_2$VATE trials. To quantify quality of life, published literature was used to first quantify utility (benefit) associated with different forms of renal replacement therapy (haemodialysis, peritoneal dialysis, transplant). Then these utilities (benefits) were adjusted for patient age and quality of life reductions associated with anaemia (through reduced Hb levels), MACE events and adverse events.

The company believes there is no aspect of anaemia in CKD or vadadustat that would impact the ability to generate high-quality evidence in determining the costs and benefits of vadadustat versus darbepoetin alfa in the target population.

What do the results of the cost-effectiveness analysis tell us?

The cost-effectiveness analysis provides an estimate of the additional costs to the healthcare system and the quality of life gains to patients that are likely associated with the use of vadadustat compared with ESAs in the treatment of anaemia in CKD. The analysis is based on the INNO$_2$VATE clinical trials which demonstrated that vadadustat controls Hb levels as well as the established ESA treatment. This benefit is reflected in the model outcomes. As no real difference was seen in the safety or tolerability of the treatments, these outcomes do not have a large impact on the model results.

Although EQ-5D data was not collected in the INNO$_2$VATE clinical trials used to inform the cost-effectiveness model, the trials showed that vadadustat was not inferior to ESAs in terms of how well the treatment worked and how safe it was for patients. Therefore, it can be expected that the health-related benefits of vadadustat will be at least similar to ESAs for the target population. Given vadadustat is an oral treatment it is also expected to provide additional value to patients compared to ESAs which are injectable treatments, and this benefit is also captured in the model. Vadadustat is a new treatment for patients with DD-CKD and does cost more than the older ESA treatments. The cost-effectiveness model weighs up the benefits associated with vadadustat with the additional costs to understand whether it will meet NICE's threshold for offering sufficient value for money for use in the NHS.

Does the treatment extend life?

The vadadustat INNO$_2$VATE trials were designed as non-inferiority trials, which means that the trials aimed to test whether vadadustat is at least as effective as the alternative standard treatment used in the trial, darbepoetin alfa. A non-inferiority trial design is not suitable for assessing whether one treatment is more effective than or has greater benefit over another treatment. The INNO$_2$VATE trials showed that vadadustat is non-inferior (i.e., not worse than) to darbepoetin alfa. However, the INNO$_2$VATE trials also reported several outcomes, including risk of MACE outcomes (myocardial infarction, stroke and all-cause mortality), that showed numerical differences between vadadustat and darbepoetin alfa in favour of vadadustat. These differences in outcomes between the treatments were not statistically significant, indicating that fewer MACE outcomes with vadadustat are unlikely to occur in clinical practice.

Benefits of the treatment not captured in the modelling

Vadadustat may reduce costs to the health service compared with ESAs. Because vadadustat is given orally, it would reduce the costs of administration and the costs of medical supplies, such as syringes, which would not be needed (unlike for ESAs, which are given by injection). It would also reduce the costs of the disposal of syringes (unlike for ESAs). ESAs also require cold storage, which is not needed for vadadustat, and therefore the use of vadadustat could reduce storage costs. Because it is taken orally in tablet form, vadadustat does not require that a qualified nurse is present to support with administering the treatment. Therefore, the use of vadadustat could also save resources by reducing nursing time. Vadadustat could also reduce costs to the NHS by allowing more patients to switch to undergoing their dialysis at home, which requires less resources for the NHS (13, 34). Home dialysis could also reduce costs for patients, as they would not need to travel to dialysis centres for their treatment (13).

Because vadadustat is taken orally, it offers added convenience compared to the existing treatment which are typically given by injection under the skin, which may have a positive effect on patients' quality of life.

In addition, because vadadustat does not require cold storage, which requires high use of energy, the use of vadadustat would also help support the NHS in its objective to reducing its CO_2 footprint (while also reducing the fridge capacity for patients). Single use injections have huge implications for environmental sustainability, therefore, reliance on single use plastics is clearly not ideal. Moreover, cold storage delivery also has environmental impact, as does incineration of hazardous waste which costs the NHS a large amount of money annually. Vadadustat would hence help NHS move towards a "green therapy" (45).

Conclusion

The analysis was designed to examine the cost-effectiveness of vadadustat in the NHS setting.

Vadadustat offers an important alternative treatment option for adult patients with anaemia in CKD who are on dialysis.

Vadadustat also addresses a key unmet need by offering an effective treatment option to patients who are resistant to ESAs, the current standard of care. This is a patient population with very poor quality of life. Vadadustat may improve the quality of life of patients with anaemia in CKD who are on dialysis by offering a more convenient oral administration route, which would allow patients to undergo dialysis at home. It also has the ability to support a gradual increase in Hb levels, thereby reducing the need for continuous testing. It has a good safety profile that allows patients to use it for a long time.

Additionally, vadadustat has the potential to help save costs associated with the use of ESAs, by reducing the costs of administration, medical supplies, disposal of clinical waste, cold storage, and nursing time.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
If vadadustat is approved, it would be the only recommended HIF-PH inhibiting treatment that is recommended for adults with anaemia in CKD who are on ongoing dialysis. Vadadustat would also provide an alternative treatment option to ESA, to be taken orally which is in contrast to the existing treatments that are usually taken by injection under the skin.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Oral treatment option could help reduce inequalities in access to care Vadadustat is to be taken orally as a tablet once a day. Unlike for ESAs, vadadustat does not require a qualified nurse to be present to give the treatment or support the patient in taking the treatment. Therefore, the availability of vadadustat can help support patients on dialysis to undergo dialysis at home instead of having their dialysis at an outpatient centre. This would improve access to treatment and provide greater choice for patients, which has been lacking. Although it has been recommended that all patients who can have dialysis at home should be offered the choice (46), only a small proportion of patients are given this option (34). A recent study on patient preferences in patients with CKD not on dialysis found that 83% of patients with anaemia in CKD preferred a treatment in oral form over the existing treatment options (39, 40). Also, oral treatment like vadadustat can support patients due to the ease of administration associated with tablets, no need of formal training or struggling with administration directions or leaflets. It may also help patients with dexterity issues or patients who gets stressed or anxious about taking injectable treatments. In a MEDICE advisory board, clinical experts have also suggested that vadadustat could benefit patients who are homeless or do not have a fixed address and lack access to a refrigerator. Unlike ESAs, vadadustat does not require cold storage.

Vadadustat could provide an important treatment option for patients who are resistant to ESA treatment

Some patients with anaemia in CKD do not respond well to treatment with ESAs, the current standard of care (41). The estimated number of patients who are resistant to ESA treatment varies, because of a lack of an agreed definition of resistance to ESAs. Depending on the definition used, resistance to ESAs affects 12.5-30% of CKD patients (28). It is uncertain how this group of patients should be treated, and this is a key area of unmet need in anaemia in CKD. Patients who are resistant to ESAs have a higher risk of death, low levels of haemoglobin despite high ESA doses, and a very poor quality of life (29).

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

- National Kidney Foundation – anaemia and chronic kidney disease: https://www.kidney.org/atoz/content/what_anemia_ckd
- Kidney Care UK – patient information booklets: https://kidneycareuk.org/get-support/free-resources/patient-information-booklets/
- UK Kidney Association – information & resources for patients: https://ukkidney.org/patients/information-resources
- NHS – chronic kidney disease: https://www.nhs.uk/conditions/kidney-disease/

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Anaemia:** A condition of not having enough healthy red blood cells or haemoglobin to carry oxygen to the body's tissues
- **Bilirubin:** A yellowish pigment that is made during the breakdown of red blood cells. Bilirubin passes through the liver and is eventually excreted out of the body
- **Chronic condition:** An illness persisting over a long time or constantly recurring
- **CKD:** Chronic kidney disease
- **Dialysis:** A procedure to remove waste products and excess fluid from the blood when the kidneys stop working properly. There are different ways in which this procedure can be carried out, e.g. haemodialysis or peritoneal dialysis.
- **End stage renal disease:** End stage renal disease, also called kidney failure, occurs when chronic kidney disease – the gradual loss of kidney function – reaches an advanced state. In end-stage renal disease, your kidneys no longer work as they should to meet your body's needs
- **Erythropoietin:** A hormone that regulates the production of red blood cells in the bone marrow
- **EQ-5D:** A standardised measure of health-related quality of life that assesses health status in terms of five dimensions of health. It is considered a 'generic' questionnaire because these dimensions are not specific to any one patient group or health condition
- **ESA:** Erythropoiesis-stimulating agent, a medication that stimulates the bone marrow to produce red blood cells
- **Haemodialysis:** A procedure which replaces some of the functions of the kidney to remove waste products and excess fluid from the blood, by using a machine to filter and clean the blood outside of the body.
- **Haemoglobin:** A protein found in the red blood cells that carries oxygen in your body and gives blood its red colour
- **HIF-PHI:** Hypoxia-inducible factor prolyl-hydroxylase inhibitor, a new class of oral drugs that are being developed to treat anaemia in patients with chronic kidney disease
- **INNO$_2$VATE – incident:** This was a phase 3 clinical study that evaluated the efficacy and safety of vadadustat in the treatment of anaemia in CKD in patients over the age of 18 undergoing dialysis, as compared with darbepoetin alfa
- **INNO$_2$VATE – prevalent:** This was a phase 3 clinical study that evaluated the efficacy and safety of vadadustat in the treatment of anaemia in CKD in patients over the age of 18 undergoing dialysis, as compared with darbepoetin alfa
- **Linear regression:** An analysis that is used to predict the value of a variable based on the value of another variable.

- **Peritoneal dialysis:** A procedure which replaces some of the functions of the kidney to remove waste products and excess fluid from the blood. In peritoneal dialysis, the blood is cleaned inside the body, with the help of a catheter inserted into the abdomen (belly)
- **Pure red cell aplasia:** A rare disease that prevents the bone marrow from producing red blood cells
- **Renal replacement therapy:** A therapy that replaces the normal blood-filtering function of the kidneys (dialysis or transplantation).
- **Transfusion:** A medical procedure that involves transferring blood products into a patient's bloodstream through a vein

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821] Clarification questions	**2**	**Yes**	**26/06/2024**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. The decision problem (Table 1, Doc B). There were differences between the population in the final scope issued by NICE and the population in the decision problem addressed in the company submission. Please can the company offer a rationale why each of the phrases 'symptomatic', 'associated with' and 'chronic maintenance' were not used to define the population addressed in the company submission.

Company response: MEDICE do not disagree with the final scope issued by National Institute for Health and Care Excellence (NICE) for the population description. Small differences in wording were an oversight and MEDICE agree the population can be defined as 'Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis' to align with the MHRA marketing authorisation.

A2. PRIORITY. Differing treatment aims in the populations recruited to the two pivotal trials. The external assessment group (EAG) considered the two trial populations of INNO$_2$VATE – incident and INNO$_2$VATE – prevalent to be different in their baseline characteristics and the dosing and aims of treatment, and therefore do not consider it appropriate to pool these populations. The aim of treatment in INNO$_2$VATE – incident was to increase low haemoglobin (Hb) levels to within the

recommended target range (10-12 g/dL). However, the population in INNO$_2$VATE – prevalent were people whose Hb levels were already within the recommended target range, and the aim of treatment was to maintain their Hb levels rather than change them. Please would the company advise whether it disagrees with this view (and if so, why). If it agrees, please advise how the company handled the differences in the trials when pooling the data and using the data in the economic model.

Company response: MEDICE agree that there are some differences in the baseline characteristics of patients enrolled into the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials (e.g., mean time on dialysis), as expected for incident and prevalent populations. However, all other characteristics and demographics were generally similar across both trials (e.g., mean age, sex, body mass index, diverse race representation, geographic region, type of dialysis, comorbidities/aetiology of CKD and many laboratory parameters and prior medications) (1). Furthermore, the trial designs, dosing and objectives were pre-specified to be the same across both the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials as they were intended to be presented in a pooled MACE analysis reflecting the entire DD CKD population eligible for treatment.

The eligibility criteria of the INNO$_2$VATE trials were chosen to maximise the generalisability of results to the wider dialysis-dependent chronic kidney disease (DD-CKD) population (1), while allowing for differences in the inclusion and exclusion criteria consistent with the incident dialysis nature of the INNO$_2$VATE – incident trial and the prevalent dialysis nature of the INNO$_2$VATE – prevalent trial (2). As a result, participants in the INNO$_2$VATE – incident trial were required to have initiated chronic maintenance dialysis within 16 weeks of screening, while participants in the INNO$_2$VATE – prevalent trial were required to be receiving chronic maintenance dialysis for at least 12 weeks prior to screening. In the INNO$_2$VATE – incident trial, participants that met the criteria of erythropoietin stimulating agent (ESA) resistance within eight weeks prior to or during screening were excluded from the study, while the INNO$_2$VATE – prevalent trial required participants to be maintained on ESA therapy at screening, with a dose received within six weeks prior to or during screening.

As mentioned, the design of the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials was similar: both were randomised, open-label (sponsor-blind), active-controlled

(darbepoetin alfa), non-inferiority efficacy and safety cardiovascular outcomes studies (2). In both studies the starting dose of vadadustat was 300 mg once daily (QD), with up-and-down titration to 150 mg to 600 mg QD to achieve target Hb levels (10.0 to 11.0 g/dL in US and 10.0 to 12.0 g/dL ex-US). In both studies participants were stratified by geographic region (United States [US] versus Europe versus Rest of World [ROW]), New York Heart Association (NYHA) Heart Failure Class, and by baseline Hb level at study entry.

Furthermore, the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials were designed to be analysed jointly to assess the safety and efficacy of vadadustat. The single primary objective of the clinical trial programme was to investigate the cardiovascular safety and haematological efficacy of vadadustat compared with darbepoetin alfa for the treatment of anaemia in patients with DD CKD (1). The objectives for the individual studies reflected this joint aim:

- *INNO$_2$VATE – incident trial objective:* to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anaemia after the correction of haemoglobin or conversion from current ESA therapy, in subjects who have recently initiated dialysis treatment for DD-CKD (3);

- *INNO$_2$VATE – prevalent trial objective:* to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anaemia in subjects with DD-CKD (4).

The primary safety analysis (time to first adjudicated major adverse cardiovascular event [MACE]), prespecified to be pooled from both INNO$_2$VATE trials, was based upon all events that accrued over the two trials. Specifically, the INNO$_2$VATE clinical trial programme was designed so that the pooled analyses included a sufficient number of independently adjudicated endpoints to allow a meaningful comparison of vadadustat and darbepoetin alfa with respect to MACE (5). Moreover, the pooled data from the two trials represents the target population. This approach was accepted for regulatory assessment (2) and MEDICE believe this evidence is more appropriate for addressing the current decision problem than using a meta-analysis approach.

A3. PRIORITY. Trial data pooling. The EAG understand that the efficacy data used in the model is taken from the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials. However, no meta-analysis was presented in Document B explaining how data from these trials were pooled. The EAG understand, after interrogating the efficacy data used in the model, that these data were pooled as if they came from a single trial. It is understood that compared to standard meta-analysis, the treat-as-one-trial method gives greater weight to large trials and disregards study-to-study variation leading to narrower confidence intervals. If any data pooling is required for this submission, please use a meta-analysis to pool the data from trials and present this meta-analysis for critique by the EAG.

Company response: As mentioned in the response to A2, the IPD have been pooled across the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials as a single trial because the clinical trial programme was designed as two prospective clinical trials that would be analysed jointly to assess the safety and efficacy of vadadustat. The single primary objective was to investigate the cardiovascular safety and haematological efficacy of vadadustat compared with darbepoetin alfa for the treatment of anaemia in patients with dialysis-dependent CKD (1). Therefore, the primary safety analysis (time to first adjudicated MACE), prespecified to be pooled from both INNO$_2$VATE trials, was based upon all events that accrued over the two trials. Specifically, the INNO$_2$VATE clinical trial programme was designed so that the pooled analyses included a sufficient number of independently adjudicated endpoints to allow a meaningful comparison of vadadustat and darbepoetin alfa with respect to MACE (5). This approach was acceptable for regulatory decision making by the European Medicines Agency (EMA) (6). The pooling of data already weights the total sample size by the size of each study and therefore the mean and variation are correctly estimated with this approach. Furthermore, the ‘study-to-study variation’ should be accounted for in the pooling when study designs are identical, as in this case (see A2 response for details). Therefore, a meta-analysis would add no additional value in this case and the correct approach is to naïvely pool the IPD given the pooled data represent the target population (i.e., combining the incident and prevalent).

MEDICE would like to again remind the EAG that the indicated population is neither that of the INNO$_2$VATE – incident trial, nor that of the INNO$_2$VATE – prevalent trial and

the eligibility criteria of the INNO$_2$VATE trials were chosen to maximise the generalisability of results to patients with anaemia of dialysis-dependent CKD (1). Importantly, the demographics and baseline characteristics of patients enrolled in the two studies are comparable to those typically observed in patients with DD-CKD, suggesting the results of the INNO$_2$VATE trials will be generalisable to a large proportion of the DD-CKD population (1).

MEDICE, therefore, believe pooling the IPD and conducting analyses provides the most robust assessment, and that a meta-analysis will not provide more reliable information. In addition, using a meta-analysis is not expected to have a substantial impact on the cost-effectiveness outcomes given a meta-analysis previously performed for the primary MACE endpoint (time to first MACE) yielded similar results to analyses of the pooled data (Table 1) (5).

Given the clear alignment of results of the prespecified analysis of pooled INNO$_2$VATE data with the meta-analyses provided in the EPAR, using data from the pooled analysis is the preferred approach to minimise uncertainty around the point estimate of treatment effect, as the pooled data represent the target population for decision making.

To further address this request, MEDICE have also provided below the results of a fixed effects meta-analysis using the published aggregate results for the other key efficacy outcomes, including change in Hb, proportion of patients within Hb target range, proportion of patients receiving rescue therapies (Table 2; forest plots for meta-analysis provided in Appendix, Figure 7 to Figure 13). As expected, the results of the fixed effects meta-analysis are more heavily weighted by the results of the INNO$_2$VATE – prevalent trial as it constitutes the majority of patients across the two trials, which would similarly be reflective of the real-world target patient population eligible for vadadustat.

Table 1. Time to first MACE (safety population)

	Vadadustat (N=1,947)	Darbepoetin alfa N = 1,955	Treatment comparison, HR (95% CI); p-value
Primary analysis (pooled)			
Subjects with events, n (%)	355 (18.2)	377 (19.3)	
Time to first event, weeks n Median Q1, Q3	 355 46.14 24.71, 77.14	 377 47.00 22.43, 74.43	 0.96[a] (0.833, 1.113); p=0.4877[b]
Supportive meta-analysis [weighting inversely proportional to the variance of the study-specific log (HR)]			
Meta-analysis (inverse-variance weighting)	-	-	0.96[c] (0.832, 1.113)

[a] From Mantel-Haenszel method, vadadustat/darbepoetin alfa. Based on a stratified Cox regression model with study as a stratification factor.
[b] Log-rank test based on non-parametric analysis. For the analysis of pooled data ($INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent), log-rank test is stratified by study.
[C] The hazard ratio (HR) is estimated by weighting log(HR), obtained from each individual study, inversely proportional to the variance of the study-specific log(HR).
Abbreviations: CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; Q, quartile.
Source: MACE report (5)

Table 2. Meta-analysis key efficacy outcomes for vadadustat (N=1,958) vs darbepoetin alfa (N=1,965) from INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials

Endpoint	Fixed effects meta-analysis[a]			Pooled IPD results from EPAR
	Mean difference (95% CI)	**z-value**	**p-value**	**LS mean difference (95% CI)**
Change from baseline in Hb to average over Weeks 24 to 36	-0.18 (-0.27, -0.10)	-4.19	<0.0001	-0.18 (-0.24, -0.12)
Change from baseline in Hb to average over Weeks 40 to 52	-0.17 (-0.27, -0.08)	-3.73	0.0002	-0.17 (-0.24, -0.11)
Change from baseline in Hb to average over Weeks 24 to 52	-0.17 (-0.25, -0.10)	-4.44	<0.0001	NR
	Odds ratio (95% CI)	**z-value**	**p-value**	
Proportion of patients with average haemoglobin value within geography-specific target range, Weeks 24 to 36	0.87 (0.76, 0.99)	-2.12	0.034	NR
Proportion of patients with average haemoglobin value within geography-specific target range, Weeks 40 to 52	0.82 (0.71, 0.94)	-2.86	0.0042	NR
	Incident rate ratio (95% CI)	**z-value**	**p-value**	
ESA rescue episodes, narrow rescue definition	3.59 (3.14, 4.10)	18.8	<0.0001	NR
ESA rescue episodes, broad-on rescue definition	2.82 (2.53, 3.15)	18.73	<0.0001	NR

a Analyses were performed in R version 4.3.2 on published aggregate data. The inverse variance method was used for estimation of weights and a restricted maximum-likelihood estimator was applied for tau^2. Meta-analyses of binary outcomes and count outcomes used the respective relative effects estimates (i.e., odds ratios or rate ratios, respectively) as data inputs. In that case, outcome measures are log-transformed in order to be able to use the assumption that the effects are normally distributed. Test of heterogeneity was met for all analyses performed.

Abbreviations: CI, confidence interval; Hb, haemoglobin; IPD, individual patient data; LS, least squares; NR, not reported in EPAR.

Source: MEDICE data on file – fixed effects meta-analysis; EPAR (2).

A4. The Final Scope issued by NICE requests previous exposure to ESA subgroups to be considered, if the evidence allows. The EAG are aware that in the INNO$_2$VATE – incident trial, 177 (48.0%) participants were using an ESA at baseline, and therefore, 192 (52.0%) of participants were not treated with ESAs at baseline. The EAG understand these people were naive to ESA treatment and may represent a subgroup of interest to the committee. Please present efficacy and safety data for this subgroup so it can be evaluated in the economic model.

Company response: Limited analyses were conducted for the subpopulation of participants naïve to ESA treatment because this was a very small proportion (n=192) of the overall population (N = 3,923 for total pooled INNO$_2$VATE population). Figure 1 in Appendix E.1.1 presents prespecified subgroup analyses of change from baseline in haemoglobin to the average over weeks 24 to 36 and weeks 40 to 52 from the INNO$_2$VATE – incident trial. In these analyses, the least square mean (LSM) difference between vadadustat and darbepoetin alfa (95% CI) for participants with no prior ESA use (n=192) was -0.13 (-0.44, 0.18) and for those with prior ESA use (n=177) -0.51 (-0.80, -0.23). Even though the point estimates are slightly different for these subpopulations, the 95% CI intervals overlap and results for both populations demonstrated non-inferiority of vadadustat compared with darbepoetin alfa (3).

Further analyses, where evidence allowed, were conducted to address the EAG's query. According to these statistical analyses no significant effect modification by the subgroup characteristic "previous ESA-treatment" was found in the INNO$_2$VATE – incident trial. Available data relevant for the cost-effectiveness analysis in this assessment are provided in Table 3 to Table 8 below.

Table 3. Time to death from any case (weeks) in subgroup 'previous ESA treatment'

Treatment	N	n (%)	Censored (%)	Median (95-%-KI)	HR (95-%-KI)	p-value
Yes						
Vadadustat	91	5 (5.5)	86 (94.5)	NA (NA; NA)	0.58 (0.18; 1.85)	0.2355
Darbepoetin alfa	84	9 (10.7)	75 (89.3)	NA (NA; NA)		
No						
Vadadustat	88	10 (11.4)	78 (88.6)	NA (NA; NA)	0.97 (0.39; 2.39)	0.8508
Darbepoetin alfa	102	11 (10.8)	91 (89.2)	NA (NA; NA)		
Post-hoc analysis: calculation of the median using the Kaplan-Meier estimator, calculation of the hazard ratios using Cox regression, calculation of the p-value using the log-rank test.						
ITT: Intention-to-treat; N: Number of patients; n: Number of patients with event; HR: Hazard ratio; CI: Confidence interval; NA: Not analysable						

Table 4. Time to cardiovascular death (weeks) in subgroup 'previous ESA treatment'

Treatment	N	n (%)	Censored (%)	CIF W52 (95% CI)	HR (95% CI); p-value
Yes					
Vadadustat	91	4 (4.4)	87 (95.6)	0.04 (0.01; 0.10)	1.21 (0.32; 4.58); 0.6702
Darbepoetin alfa	84	5 (6.0)	79 (94.0)	0.04 (0.01; 0.11)	
No					
Vadadustat	88	5 (5.7)	83 (94.3)	0.06 (0.02; 0.12)	1.26 (0.38; 4.15); 0.7712
Darbepoetin alfa	102	5 (4.9)	97 (95.1)	0.01 (0.00; 0.05)	
Post-hoc analysis: calculation of the p-value using the Gray test for competing risks, calculation of the hazard ratios using the proportional sub distribution hazard regression model, cumulative incidence functions (CIF) represent the probability of occurrence of the endpoint in competition with the other risks for the corresponding week (W).					
N: number of patients; n: number of patients with event; CIF: cumulative incidence function; HR: hazard ratio; W: week; CI: confidence interval; NA: not analysable					

Table 5. AE (total rate) in subgroup 'previous ESA treatment'

Treatment	N	n (%)	RR (95% CI)	OR (95% CI)	RD (95% CI)	p-value
No						
Vadadustat	88	70 (79.5)	0.92 (0.81; 1.05)	0.62 (0.29; 1.33)	-0.07 (-0.17; 0.04)	0.2466
Darbepoetin alfa	102	88 (86.3)				
Yes						
Vadadustat	91	80 (87.9)	1.04 (0.92; 1.17)	1.33 (0.56; 3.16)	0.03 (-0.07; 0.14)	0.6608
Darbepoetin alfa	84	71 (84.5)				
Post-hoc analysis: calculation of the p-value using Fisher's test, unstratified calculation of all effect estimates (RR, OR and RD) using a four-field table, calculation of the CI using normal distribution approximation.						
N: Number of patients; n: Number of patients with event; RR: Relative risk; OR: Odds ratio; RD: Risk difference; CI: Confidence interval; NA: Not analysable						

Table 6. Severe AE (total rate) in subgroup 'previous ESA treatment'

Treatment	N	n (%)	RR (95% CI)	OR (95% CI)	RD (95% CI)	p-value
No						
Vadadustat	88	32 (36.4)	1.16 (0.78; 1.73)	1.25 (0.68; 2.28)	0.05 (-0.09; 0.18)	0.5386
Darbepoetin alfa	102	32 (31.4)				
Yes						
Vadadustat	91	28 (30.8)	0.81 (0.54; 1.22)	0.72 (0.39; 1.35)	-0.07 (-0.21; 0.07)	0.3411
Darbepoetin alfa	84	32 (38.1)				
Post-hoc analysis: calculation of the p-value using Fisher's test, unstratified calculation of all effect estimates (RR, OR and RD) using a four-field table, calculation of the CI using normal distribution approximation.						
N: Number of patients; n: Number of patients with event; RR: Relative risk; OR: Odds ratio; RD: Risk difference; CI: Confidence interval; NA: Not analysable						

Table 7. Time to first MACE event (defined as death from any cause, non-fatal myocardial infarction or non-fatal stroke; weeks) in subgroup 'previous ESA treatment'

Treatment	N	n (%)	Censored (%)	Median (95% CI)	HR (95% CI)	p-value
Yes						
Vadadustat	91	9 (9.9)	82 (90.1)	NA (NA; NA)	1.04 (0.39; 2.78)	0.9653
Darbepoetin alfa	84	9 (10.7)	75 (89.3)	NA (NA; NA)		
No						
Vadadustat	88	13 (14.8)	75 (85.2)	NA (NA; NA)	0.99 (0.46; 2.16)	0.9343
Darbepoetin alfa	102	15 (14.7)	87 (85.3)	NA (NA; NA)		
Post-hoc analysis: calculation of the median using the Kaplan-Meier estimator, calculation of the hazard ratios using Cox regression, calculation of the p-value using the log-rank test.						
N: Number of patients; n: Number of patients with event; HR: Hazard ratio; CI: Confidence interval; NA: Not analysable						

Table 8. Time to first MACE event plus hospitalisation due to heart failure or a thromboembolic event other than vascular access thrombosis (weeks) in subgroup 'previous ESA treatment'

Treatment	N	n (%)	Censored (%)	Median (95% CI)	HR (95% CI)	p-value
Yes						
Vadadustat	91	16 (17.6)	75 (82.4)	NA (NA; NA)	1.41 (0.65; 3.07)	0.4531
Darbepoetin alfa	84	12 (14.3)	72 (85.7)	NA (NA; NA)		
No						
Vadadustat	88	13 (14.8)	75 (85.2)	NA (NA; NA)	0.81 (0.39; 1.69)	0.5905
Darbepoetin alfa	102	19 (18.6)	83 (81.4)	NA (NA; NA)		
Post-hoc analysis: calculation of the median using the Kaplan-Meier estimator, calculation of the hazard ratios using Cox regression, calculation of the p-value using the log-rank test.						
ITT: intention-to-treat; N: number of patients; n: number of patients with event; HR: hazard ratio; CI: confidence interval; NA: not analysable						

A5. Relevant RCTs excluded from the systematic literature review (SLR). In section D.1.7 of the CS you state that four trials of vadadustat versus ESAs for people with CKD on chronic maintenance dialysis met the SLR inclusion criteria but were excluded from the submission for reasons not detailed in the SLR protocol.

- FO2CUS [NCT04707768]: excluded because it was conducted in the US.
- MT-6548-J03 [NCT03439137]: excluded because it was conducted in Japan.

The EAG's clinical expert is not aware of any differences in the efficacy of ESAs or vadadustat for anaemia in adults with CKD who are dialysis-dependent (DD), linked to a person's ethnic background, and as such, the EAG do not consider the stated reasons for excluding FO2CUS and MT-6548-J03 to be valid.

- FO2RWARD-2 [NCT03799627]: excluded because it was a phase II trial.
- AKB-6548-CI-0018 [NCT03140722]: excluded because it was a phase II trial.

The SLR protocol in Appendix D stated that Phase I trials would be excluded but the FO_2RWARD-2 and AKB-6548-CI-0018 were phase II trials. Therefore, the EAG do not consider this to be a valid reason for exclusion from the SLR.

Please justify their exclusion based on the exclusion criteria or incorporate them in the analysis.

Company response: MEDICE believe that the most robust evidence to support the assessment of vadadustat in the treatment of symptomatic anaemia in DD-CKD patients comes from the INNO$_2$VATE clinical trial programme. This programme was comprised of two randomised clinical trials designed to be pooled to address the primary objective of investigating the cardiovascular safety and haematological efficacy of vadadustat compared with darbepoetin alfa for the treatment of anaemia in patients with dialysis-dependent CKD (1). The pivotal INNO$_2$VATE trials were the focus of regulatory assessment, with other trials, including MT-6548-J03 (NCT03439137) and FO_2RWARD-2 (NCT03799627), mentioned only as supportive studies (2).

Regarding the Phase II studies, Study AKB-6548-CI-0018 (NCT03140722) specifically investigated vadadustat in DD-CKD patients hyporesponsive to ESA (vadadustat

versus epoetin alfa) and was conducted only in the US. This study only enrolled two patients and was terminated, therefore, results are unavailable for inclusion (7). The other Phase II study, FO_2RWARD-2 (NCT03799627), was only conducted in the US with potentially significant patient demographic and healthcare system disparities versus the European or English setting. The FO_2RWARD-2 trial investigated vadadustat in participants converting from epoetin alfa therapy to vadadustat and comprised three treatment arms: daily vadadustat versus epoetin alfa versus vadadustat three times per week (8). A variety of vadadustat starting doses were tested. To date, the data from this trial have not been published in a peer-reviewed manuscript although some data are available via CT.gov (e.g., participant information, baseline characteristics, mean change in haemoglobin, haemoglobin values within target range, iron supplementation, ESA rescue therapy, RBC transfusion, treatment-emergent adverse events, changes from baseline in laboratory parameters, vital signs, adverse events) (8); the IPD are unavailable to MEDICE for inclusion in the CEM.

Regarding the Phase III trials, Study MT-6548-J03 (NCT03439137) was conducted in Japan by the Mitsubishi Tanabe Pharma Corporation. In this trial, there were differences in subject characteristics and the endpoints analysed in comparison to the pivotal global studies; as a result regulatory assessment did not consider this trial relevant (2). The Phase III FO_2CUS (NCT04707768) study was conducted in the US only and, as for the FO_2RWARD-2 (NCT03799627) study above, MEDICE considered it less relevant for NICE assessment given the potential disparities between US and United Kingdom (UK) patient demographics and healthcare systems. In addition, the vadadustat dosing and frequency were different in the FO_2CUS study (starting dose 600 mg or 900 mg; with 300 mg minimum dose and 1200 mg maximum dose; three time weekly frequency) compared with the INNO_2VATE clinical trial programme (starting dose 300 mg as per marketing authorisation, with flexible titration of 150-600 mg/day; once daily frequency) further reducing the relevance to this assessment [please refer to Table 24 of EPAR (2)]. Furthermore, the IPD are unavailable to MEDICE for inclusion in the CEM.

For the reasons above, MEDICE believe including data from the listed clinical trials does not provide relevant evidence to inform the current assessment of vadadustat in

the treatment of anaemia in CKD, particularly given the different populations and dosages used do not reflect the decision problem.

A6. PRIORITY. In Section B.2.8 of the CS the company refers to the class effect of ESAs as well established and quote the Cochrane review from 2014 that concluded insufficient evidence to suggest the superiority of any ESA formulation. As the company notes, this review was updated in 2023 with 61 more trials and the author concluded that current data from RCTs were insufficient to definitively inform on the comparative efficacy and safety of differing ESA formulations. The EAG is concerned that the current evidence base for ESA treatment of anaemia in CKD does not establish a class effect for ESAs. Please do not use an assumption of a class effect. Please include all ESAs used in UK practice for people with anaemia who have dialysis treatment for DD-CKD as separate comparators in the analysis.

Company response: The assumption by MEDICE that the effectiveness of vadadustat compared to darbepoetin alfa is generalisable to the broader ESA therapeutic class is based on the NICE treatment guidelines for managing anaemia in CKD, which states that available evidence on efficacy suggest no difference between darbepoetin alfa and epoetin alfa, or between darbepoetin alfa and epoetin beta (9, 10). The position taken by NICE is further supported by MEDICE's discussions with UK clinical experts as well as several studies which similarly conclude equivalent efficacy between ESAs (having similar duration of action) at equivalent doses within the target population (9, 10). Further, several studies similarly conclude either there are uncertain differences or equivalent efficacy between ESAs (having similar duration of action) at equivalent doses (11, 12, 13, 14, 15, 16, 17). Hence, MEDICE is unaware of any evidence that would reject a class effect.

Regarding the recently updated Cochrane review, which MEDICE considers to be the most relevant, complete review of all available evidence for ESAs in the target population, MEDICE agrees with the EAG's interpretation that the clinical efficacy evidence is insufficient evidence to suggest the superiority of any ESA formulation (17). However, it equally believes that the review is neither able to confirm nor reject the class effect assumption due to the unclear to high risk of the individual studies, which lends the meta-analysis of unclear to high uncertainty based on the GRADE criteria for network meta-analysis. High uncertainty in the available ESA evidence

base exists for a number of reasons. As concluded by the Cochrane authors, observed events for most outcomes were relatively low, resulting in significant imprecision and inconclusive evidence for most outcomes. Most studies were not powered to detect differences in patient-level outcomes such as death, cardiovascular events and kidney failure, with a median study size of 137 participants and a median follow-up duration of seven months. Methodological limitations (i.e., allocation concealment, blinding of outcome assessment and attrition from follow-up), heterogeneity, inconsistency and selective reporting of outcomes further contributed to uncertainty. The Cochrane authors conclude, therefore, that other considerations should be made when determining choice of ESA, such as drug cost, availability, and dosing frequency preferences, which is aligned with the NICE guidelines as well as expert advice sought in preparation for this submission. Given the high uncertainty and risk of bias, MEDICE believes that making use of the evidence available for alternative ESAs within a scenario analysis would only increase uncertainty of vadadustat's cost-effectiveness.

MEDICE would further like to note that darbepoetin alfa is the most commonly used ESA in NHS clinical setting for the target population of DD-CKD patients, representing 80% of total ESA use by the NHS to treat symptomatic anaemia in this population. The remaining ESA use is distributed across epoetin alfa, beta and zeta and methoxy polyethylene glycol-epoetin bet, each of which constitute individually a small proportion of overall use (i.e., <5%).

Therefore, based on the overwhelming representation of darbepoetin alfa for ESA use and the clinical guidelines for ESA use in this population, MEDICE believes that the INNO$_2$VATE trials comparing vadadustat to a single ESA (i.e., darbepoetin alfa) serves as high quality evidence to establish the benefits of vadadustat compared to the entire class of ESAs when administered as standard of care to DD-CKD patients in the NHS.

Finally, MEDICE would like to note that the 2022 NICE appraisal for roxadustat (TA807) in the NDD-CKD population was also supportive of the assumption of a class effect for ESAs in a NDD-CKD population (18). While acknowledging some differences in the frequency of administration, the TA807 committee concluded that the effectiveness of ESAs is similar, supporting a class effect. MEDICE is not aware of any reasons why the class effect would exist in a non-DD population and not the DD

population. This also aligns with the views of the clinical experts that EAG referenced and discussed during the clarification call with MEDICE.

MEDICE has already proactively provided scenario analyses which alters the cost of the ESA comparator to reflect the relevant decision-making criteria applied when deciding between alternative options available to NHS patients, i.e., costs and convenience.

A7. PRIORITY. Table 13: Summary of patients with any events (first and subsequent MACE) – overall (safety population) in Appendix F:

- Please present Table 13 using only data from INNO$_2$VATE – incident.
- Please present Table 13 using only data from INNO$_2$VATE – prevalent.

Company response: The requested data are provided below (Table 9 and Table 10).

Table 9: Summary of patients with any events (first and subsequent MACE) – overall (safety population) from INNO$_2$VATE – incident

Event, n (%)	Vadadustat (N=179)	Darbepoetin Alfa (N=186)	Total (N=365)
Patients with Any MACE	22 (12.3)	24 (12.9)	46 (12.6)
All-cause Mortality	15 (8.4)	20 (10.8)	35 (9.6)
Non-fatal Myocardial Infarction	5 (2.8)	3 (1.6)	8 (2.2)
Non-fatal Stroke	4 (2.2)	3 (1.6)	7 (1.9)
Patients with Any CV MACE	16 (8.9)	14 (7.5)	30 (8.2)
CV Death	9 (5.0)	10 (5.4)	19 (5.2)
Non-fatal Myocardial Infarction	5 (2.8)	3 (1.6)	8 (2.2)
Non-fatal Stroke	4 (2.2)	3 (1.6)	7 (1.9)
Patients with Any Thromboembolic Events	7 (3.9)	13 (7.0)	20 (5.5)
Vascular Access Thrombosis	7 (3.9)	9 (4.8)	16 (4.4)
Arterial Thrombosis	0	0	0
Deep Vein Thrombosis	0	3 (1.6)	3 (0.8)
Pulmonary Embolism	0	1 (0.5)	1 (0.3)
Patients with Any Hospitalisations for Heart Failure	11 (6.1)	7 (3.8)	18 (4.9)
Patients with Any Expanded MACE			
Any MACE plus Thromboembolic Events	29 (16.2)	35 (18.8)	64 (17.5)
Any MACE plus Thromboembolic Events Excluding Vascular Access Thrombosis	22 (12.3)	27 (14.5)	49 (13.4)
Any MACE plus Hospitalisations for Heart Failure	29 (16.2)	28 (15.1)	57 (15.6)
Any MACE plus Hospitalisations for Heart Failure or Thromboembolic Events	34 (19.0)	39 (21.0)	73 (20.0)
Any MACE plus Hospitalisations for Heart Failure or Thromboembolic Events Excluding Vascular Access Thrombosis	29 (16.2)	31 (16.7)	60 (16.4)
Patients who Died (All-cause Mortality)	15 (8.4)	20 (10.8)	35 (9.6)
CV Deaths	9 (5.0)	10 (5.4)	19 (5.2)
Non-CV Deaths	5 (2.8)	8 (4.3)	13 (3.6)
Unknown Deaths	1 (0.6)	2 (1.1)	3 (0.8)

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular events; n (%), number (percent) of patients with events
Note: A subject can have more than one event.
Source: MACE Report: INNO$_2$VATE (5)

Table 10: Summary of patients with any events (first and subsequent MACE) – overall (safety population) from INNO$_2$VATE – prevalent

Event, n (%)	Vadadustat (N=1,768)	Darbepoetin Alfa (N=1,769)	Total (N=3,537)
Patients with Any MACE	333 (18.8)	353 (20.0)	686 (19.4)
All-cause Mortality	276 (15.6)	290 (16.4)	566 (16.0)
Non-fatal Myocardial Infarction	77 (4.4)	85 (4.8)	162 (4.6)
Non-fatal Stroke	28 (1.6)	40 (2.3)	68 (1.9)
Patients with Any CV MACE	209 (11.8)	228 (12.9)	437 (12.4)
CV Death	141 (8.0)	150 (8.5)	291 (8.2)
Non-fatal Myocardial Infarction	77 (4.4)	85 (4.8)	162 (4.6)
Non-fatal Stroke	28 (1.6)	40 (2.3)	68 (1.9)
Patients with Any Thromboembolic Events	162 (9.2)	135 (7.6)	297 (8.4)
Vascular Access Thrombosis	139 (7.9)	111 (6.3)	250 (7.1)
Arterial Thrombosis	7 (0.4)	4 (0.2)	11 (0.3)
Deep Vein Thrombosis	15 (0.8)	17 (1.0)	32 (0.9)
Pulmonary Embolism	5 (0.3)	8 (0.5)	13 (0.4)
Patients with Any Hospitalisations for Heart Failure	73 (4.1)	82 (4.6)	155 (4.4)
Patients with Any Expanded MACE			
Any MACE plus Thromboembolic Events	452 (25.6)	455 (25.7)	907 (25.6)
Any MACE plus Thromboembolic Events Excluding Vascular Access Thrombosis	350 (19.8)	370 (20.9)	720 (20.4)
Any MACE plus Hospitalisations for Heart Failure	375 (21.2)	405 (22.9)	780 (22.1)
Any MACE plus Hospitalisations for Heart Failure or Thromboembolic Events	485 (27.4)	500 (28.3)	985 (27.8)
Any MACE plus Hospitalisations for Heart Failure or Thromboembolic Events Excluding Vascular Access Thrombosis	391 (22.1)	418 (23.6)	809 (22.9)
Patients who Died (All-cause Mortality)	276 (15.6)	290 (16.4)	566 (16.0)
CV Deaths	141 (8.0)	150 (8.5)	291 (8.2)
Non-CV Deaths	107 (6.1)	108 (6.1)	215 (6.1)
Unknown Deaths	28 (1.6)	32 (1.8)	60 (1.7)

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular events; n (%), number (percent) of patients with events
Note: A subject can have more than one event.
Source: MACE Report: INNO$_2$VATE (5)

A8. There are 2 rescue therapy outcomes reported in the pivotal trials. Narrow rescue therapy is “for worsening anaemia” and broad-on treatment rescue therapy is “for any reason”. Our clinical expert was unsure why people might be administered rescue therapy if it was not linked to worsening anaemia.

- Please explain why the outcome was categorised into narrow rescue therapy and broad-on treatment rescue therapy.
- What different conclusions can be drawn from narrow rescue therapy results as compared to broad-on treatment rescue therapy results?
- Please outline the reasons why people received a RBC transfusion as rescue therapy when it was not linked to worsening anaemia.
- Please outline the reasons why people received an ESA as rescue therapy when it was not linked to worsening anaemia.
- Please offer a rationale why it was appropriate to use narrow rescue therapy rather than the broad-on treatment rescue therapy for RBC transfusion and ESAs rescue therapies in the cost-effectiveness model.

Company response: Rescue was defined from narrow to broad, based on the type, timing, intensity, and reason for treatment. ESA medication and RBC transfusion were considered rescue therapy for anaemia secondary to chronic kidney disease (19, 20). The possible reasons for such treatments included:

- Investigator-ordered rescue (per protocol for worsening of anaemia),
- Adverse events (unrelated to anaemia),
- Maintenance during prolonged interruption of study treatment, and
- Inadvertent use (at hospital or dialysis centre).

The case report forms collected reasons for ESA medication and RBC transfusion. The series of rescue definitions are defined as follows (19, 20):

- *Narrow:* Rescue for worsening anaemia with ESA medication or RBC transfusion not starting after permanent study treatment discontinuation.

- *Broad-on-treatment:* Any exposure to ESA medication (aside from darbepoetin alfa not designated as rescue in the control arm) or RBC transfusion for any reason not starting after permanent study treatment discontinuation.

Thus, while the narrow definition focussed on the intended indication of renal anaemia, the broad definition provided additional information related to rescue therapy in the trial population as supporting analysis. Generally, results from the INNO$_2$VATE clinical trial programme were consistent across the two rescue therapy definitions (2).

In the pivotal global INNO$_2$VATE studies, the protocol-specified criteria for narrow ESA rescue for vadadustat-treated participants was strictly defined as a decline in Hb to <9.5 g/dL and/or an associated worsening of symptoms of anaemia (2). For broad-on-treatment rescue, any ESA exposure, including inadvertent administration of ESA, was deemed ESA rescue therapy in vadadustat-treated participants. For darbepoetin alfa-treated participants, ESA rescue was defined in the protocol as the receipt of any ESA agent other than darbepoetin alfa, i.e., increases in the darbepoetin alfa dose were not considered ESA rescue unless the Investigator designated the administration as such. In other words, there were no protocol prespecified dose-related criteria to define ESA rescue with darbepoetin alfa in individuals randomised to the darbepoetin alfa treatment group (2).

However, the definitions of rescue therapy in the statistical analysis plans for the INNO$_2$VATE trials represent a limitation that did impact the ability to demonstrate the full extent of efficacy for vadadustat. The administration of rescue for vadadustat-treated subjects was clearly defined. Conversely, dosing changes in darbepoetin alfa was not consistently defined as a rescue therapy in the protocols, but rather was classified as a protocol deviation, which led to underreporting of ESA rescue in this treatment group. In subjects randomised to darbepoetin alfa, the Investigator was responsible for the proper reporting of reasons for changes in ESA dose. In practice, in the global clinical studies, dose increases of ≥50% and ≥100% were observed frequently in the darbepoetin alfa group. As the prescribing information recommends dose adjustments of ≤25%, the incremental changes in dose that were 2-fold to 4-fold

higher than recommended fit the profile of rescue therapy in the darbepoetin alfa group.

As a result, post-hoc analyses were conducted for ESA rescue that, in addition to the prespecified narrow and broad-on-treatment ESA rescue definitions, also included individuals who received ≥50% or ≥100% increase in the dose of darbepoetin alfa from the previous closest reported dose. The ≥50% or ≥100% dose increases were selected because they are substantially higher than what is recommended in the darbepoetin alfa US prescribing information and the EMA SmPC, which is an increase of 25% from the previous dose and potentially represents a need for ESA 'rescue' treatment for individuals on darbepoetin alfa as relevant to real-life clinical practice. The post-hoc analysis performed to explore this definition of rescue therapy demonstrated that a greater proportion of subjects taking darbepoetin alfa required rescue therapy (approximately 25% using the ≥50% criterion and approximately 10% using the ≥100% criterion) compared with subjects who received vadadustat (approximately 5% to 8%) (2).

RBC transfusion as rescue therapy was defined as RBC transfusion therapy grouped temporally into episodes, which contained multiple administrations based on the gap in time between the end of one episode and the start of the next with a maximum gap for an episode of seven days (2). Investigators used their local institution's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, a RBC transfusion was administered as clinically indicated. In less severe instances but where there may have been worsening of anaemia or moderate to severe symptoms of anaemia, RBC transfusions were permitted at the discretion of the Investigator given medical necessity. Reasons for RBC transfusion were captured in the appropriate case report form. Study drug (vadadustat or darbepoetin alfa) could be continued during the transfusion period.

Rescue episodes were defined as exposure to the therapy grouped temporally, which contained multiple administrations based on the gap in time between the end of one and the start of the next (2) . The maximum gap for ESA medication within a single episode was 30 days. Concomitant use of an ESA with study drug was strictly prohibited. Starting at Week 6, subjects in both treatment groups were allowed (although not required) to have their Hb rescued with ESA therapy. When possible, a

subject on vadadustat had to be on the maximum dose of vadadustat for two weeks prior to ESA rescue. A subject on darbepoetin alfa could be rescued with another ESA per the standard of care. To qualify for ESA rescue, a subject had to fulfil both of the following criteria:

- Experienced worsening of the symptoms of anaemia (e.g., fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared to baseline.
- Hb of <9.5 g/dL.

However, in the event the subject did not meet the above criteria for ESA rescue, ESA rescue was permitted when medically necessary at the discretion of the Investigator. Following ESA rescue, the study drug was resumed at the same dose as previously used or one dose higher and adjusted according to the Dose Adjustment Algorithms (2).

MEDICE believe it is more appropriate to use the narrow therapy definition, rather than broad therapy, in the cost effectiveness model as the narrow definition better captures the indication and scope that is the subject of this assessment (i.e., renal anaemia). Broad-on treatment rescue therapy included other instances unrelated to anaemia, such as use of ESA due to accidents, operations, etc.

A9. In the INNO$_2$VATE – incident trial, 60 (33.1%) people in the vadadustat arm and 49 (26.1%) people in the darbepoetin alfa arm discontinued from the study drug.

- The most frequently cited reason for discontinuation in the vadadustat arm was “subject no longer wants to receive study drug”. Twice as many people discontinued for this reason in the vadadustat arm than the darbepoetin alfa arm. Please would the company expand on the reasons why a larger proportion of people no longer want to receive vadadustat than darbepoetin alfa.

Company response: The pivotal studies used the active comparator, darbepoetin alfa as it is marketed and available globally and it has a well-characterised safety profile (2). Due to practical considerations to execute a double blind, double dummy design (the potential for dosing errors and inappropriate dose adjustments, delays in dosing, discomfort and risks inherent in repeated injections of placebo, extensive

coordination to maintain the blind, the endpoints both efficacy and safety were outcomes that required laboratory and/or diagnostic measurements) an open-label study design with measures to keep only key sponsor personnel and external adjudication committee blinded was used. This open label design may have contributed to difficulties in assessment of discontinuations and discontinuations up to the end of the primary efficacy period (26 or 39 weeks) were higher for vadadustat than darbepoetin alfa in the INNO$_2$VATE trials (33.1% vs 26.1%, and 50.6% vs 36.7% in INNO$_2$VATE – incident and INNO$_2$VATE – prevalent, respectively) (2). One of the major reasons for treatment discontinuation was related to subjects no longer wanting to receive study drug. The difference in early discontinuations between vadadustat and darbepoetin alfa may be due to the open-label design (2). The most frequent reasons for discontinuations suggest that subjects may have preferred to switch to a product which effect and dosing were well known (standard of care). Even though discontinuations were more frequent in the vadadustat treatment group, the frequency of subjects completing the trial was similar for vadadustat and darbepoetin alfa, showing that subjects in both groups were followed-up for MACE and TEAEs even though they discontinued. The post-hoc sensitivity analyses show no significant impact of missing data due to discontinuations on the results. The sensitivity analysis handled the missing data due to discontinuations with multiple imputation. Also, the potential missing data did not have an impact on the overall number of reported TEAEs, serious TEAEs, and TEAEs leading to death in the CKD population, since they were similar (2).

A10. In the INNO$_2$VATE – prevalent trial, 899 (50.6%) people in the vadadustat arm and 653 (36.7%) people in the darbepoetin alfa arm discontinued from the study drug.

- The EAG's clinical expert indicated that this was a larger proportion than he expected. Please would the company provide a rationale why a substantially higher proportion of people in the vadadustat arm discontinued from the treatment than the darbepoetin alfa arm.

- The most common frequently cited reason was "subject no longer wants to receive study drug". This was 213 people in the vadadustat arm and 103 in the darbepoetin alfa arm. Please would the company expand on the reasons why

a higher proportion of people no longer wanted to receive vadadustat than darbepoetin alfa.

Company response: As mentioned in response to question A9 above, the open label design of the INNO$_2$VATE trials may have contributed to difficulties in assessment of discontinuations, contributing to the differences observed between treatment arms. As stated in the EMA public assessment report, subjects may have preferred to switch to a product whose effect and dosing were well known (standard of care) (2). However, even though discontinuations were more frequently reported for vadadustat than darbepoetin alfa, the frequency of subjects completing the trial was similar for vadadustat and darbepoetin alfa and potential missing data were not found to impact results.

A11. PRIORITY. How many people were lost to follow-up in each treatment arm for:

- INNO$_2$VATE – incident.
- INNO$_2$VATE – prevalent.

Company response: Table 11 presents the number of patients lost to follow-up in each treatment arm for the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials.

Table 11. Subjects lost to follow-up in the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials

INNO$_2$VATE – incident	**Vadadustat N=181 n (%)**	**Darbepoetin alfa N=188 n (%)**	**Total N=369 n (%)**
Patients lost to follow-up	3 (1.7)	2 (1.1)	5 (1.4)
INNO$_2$VATE – prevalent	**Vadadustat N=1,777 n (%)**	**Darbepoetin alfa N=1,777 n (%)**	**Total N=3,554 n (%)**
Patients lost to follow-up	37 (2.1)	31 (1.7)	68 (1.9)

Source: CSR INNO$_2$VATE – incident (3); CSR INNO$_2$VATE – prevalent (4)

A12. The outcomes reported in appendix F, table 13 are only partially consistent with the outcomes reported in the SPC table 4. For example, the values reported for ‘any MACE’ are consistent between appendix F and the SPC whereas the values reported for the outcomes ‘all-cause mortality, non-fatal myocardial infarction, and

non-fatal stroke' differ between these sources. Please explain the reason for these differences.

Company response: The SPC presents analysis of "time to first event" whereas appendix F presents analysis of "time to first and subsequent events" (5, 21, 22, 23). This leads to the observed differences in results. The number of events for "Any Major Adverse Cardiovascular Events (MACE)" is the same because it is irrelevant whether it is a "first" or "subsequent" MACE event.

Section B: Clarification on cost-effectiveness data

Model structure

B1. <u>PRIORITY.</u> Model structure. Please justify the chosen model structure and health states and how this relates to the value of vadadustat as a treatment for anaemia compared to ESAs.

Company response: The model employs a Markov cohort design and is comprised of three mutually exclusive and exhaustive health states reflective of the clinical course of DD-CKD, including DD, transplant, and death. Compared to the roxadustat model, the Markov model developed for vadadustat offers a simpler modelling approach as it defines health states according to the renal care received (dialysis, transplant), with sub-health states (No MACE, New MACE and History of [Hx] MACE) based on the history and occurrence of MACE, all of which are associated with relevant differences in costs, HRQoL and survival. The novel vadadustat model structure also offers advantages compared to currently published models identified from the SLR as it reflects the clinical course of CKD patients with anaemia through distinct clinically meaningful health states that can be modelled directly using the INNO$_2$VATE trial results.

The model accommodates Hb level cut-offs for patients initiating vadadustat or ESAs of <10 g/dL, 10 - <12 g/dL, and ≥12 g/dL as they are the most commonly reported values in the UK (confirmed by clinical experts). This approach was chosen because different Hb levels have been associated with different levels of anaemia-related disutilities which affect the quality of life of patients (i.e., anaemia-related disutility is larger for patients with lower Hb level) (24).

Division of the DD and transplant states into three sub-states based on MACE status was performed to account for important differences in costs and treatments associated with each of the sub-states.

B2. Hb level cut offs. In Document B Section B.3.2.2, Page 65, the submission states *"The model accommodates Hb level cut-offs for patients initiating vadadustat or ESAs of <10 g/dL, 10 - <12 g/dL, and ≥12 g/dL as they are the most commonly reported values in the UK (confirmed by KOLs)."* The EAG note that in Appendix N, there appears to be no discussion on the Hb levels with the clinical expert. Please explain and provide reference to how the Hb level groups have been derived and why these are the most appropriate groups to inform the model.

Company response: The choice of Hb level cut-offs was presented as part of the background details required to answer the questions discussed with the clinical expert. The clinical expert did not express any concern or disagreement regarding the Hb level choice for the model during the discussion. Furthermore, the NICE guidelines for the treatment of anaemia in CKD which were revised in 2015, recommend not to initiate ESA treatment unless Hb is <10 g/dL and that target Hb should be 10-12 g/dL (25).

B3. Cycle length. In Document B Section B.3.2.2, Page 67, Table 17, the submission states that justification of the 3-month cycle length was due to the appropriateness of monitoring iron deficiency and Hb levels. However, given the inclusion of transplant and MACE events, the EAG consider it possible for a patient to transition to multiple health states within a 3-month timeframe (e.g., from DD to transplant to death via any MACE sub-state). Please confirm that any costs and utilities associated within multiple movements per cycle are accounted for? Please also justify the appropriateness of a 3-month cycle length with regard to MACE events.

Company response: The published cost-effectiveness studies identified in the economic SLR found models with cycle lengths ranging from 4 weeks to annual cycles for those models that were defined by cardiovascular events and/or renal events that occur in patients with anaemia (26, 27, 28, 29). Furthermore, the roxadustat appraisal in a similar indication [TA807] (18) used a 3-month cycle length.

MEDICE expect that the 3-month cycle length in the model is conservative for vadadustat when compared to a shorter cycle length for the following reasons: 1) the

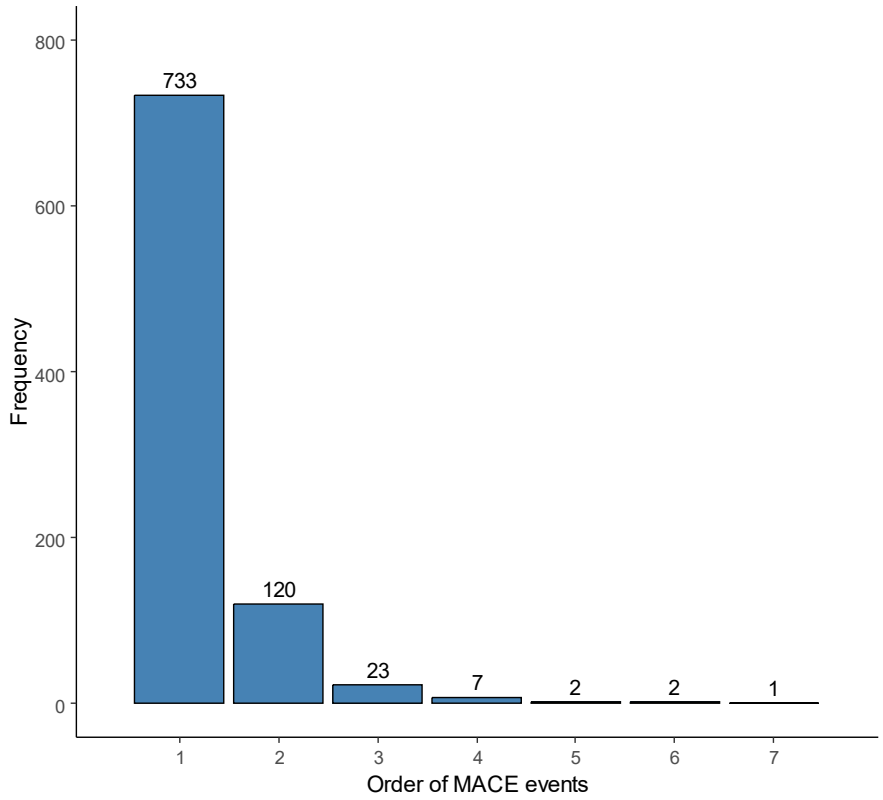
treatment effect of vadadustat is likely to be underestimated if multiple transitions occur within a cycle as the modelling of vadadustat lowers progression events; and, 2) the additional time spent in the active treatment health states is likely to overestimate treatment costs for vadadustat.

According to INNO$_2$VATE trial data, subsequent MACE events were rather infrequent with most patients experiencing just one MACE event within the study period of 52 weeks, as shown in Figure 1.

Furthermore, an analysis of MACE outcomes from the INNO$_2$VATE trials showed that a second MACE event occurred, on average, 97.3 days after a first MACE event; a third MACE event occurred, on average, 91.3 days after a second MACE event. Given that MACE events took place, on average, 94.3 days apart in the INNO$_2$VATE population, MEDICE believe that a 3-month cycle length is likely sufficient to capture MACE event occurrence in the modelled cohort.

It was assumed that use of 3-month cycle, which is compatible with the frequency of MACE events in the INNO$_2$VATE trials, would not generate multiple transitions. Therefore, the model does not account for multiple transitions per cycle in terms of costs or utilities.

Figure 1. Frequency of MACE events in the total population of INNO$_2$VATE trial program by event order



B4. <u>PRIORITY.</u> Clarification on data used for each health state. For each treatment arm, please clarify what data are being used to inform transitions for each health state (as depicted in the table below) at each specific time point (Cycles 0-2, Cycles 3-4, Cycles 5-20, Cycles 20+):

Main health state	Treatment status	MACE substate	Haemoglobin substate
DD	On	No MACE	<10
			≥10-<12
			≥12
		New MACE	<10
			≥10-<12
			≥12
		Hx MACE	<10
			≥10-<12
			≥12
	Off	No MACE	<10
			≥10-<12
			≥12
		New MACE	<10
			≥10-<12
			≥12
		Hx MACE	<10
			≥10-<12

Main health state	Treatment status	MACE substate	Haemoglobin substate
			≥12
Transplant	Off	No MACE	<10
			≥10-<12
			≥12
		New MACE	<10
			≥10-<12
			≥12
		Hx MACE	<10
			≥10-<12
			≥12
Death	-	MACE-related	-
		Non-MACE related	

Company response: For the main health states of dialysis dependent (DD), Transplant and Death, the transition probabilities are informed by the following data in both treatment arms: baseline transition probabilities of dialysis, transplant receipt, or death for Cycles 0-2, Cycles 3-4, and Cycles 5-20 in line with Table 2.8 of the 25th United Kingdom renal registry (UKRR) report data (30) (Table 12). Beyond cycle 20, probabilities of transition between DD and transplant are held constant and are re-weighted to take into account mortality at each specific cycle. The mortality probabilities for cycle 0-20 are based on Table 2.8 of the 25th UKRR report data (30); the mortality probability beyond week 20 was estimated using linear regression utilising survival data since kidney replacement therapy start from Figure 2.21 of the 25th UKRR report (30). As survival data allow the estimation of mortality but does not allow distinction between causes of death (MACE and non-MACE related), the probability of death at every timepoint was re-weighted into MACE-related and non-MACE related deaths using mortality causes data from Table 3.10 of the 25th UKRR report (30). The proportion of MACE-related deaths was estimated using the frequency of death from cardiac and cerebrovascular diseases Cycles 0-2, Cycles 3-4, Cycles 5-20, and Cycles 20+.

To account for MACE and mortality risks in DD CKD patients with and without prior MACE history, IPD data from the INNO$_2$VATE trials for the ESA arm was used for all health states (DD and Transplant) in Cycles 0-2, Cycles 3-4, and Cycles 5-20. For the vadadustat arm, probabilities of MACE and death were calculated using probabilities estimated for the ESA arm corrected for the hazard ratio (HR) of MACE for Cycles 0-

2, Cycles 3-4, and Cycles 5-20. Probabilities were held constant beyond Cycle 20 and were adjusted for changing mortality. Beyond the treatment waning timepoint for vadadustat, the ESA arm probabilities for transitioning between health states were applied to the vadadustat arm in the model.

Patients on and off treatment were estimated using discontinuation rates from the INNO$_2$VATE trials for vadadustat and ESA arms in DD health state in Cycles 0-2, Cycles 3-4, and Cycles 5-20. Vadadustat treatment discontinuation in the DD health state in cycle 1 was estimated as the proportion of patients having Hb level of less than 10 g/dL in line with the stopping rule. No patients received vadadustat while in the Transplant health state, at any cycle when transplantation has occurred, which was in line with the INNO$_2$VATE trials' design where transplant patients did not continue to receive study treatment. Beyond cycle 20, the proportion of patients discontinuing vadadustat was held constant in line with Cycle 5-20.

The proportion of patients falling into the different Hb level cut-offs was estimated using IPD data from the INNO$_2$VATE trials for Cycles 0-2, Cycles 3-4, and Cycles 5-20. Beyond cycle 20, the proportion of patients falling into defined Hb levels was held constant in line with Cycle 5-20.

Application of transition probabilities to the patient flow were corrected to median time on dialysis as mortality probabilities were extrapolated using data on survival since kidney replacement therapy start. This adjustment was necessary to accurately apply respective probabilities patients with history of dialysis use in line with the total cohort of the INNO$_2$VATE trials.

Table 12. Data used for each health state

Modelling feature	Data source
Main health state	• 25th UKRR report (30) for baseline transitions between dialysis, transplant and death in DD CKD patients is applied through model time horizon except for mortality • Long-term mortality data (beyond cycle 20) is based on linear regression estimates of survival since kidney replacement therapy start in line with 25th UKRR report (30)
Treatment status	• Discontinuation rates from INNO$_2$VATE trials for Cycles 0-2, Cycles 3-4, Cycles 5-20 • Discontinuation rates were assumed to be constant beyond cycle 20 • All transplant patients discontinued vadadustat in line with INNO$_2$VATE trials' design

Modelling feature	Data source
	• In cycle 1 in vadadustat arm, proportion of patients with Hb level <10 g/dL in line with the stopping rule was used to estimate rate of discontinuation
MACE substate	• $INNO_2VATE$ trial IPD data for estimating risk of MACE and death in anaemia DD CKD patients with and without prior history of MACE is applied through model horizon for ESA arm and for vadadustat arm beyond treatment waning timepoint • HR of MACE risk for vadadustat relative to darbepoetin alfa from $INNO_2VATE$ trials is applied up to a point of treatment waning of vadadustat
Haemoglobin substate	• Proportion of patients falling into different Hb level cut-offs from $INNO_2VATE$ trials' IPD data was applied for Cycles 0-2, Cycles 3-4, Cycles 5-20 • Distribution of patients between Hb level cut-offs was assumed to be constant beyond cycle 20

Efficacy data

B5. <u>PRIORITY.</u> Data availability. The efficacy inputs used for the economic model are based on the $INNO_2VATE$ trials' data up to 52 weeks with the exception of dosing data which uses up to 3 years of data. Please explain why further data is not available for all the efficacy inputs. If available, please update all the model inputs to incorporate the longer follow-up data.

Company response: The primary analysis period of the $INNO_2VATE$ trials was 52 weeks (3, 4) and these are the efficacy data available to MEDICE as IPD to support the cost effectiveness model. However, it should be clarified that the HRs for MACE and expanded MACE used in the model were based on approximately 3 years of observation (Kaplan-Mayer curves of time to first event display probability of event up to Week 168); therefore, MACE risks in the model are based on the longer-term 3 year data (5).

Further long-term IPD were sought to enable updating all other model inputs with longer follow-up data, but these were not available within the response timeframe. However, use of longer-term efficacy data would not be expected to have a large impact on model outcomes given changes to Hb concentrations were observed to stabilise well before the 52-week cut-off (31). In addition, MACE outcomes (including MACE, expanded MACE, death from cardiovascular causes, and death from any

cause) showed a consistent trend, non-inferior to darbepoetin, beyond 52 weeks to approximately 36 months (after which patient numbers become very small) (31).

B6. PRIORITY. Mortality. Please provide further details on mortality described in Document B Section B.3.3.2.1, Pages 74-75.

- Please explain how mortality is applied within the model and how this interacts with Hb levels, MACE events, dialysis, and transplant.

- Please explain why regression models were used to inform long-term survival over the use of parametric survival models as per NICE Technical Support Document (TSD) 14 (32).

- Please provide a scenario analysis where the long-term survival from the 25th UKRR annual report are estimated using parametric survival models as per NICE TSD 14 (32) [based on the digitised data and estimating patient-level data using the Guyot algorithm (33)]. The relevant curve for the base case should be informed by goodness of fit statistics, visual fit and clinical plausibility as described in NICE TSD 14.

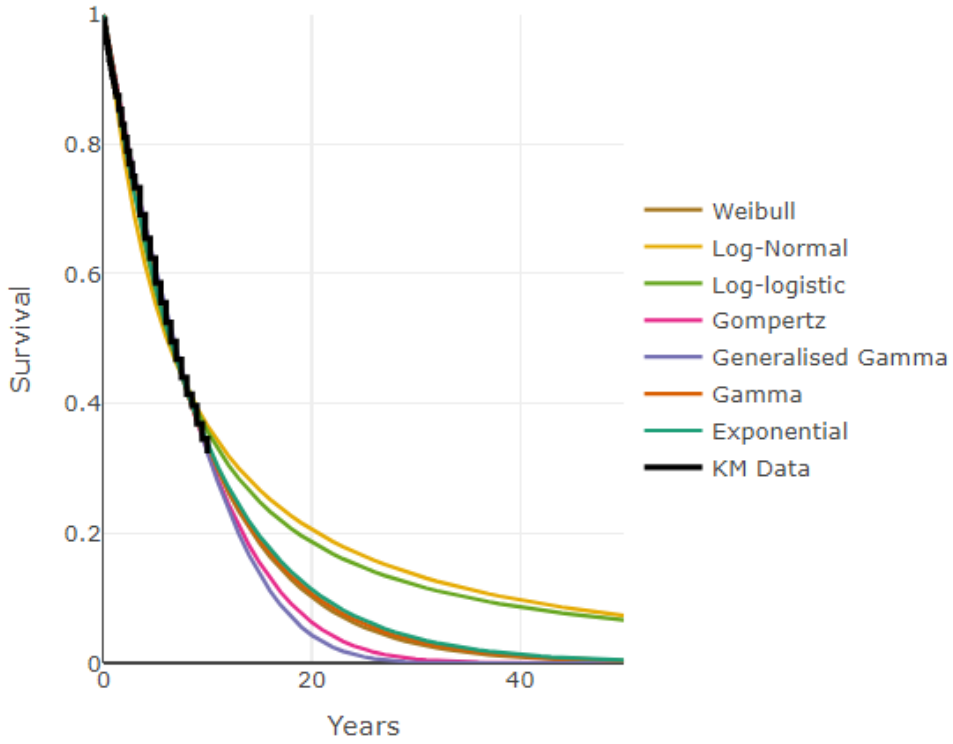
Company response: Mortality estimates based on UKRR report data (30), which reflect mortality following the start of kidney replacement therapy, were incorporated into the model starting from cycle 21. Prior to cycle 21, mortality estimates were based on transition probabilities calculated based on UKRR data (30) for patients moving between kidney replacement therapy types and death. As UKRR data did not provide estimates for MACE-related and non-MACE-related deaths, it was assumed that total mortality represents all-cause death. Thus, for the purpose of the model, death probabilities were re-weighted using data on the proportion of patients dying from cardiac and cerebrovascular diseases.

As outlined in the company's Evidence Submission Document B, long-term mortality data were extrapolated using a regression model to determine the relationship between time since kidney replacement therapy start and mortality. Several regression models were tested including linear and logarithmic regressions. Both regression types explained more than 95% of variation in mortality data. The clinical expert consulted by MEDICE advised that linear regression is not representative, as after

10 years on KRT a plateau in mortality would be expected. Therefore, logarithmic regression was chosen for the mortality extrapolation method in the current model. A regression model approach was chosen, as opposed to a parametric survival model, as additional data would be required, which is not provided in the UKRR report (30). The Guyot algorithm, used in the parametric survival approach, requires at least the initial numbers at risk; however, this is not available from the UKRR report.

Nonetheless, to address the query from the EAG, the Guyot algorithm was applied to the UKRR data (30) using assumptions for numbers at risk to allow parametric survival models to be fit using the flexsurv package in R. The total cohort size of patients under 65 years old from 2020 to 2011 was used for the initial numbers at risk as there was no reported value for the 55 to 64 years old subgroup. This affects the uncertainty in the Kaplan-Meier estimator. Figure 2 and Table 13 show the visual and statistical fits, respectively. The log-normal and log-logistic models were found to be too optimistic with landmark survival estimated at approximately 10% after 40 years, resulting in a hazard less than the general population mortality. The Gompertz and generalised gamma models were more pessimistic compared to the Weibull, exponential and gamma models. The Gompertz was the best fitting model compatible with proportional hazards.

Figure 2. Parametric models fit to UKRR survival data



Abbreviations: UKRR, United Kingdom renal registry
Source: 25th UKRR report data (30)

Table 13. Statistical fits for parametric models fit to UKRR survival data

Model	AIC	AIC Rank	BIC	BIC Rank
Generalised Gamma	150,505	1	150,530	1
Gamma	150,815	4	150,832	4
Log-logistic	152,083	6	152,100	6
Log-Normal	153,683	7	153,700	7
Gompertz	150,588	2	150,604	2
Weibull	150,780	3	150,797	3
Exponential	150,855	5	150,863	5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; UKRR, United Kingdom renal registry
Source: 25th UKRR report data (30)

Table 14 provides the results using the Gompertz model for extrapolating mortality in the model.

Table 14. Deterministic results with Gompertz model fit to UKRR data, after corrections listed in C8 (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	258,738	6.500	3.467	902	0.06	0.01	72,609

Darbepoetin alfa	257,836	6.443	3.455	Reference

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Table 15 presents scenarios implementing alternative distributions for mortality extrapolation that were compatible with proportional hazards.

Table 15. Incremental deterministic scenario results with exponential, and Weibull models, fit to UKRR data, after corrections listed in C8 (at list price)

Model fit	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Exponential	1,016	0.07	0.02	58,131
Weibull	999	0.06	0.02	60,679

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

B7. PRIORITY. Cycle adjustment for median time on dialysis. Please clarify what is meant by *"For implementing death probabilities into the model, time since KRT was tracked based on patients having had a median of 2.4 years on dialysis at baseline in the INNO$_2$VATE trials."* And *"Cycle corrected for baseline time since dialysis"* in regard to its application in the model (see Document B Section B.3.3.2.1, Pages 74-75).

- Further to this, the EAG are unclear why the transition probabilities for Cycles 1-5 are not used to inform any transition probabilities (see Model tab 'PatFlow'). Please explain the application of the transition probabilities.

Company response: Model transition probabilities are based on UKRR data (30), which provide data on patients moving between kidney replacement therapy types, and mortality data since the start of kidney replacement therapy. To account for the fact that the prevalent patients in the INNO$_2$VATE trials are not kidney replacement therapy naïve (they use dialysis), the model accounts for the median time to dialysis by correcting the UKRR data (30) starting from a timepoint that corresponds to the patients' median time on dialysis. For the above reason, transition probabilities from cycle 1-5 are not used. As median time on dialysis for the total cohort in the INNO$_2$VATE trials was 2.4 years (corresponding to cycle 10), the patient flow starts at cycle 0 using transition probabilities corresponding to cycle 5-12.

B8. PRIORITY. Hb level distributions. Please explain why baseline Hb level distributions are treatment specific. The EAG note that treatment specific outcomes

should be based on relative treatment specific differences from baseline and not aggregate treatment specific outcomes.

- Please provide a scenario applying pooled Hb baseline distributions (i.e., same across treatment arms) with transitions between cycles based on relative differences from baseline on each arm (e.g., by applying the count methodology). Please describe the methodology undertaken and any assumptions made (e.g., in regard to missing data).
    - Please provide one scenario using treatment specific transitions using treatment specific data from the INNO$_2$VATE trials.
    - Please provide another scenario using treatment independent transitions using pooled data from the INNO$_2$VATE trials.
- Please comment on the appropriateness of assuming the treatment specific Hb distribution from cycle 4 (week 52) throughout the remainder of the time horizon. Please also consider how this interacts with the treatment waning effect assumption for the main health states and transition probabilities.

Company response: The baseline Hb level distribution used was implemented to be treatment specific in line with IPD data, which was expected to be balanced due to randomisation. To address the EAG clarification, scenarios were conducted using treatment specific and treatment independent transitions using INNO$_2$VATE trial data. Transition probabilities were generated from patient counts per quarter from the trial data. Missing data was assumed to be random and therefore was excluded from transition probability calculations. The distribution across Hb levels was generated from using the Hb level transition probabilities applied to the pooled Hb baseline distribution. This was then weighted by the patients in the DD health state. Table 16 and Table 17 below presents scenarios using treatment specific transitions using treatment specific data and treatment independent transitions using pooled data for Hb level distribution from INNO$_2$VATE trials.

Table 16. Deterministic scenario analysis using treatment specific transitions using treatment specific data from the INNO2VATE trials for Hb levels distribution in the cost effectiveness analysis after corrections listed in C8 (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	314,608	8.892	4.930	1,098	0.08	0.02	61,403
Darbepoetin alfa	313,510	8.815	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Table 17. Deterministic scenario analysis using treatment independent transitions using pooled data from the INNO2VATE trials for Hb levels distribution in the cost effectiveness analysis after corrections listed in C8 (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	314,608	8.892	4.942	1,098	0.08	0.04	25,875
Darbepoetin alfa	313,510	8.815	4.900	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Regarding the appropriateness of assuming the treatment specific Hb distribution from cycle 4 (week 52) throughout the remainder of the time horizon, this was considered appropriate for two reasons. Firstly, changes in Hb levels for both vadadustat and darbepoetin alfa were observed to stabilise around Week 48 in the $INNO_2VATE$ trials (for example see mean changes from baseline in haemoglobin presented in Figure 7, Document B). Secondly, given the SmPC stopping rule was applied in the vadadustat arm for patients not achieving a clinically meaningful increase in Hb levels by week 24, it is not expected that the cohort will experience a dramatic drop in Hb levels beyond week 52 as the stopping rule will have already excluded patients not benefiting from vadadustat from those remaining on treatment. Patients who initially benefited from therapy are assumed to maintain Hb levels long-term. Treatment waning is mostly affecting MACE as it the main driver of benefits once a patient has stabilised Hb levels in the model.

B9. <u>PRIORITY.</u> MACE events and treatment waning. Treatment-related benefit of vadadustat in terms of MACE events was based on a HR of time to first MACE event from the INNO$_2$VATE trials. Please provide further details of this benefit.

- **A)** The HR is 0.96 with a 95% confidence interval 0.833 – 1.113. Based on this value being close to 1 and not being significant at a 5% level, please provide further evidence to support the reduction of MACE events for vadadustat in comparison to ESAs.

- **B)** Please justify the approach to use a HR applied to the ESA probabilities within the economic model and if possible, provide a scenario using the direct trial data as per approach taken to inform the ESA arm to inform the transitions of MACE events for vadadustat.

- **C)** Please provide evidence to support a treatment waning effect at 5 years and justification for the selection of a 5-year time point – particularly given the treatment benefit applied is close to 1 and not statistically significant.

- **D)** Please justify why the MACE HR (based on time to first MACE event), is appropriate to inform differences in mortality between vadadustat and ESAs when these also include non-MACE related deaths.

Company response:

A) Given that a cost-utility analysis was requested to address the current decision problem, the economic evaluation provided by MEDICE has used the point estimates from the INNO$_2$VATE trials to inform the cost effectiveness model. The approach to use the point estimate for the HR of MACE events was deemed appropriate as it allows modelling of the vadadustat relative benefit of a generally lower risk of MACE as observed throughout the trial duration. The MACE HR used in the model was based on 3 years of data from the INNO$_2$VATE trials. In comparison, IPD MACE data from INNO$_2$VATE trials was available for 1 year only. To model longer term average risk reduction in MACE using the MACE HR based on 3 years data, instead of IPD data of shorter duration, was considered more appropriate.

B) Estimates for MACE were generally lower for vadadustat compared with darbepoetin alfa, as reflected by the point estimate for the HR. The base line curve for

darbepoetin alfa was then used in combination with the HR to reflect this general trend of lower MACE for vadadustat. Furthermore, the time to first MACE event was assessed for proportional hazards and no violation was shown from the Schoenfeld residuals plot (Figure 3). Therefore, it was considered appropriate to apply the HR methodology.

Figure 3. Schoenfeld residuals plot of time to first MACE event

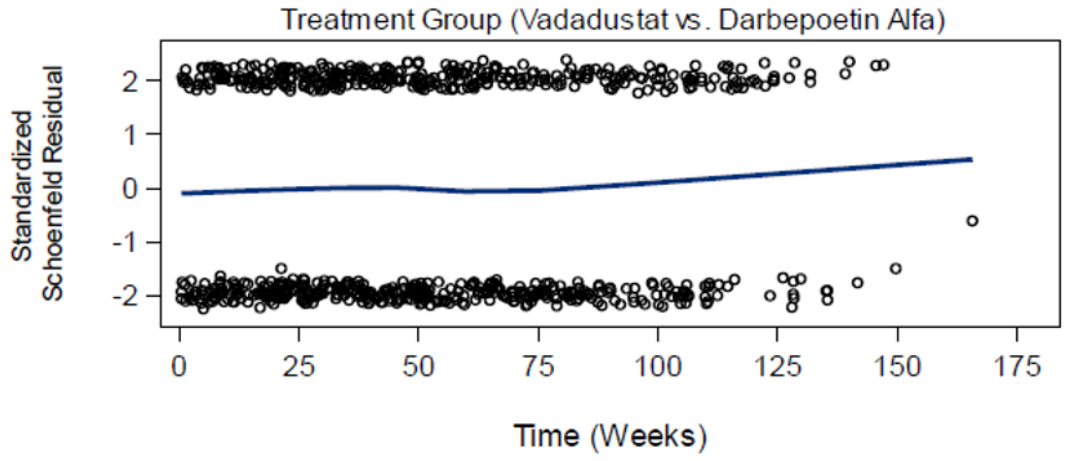


Table 18 provides the results for the requested scenario using direct trial data for vadadustat MACE transitions instead of applying a HR, while applying all other base case assumptions. Examination of the IPD data have led to a conclusion that later cycles (IPD trial data for quarters 3 and 4 corresponding to cycles 5 to 20) have slightly worse point estimates for MACE and/or death, while earlier cycles (IPD trial data for quarters 1 and 2 corresponding to cycles 1 to 5) have demonstrated less events with vadadustat leading to overall lower number of events in the vadadustat arm across the trial horizon. In this scenario, transition probabilities were corrected for median time on dialysis similarly to darbepoetin alfa arm IPD so that only the transition probability data for vadadustat from quarter 3 onwards is used in this scenario. As a result, this scenario uses less data from the trial to demonstrate the vadadustat treatment effect in the model Consequently, applying IPD data directly for vadadustat arm would not account for the full relative benefit of vadadustat in MACE reduction that was observed across total trial time horizon. Because of this, the ICER is in the southwest quadrant of the cost-effectiveness plane (less costly, less effective) as improvements in MACE reduction from cycle 1 to 5 (IPD trial data from quarters 1 and 2) are not reflected. Due to the model specifics above, accounting for vadadustat efficacy using the point

estimate for the HR of MACE events was deemed appropriate as it allows modelling of the vadadustat relative benefit in full using estimates reflecting the generally lower risk of MACE as observed throughout the trial duration.

Table 18. Deterministic results with direct trial data for vadadustat MACE transitions, after corrections listed in C8 (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	309,814	8.764	4.872	-3,695	-0.05	-0.04	93,861 (SW)
Darbepoetin alfa	313,510	8.815	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; SW, southwest

C) Implementation of the treatment waning assumption affects the application of the MACE HR for the vadadustat arm. Given the MACE HR was estimated based on data up to week 168 in the current model, there is uncertainty regarding any treatment effect in the long-term, beyond the 3-year timepoint. Because of this uncertainty, a conservative approach was taken to apply a treatment waning effect. The assumption of treatment waning from 5 years was used in the base case analysis after consultation with a health economic expert and is supported by a set of sensitivity analysis to show the impact of this assumption (the scenario analysis showed not applying this assumption generated a more favourable ICER, see Table 51 in Document B).

Uncertainty regarding treatment effect waning time will remain as no longer-term data for vadadustat use in this population is available. It should be noted that an assumption of treatment waning at 5 years appears to be consistent with previous NICE appraisals. A recent review found that 37.9% (25/66) of previous appraisals analysed assumed treatment effect waning to take place at 5 years; 22.7% (15/66) of appraisals analysed implemented treatment waning similar to the current model with sudden treatment effect loss at year 5 (34). The scenario results for 1 year (most pessimistic) and lifetime (most optimistic) treatment waning effect timepoints are shown in Table 19, which also reflect the correction for the technical error identified in clarification C8.

Table 19. Deterministic scenario results for treatment waning, after corrections listed in C8 (at list price)

Scenario	Description	ICER (£/QALY)	% change relative to base-case ICER
Base case	**-**	**47,532**	**0%**
Vadadustat treatment waning, efficacy stop at cycle 5 (beyond 1 year)	Vadadustat reduced risk of MACE is applied for 1 year in line with INNO$_2$VATE trial length	Less costly, less effective	**-**
Vadadustat treatment waning not applied, indefinite efficacy of vadadustat	Vadadustat reduced risk of MACE is applied through modelling horizon	38,691	**-19%**

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

D) As the MACE endpoint includes all-cause mortality, the time to first MACE event HR is reflective of all events within the MACE definition including death. Analysis of time to all cause death shows that the HR for vadadustat versus darbepoetin alfa is 0.95 (CI: 0.812, 1.118), which is slightly lower than the HR for time to first MACE. Therefore, it is conservative to apply the time to first MACE event HR to mortality.

B10. Model transitions. In Document B Section B.3.2.2, Page 66, the submission states that the advantage of the model structure is that is reflects the *"clinical course of CKD patients with anaemia…that can be modelled directly using the INNO$_2$VATE trials*". However, some transitions have been informed by external data sources. The transitions between dialysis, transplant and death are informed by 25th UKRR annual report (see Document B Section B.3.3.2, Pages 69-70). Please explain why these transitions could not be informed by the INNO$_2$VATE trials.

- Please provide a scenario using transitions derived from the INNO$_2$VATE trials.

Company response: The primary analysis period of the INNO$_2$VATE trials was 52 weeks (3, 4), which was considered insufficient to inform transition probabilities for a model with a lifetime horizon. Furthermore, the trial durations were unlikely to provide data to capture transition from transplant back to dialysis. In contrast, the UKRR data (30) used to estimate baseline transition probabilities is available for 5 years in a patient population largely representative of the vadadustat target population and did

suggest the possibility of transition from transplant to dialysis; therefore, this was considered a better source for model inputs. In hindsight, it would have been more accurate to have stated in Document B Section B.3.2.2 that the *"clinical course of CKD patients with anaemia…that can predominantly be modelled directly using the INNO$_2$VATE trials*".

MEDICE sought data from the INNO$_2$VATE trials to support the scenario analyses requested; however, suitable data were not identified within the response timeframe. Nonetheless, the INNO$_2$VATE dataset is unable to support the requested analyses. This is because once patients received a transplant, they discontinued the study drug permanently and follow-up was reduced to safety endpoints only. Thus, it was not recorded whether patients on transplant subsequently received dialysis, thereby preventing use of the trial data to calculate this transition probability.

According to the 25th UKRR report data (30), a fraction of patients on transplant will experience death, and another fraction will switch back to dialysis. Given that trial data could not inform all required model transitions, it was considered more appropriate to use transition probabilities based on the 25th UKRR report (30) in the current model instead of using transition probabilities based on inadequate trial data.

B11. PRIORITY. Subgroup analyses. Please provide subgroup analyses considering the 'incidence' and 'prevalent' patients separately within the economic model. Inputs for these subgroups should use the respective trial data. Further to this, please provide results of the scenarios from questions B5, B6, B8, and B9 using the data separately for the incidence and prevalent patients.

Company response: Although INNO$_2$VATE clinical trial programme consists of two studies (3, 4), these two studies represent a full cohort of patients within the vadadustat indication. The eligibility criteria of the INNO$_2$VATE trials were chosen to maximise the generalisability of results to the wider dialysis-dependent chronic kidney disease (DD-CKD) population (1), while allowing for differences in the inclusion and exclusion criteria consistent with the incident dialysis nature of the INNO$_2$VATE – incident trial and the prevalent dialysis nature of the INNO$_2$VATE – prevalent trial (2). The demographics and baseline characteristics of patients enrolled in the two studies are comparable to those typically observed in patients with DD-CKD, suggesting the

results of the INNO$_2$VATE studies will be generalisable to a large proportion of the DD-CKD population (1).

As mentioned earlier the responses to A2 and A3, the IPD were pooled across the INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials as a single trial to investigate the cardiovascular safety and haematological efficacy of vadadustat compared with darbepoetin alfa for the treatment of anaemia in patients with dialysis-dependent CKD (1). Because of this design, the primary safety analysis (time to first adjudicated MACE), prespecified to be pooled from both INNO$_2$VATE trials, was based upon all events that accrued over the two trials. Specifically, the INNO$_2$VATE clinical trial programme was designed so that the pooled analyses included a sufficient number of independently adjudicated endpoints to allow a meaningful comparison of vadadustat and darbepoetin alfa with respect to MACE (5). As such, MACE outcomes, which are key inputs for the model, are only available for the pooled data which prevents the subgroup analyses requested; the individual trials are insufficiently powered for separate analysis of MACE outcomes.

Furthermore, MEDICE are unclear on the value of the requested analyses given that only about half of the patients in the INNO$_2$VATE – incident trial were ESA naïve (a very small proportion of the total as discussed in A4) (3), and in practice it would be difficult to treat only the incident or prevalent populations; after all, incident patients swiftly become prevalent patients in the chronic treatment setting. In addition, restricting access to one or the other subgroup raises a question of equity of treatment and patient choice, particularly for those who may need to switch treatments for reasons other than Hb control (e.g., tolerability issues, administration issues).

The INNO$_2$VATE clinical trial programme demonstrated vadadustat is not inferior to darbepoetin alfa, the ESA used by the majority of patients in the UK, in both the incident and prevalent DD-CKD populations, for both of which it has received marketing authorisation. Given the evidence base does not support separate analyses of the subpopulations, MEDICE firmly believe the cost-effectiveness analysis reflecting the full indicated population as presented in this submission is appropriate for decision making for vadadustat in the DD-CKD population.

Treatment costs and durations

B12. Treatment discount. Please confirm what discount has been used to inform the results tables 45-48.

Company response: [redacted]

B13. Costs of IV iron as rescue therapy. Document B section B.3.5.4.1 explains how costs associated with IV iron rescue therapy were calculated and includes the cost per cycle, administration cost and cost per mg. However, the source of the unit cost (cost per mg) is not described in appendix K. Please clarify the source of this cost.

Company response: As described in Document B section B3.5.4.1, IV iron cost per mg were sourced from the British National Formulary (BNF). To calculate per mg IV iron cost, the weighted average cost of 1 mg of IV iron medications presented in the BNF was multiplied by the IV iron dose reported in INNO$_2$VATE trials. IV iron market shares from the NHS PCA database for 2022 were used to weight the cost per mg. Table 20 presents the IV iron medications costs used in the model which are in line with the BNF.

Table 20. IV iron medications costs

Name	Form	Dose per unit	Pack size	List price (£)	Cost per application (£)	Cost per unit (mcg/IU) (£)	Source
Iron dextran	Iron dextran 100mg/2ml solution for injection ampoules	50 mg per 1 ml	5	39.85	7.97	0.0797	BNF (iron dextran) (35)
	Iron dextran 500mg/10ml solution for injection ampoules		2	79.7	39.85	0.0797	
Iron sucrose	Iron sucrose 100mg/5ml solution for injection ampoules	20 mg per 1 ml	5	51.2	10.24	0.1024	BNF (iron sucrose) (36)

Name	Form	Dose per unit	Pack size	List price (£)	Cost per application (£)	Cost per unit (mcg/IU) (£)	Source
Ferric carboxymaltose	100mg/2ml solution for injection vials	50 mg per 1 ml	1	95.5	19.1	0.191	BNF (ferric carboxy-maltose) (37)
	Ferric carboxymaltose 500mg/10ml injection vials		5	477.5	95.5	0.191	
	Ferric carboxymaltose 1g/20ml solution for injection vials		5	154.23	154.23	0.15423	

B14. <u>PRIORITY.</u> Treatment discontinuation. Please provide further clarity and analyses to support the approach to treatment discontinuation:

- **A)** The stopping rule of vadadustat is that patients who fall under <10 g/dL at week 24 will discontinue treatment. In the model, a proportion of patients who were under 10 g/dL discontinued treatment in cycle 1 and then assumed to follow the ESA transition probabilities. Please confirm why these patients were discontinued at cycle 1 (week 11) instead of cycle 2 in the model. See cells "PatFlowBQ16:BX16" in the economic model. This results in 81.7% of patients receiving treatment at the start of the model (see "PatFlow column DR").

- **B)** On page 75, the submission states *"As the proportion of patients with Hb level <10 g/dL was higher than discontinuation rate in vadadustat arm in cycle 2, to avoid potential double-counting general discontinuation of vadadustat was not applied in cycle 2 of the model."* Please clarify how this approach avoids double-counting and confirm if the discontinuation rates in Table 25 include those who discontinued due to the 24-week stopping rule.

- **C)** In the economic model, the proportion of patients on treatment is applied to patients in the 'DD' health state. Based on the discontinuation rates taken from the INNO$_2$VATE trials, please comment on how these rates interact with the movement between the DD and transplant health states to ensure no double counting of discontinuation has occurred.

- **D)** Further to this, please provide the proportion of patients who were on treatment each cycle for patients on 'DD' and the proportion of patients who had 'Transplant' and 'Died' separately from the INNO$_2$VATE trials:

INNO$_2$VATE – incident

Quarter	Vadadustat				Darbopoetin alfa			
	DD		Transplant	Death	DD		Transplant	Death
	On Tx	Off TX			On Tx	Off TX		
Q1								
Q2								
Q3								
Q4+								

INNO$_2$VATE – prevalent

Quarter	Vadadustat				Darbopoetin alfa			
	DD		Transplant	Death	DD		Transplant	Death
	On Tx	Off TX			On Tx	Off TX		
Q1								
Q2								
Q3								
Q4+								

- **E)** Patients who discontinue treatment due to the stopping rule are assumed to use the darbepoetin alfa transition probabilities for the rest of the time horizon. However, the patients who discontinue after this time point for other reasons, still appear to follow the vadadustat transition matrices. Please confirm if this is how the treatment discontinuation has been applied and if so, please justify why patients who discontinue for other reasons would not also follow the darbepoetin alfa transitions for the remainder of the time horizon.

- **F)** Please provide justification and further rationale why no patients would discontinue treatment after the first year.

- **G)** Please provide Kaplan-Meier plots of treatment discontinuations in the INNO$_2$VATE trials split by treatment arm with the event being either treatment discontinuation (for any reason) or death. Please provide a plot for each trial separately and then one that pools the trial data.

- **H)** Please fit parametric curves to the treatment discontinuation data for each arm of the INNO$_2$VATE trials as per NICE TSD 14(32) and provide a scenario in the model using these curves to estimate the proportion of patients on treatment per cycle. Use goodness of fit statistics, visual fit and clinical plausibility to choose the most appropriate curve in the base case.

Company response:

A) The vadadustat SmPC states that treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved (21, 22, 23). This stipulation was reflected in the model by implementing a stopping rule. However, as cycle 2 of the model starts at Week 26, which is beyond the stopping rule timepoint (24 weeks), treatment for these patients is halted in the model at cycle 1 (week 13) to avoid going beyond what is recommended in the SmPC.

B) The stopping rule was not a part of the INNO$_2$VATE clinical trial programme; therefore, the proportion of patients who may discontinue due to the SmPC requirement could not be established from the trials. Furthermore, the discontinuation rates observed within the INNO$_2$VATE trials are challenging to align with the stopping rule specified in the SmPC (21, 22, 23). As such, it was considered that accounting for discontinuation rates as observed in the trials and due to a stopping rule may potentially overestimate the total vadadustat discontinuation.

C) The proportion of patients on treatment is applied to patients in the 'DD' health state only, because according to the INNO$_2$VATE trials' study design, patients who received a renal transplant remained in the study but permanently discontinued vadadustat treatment. Therefore, the proportion of patients on treatment was calculated using number of subjects not discontinuing study treatment permanently data from the INNO$_2$VATE trials, which is fully attributed to patients on dialysis; as such, double counting is not expected to occur.

D) Table 21 and Table 22 provide the proportion of patients who were on treatment each cycle for patients on 'DD', and the proportion of patients who had 'Transplant' and 'Died', separately for the INNO$_2$VATE trials.

Table 21. Proportion of patients who were on treatment each cycle in the INNO$_2$VATE – incident trial

Quarter	Vadadustat				Darbepoetin alfa			
	DD		Transplant	Death	DD		Transplant	Death
	On Tx	Off TX			On Tx	Off TX		
Q1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DD, dialysis dependent; Tx, treatment.

Table 22. Proportion of patients who were on treatment each cycle in the INNO$_2$VATE – prevalent trial

Quarter	Vadadustat				Darbepoetin alfa			
	DD		Transplant	Death	DD		Transplant	Death
	On Tx	Off TX			On Tx	Off TX		
Q1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DD, dialysis dependent; Tx, treatment.

E) Patients who discontinue vadadustat treatment due to the stopping rule are certain to have suboptimal Hb levels indicating efficacy in these patients was suboptimal while using vadadustat. Thus, for these patients the darbepoetin alfa transition probabilities were applied for the rest of the time horizon. However, patients who discontinue vadadustat for other reasons may not have experienced suboptimal Hb levels; therefore, it was deemed appropriate to assign these patients vadadustat efficacy estimates and transition probabilities similarly to patients discontinuing ESAs in the darbepoetin alfa arm. The above approach corresponds to randomised population analyses in the INNO$_2$VATE trials from which the majority of data is drawn (3, 4). Available analyses from the INNO$_2$VATE trials did not analyse results by responder status; therefore, the observed treatment effect drawn from the trials represents the overall patient cohort of those continuing and discontinuing the treatment.

F) Discontinuations were assumed to primarily happen within the first study year as this time was assumed sufficient for patients to discontinue due to adverse events or suboptimal Hb level.

G) Figure 4 presents the Kaplan-Meier plot of treatment discontinuations for any reason or death in the INNO$_2$VATE trials (pooled) split by treatment arm. Plots for each

trial separately were sought however were not available within the response timeframe.

Figure 4. Kaplan-Meier plot of treatment discontinuations in the INNO$_2$VATE – total population of INNO$_2$VATE trials (pooled)

H) As requested by the EAG, parametric extrapolation was explored using treatment discontinuation data for each arm of the INNO$_2$VATE trials. Patients discontinue treatment upon moving to the transplant or death health state, hence 'on treatment' was bounded by the total patients alive in the DD health state. Analysing time to treatment discontinuation (TTD), using any reason for discontinuation and death as events, generated a TTD extrapolation that can violate this restriction in some cycles due to the increased mortality and frequency of transplantation that the model predicted from the UKRR data. It was therefore more appropriate to use the trial

discontinuation data where transplant and death were censored events in order to generate the percentage of treatment discontinuation within the DD health state (Figure 5 and Figure 6 for vadadustat and darbepoetin alfa, respectively). The corresponding goodness of fit analyses are shown in Table 23 (vadadustat) and Table 24 (darbepoetin alfa). Based on these results, the Weibull model was considered to provide a better overall statistical fit with less than 3 difference in AIC and BIC. Table 25 presents a deterministic scenario using the Weibull model to estimate treatment discontinuations in the cost effectiveness model.

Figure 5. Parametric curves fitted to the treatment discontinuation data for each arm of the INNO$_2$VATE trials for vadadustat arm

Figure 6. Parametric curves fitted to the treatment discontinuation data for each arm of the INNO$_2$VATE trials for darbepoetin alfa arm

Table 23. Statistical fits for parametric models fit to time to treatment discontinuation data from INNO$_2$VATE trials for vadadustat arm

Model	AIC	AIC Rank	BIC	BIC Rank
Generalised Gamma	10,972	1	10,989	5
Gamma	10,974	4	10,985	3
Log-logistic	10,972	2	10,983	1
Log-Normal	10,990	6	11,001	7
Gompertz	10,976	5	10,987	4
Weibull	10,973	3	10,984	2
Exponential	10,995	7	11,000	6

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 24. Statistical fits for parametric models fit to time to treatment discontinuation data from INNO$_2$VATE trials for darbepoetin alfa arm

Model	AIC	AIC Rank	BIC	BIC Rank
Generalised Gamma	6,977	2	6,994	5
Gamma	6,978	4	6,989	4
Log-logistic	6,983	6	6,994	6
Log-Normal	7,011	7	7,022	7
Gompertz	6,975	1	6,986	2
Weibull	6,978	3	6,989	3
Exponential	6,979	5	6,984	1

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 25. Deterministic scenario analysis using Weibull model fit for vadadustat and darbepoetin alfa arms to estimate treatment discontinuations in the cost effectiveness analysis after corrections listed in C8 (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	304,493	8.892	4.935	-718	0.08	0.02	Dominant
Darbepoetin alfa	305,210	8.815	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Management costs

B15. Management cost categories. In Document B Section B.1.3.1.5, Pages 18-19, it states that *"Management of anaemia in CKD involves various healthcare resources, including nephrologists, cardiologists, anaemia nurses, specialist renal nurses, general practitioners, dieticians, home care, blood tests, ESAs, blood transfusions, and facilities for diagnostic and intensive care. Other resources required include cold storage and cold chain delivery for ESAs, consumables, sharps bins and the necessary specialist disposal of sharps and bins."* In Section B.3.5.2, Pages 86-88, the disease management costs only cover dialysis and transplant costs, and administration of ESAs only includes a hospital appointment.

- Please clarify why the other costs mentioned above, such as diagnostic tests and cold storage have not been included within the economic model.

- Please provide a scenario incorporating these costs into the economic model.

Company response: The above-mentioned costs were considered minor and equal across treatment arms; therefore, the current economic analysis assumed it appropriate to exclude most of these costs from consideration. MEDICE excluded other costs associated with ESA administration such as cold storage and cold chain delivery for ESAs, consumables, sharps bins and the necessary specialist disposal of sharps and bins due to limited available evidence and because they would go beyond the scope of the reference case. In an attempt to provide conservative base case economic analyses, other costs related to use of ESAs were also neglected. To give an impression of the impact these costs may have, two scenario analyses assuming

+5% and +10% ESA cost increase associated with cold chain storage and disposal have been presented in Document B (Section B.3.11.4, Table 51).

B16. Frequency of visits. Please explain the number of visits per quarter inputs presented in Document B Section B.3.5.2.2, Page 86, Table 33, and why these visits reduce after one year and provide references where relevant, or any details of assumptions made.

Company response: Based on NICE TA807 (18), anaemia was associated with four monitoring visits in the first 12 weeks (cycle 1) and then with 1.5 visits in subsequent cycles. It was assumed that the frequency of visits for monitoring anaemia control in non-dialysis dependent CKD is equal to the number of visits in patients in receipt of kidney replacement therapy (dialysis and transplant).

Health-related quality of life

B17. Utility input sources. Please provide further details of the sources used to inform the utility values in Document B Section B.3.4.5, Table 29:

- Aside from prior use in TA807, please explain how these sources are more relevant to the UK setting over those found in the SLR.

- The health states for 'DD no MACE' in the model were informed by Liem et al (2008) which is an SLR and meta-analysis of quality of life of patients on renal replacement therapy. A study by Cooper et al (2020) (38) provides a more recent systematic review to identify utilities for economic evaluation in CKD (and specifically reports utility values at CKD stage and by HD and PD). Please confirm why this more recent study for utilities in CKD was not used to inform the main health states. Please consider a scenario which utilises the data provided in this more recent source.

Company response: The publication by Liem et al., 2008 (39) was used to inform health state utility values for dialysis and transplantation health states. It summarises evidence on health state utility values from studies with various geographic origin including the UK. Given limited evidence from the UK on health state utilities by renal replacement therapy type, meta-analyses values reported by Liem et al., 2008 (39) were considered representative for the UK population. Liem et al., 2008 (39) was

deemed most appropriate in the context of the current cost-utility model as, in contrast to studies found in the SLR, it can be used to account for utility in dialysis types (haemodialysis and peritoneal dialysis) and transplantation.

Disutilities associated with adverse events and anaemia were not identified from the SLR; therefore, disutilities were sourced from previous NICE technology appraisals including TA807 (18), TA599 (40), TA877 (41) or from the catalogue of EQ-5D scores in the UK reported by Sullivan et al., 2011 (42).

The publication by Cooper et al., 2020 (38) was not identified from the SLR as it does not concern patients with anaemia. In the updated cost-utility model file version, the mean health state utilities as per EQ-5D-3L instrument were added as an option. Deterministic results of this scenarios analysis are presented in Table 26 after correction for the technical error identified in question C8.

Table 26. Deterministic results of scenario analysis using utilities as per Cooper et al., 2020 after corrections listed in C8 (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	314,608	8.892	5.547	1,098	0.08	0.03	39,316
Darbepoetin alfa	313,510	8.815	5.519	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

Section C: Textual clarification and additional points

C1. Document B Section B.1.1, Page 10-11. The decision problem table states that some subgroups are presented. However, the EAG notes that no subgroups are presented in the economic section. Please clarify the use of subgroups within the submission dossier and if these have been omitted, please provide them.

Company response: Clinical data were provided for subgroup analyses from the INNO$_2$VATE trials in Appendix E. These analyses included prior ESA use (yes/no) in the INNO$_2$VATE – incident trial (3) and three subgroups based on baseline ESA doses (≤90 U/kg/week, >90 and <300 U/kg/week, ≥300 U/kg/week) in the INNO$_2$VATE –

prevalent trial (4). The prespecified subgroup analyses consistently supported the primary and key secondary efficacy endpoint results and met the non-inferiority criterion (3, 4). Furthermore, the results of prespecified subgroup analyses of a first occurrence of a MACE and a first occurrence of an expanded MACE were consistent across subgroups (31). As both efficacy and safety endpoints were generally consistent across all subgroups in the INNO$_2$VATE trials, no cost-effectiveness analyses in particular subpopulations were undertaken in the economic assessment.

C2. Document B Section B.1.3.1.2, Page 15. The submission states that "*In 2020, there were 29,354 adults receiving dialysis for ESRD in the UK, estimated to increase to 33,845 by 2033. As of 2020, in-centre dialysis was the most common form of dialysis delivered in the UK (24,155 adults), followed by PD (3,822 adults) and HD (1,377 adults)".* Please confirm if 'HD' here refers to haemodialysis in the home setting.

Company response: MEDICE can confirm that 'HD' in the above statement refers to haemodialysis in the home setting.

C3. Document B Section B.3.2.2, Page 65. The submission states that *"The distribution of patients across the nine Hb levels changes at each cycle according to the Hb outcomes reported in the INNO$_2$VATE trial."* However, the EAG note that only three categories of Hb levels have been included. Please confirm if this is a typo.

Company response: The above is a typographical error. MEDICE can confirm the model used <u>three</u> Hb levels applied to DD and transplant states.

C4. Document B Section B.3.2.2, Page 66. The submission states that "*Similarly, patients in the DD or transplant health states with a prior history of MACE who experience a non-fatal MACE event during a modelling cycle transit into 'Hx MACE' sub-state of that respective health state."* It is the EAG's understanding that patients with a history of MACE would already be in the 'Hx MACE' sub-state. Please clarify the transition of those patients with a history of MACE experiencing a new MACE event.

Company response: Patients with an underlying prior history of MACE pre-occupy the Hx MACE sub-health state in either DD or Transplant health states at the beginning of the modelling period. As new MACE events occur in these patients, they transition

to the New MACE health state for the respective cycle and then returning to the Hx MACE health state.

C5. Document B Section B.3.2.2, Page 67, Table 17. The justification for the chosen time horizon is based on 100% of patients dying by year 13 (cycle 52). However, in the economic model, patients don't die until year 41 (cycle 165). Please clarify if this is a typographical error.

Company response: The above-mentioned text from the company's Evidence Submission Document B is a typographical error and should have mentioned 41 years, not 13. The model time horizon of 42 years was based on the fact that at a mean age of 58 years (as indicated in Document B Table 18) patients will reach 100 years old within a 42-year time horizon. It is reasonable to assume that at 100 years of age, death will have occurred for the majority of patients. Indeed, in the economic model the patient cohort do not die fully until Year 41. Therefore, a 42-year time horizon is appropriate for the decision problem taking into account patients underlying age and expect survival time.

C6. Document B Section B.3.3.4 & B.3.3.5, Page 77, Tables 25 & 26. The 'Week' labels in Table 25 and Table 26 start from week 2 and miss certain weeks in between the categories (e.g., week 9). Please confirm if these are correct and if so, please clarify why these are inconsistent and have weeks missing and how they are applied within the model.

Week
Week 2-8
Week 10-20
Week 24-36
Week 40-52
Week 64+

Company response: Tables 25 and 26 in Document B Sections B.3.3.4 and B.3.3.5 reflect how INNO$_2$VATE trial data are reported in the CSRs (3, 4), using the time periods mentioned above which represent the classification of assessments in the clinical trials (Table 27).

The cost-utility model aimed to utilise available data fully and thus used every available time cut-off for each separate cycle in the following fashion: data for weeks 2-8, 10-

20, 24-36, 40-52, 64 was assumed to be relevant for cycles 1, 2, 3, 4, 5, respectively, in the model. Data from the latest available timepoint was assumed to be carried out to the later timepoint.

Table 27. Classification of assessments at every visit for Years 1 through 4 of the INNO$_2$VATE trials

Time period	Visit classification	Target week	Target day	Actual study day of visit
Baseline	Screening visit 1[a]	-	-	-
	Screening visit 2[a]	-	-	-
	Visit 1	Week 0	Day 1	Day 1 (first dose date)[b]
1) **Weeks 2–8**	Visit 2	Week 2	Day 14	Day 2–21
	Visit 3	Week 4	Day 28	Day 22–35
	Visit 4	Week 6	Day 42	Day 36–49
	Visit 5	Week 8	Day 56	Day 50–63
2) **Weeks 10–20**	Visit 6	Week 10	Day 70	Day 64–77
	Visit 7	Week 12	Day 84	Day 78–98
	Visit 8	Week 16	Day 112	Day 99–126
	Visit 9	Week 20	Day 140	Day 127–154
3) Primary Efficacy Period, **Weeks 24–36**	Visit 10	Week 24	Day 168	Day 155–182
	Visit 11	Week 28	Day 196	Day 183–210
	Visit 12	Week 32	Day 224	Day 211–238
	Visit 13	Week 36	Day 252	Day 239–266
4) Secondary Efficacy Period, **Weeks 40–52**	Visit 14	Week 40	Day 280	Day 267–294
	Visit 15	Week 44	Day 308	Day 295–322
	Visit 16	Week 48	Day 336	Day 323–350
	Visit 17	Week 52	Day 364	Day 351–406
Weeks 64+	Visit 18	Week 64	Day 448	Day 407–490
	Visit 19	Week 76	Day 532	Day 491–574
	Visit 20	Week 88	Day 616	Day 575–672
	Visit 21	Week 104	Day 728	Day 673–770
	Visit 22	Week 116	Day 812	Day 771–854
	Visit 23	Week 128	Day 896	Day 855–938
	Visit 24	Week 140	Day 980	Day 939–1036
	Visit 25	Week 156	Day 1092	Day 1037–1134
	Visit 26	Week 168	Day 1176	Day 1135–1218
	Visit 27	Week 180	Day 1260	Day 1219–1302
	Visit 28	Week 192	Day 1344	Day 1303–1400
	Visit 29	Week 208	Day 1456	Day 1401–1498

[a]The Screening period, which starts when the informed consent form is signed, will last a maximum of 8 weeks. Two Screening visits (Screening Visit 1 and Screening Visit 2) must be performed within 8 weeks prior to dosing (Baseline visit or Day 1). There must be a minimum of 4 days between the two Screening visits and a minimum of 4 days between Screening Visit 2 or last retest and the Baseline visit.

[b]If patient has no first dose date, day 1 will be the randomisation date.

Source: Statistical analysis plan (SAP) – INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials (43)

C7. Document B Section B.3.11.3, Page 122, Table 49. The parameter labels in Table 49 appear incorrect and do not match the tornado plot. Please provide an updated and corrected table.

Company response: Table 49 in Document B Section B.3.11.3 contained a typographical error with incorrect parameters listed in the first column. The updated table is presented below (Table 28).

Table 28: Deterministic one-way sensitivity analysis inputs and results (at list price), updated

Parameter	Input -Low	INMB (£) Input-Low	Input -High	INMB (£) Input-High
Utility, DD, No MACE, vadadustat	0.45	-12,592	0.67	11,574
Utility, DD, No MACE, ESA	0.45	11,482	0.67	-12,500
Utility, Transplant, No MACE, vadadustat	0.65	-10,188	0.97	9,170
Utility, Transplant, No MACE, ESA	0.65	9,070	0.97	-10,088
Vadadustat efficacy, HR of MACE, no history of MACE	0.83	-3,462	1.11	2,880
Vadadustat efficacy, HR of MACE, history of MACE	1	-1,763	1	970
Cost of hospital ESA administration	24.82	-1,267	36.93	249
Discount rate - Outcomes	0	-97	0	-681
Cost of IV iron administration, per episode	287	-756	426	-262
Discount rate – Costs	0.00	-826	0.06	-335

Abbreviations: HR, hazard ratio; DD, dialysis-dependent; ESA, erythropoietin stimulating agent; INMB, incremental net monetary benefit; IV, intravenous; MACE, major adverse cardiovascular events
Note: INMB reported (vs ICER/QALY gained) due to ICER results being less effective-less costly for some parameter variation

C8. Economic model file, tab "PatFlow", cell reference "AU:AV" and "DK:DL". Please clarify the formula used to estimate the proportion of patients receiving rescue therapy per cycle. There appears to be an adjustment for cycle length when the inputs 'RBC_rescue_rate_vada', 'RBC_rescue_rate_ESA', ESA_rescue_rate_vada', 'ESA_rescue_rate_ESA' are already labelled as probability per cycle. Please also justify why the formula is further divided by 100, when they are already labelled as a proportion.

Company response: The above formula contained a technical error. This has been corrected in the updated cost-utility model shared with the clarification responses by applying probability of rescue therapy received corrected for cycle length within inputs 'RBC_rescue_rate_vada', 'RBC_rescue_rate_ESA', ESA_rescue_rate_vada', 'ESA_rescue_rate_ESA' directly to the patient flow. Updated deterministic results from the corrected model are presented in Table 29 below.

Table 29. Deterministic results after correction for technical error identified in question C8 (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	314,694	8.892	4.935	1,184	0.08	0.02	51,254
Darbepoetin alfa	313,510	8.815	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

In addition to the correction above, another technical error has been identified on "PatFlow" tab in column DS. In cycle 2 (cell DS17) the formular refers to number of patients from cycle 1 (row 16) whereas it should have referred to number of patients in cycle 2 (row 17). This mistake is being carried out further in column DS. Updated deterministic results from the corrected model for technical error identified by EAG together with correction for technical error identified by Medice are presented in Table 30 below.

Table 30. Deterministic results after correction for technical error identified in question C8 together with correction of error identified by Medice in column DS from "PatFlow" tab (at list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Vadadustat	314,608	8.892	4.935	1,098	0.08	0.02	47,532
Darbepoetin alfa	313,510	8.815	4.912	Reference			

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years

C10. Figure 3. Patient flow in the INNO$_2$VATE – incident trial in Appendix D.2. In the darbepoetin alfa patient flow, 139 patients completed treatment and 49 patients discontinued from study drug. There were 10 further patients randomised to darbepoetin alfa. Please would the company present this table corrected to include all the patients.

Company response: MEDICE has checked the patient flow in Figure 3 Appendix D.2. As shown in this figure, 188 patients were randomised to the darbepoetin alfa treatment group, out of which 139 patients completed the treatment and 49 patients discontinued from the study (139+49=188) (3). The additional 10 patients mentioned

in this query as randomised to darbepoetin alfa were not identified; the figure is correct as shown in Appendix D.2.

C11. PRISMA diagram. The numbers provided in the first box (databases) of the PRISMA diagrams in Appendixes B, G, H and I consistently do not align with the numbers reported in the search strategies. The EAG notes that this could be due to a lack of reporting of duplicates removed. Please would the company clarify why there is this discrepancy and which are the correct figures.

Company response: The EAG is correct, however, please note that this inconsistency was due to the presence of duplicates in the search strategy numbers. The correct figures, that is with duplicates removed, have now been updated in the PRISMA diagrams in Appendixes D, G, H and I.

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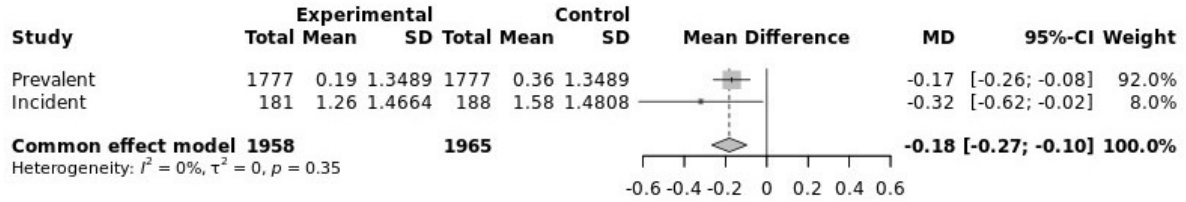
Appendix

Forest plots for meta-analysis of key efficacy outcomes for vadadustat vs darbepoetin alfa from INNO$_2$VATE – incident and – prevalent trials

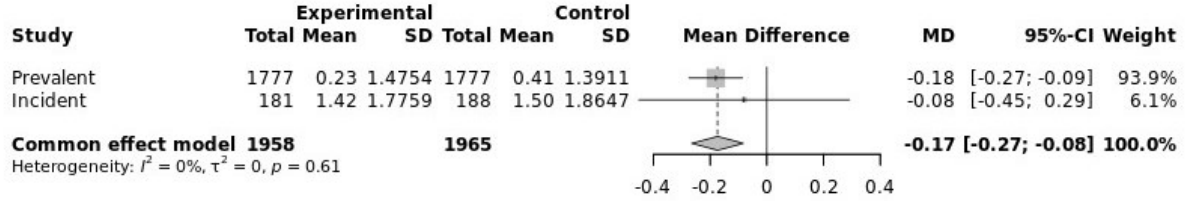
Analyses were performed in R version 4.3.2. The inverse variance method was used for estimation of weights and a restricted maximum-likelihood estimator was applied for tau^2. Meta-analyses of binary outcomes and count outcomes used the respective relative effects estimates (i.e., odds ratios or rate ratios, respectively) as data inputs. In that case, outcome measures are log-transformed in order to be able to use the assumption that the effects are normally distributed. Test of heterogeneity was met for all analyses performed.

Figure 7. Forest plot of change from baseline in Hb to average over Weeks 24 to 36, vadadustat vs darbepoetin alfa



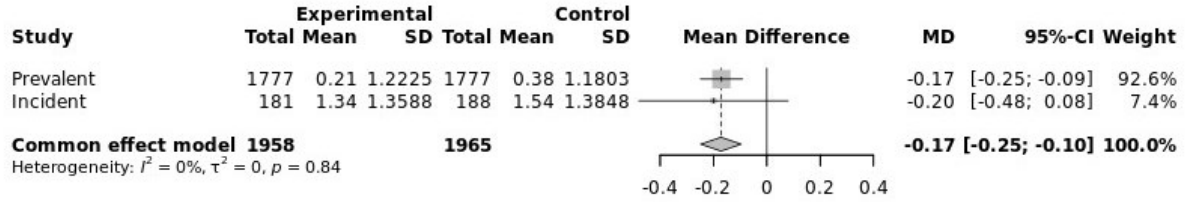
Experimental = vadadustat; Control = darbepoetin alfa
Abbreviations: CI, confidence interval; MD, mean difference; SD, standard deviation.
Source: MEDICE data on file – fixed effects meta-analysis

Figure 8. Forest plot of change from baseline in Hb to average over Weeks 40 to 52, vadadustat vs darbepoetin alfa



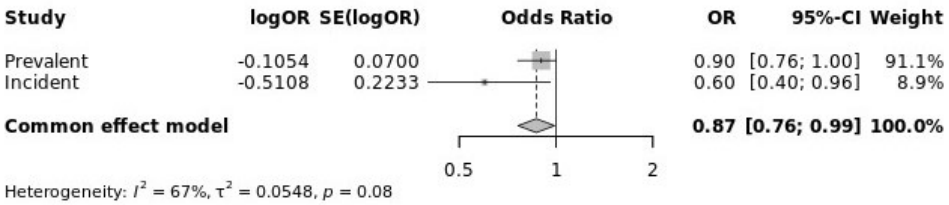
Experimental = vadadustat; Control = darbepoetin alfa
Abbreviations: CI, confidence interval; MD, mean difference; SD, standard deviation.
Source: MEDICE data on file – fixed effects meta-analysis

Figure 9. Forest plot of change from baseline in Hb to average over Weeks 24 to 52, vadadustat vs darbepoetin alfa



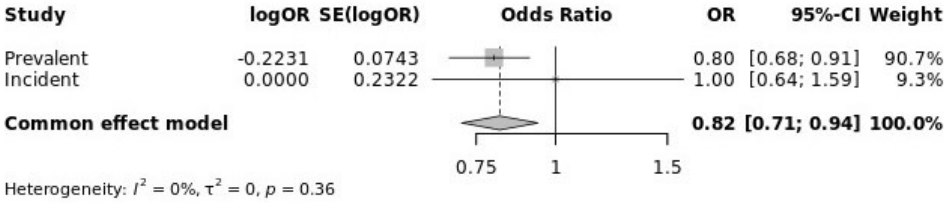
Experimental = vadadustat; Control = darbepoetin alfa
Abbreviations: CI, confidence interval; MD, mean difference; SD, standard deviation.
Source: MEDICE data on file – fixed effects meta-analysis

Figure 10. Forest plot of proportion of patients with average haemoglobin value within geography-specific target range, Weeks 24 to 36



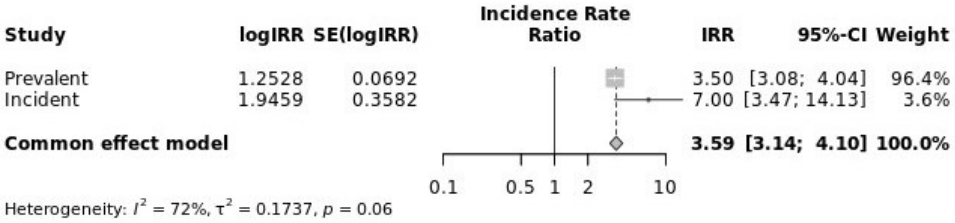
Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error.
Source: MEDICE data on file – fixed effects meta-analysis

Figure 11. Forest plot of proportion of patients with average haemoglobin value within geography-specific target range, Weeks 40 to 52



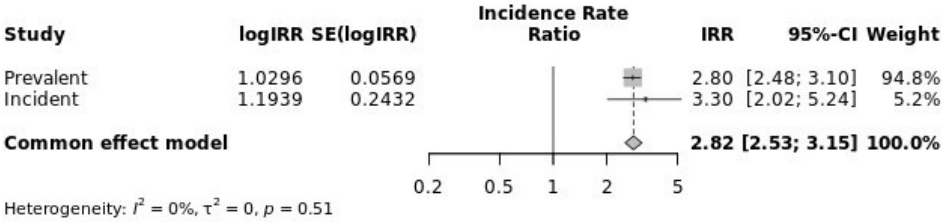
Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error.
Source: MEDICE data on file – fixed effects meta-analysis

Figure 12. Forest plot of ESA rescue episodes, narrow rescue definition



Abbreviations: CI, confidence interval; IRR, incidence rate ratio; SE, standard error.
Source: MEDICE data on file – fixed effects meta-analysis

Figure 13. Forest plot of ESA rescue episodes, broad-on definition



Abbreviations: CI, confidence interval; IRR, incidence rate ratio; SE, standard error.
Source: MEDICE data on file – fixed effects meta-analysis

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [3821]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Kidney Research UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Research UK is the leading kidney research charity in the UK. We fund and promote research into kidney disease and related topics; bring together patients and researchers in networks and clinical study groups; campaign for the adoption of best practice by the NHS and improved health outcomes for patients. The majority of our income is from donations, gifts, and legacies. The remainder is from trusts, partnerships, investments, trading, and government funding. We are not a membership organisation but have an extensive supporter base and a significant number of active volunteers, many of whom are kidney patients.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Medice - £3000 – sponsorship of the industry partnership programme

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Kidney Research UK spoke to a range of people living with chronic kidney disease, both in a focus group, and in one-on-one interviews. We identified participants through our 'Kidney Voices' patient network.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Chronic kidney disease related anaemia is described as being “really really extreme fatigue”, “hitting you like a wave”, the resulting uncertainty catching you out so much that “sometimes you just have to sit on the floor… wherever you are”. Common symptoms described are breathlessness, loss of appetite and weakness. These can be moderate or severe. A transplanted kidney patient described to us how at one point in time, they were so fatigued that they could not hold up their toothbrush to clean their teeth. Other patients outlined how this impacted on their ability to shower or to use the bathroom. Patients sometimes experience a stigma attached to living with the condition, due to a lack of its understanding by others, where “people think you’re lazy…”. This is exacerbated by the nature of the condition often not being visually perceptible. When starting to “rely” more on loved ones, this can also lead to a feeling that you are “becoming a burden to them”. An aspect of the condition can also be ‘brain fog’ – “I can’t always focus properly”. A patient we spoke to, who first experienced the condition as a teenager, outlined the impact this had on their studies. This was difficult to come to terms with, already understand their physical ailments – “this affected me even more”. It later led to their withdrawal from their university studies.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	It is highlighted by patients that injecting oneself with ESA therapy can be challenging, particularly as a young person. It was highlighted by a patient, who experienced the condition both as a young person and an adult, how there could be lessons learned by paediatric care. The patient was told about the condition in a holistic and engaging way as a young person, but information received by adults can be quite stale and difficult to understand in comparison.
8. Is there an unmet need for patients with this condition?	There is an unmet need for patients with this condition. Treatment options are presently limited, particularly for those who are dialysis dependent. For those who are dialysis dependant, and therefore, already undergoing extremely burdensome treatment, comparative treatments are unavailable.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Not having to inject oneself is described as being ideal by those living with kidney disease anaemia, with mixed reflections on how burdensome it is to inject yourself. If treatment can help enable a consistent ability to work, this is described as particularly important to patients – "we have to look after our families, we have lives to live…". The hope that treatment can provide greater certainty to understanding highs and lows is frequently mentioned as being important to patients. Clinical trial data indicates that the treatment is not inferior to ESA in raising haemoglobin levels.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Side effects of treatments can be hugely impactful. A patient we spoke to experienced severe diarrhoea after being treated with iron tablets. This affected their quality of life, as they could not travel far, not being able to commute into work or go on holiday.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Kidney disease disproportionally impacts people from deprived communities and ethnic minority groups. They are more likely to develop kidney disease, progress faster to renal failure and therefore require dialysis or a transplant. People from ethnic minority groups wait on average longer for a kidney transplant due to a shortage of kidneys with a suitable tissue and blood match. People from deprived communities are also more likely to be diagnosed at a later stage of disease progression and die earlier than other socio-economic groups.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Chronic kidney disease related anaemia has a significant affect on a person's physical wellbeing, and their ability to undertake what may be considered simple tasks. • There is a great 'mental' strain of anaemia, which can include depression, brain fog, and other symptoms stemming from either the direct effects of the condition or the stigma attached to it. • The condition can prove an obstacle to participating in work, and the economy. • Treatment options are presently limited, particularly for those dependant on dialysis. • Kidney disease disproportionately impacts people from deprived communities and ethnic minority groups.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [3821]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	UK Kidney Association (UK Renal Pharmacy Group)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **No** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The UKKA was created through merger of the Renal Association, British Renal Society and its affiliates, to support the multi-professional team with delivery of kidney care, education and research – enabling people to live well with kidney disease. UKKA is funded by its members, grants, events, project work and capitation. Governance & structure | The UK Kidney Association
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	UKKA (amount received since 01/01/23 Medice £4,200.00 in sponsorship Pfizer £75,000.00 – project work (RaDaR)
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent and correct anaemia of Chronic Kidney Disease in people receiving chronic dialysis. To prevent and improve symptoms associated with anaemia such as tiredness, weakness, or shortness of breath. Preserve or improve quality of life, and reduce morbidity and mortality.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvements in haemoglobin (Hb) concentration and maintenance between 100 and 120 g/L. Prevent and improve symptoms associated with anaemia such as tiredness, weakness, or shortness of breath.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	For people receiving HD, iron deficiency is treated with intravenous (IV) iron. IV or subcutaneous (SC) Erythropoiesis-stimulating Agents (ESAs) are used to correct anaemia and maintain Hb levels between 100 and 120g/L. People receiving peritoneal dialysis (PD) are usually offered the choice of oral and parenteral iron. ESAs are used to correct anaemia and maintain Hb levels between 100 and 120g/L. If roxadustat was initiated when the patient was not dialysis-dependent, it may be continued if the patient subsequently requires dialysis.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	UK Kidney Association Clinical Practice Guideline: Anaemia of Chronic Kidney Disease NICE CG 203 KDIGO
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	I work in NHS Wales. The pathways of care for anaemia of CKD are generally well defined across the UK, although there may be regional variation. Renal teams assume responsibility for the initiation and continuation of treatment for anaemia of CKD for people with end-stage kidney disease and kidney failure. Iron, ESA and HIF-PH inhibitors are often prescribed by specialist renal nurses and pharmacists, as well as renal physicians. HIF-PH inhibitors provide a valuable alternative to ESA therapy. The extent to which HIF-PH inhibitors are currently used, and their place in therapy depend on factors such as clinical need (including ESA resistance, needle phobia or allergy to iron preparations), clinician and patient preference, and drug acquisition cost. National and local guidelines support decision-making.

9c. What impact would the technology have on the current pathway of care?	Vadadustat would be a valuable alternative to ESA therapy for people receiving dialysis. Vadadustat will be prescribed by renal clinicians with experience in the management of anaemia, as is the case with ESA and roxadustat. Vadadustat's place in therapy relative to ESA will depend on clinical need (including ESA resistance and needle phobia), clinician and patient preference, and acquisition cost. The cost effectiveness of vadadustat relative to ESA will depend on the price paid for ESAs in renal centres across the UK. In Wales, ESAs are procured against to a single national framework. For people receiving PD and subcutaneous ESA therapy, vadadustat would provide a valuable oral alternative. Vadadustat does not need to be stored in the fridge which facilitates drug distribution and storage in pharmacies and patients' homes. General Practice, District and Renal Specialist nurses sometimes administer SC ESA for people who require assistance. This would not be required with vadadustat, unless the patient happened to need support in administering oral medication at home.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Vadadustat would be initiated, continued and monitored by clinicians (doctors, pharmacists and nurses) within a specialist renal team, as is currently the case with IV iron, ESA and roxadustat therapy. Roxadustat is currently offered to people who are not on dialysis, but people starting roxadustat are able to continue treatment if they start dialysis. Switching from ESAs to roxadustat for people who are on dialysis and whose anaemia is stable on ESAs should only be considered if there is a valid clinical reason. If recommended in this technology appraisal, vadadustat could be offered to people after starting dialysis.

10a. How does healthcare resource use differ between the technology and current care?	Vadadustat would be initiated, continued and monitored by clinicians (doctors, pharmacists and nurses) within a specialist renal team, as is currently the case with IV iron, ESA and roxadustat therapy. General Practice, District and Renal Specialist nurses sometimes administer SC ESA for people who require assistance. This would not be required with vadadustat, unless the patient happened to need support in administering oral medication at home. Haemodialysis nurses would not need to administer IV or SC ESA on dialysis if vadadustat was prescribed instead. Renal teams, particularly pharmacy professionals, will need to consider the most convenient and cost-effective way to provide people on peritoneal dialysis and haemodialysis with vaduadustat; whether from hospital stock, via home care delivery or from a community pharmacy by prescribing on a community (FP10) prescription.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Vadadustat would be prescribed by renal specialists in secondary care, primarily in an outpatient setting. Inpatients may require continuation of therapy during a hospital stay. Renal centres may decide to supply vadadustat from hospital stock, arrange home care delivery or prescribe vadadustat on a community (FP10) prescription, depending on local arrangements and patient preference.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	• Financial investment may be required if vadadustat is more expensive than ESA preparations • Renal teams (particularly pharmacy and anaemia teams) will need to adapt working practices if a significant number of patients under their care are prescribed vadadustat; mainly in relation to the activity of prescribing and supply. This may or may not require investment • Frequent blood tests are required when initiating vadadustat • Renal health professionals and primary are colleagues may benefit from information sessions and resources

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Vadadustat has been shown to be non-inferior to ESA therapy in changing Hb levels from baseline in clinical trials. I expect vadadustat to be particularly beneficial for people with ESA resistance and needle phobia.
11a. Do you expect the technology to increase length of life more than current care?	Potentially in people with ESA resistance or needle phobia.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Potentially in people with ESA resistance or needle phobia.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	People with ESA resistance or needle phobia may benefit more from vadadustat. Vadadustat improves iron utilisation and availability to erythroid cells. Oral and IV iron use was similar in vadadustat and comparator groups in clinical trials, and the effects of vadadustat on oral iron absorption could not be determined. More experience and evidence is required to determine whether vadadustat can achieve and maintain target Hb concentrations in people on dialysis while reducing or eliminating intravenous iron administration. A reduction in iron requirements would be broadly beneficial.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	For people receiving HD, ESAs can be administered intravenously via the dialysis machine by the nurse, which is likely to be more convenient for the patient than taking a tablet every day. Some ESAs, for example epoetin beta, are often administered subcutaneously on HD due to improved ESA efficacy at the EPO receptor when given by this route, allowing for smaller doses to be used. Patients may prefer to take a tablet every day to regular subcutaneous injections. For people receiving PD and subcutaneous ESA therapy, vadadustat would provide a valuable oral alternative. Vadadustat does not need to be stored in the fridge which facilitates drug distribution and storage in pharmacies and patients' homes. General Practice, District and Renal Specialist nurses sometimes administer ESA subcutaneously for people who require assistance. This would not be required with vadadustat, unless the patient happened to need support in administering oral medication at home. Vadadustat will be prescribed by renal specialists, but depending on local arrangements, patients could receive vadadustat from the hospital, via home care delivery or from their community pharmacy. This could provide flexibility and convenience for patients. People receiving ESA during in-centre HD do not need to order this medication from the renal pharmacy department (it is taken from stock and administered on the dialysis unit), which is likely to be more convenient for patients and renal services.

	Vadadustat does not need to be refrigerated. This is beneficial with regard to transportation and storage in pharmacies and patients' homes. According to the manufacturer, once stable, haemoglobin should be monitored at least monthly in people taking vadadustat. This generally mirrors practice for the monitoring of ESA on HD. People receiving PD with stable Hb (and other laboratory) levels often attend outpatient clinic less frequently than once a month. More experience and evidence is required to determine whether vadadustat can achieve and maintain target Hb concentrations in people on dialysis while reducing iron administration. A reduction in iron requirements would be beneficial when considering the risks associated with IV iron therapy, the GI side effects associated with oral iron preparations particularly and drug costs. A reduction in the need for IV iron infusions for PD patients in particular (IV iron is given via the HD machine), would liberate renal nurse and patient time.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Local guidelines will likely be developed or amended to include vadadustat, considering prescribing information in the technology's Summary of Product Characteristics, and NICE and other national recommendations (for example UK Kidney Association).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Vadadustat belongs to an innovative class of medication and would be the first HIF-PH inhibitor with NICE endorsement for use in dialysis at the start of treatment. I see this technology as a valuable alternative to ESA therapy.
16a. Is the technology a 'step-change' in the management of the condition?	This technology would be a valuable alternative to ESA; perhaps a step forward as opposed to a step change.
16b. Does the use of the technology address any particular unmet need of the patient population?	This technology would be useful for people with an inadequate response to ESA therapy and for people with needle phobia. Vadadustat may also reduce IV iron requirements, but more evidence is required to establish this.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	According to the manufacturer, the most frequent (> 10%) adverse reactions in patients treated with vadadustat are thromboembolic events (13.7%), diarrhoea (12.7%) and hypertension (11.1%). The most frequent (≥ 1%) serious adverse reactions in patients treated with vadadustat are thromboembolic events (10.0%), hypotension (1.6%) and hypertension (1.1%). Similar adverse effects have been observed with ESA therapy. Diarrhoea is not commonly associated with ESA therapy which can be problematic for people with CKD who often suffer with gastro-intestinal issues.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Efficacy: Increase and maintain Hb levels Safety: Favourable MACE outcomes (all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke) These non-inferiority outcomes (versus ESA) were measured in trials.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not as far as I'm aware.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	I'm not familiar with real-world experience data for vadadustat.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Vadadustat would be a valuable option for treating anaemia of CKD in people receiving dialysis • Vadadustat's place in therapy will depend on the acquisition cost of the drug as well as clinical and logistical considerations • Renal departments, particularly pharmacy teams, will need to consider the most convenient and cost-effective way to provide vaduadustat to people having dialysis.

Thank you for your time.

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Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **09 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating symptomatic anaemia in adults having dialysis for chronic kidney disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof Sunil Bhandari
2. Name of organisation	Hull University Teaching Hospitals NHS Trust – representing Self as Clinical Expert
3. Job title or position	Consultant Nephrologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of adults with symptomatic anaemia while having dialysis for chronic kidney disease? ☒ A specialist in the clinical evidence base for symptomatic anaemia in adults having dialysis for chronic kidney disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

8. What is the main aim of treatment for symptomatic anaemia in adults having dialysis for chronic kidney disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	**The key aim for the treatment of symptomatic anaemia is to improve quality of life, functional capacity, reduce cardiovascular risk in people with Chronic Kidney Disease on regular kidney replacement therapy and maintain the haemoglobin concentration within the current recommended range of 100-120g/L while maintaining safety with an acceptable side effect profile.**
9. What do you consider a clinically significant treatment response in terms of change in hb? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	1. At least a 10g/L rise in Hb 2. % of patients in the recommended target range as above. 3. Reduction in the need for blood transfusions
10. In your view, is there an unmet need for adult patients and healthcare professionals in symptomatic anaemia while having dialysis for chronic kidney disease?	1. The need for an effective therapy in patients with chronic inflammation who are on receiving dialysis 2. The need for effective therapy in those with ESA hyporesponsiveness – areas of clinical need where an alternative therapy is needed for this group of patients to improve their haemoglobin levels and hence quality of life. 3. Use in patients who are not keen or struggle with injections – especially those receiving peritoneal dialysis.
11. How is symptomatic anaemia in adults having dialysis for chronic kidney disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Currently guidelines recommend iron repletion first with iv iron therapy in those who have no contraindications. The regime which is Nice and UKKA (UK Kidney Association guidelines) is based on the PIVOTAL Trial NEJM 2019. Once iron replete the next step to achieve the haemoglobin in the target range (100-120g/L), is use of subcutaneous or intravenous erythropoietin stimulating agents. Sub-cutaneous (Peritoneal Dialysis patients and in some units haemodialysis patients) or intravenous (usually in haemodialysis patients) injection together with iron.

• What impact would the technology have on the current pathway of care?	ESA agents can be short acting agents given up to three times a week or long acting agents given weekly or even less frequently (monthly). The pathway of care is well defined with variations in use of formulations of ESA therapy. The current treatment for anaemia of CKD is 1. First, oral or intravenous iron – usually IV iron in HD and oral PD 2. Then subcutaneous (intravenous in haemodialysis patients) erythropoietin stimulating agents (ESAs). 3. Blood transfusions when the above fail or Hb is extremely low and the patient symptomatic. Choice of ESA used by sub-cutaneous injection is variable throughout the UK from short acting thrice weekly preparations to longer acting monthly preparations. This is based on contracts. NICE Chronic kidney disease: managing anaemia. NICE guideline [NG8] Published: 03 June 2015 and revised in August 2021 Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease 2017 – revised 2024 (pending publication) Management is well documented in the current NICE and KDIGO guidelines (kidney disease improving global outcomes) and the UKKA anaemia guidelines. These are all broadly similar with slight difference to target Hb ranges.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This technology would add an additional choice to clinicians and patients in optimisation of their anaemia. The majority of treatment is given in secondary care and monitored by specialists. Choice for patients is critical as detailed by the Government and Health Education England Certain groups would particularly benefit: 1. ESA naive patients as their primary treatment after iron for anaemia 2. Patients who are unable to take ESA therapy 3. ESA hyperresponsiveness 4. Those unable to self-inject ESA therapy 5. People receiving peritoneal dialysis. As an oral therapy – no investment is required except in training in the utilization – this is made simpler with the imminent publication of the recent UKKA 2024 Anaemia of chronic kidney Disease guidelines. The technology is already in use in the UK in the CKD non dialysis population with the ability to continue when progressing to dialysis so there is accumulating experience of use of HIF-proply hydroxylase drugs.
13. In your clinical understanding does vadadustat have the same or a similar mechanism of action to injectable ESAs (are there differences between treatments other than how it is administered)? Would you describe vadadustat as an oral ESA?	The mechanism of action is different to ESA therapy. It is novel and the more physiological approach may have longer term benefits as yet not identified including its widespread pleotropic effects which may be positive as in the impact on lipids but also negative in other areas. The combination of increasing

	haemoglobin with endogenous erythropoietin production and improved iron metabolism is very attractive to simplify management. Vadadustat could not be described as an oral ESA.
14. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The technology with be as effective in patients who require ESA therapy both chronic kidney disease and dialysis patients. It would seem more attractive in those receiving peritoneal dialysis, as an oral tablet may be preferred to an injection. In haemodialysis patients this is less attractive as currently ESA therapy is given in the dialysis machine in many units so there is no injection, and the additional tablet may not be as attractive to that group of patients. Meaningful benefit will be related to patient choice and options and in the group of 10-15% of patients who do not respond to ESA therapy An increase in length of life would be unlikely. We know that improving Hb in patients with CKD reduces mortality and cardiovascular risk. The data available show comparable risk. The trials published do show some benefit, but this needs further data
15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? **For example:** **- is there any reason to expect that a person's anaemia may respond differently to vadadustat if it has previously not responded to ESAs? (i.e. there is ESA resistance)**	More appropriate for: • Patients with chronic inflammation and a high CRP • Patients hyporesponsive to ESA therapy • Those with ESA antibodies and ESA resistance • CKD patients on dialysis • Those who are unable to self-inject.

- would you expect vadadustat to have a different treatment effect, depending on the stage of their treatment? (I.e. if they have just started or are established on dialysis)	Data is lacking at present but preliminary evidence does suggest a potentially more physiological response and possible better use of available iron but this latter aspect requires more trials. Potentially less appropriate for: • Unit haemodialysis patients who get IV ESA in the dialysis machine • Those with fistula problems • Those with clotting disorders • Those with allergy to drug
16. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) **Would you expect vadadustat to appeal mostly to people taking peritoneal dialysis? And, for people taking haemodialysis, is there a benefit to taking vadadustat orally over ESAs that are given as part of dialysis? Would it primarily be used for people taking haemodialysis if their anaemia is resistant to ESAs or are there other reasons why they may prefer vadadustat over ESAs?**	It will potentially be easier to use as it is a tablet. Versus injection– this might present issues with compliance. This will be easier for patients. 1. The therapy may lead to a reduction in the need for iv iron therapy and hence visits to hospital as a result of its action on improving iron absorption and mobilisation. It will be more “green” with the reduced need for special disposal requirements that are needed for sharps with ESAs and need for cold chain storage requirements for ESAs. Reduction in patient training in administration of ESA versus none with technology Reduction in training healthcare professionals such as district nurse to deliver if patient cannot.
17. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• There are certain groups which might need to be excluded based on the trials.

	• For example cancer patients; patients with polycystic kidney disease; abnormal liver function tests; myeloma patients – this is in part similar to ESA therapy for cancer patients. Monitoring will be no different to current pathways of care
18. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	There is limited clinical data available examining this but it is unlikely to demonstrate any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?
19. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is an innovate technology which has developed from the Nobel prize winning work of the oxford group under the auspices of Sir Peter Radcliffe. This technology will add to the nephrologist armoury in the effective management of dialysis patients and in particular those who do not respond to ESA therapy. Health related benefits data is limited at present and it is difficult to comment on this and if this therapy will be better than current therapies; is all one can say is that it is as effective and safety is comparable. This novel and the more physiological approach may have longer term benefits as yet not identified including its widespread pleotropic effects which may be positive as in lipids but also negative in other areas. The combination of

	increasing haemoglobin with endogenous erythropoietin production and improved iron metabolism is very attractive to simplify management. See above – certain groups may particularly benefit from this therapy.
20. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• Side effects are important and need to be considered when prescribing. 1. Increased risk of hypertension – this may require additional therapy 2. Potential increased risk of vascular access thrombosis – more gradual increase in haemoglobin may be important to offset this effect 3. Gastro-intestinal side affects 4. Headache 5. Other thrombotic events This may require care in those "high risk groups"
21. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? • Do you consider the clinical trials to include people with ESA resistance? As a reminder, the exclusion criteria in the INNO2VATE – incident trial was, as follows:	Yes in part – in dialysis patients the current therapy is iron repletion then ESA. The trials compared against standard of care but with varying degrees of iron repletion. The haemoglobin target ranges also varied due to differences in worldwide practice. The outcomes measures were non inferiority to ESA therapy: 1. Efficacy – measured against the current active comparator - ESA Therapy

"Patients that met criteria of ESA resistance within eight weeks prior to or during screening defined as follows: - epoetin >7,700 units/dose three times per week or >23,000 units per week; - darbepoetin alfa >100 µg/week; - methoxy polyethylene glycol-epoetin beta >100 µg every other week or >200 µg every month."	2. Safety of drug against an active comparator – data does show this and the pooled analysis does confirm no increase adverse cardiovascular risk but also no additional benefit. 3. Health related quality of life – these were measured and comparable to active comparator 4. Primary outcome of CV events and death – not measured as a primary outcome but a secondary outcome and pooled analysis. We do have data on other HIF-PHI outcomes. The current trials had approximately 10% pf patients with possible ESA resistance or chronic inflammation, but this was not studied and the trials were not stratified to specifically answer the question of efficacy in the group. Trials were only up to 2 years so longer term side affects are unknown at present.
22. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No – there are studies now 5 other molecules in the same family, but the question remains can it be assumed this is a class affect or are there differences. – As an expert in the field, I suspect there maybe differences due to actions on various proteins. A recent metanalysis from Chen of 21 placebo controlled trials and 17 ESA trials confirmed comparable effects of the molecules and safety.

23. How do data on real-world experience compare with the trial data?	not available at present or at least very little. Real world data is similar but is based on non UK data as the UK population is limited.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	N/A

Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Iron repletion is essential before consideration of any other intervention such as ESA or vadadustat

Vadadustat is comparable to ESA therapy in increasing and maintaining Hb in the target range.

Vadadustat offers an alternative to ESA therapy in those patients who cannot tolerate ESA therapy or have a poor response to it

An oral therapy providing increased choice to clinicians and patients

Other benefits may become apparent with more trials such as better utilisation of iron.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **09 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating symptomatic anaemia in adults having dialysis for chronic kidney disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Karen Jenkins
2. Name of organisation	East Kent Hospitals University NHS Trust (Clinical advisor to Medice, consultancy basis)
3. Job title or position	Nurse Consultant Renal Medicine
4. Are you (please tick all that apply)	X An employee or representative of a healthcare professional organisation that represents clinicians? X A specialist in the treatment of adults with symptomatic anaemia while having dialysis for chronic kidney disease? X A specialist in the clinical evidence base for symptomatic anaemia in adults having dialysis for chronic kidney disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	Yes, I agree with it – nomination by Medice ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE

8. What is the main aim of treatment for symptomatic anaemia in adults having dialysis for chronic kidney disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve physical function, concentration levels, quality of life. To reduce the adverse effects of anaemia such as left ventricular hypertrophy. Reduce symptoms such as fatigue, breathlessness on exertion Improve the ability to carry out daily activities of living.
9. What do you consider a clinically significant treatment response in terms of change in hb? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A rise in haemoglobin level to within aspirational range of 100-120g/L Reduction in symptoms Improvement in physical function and quality of life indicators
10. In your view, is there an unmet need for adult patients and healthcare professionals in symptomatic anaemia while having dialysis for chronic kidney disease?	IV or sub cut ESA therapies are the only drug group licensed for use in the dialysis population in the UK. These are used alongside IV iron and in some cases oral iron. For people having peritoneal dialysis this means injecting themselves up to three times a week with an ESA subcutaneously. No choice of an alternative For people having haemodialysis ESAs can be given IV during dialysis or self-administered subcutaneously at home. No choice of an alternative For those who do not respond to ESA therapy there is currently no alternative treatment apart from blood transfusion, which is not recommended for those on the Transplant list due to risk of developing antibodies. If an oral HIF stabiliser has been commenced pre-dialysis it can be continued when a person starts dialysis as per NICE guidance. Whether this is common practice is unknown
11. How is symptomatic anaemia in adults having dialysis for chronic kidney disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	Use of Intravenous/oral iron, ESA therapy NICE guidance ng 8 Chronic kidney disease: managing anaemia | Guidance | NICE UK kidney Association Clinical Practice Guideline: Anaemia of chronic Kidney Disease (2022) under review

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Yes, the pathway is well defined and has been established in kidney care for many years. NICE/UKKA guidance used to shape local protocols for managing anaemia of CKD in Renal units **Impact** The technology would give an alternative to ESA therapy for people receiving dialysis (patient choice) and an opportunity to try an alternative treatment if not responding to ESA therapy
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	**Resource** It would be an addition to the current model of care for dialysis patients, prescribed and monitored by secondary care. It would reduce the burden of self-injection for patients receiving peritoneal dialysis, reduce the need for specialist transport of refrigerated products to patient's homes. It could reduce inequalities to access to anaemia treatment and support self-management for those dependent on others for their treatment e.g. carer/healthcare professional to administer injections, particularly for home-based dialysis e.g. peritoneal dialysis **Clinical setting** Secondary care prescribed for use for any patient requiring in-centre, satellite, home haemodialysis and Peritoneal dialysis **Training** Staff training for prescribing/ monitoring response. Drug interactions, Patient information & education, awareness of drug interactions/side effects Self-medicate so no special storage required in a renal unit. Could reduce the need for temperature-controlled drug fridges in dialysis units.

13. In your clinical understanding does vadadustat have the same or a similar mechanism of action to injectable ESAs (are there differences between treatments other than how it is administered)? Would you describe vadadustat as an oral ESA?	There are pharmacological differences between Vadadustat and injectable ESAs Vadadustat acts on the HIF-PH enzyme which regulates physiological response to hypoxia and stimulate the synthesis of endogenous erythropoietin production, supresses hepcidin production and improves iron availability by increasing iron absorption and transportation and release from stores. ESAs stimulate erythropoiesis in the bone marrow to activate the red blood cell cycle. I would not describe Vadadustat as an oral ESA as it has a different mechanism I would describe it as an alternative oral treatment which has the same end point as an ESA.
14. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Evidence for this is unknown but would be comparable with current care It will give a choice to Peritoneal dialysis patients and relieve the burden of the only current option being self-administering a subcutaneous injection or attending a GP practice/ require a community nurse to administer. It lifts the restrictions of storage and travel with a cold chain drug. It would reduce the need IV iron supplementation & attendance for this as an outpatient for home Haemodialysis and Peritoneal Dialysis patients/ reduce the need for oral iron and therefore side effects of oral iron. It would give more freedom with daily activities and enhance independent/self-management for home-based therapies in particular and hence QOL.

15. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? **For example:** **- is there any reason to expect that a person's anaemia may respond differently to vadadustat if it has previously not responded to ESAs? (i.e. there is ESA resistance)** **- would you expect vadadustat to have a different treatment effect, depending on the stage of their treatment? (I.e. if they have just started or are established on dialysis)**	A person may respond differently to Vadadustat due to the pharmacological effect of the drug and the inhibition of the HIF enzyme mechanism. ESA resistance is multifactorial. Often when ESAs are administered in high doses and a reduced response occurs they are stopped and the only current alternative is blood transfusion, which is detrimental for those wishing to be transplanted due to risk of developing antibodies. I wouldn't expect it to have a different treatment effect depending on when they commenced dialysis
16. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) **Would you expect vadadustat to appeal mostly to people taking peritoneal dialysis? And, for people taking haemodialysis, is there a benefit to taking vadadustat orally over ESAs that are given as part of dialysis? Would it primarily be used for people taking haemodialysis if their anaemia is resistant to ESAs or are there other reasons why they may prefer vadadustat over ESAs?**	It would potentially reduce the amount of intravenous iron required for haemodialysis patients. Current guidelines recommend 400mg/month, 200mg given on consecutive Haemodialysis sessions. Home Haemodialysis patients have to come into a unit to have IV iron as can no longer administer at home due to possible risk of anaphylaxis and MHRA recommendations. Initial increase in monitoring if switching or new starter. SPC suggests every 2wks until stable, thereafter monthly. For PD patients this may be a concern as extra blood tests and access to phlebotomy services Unit based Haemodialysis patients, samples taken in the unit from dialysis access Home haemodialysis, samples taken from dialysis access but process needed to get samples to the lab. Vadadustat would appeal mostly to people having peritoneal dialysis or home haemodialysis, and dialysis patients wishing to travel regularly.

	Vadadustat would reduce the burden of staff administering IV or SC ESA in the dialysis unit on a daily basis, freeing up time to focus on other patient needs. Vadadustat would be an option for those who are ESA resistant
17. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Renal Units will need to adjust existing protocols and have agreed criteria for starting/stopping Vadadustat. No additional tests should be required.
18. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Treatment regimens are not specifically included in QALY calculations and ought to be considered
19. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes Yes
20. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Awareness of interactions with other medications and adjustment to timing of medication e.g. phosphate binders, oral iron

21. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? • Do you consider the clinical trials to include people with ESA resistance? As a reminder, the exclusion criteria in the INNO2VATE – incident trial was, as follows: "Patients that met criteria of ESA resistance within eight weeks prior to or during screening defined as follows: - epoetin >7,700 units/dose three times per week or >23,000 units per week; - darbepoetin alfa >100 µg/week; - methoxy polyethylene glycol-epoetin beta >100 µg every other week or >200 µg every month."	Vadadustat was non- inferior in terms of cardiovascular safety, correction and maintenance of haemoglobin levels in the dialysis population. Safety profiles were similar. Included patients at different stages and types of dialysis. Not that I am aware of Excluded in INNO2VATE – but criteria for exclusion was different to guideline recommendation 'ESA therapy is defined as failure to reach the target Hb level despite SC epoetin dose >300 IU/kg/week (450 IU/kg/week IV epoetin), or darbepoetin dose >1.5 microgram/kg/week' Not mentioned in the other studies
22. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
23. How do data on real-world experience compare with the trial data?	I have not seen any publications to this effect

24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This technology is comparable to ESA therapy in terms of efficacy and safety

This technology would be of most benefit to those receiving home-based dialysis, enhancing independent/self-management

This technology would give patients receiving dialysis an additional option for treatment of their anaemia

This technology would reduce requirement of IV iron supplementation/oral iron

This technology offers an alternative to those who are resistant to ESA therapy

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with symptomatic anaemia while having dialysis for chronic kidney disease or caring for an adult patient with symptomatic anaemia who is having dialysis for chronic kidney disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **09 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for an adult patient with symptomatic anaemia who is having dialysis for chronic kidney disease

Table 1 About you, symptomatic anaemia during dialysis for chronic kidney disease, current treatments and equality

1. Your name	Faizan Awan
2. Are you (please tick all that apply)	☐ A patient with symptomatic anaemia while having dialysis for chronic kidney disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of an adult patient with symptomatic anaemia who is having dialysis for chronic kidney disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Kidney Research UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with symptomatic anaemia while having dialysis for chronic kidney disease? **If you are a carer (for an adult with symptomatic anaemia who is having dialysis for chronic kidney disease) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for symptomatic anaemia in adults having dialysis for chronic kidney disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for symptomatic anaemia in adults having dialysis for chronic kidney disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of vadadustat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability	

to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does vadadustat help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of vadadustat over current treatments on the NHS please describe these. For example, are there any risks with vadadustat? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from vadadustat or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering symptomatic anaemia in adults having dialysis for chronic kidney disease and vadadustat? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	That anaemia does not just affect the dialysis population who have CKD, but can also affect those transplanted as transplant is not a cure, which itself has its own side effects , and anaemia can still persist so making something which could be helpful to the CKD population, should be available for all not just the dialysis community.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with symptomatic anaemia while having dialysis for chronic kidney disease or caring for an adult patient with symptomatic anaemia who is having dialysis for chronic kidney disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **09 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for an adult patient with symptomatic anaemia who is having dialysis for chronic kidney disease

Table 1 About you, symptomatic anaemia during dialysis for chronic kidney disease, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with symptomatic anaemia while having dialysis for chronic kidney disease? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of an adult patient with symptomatic anaemia who is having dialysis for chronic kidney disease? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Kidney Care UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing

	on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with symptomatic anaemia while having dialysis for chronic kidney disease? **If you are a carer (for an adult with symptomatic anaemia who is having dialysis for chronic kidney disease) please share your experience of caring for them**	The anaemia control began in pre dialysis when significant symptoms of low HB and associated tiredness were directly affecting quality of life and social issues of employment and income generation. Epo was prescribed and so there was a significant recovery in health and cognitive alertness at a time when dialysis choices needed to be made. Sadly other issues like increased urea and potassium from severe kidney failure were also contributing to significant quality of life issues The 3 issues where 1. the self needling 2. cold storage of the epo 3. Maintaining Iron levels Once on dialysis these became easier as the epo and iron where directly injected into the lines.
7a. What do you think of the current treatments and care available for symptomatic anaemia in adults having dialysis for chronic kidney disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**Epo regimes has a significant track record of success with a whole variety of patients and presentations, some of whom can present a significant risk to uncontrolled fluctuations in HB levels. No apparent side effects to patients are regularly reported on patient bulletins and social media feeds** **Most patients suffering from anaemia have found Epo a very positive drug . Our hospital have worked well with dialysis suppliers to make it a relatively easy drug to prescribe and obtain by patients**
8. If there are disadvantages for patients of current	Needle phobia is a common concern with pre dialysis patients but once shown the

NHS treatments for symptomatic anaemia in adults having dialysis for chronic kidney disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	technique few patients actually continue with the concern. Cold storage can be an issue as a typical subscription can be 4 plus boxes taking up refrigerator space Maintaining iron supplies by infusion has been regulated back to the hospital and involves yet another visit to hospital.
9a. If there are advantages of vadadustat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does vadadustat help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**1.This is a pill , which is usually preferable to self injection by patients. Although patients in ESRF can be 'fed up ' with pill taking and issues of compliance.** **2. Not having to store in a fridge is useful and easier for prescription delivery** **3. If V. can reduce the need for iron infusions because of its different method of biological interaction , this would be welcomed by patients and clinical team.** **Retaining Iron stores is the most significant advantage** **Awaiting details**
10. If there are disadvantages of vadadustat over current treatments on the NHS please describe these. For example, are there any risks with vadadustat? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Many patients will be concerned about the over stimulation of HB and possible cardio vascular issues in a NHS system that can be inefficient in monitoring HB levels . EPO took 3 generations of adaption to get to a point where it is well understood and monitored. EPO does not appear to affect the bowels or feeling of sickness or headaches. Any drug that gets a reputation for providing side effects that have adverse reactions in everyday living, like feeling sick or diarrhoea will lead to significant non-compliance by patients.

11. Are there any groups of patients who might benefit more from vadadustat or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	This drug appears to have its main advantage in application only. It is possible to be 'resistant ' to Epo , if V. can help this group of patients then it will certainly be welcomed.
12. Are there any potential equality issues that should be taken into account when considering symptomatic anaemia in adults having dialysis for chronic kidney disease and vadadustat? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I cannot see any ethnic , age or gender being a barrier to using V. Only patients who have high risk co-morbidities that will affect their ability to use the drug.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Anaemia is a very deliberating condition for patients with kidney failure with severe tiredness and lack of energy and cognitive issues that significantly affect quality of life and social issues .
- Epo regimes are a trusted and efficiently prescribed drug for the treatment of Anaemia in patients with kidney failure
- A pill is much easier for patients and easier to prescribe.
- retaining iron stores is critical for HB production , any drug that retains iron longer will help patients significantly
- No everyday side effects of any drug is preferable for patients and will ensure compliance

Thank you for your time.

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Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]:

A Single Technology Appraisal

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School

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Author contributions

Alex Allen	Critical appraisal of the company's clinical effectiveness evidence and drafted sections of the report
Rachael Batteson	Critical appraisal of the company's economic evidence, conducted additional economic analysis, and drafted sections of the report
Simone Critchlow	Critical appraisal of the company's economic evidence, conducted additional economic analysis, and drafted sections of the report
Tommy Douglas	Critical appraisal of the company's economic evidence, conducted additional economic analysis, and drafted sections of the report
Millie Woodrow-Hill	Critical appraisal of the company's economic evidence, conducted additional economic analysis, and drafted sections of the report
Alan Lovell	Project manager. Critical appraisal of the company's literature search strategies and editorial input.
G.J. Melendez-Torres	Critical appraisal of the company's statistical analysis
Jemma Perks	Critical appraisal of the company's statistical analysis
Dominic de Takats	Expert clinical advice to the EAG about anaemia in CKD and its treatment
Adam Rumjon	Expert clinical advice to the EAG about anaemia in CKD and its treatment
Edward C.F. Wilson	Project director and guarantor. Critical appraisal of the company's economic evidence and edited the report

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Abbreviations

Acronym	Definition
AE	Adverse effect
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
APD	Automated peritoneal dialysis
ASN	American Society of Nephrology
BIC	Bayesian information criterion
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPD	Continuous ambulatory peritoneal dialysis
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CERA	Continuous erythropoietin receptor activator
CHF	Congestive Heart Failure
CI	Confidence interval
CKD	Chronic Kidney Disease
CMU	Commercial Medicines Units
cPAS	Confidential Comparator Patient Access Scheme
CQ	Clarification question
CRD	Centre for Reviews and Dissemination
CS	Company submission
CV	Cardiovascular
CVD	Cardiovascular disease
DARE	Database of Abstracts of Reviews of Effects
DD	Dialysis dependent
DD-CKD	Dialysis dependent chronic kidney disease
DL	Decilitre
DSA	Deterministic sensitivity analyses
EAG	External Assessment Group
EDTA	European Dialysis and Transplant Association
EED	Economic Evaluation Database
EMA	European Medicines Agency
EN	European Nephrology

Acronym	Definition
EOT	End of treatment
EPAR	European public assessment report
ERA	European Renal Association
ESA	Erythropoiesis-stimulating agent
EUR	Euro
FAS	Full set analysis
FDA	Food and Drug Administration
GBP	GB Pound
GP	General practitioner
HAS	Haute Autorité de Santé
Hb	Haemoglobin
HD	Haemodialysis
HDL	High-density lipoprotein
HF	Heart failure
HIF-PhI	Hypoxia-inducible factor–prolyl hydroxylase inhibitor
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IDMC	Independent data monitoring committee
IPD	Individual patient data
ISPOR	Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
IU	International unit
IV	Intravenous
IWR	Interactive Web Response
KM	Kaplan-Meier
KRT	Kidney replacement therapy
LDL	Low-density lipoprotein
LSM	Least squared mean
LY	Life years

Acronym	Definition
MACE	Major adverse cardiovascular event
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MOA	Mode of administration
MPSC	Medicines Procurement and Supply Chain
MVH	Measurement and Valuation of Health
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NKF	National Kidney Federation
NR	Not reported
NYHA	New York Heart Association
ONS	Office for National Statistics
OWSA	One-way sensitivity analyses
PAS	Patient access scheme
PCA	Prescription Cost Analysis
PD	Peritoneal dialysis
PEP	Primary efficacy period
PFS	Progression free survival
PICO	Population intervention comparator outcome
PP	Pre protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality assessment
QALY	Quality-adjusted life year
QC	Quality-control
RBC	Red blood cell
RCT	Randomised controlled trial
RRT	Renal replacement therapy
SAE	Serious adverse event
SC	Subcutaneously
SCE	Summary of clinical efficacy

Acronym	Definition
SD	Standard deviation
SE	Standard error
SEM	Standard errors of mean
SEP	Secondary efficacy period
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TE-SAE	Treatment-emergent serious adverse event
TSAT	Transferrin saturation
TTD	Time to treatment discontinuation
UK	United Kingdom
UKKA	UK Kidney Association
UKKW	UK Kidney Week
UKRR	UK Renal Registry
US	United States

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 and 1.4 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.2 to 1.5.

Broadly speaking, the key clinical issues related to the pooling of data from the two pivotal trials ('INNO$_2$VATE – prevalent' and 'INNO$_2$VATE – incident') and the relatively high discontinuation rate in the vadadustat arm, possibly due to the increased pill burden. In terms of cost effectiveness issues, the EAG noted that 1) there was a lack of evidence to support the differences in rates of major adverse cardiovascular events (MACE) in the model, 2) there were questions regarding the appropriateness of the company's approach to treatment discontinuation and treatment waning, and 3) the model structure was overly complex with a number of limitations.

Table 1: Summary of key issues

ID	Summary of issue	Report sections
Key Issue 1	Appropriateness of pooling data from the two pivotal trials	3.2.2.2, 3.2.3.1
Key Issue 2	Drug discontinuations and the impact of additional medication on a person's pill burden	2.4, 3.2.2.2, CQ A9 and A10, 6.2.5
Key Issue 3	Lack of evidence to support differences in MACE	4.2.2

ID	Summary of issue	Report sections
Key Issue 4	The company's model structure is overly complex	4.2.2
Key Issue 5	The company's approach to treatment discontinuations is inappropriate	4.2.6.6
Key Issue 6	Appropriateness of treatment waning	4.2.6.3

Abbreviations: CQ, clarification question; MACE, major adverse cardiovascular events

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Model structure	Sub-states including MACE	Sub-states including Hb levels	4.2.2
Treatment discontinuation	Landmark estimates	Parametric curves	4.2.6.6
Vadadustat stopping rule	Applied at Cycle 1	Applied at Cycle 2	4.2.6.6
MACE	HR to inform treatment effectiveness	Removed	4.2.6.3
Utility source	Liem et al	Cooper et al	4.2.7
Cost sources	PSSRU 2019	PSSRU 2022	4.2.8
Mortality	Logarithmic regression	Parametric curves	4.2.6.4
Treatment waning	Applied at 5 years to MACE	Removed	4.2.6.3
Rescue therapy definition	Narrow	Broad-on-treatment	6.2.3
Rescue rates and IV iron costs	Applied vadadustat rates throughout time horizon	Applied injectable ESA rates to those who discontinued vadadustat due to the stopping rule	6.2.4

Abbreviations: HR, hazard ratio; MACE, major adverse cardiovascular events; PSSRU, Personal Social Services Research Unit

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology was modelled to affect QALYs by:

- Improved MACE events including mortality in company base case.
- Distribution of Hb levels.

Overall, the technology was modelled to affect costs by:

- Drug acquisition costs for vadadustat.
- Reduction in administration costs for vadadustat.

The modelling assumptions that had the greatest effect on the ICER were:

- Treatment discontinuation assumptions.
- MACE events and mortality assumptions.

1.3. The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 1: Appropriateness of pooling data from the two pivotal trials

Report sections	**Sections: 3.2.2.2, 3.2.3.1.**
Description of issue and why the EAG has identified it as important	The two INNO$_2$VATE clinical trials presented in the CS recruited people at different stages of treatment for anaemia in DD-CKD. Therefore, both the baseline characteristics of the trial participants and the treatment aims in the trials primary efficacy periods were not well aligned. This clinical diversity led to inconsistency between the trials in the results of the efficacy outcomes reported. Given the misalignment of the trials and the heterogeneity of the outcome data, the EAG considered it inappropriate for the efficacy data to be pooled for use in the economic model. The INNO$_2$VATE – prevalent trial was nearly ten times larger than the INNO$_2$VATE – incident trial and therefore dominated the pooling/meta-analysis. Consequently, the efficacy data used in the model reflected the efficacy of vadadustat versus darbepoetin alfa in the population recruited to the INNO$_2$VATE – prevalent trial and not those recruited to the INNO$_2$VATE – incident trial.
What alternative approach has the EAG suggested?	The EAG, where possible, has explored analyses for the INNO$_2$VATE - incident and INNO$_2$VATE - prevalent trials separately. However, this was subject to some limitations, for separated data were not made

Report sections	Sections: 3.2.2.2, 3.2.3.1.
	available to the EAG for some model inputs. Therefore, some key inputs still relied on pooled estimates.
What is the expected effect on the cost-effectiveness estimates?	The subgroup analyses explored by the EAG showed that for both the incidence and prevalent populations vadadustat remained dominant over injectable ESAs in the company's base case. Using the EAG's preferred assumptions, however, vadadustat was dominated in the prevalent group, but showed lower costs and QALYs in the incident group, resulting in a cost-effectiveness South-West ICER. These results should be interpreted with caution due to the limited availability of data. It remained unclear how the results may change if all inputs were available to do a thorough subgroup analyses.
What additional evidence or analyses might help to resolve this key issue?	The company could provide the separate inputs, as requested at the clarification stage. In particular, the treatment discontinuation parametric models and transition matrices for Hb levels.

Abbreviations: DD-CKD, dialysis-dependent chronic kidney disease; EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio.

Key Issue 2: Drug discontinuations and the impact of additional medication on a person's pill burden

Report sections	Sections: 2.2, 2.4, 3.2.2.2, CQ A9 and A10, 6.2.5.
Description of issue and why the EAG has identified it as important	A substantially higher proportion of participants in the vadadustat arm of the INNO2VATE – prevalent trial discontinued study drug treatment than in the darbepoetin alfa arm (50.6% versus 36.7%). This was due, in part, to unacceptable toxicity (6.6% versus 3.1%) or lack of efficacy (3.5% versus 0.3%). However, it was reportedly primarily due to participants preferring to switch to a product for which effect and dosing were well known, i.e. their injectable ESA used prior to the trial (12.0% versus 5.8%). After feedback from their clinical experts, the EAG understood the differential in discontinuations between treatment arms may have resulted from the increased pill burden borne by people in the vadadustat arm. They were required to take a further oral drug daily. The EAG noted that an increased treatment burden could lead to poorer medication adherence, and reduced quality of life. Outside of study drug discontinuations, the effects of pill burden were not included in the company's model.
What alternative approach has the EAG suggested?	The EAG explored applying a utility decrement to patients on HD in the vadadustat arm, to account for changes to quality of life associated with pill burden. Details of this scenario can be found in Section 6.2.5.
What is the expected effect on the cost-effectiveness estimates?	The impact of applying a utility decrement did not change the overall conclusion of cost-effectiveness. However, it did decrease the incremental net monetary benefit.
What additional evidence or analyses might help to resolve this key issue?	A review of the literature could be performed to find alternative sources of utility decrement associated with pill burden. These could then be explored in scenario analysis.

Abbreviations: CVD, cardiovascular disease; DD-CKD, dialysis dependent chronic kidney disease; EAG, External Assessment Group; ESA, erythropoiesis-stimulating agent; HD, haemodialysis.

1.4. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 3: Lack of evidence to support differences in MACE

Report sections	Section 4.2.2
Description of issue and why the EAG has identified it as important	A key element of the company's overall differences in life-years was estimated based on the differences assumed regarding the number of major adverse cardiovascular events (MACE), using a HR of 0.96. However, given the non-inferiority design, there was no evidence from the INNO$_2$VATE trials that suggested there is any difference for vadadustat regarding MACE.
What alternative approach has the EAG suggested?	The EAG has removed MACE from their base case (see Key Issue 4 and Section 6.2.1).
What is the expected effect on the cost-effectiveness estimates?	Setting the HR of MACE to 1 in the company's base case results in a South-West ICER of [redacted] (lower incremental costs and QALYs). In addition to other model changes (see Key Issue 4), the EAG's model results in a dominated ICER.
What additional evidence or analyses might help to resolve this key issue?	Further evidence to support a robust MACE improvement for vadadustat would be required.

Abbreviations: EAG, External Assessment Group; HR, hazard ratio; ICER, Incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event.

Key Issue 4: The company's model structure is overly complex

Report sections	Section 4.2.2
Description of issue and why the EAG has identified it as important	The company's model structure was overly complex for the decision problem and evidence base. There were also several model limitations: • The company made an adjustment to account for the median time since dialysis to align the UKRR source with the INNO$_2$VATE trials. The EAG disagreed with how the company had applied this adjustment to both the UKRR source as well as the INNO$_2$VATE trial inputs, rather than just the UKRR source. • The incorporation of MACE events into the health states added complication to the transition matrices. This did not seem necessary, given the lack of evidence to support any difference in MACE (see Section Key Issue 3).

Report sections	Section 4.2.2
	• The model structure did not formally account for Hb levels, which is the primary intention of the intervention. • The model structure created issues in the application of treatment discontinuation in relation to Hb levels. The EAG were concerned that treatment discontinuation was double counted, and the timing of when patients were discontinued in the model meant that the proportion who discontinued treatment for being <100g/L did not align with the proportion of patients with <100g/L in the model at the same cycle.
What alternative approach has the EAG suggested?	The EAG has modified the model structure. This simplified the company's approach, removed the MACE sub-states, and incorporated Hb levels. Further details can be found in Section 6.2.1.
What is the expected effect on the cost-effectiveness estimates?	The EAG's model resulted in a dominated ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG noted that there is no evidence that would resolve the uncertainty associated with the model structure itself, outside of the usual sensitivity analyses.

Abbreviations: EAG, External Assessment Group; Hb, haemoglobin; ICER, Incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event; UKRR, UK Renal Registry.

Key Issue 5: The company's approach to treatment discontinuations is inappropriate

Report sections	Section 4.2.6.6
Description of issue and why the EAG has identified it as important	The company modelled treatment discontinuation using landmark proportions of patients on treatment at each cycle from the INNO$_2$VATE trials. The company also assumed that beyond cycle 4 (week 52), no patients discontinued treatment. The EAG considered this approach unlikely to reflect practice, and that therefore the treatment costs were not captured appropriately. In addition, the company removed a proportion of patients from treatment in the model, in keeping with the licensed stopping rule. However, the company removed patients in cycle 1 (week 11), whereas the SmPC stopping rule should be considered up to 24-weeks. Therefore, the EAG was concerned that the company's approach did not reflect how the stopping rule would be used in clinical practice.
What alternative approach has the EAG suggested?	The EAG considered it more appropriate to use parametric survival models to inform the proportion of patients on treatment per cycle, extrapolated from the INNO$_2$VATE trial data. Scenarios around the long-term treatment discontinuation rates were also explored. This approach was informed by data provided by the company at clarification stage.

Report sections	Section 4.2.6.6
	The EAG has also used the modified model structure (see Key Issue 4), to inform the proportion of patients who would stop treatment due to vadadustat's stopping rule (using data from the INNO$_2$VATE trials to establish which patients did not achieve an adequate response to treatment). This was in line with the SmPC,[1] that indicates that patients with an inadequate response at 24-weeks should discontinue treatment. This approach also meant that patients within the model can discontinue treatment after one year. See Section 6.2.2 for further details of the EAG's preferred approach.
What is the expected effect on the cost-effectiveness estimates?	The scenario using treatment discontinuation parametric models resulted in an ICER of [redacted] using the company's other base case settings. In addition to other model changes (see Key Issue 4), the EAG's model results in an ICER where vadadustat is dominated by the use of injectable ESAs.
What additional evidence or analyses might help to resolve this key issue?	The company provided treatment discontinuation data for up to three years at clarification stage. This showed that within the INNO$_2$VATE trials patients discontinued treatment beyond one year (contradicting the company's assumption of no discontinuation after one year within the model). As such, the EAG considered this an area of uncertainty which could only be resolved with longer-term follow-up data or clinical expert opinion.

Abbreviations: EAG, External Assessment Group; ICER, Incremental cost-effectiveness ratio; SmPC, summary of product characteristics.

Key Issue 6: Appropriateness of treatment waning

Report sections	Section 4.2.6.3
Description of issue and why the EAG has identified it as important	The company assumed a treatment waning effect of vadadustat at five years. After this time point, any treatment effect associated with MACE within the transition probabilities are removed, and the transition probabilities for the injectable ESA arms are applied to the vadadustat arm. No waning effect was applied to the Hb levels. With the company's assumption of no discontinuation from treatment after 52 weeks, and without clinical rationale, it was unclear why a treatment waning effect had been applied. Furthermore, the company did not provide any justification for why a waning effect was considered appropriate to MACE events at 5-years when there was no waning effect applied to Hb levels (with any corresponding impact on HRQoL).
What alternative approach has the EAG suggested?	The EAG has removed the inclusion of MACE from their preferred model structure (see Key Issue 3). This therefore removed the need for any treatment waning application.
What is the expected effect on the cost-effectiveness estimates?	Removing the treatment waning affect from the company's base case had little impact on the ICER and vadadustat remained dominant. In addition to other model changes (see Key Issue 4), the EAG's model resulted in an ICER where vadadustat was dominated by treatment with injectable ESAs.

Report sections	Section 4.2.6.3
What additional evidence or analyses might help to resolve this key issue?	Additional evidence which could support vadadustat having a MACE benefit over injectable ESAs. Also, further evidence to support treatment waning using longer follow-up from the trial.

Abbreviations: EAG, External Assessment Group; ESA, erythropoiesis-stimulating agent; HD, haemodialysis; Hb, haemoglobin; HRQoL, Health-related quality of life; ICER, Incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event

1.5. Summary of EAG's preferred assumptions and resulting ICER

Amendments made to the company's model and base case included:

- Changes based on technical errors and 'matters of judgement' (see Section 6.1)
- Revised model structure (see Section 6.2.1)
  - Including health states for Hb levels using transition probabilities and matched baseline.
  - Removing MACE from the health states.
- Amending the definition of rescue therapy to be 'broad-on-treatment' (see Section 6.2.3).
- Applying injectable ESA treatment specific rescue rates to patients discontinuing vadadustat (see Section 6.2.4).
- Treatment discontinuation using parametric survival curves (see Section 6.2.2).
- Long-term mortality using parametric survival models (see Section 4.2.6.4).
- Changing some cost sources to the latest sources (see Section 6.2.6).
- Change of health-state utility source (see Section 4.2.7.1).

A summary of the EAG's preferred assumptions and resulting ICERs is provided in Table 3.

Table 3: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case			
Amended model post-clarification questions	[redacted]	0.02	Dominant
EAG corrected company base case			
Correcting technical errors and applying EAG's 'matters of judgement' modelling approaches	[redacted]	0.02	Dominant
EAG's preferred base case			
See section 6.3	[redacted]	-0.003	Dominated

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by MEDICE in support of vadadustat (Vafseo®) for treating symptomatic anaemia in dialysis-dependent (DD) adults with chronic kidney disease (CKD). While vadadustat was developed by Akebia Therapeutics, MEDICE is licensed to market the drug in Europe.

2.2. Background

The EAG agreed with the company's description of DD-CKD presented in Section B.1.3.1 of the CS. The EAG considered it important to note that CKD is prevalent in people with diabetes, hypertension, and obesity, and compared with the general population, CKD is associated with an increased risk of cardiovascular disease, decreased health-related quality of life, and premature mortality. Little et al. (2023) used data from the UK Clinical Practice Research Datalink (CPRD) to describe baseline characteristics and rates of adverse clinical events in people with CKD in the UK between January 1, 2004, and December 31, 2017.[2] By the end of the study 3,931 people had DD-CKD and the medical history and comorbidities reported were: angina pectoris 470 (12.0%), coronary artery disease 761 (19.4%), myocardial infarction 322 (8.2%), atrial fibrillation 248 (6.3%), atrial flutter 780 (19.8%), diabetes (type 1 or 2) 1,577 (40.1%), diabetic nephropathy 660 (16.8%), cardiac valve disease 576 (14.7%), dyslipidemia 855 (21.8%), hypertension 2,375 (60.4%), peripheral artery disease 683 (17.4%), thrombosis 423 (10.8%). Treatment of these conditions places a large medication burden on people with DD-CKD. A review found that that the combined pill burden (SD) was 14.6 (7.6) per day in people on haemodialysis (HD) and 14.6 (6.3) in people on peritoneal dialysis (PD).[3] The review also noted that excessive medication burden can lead to poorer medication adherence and reduced quality of life.

2.3. Critique of the company's overview of current service provision

2.3.1. Current care pathway

The company detailed the current clinical pathway of care in Section B.1.3.2 of the CS. The EAG's clinical experts emphasized that a diagnosis of anaemia in CKD is only made after other causes of anaemia have been ruled out. At that point, the treatment pathway presented (Figure 2, Doc B) is the pathway used in the UK.

The pathway describes how anaemia is initially corrected using intravenous (IV) iron. If IV iron does not correct a person's anaemia, then an injectable erythropoiesis stimulating agent (ESA) is considered. The injectable ESAs used for this indication in the UK include erythropoietin, epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta. The EAG's clinical experts explained that all the injectable ESAs had similar efficacy and safety and that Medicines Procurement and Supply Chain (MPSC) (formally Commercial Medicines Units (CMU)) negotiate with suppliers of injectable ESAs to acquire the medication at the lowest cost.

Injectable ESAs are used to correct a person's Hb level. In the initial stages of injectable ESA treatment, a person's haemoglobin (Hb) levels are closely monitored until they reach the recommended target range (100-120 g/L in the UK). When a person's Hb has been corrected, injectable ESA treatment is used to maintain their Hb within the recommended target range. This is achieved through effective monitoring and injectable ESA dose adjustment. When a person leaves the recommended target range they may be offered "rescue therapy" to address this in the short term. This could be an additional dose of an ESA or a red blood cell (RBC) transfusion. The EAG's clinical experts highlighted that these are rare events as small changes in dose in response to monthly monitoring of Hb are usually sufficient to maintain a person's Hb.

The EAG's clinical experts confirmed that if ESA therapy is effective, it would likely continue for the rest of a person's life, or until they receive a kidney transplant. However, a minority of people may develop resistance to injectable ESAs. ESA resistance, or hyporesponsiveness, is a term used to describe people who do not achieve the desired Hb concentration despite higher than usual doses of ESAs or who require increasingly higher ESA doses to maintain an Hb concentration. If a cause for the ESA resistance can be identified, then it is treated. When the ESA resistance cannot be treated, the EAG's clinical experts stated that a person's ESA dose can be increased up to the maximum permitted and, if their Hb is not controlled at the highest dose, then a person receives RBC transfusions.

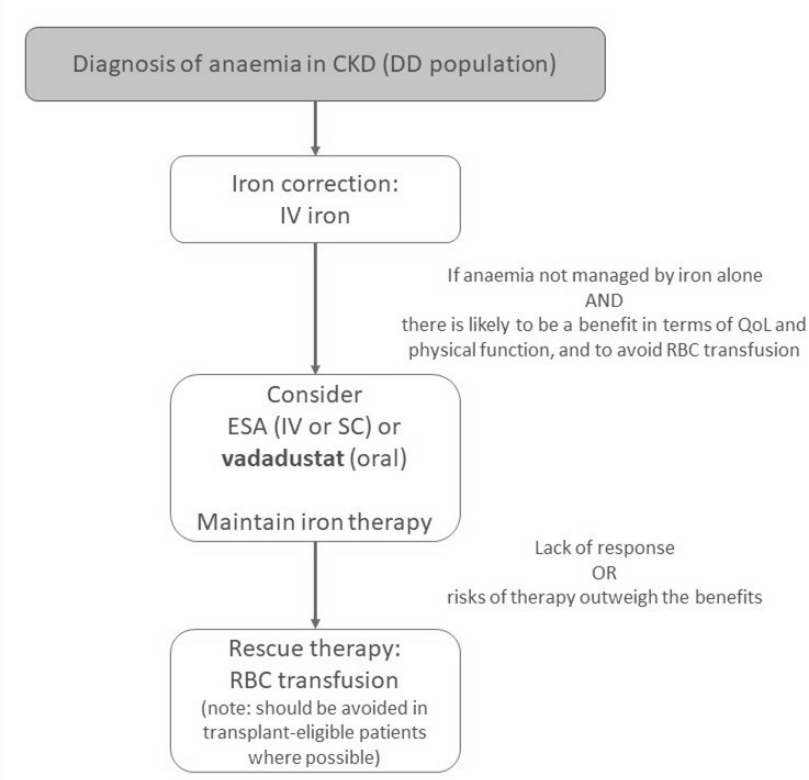
While the above treatments are referred to as injectable ESAs in this report, the EAG's clinical experts explained that people on haemodialysis (HD), whether at home or in hospital, would receive their injectable ESA administered IV into the dialysis lines, rather than needing a separate injection. However, people on peritoneal dialysis (PD), cannot be given an ESA as part of the dialysis. They would need to self-inject or be injected by a family member or a healthcare professional.

An EAG clinical expert stated that in their practice approximately 10% of people with DD-CKD were on PD while the rest were on HD, mainly administered in hospital. A key finding of the UK Renal Registry 25th Annual Report[4] that collected data annually on approximately 70,000 kidney patients on kidney replacement therapy (KRT) in the UK reported that 3,621 adult patients were receiving PD for end-stage kidney disease in the UK on 31 December 2018, which represented 5.5% of the renal replacement therapy (RRT) population.

2.3.2. Proposed positioning of vadadustat

Figure 1 shows the proposed positioning of vadadustat, an hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) enzyme inhibitor (HIF-PHI), as an alternative to injectable ESAs in the treatment pathway for people with DD-CKD. The EAG's clinical experts confirmed this positioning was appropriate given current care. In the positioning proposed by the company, vadadustat could be offered to people as an alternative to injectable ESA treatment to correct their low Hb levels and then used to maintain a person's Hb within the UK recommended target range (100 to 120 g/L).

Figure 1: Proposed positioning of vadadustat in the treatment pathway for people with DD-CKD (reproduced from Doc B, Figure 3)



Abbreviations: CKD, Chronic kidney disease; DD, dialysis-dependent; ESA, erythropoietin stimulating agents; IV, intravenous; QoL, quality of life; RBC, red blood cell; SC, subcutaneous.

The company proposed a range of benefits of using an HIF-PHI over an injectable ESA. These are detailed and critiqued below.

Administration: oral versus injection

The company noted that self-administration of an injectable ESA can pose a challenge for many people and that the NHS was experiencing a severe shortage of medical staff, including qualified nurses required to administer ESAs. However, as noted in Section 2.3.1, the EAG's experts explained that over 90% of people with DD-CKD were on home or hospital HD and the injectable ESA is administered IV into the dialysis lines rather than as a separate injection. Therefore, only those who are on PD, 5.5% of the UK DD-CKD population, would require an IV or SC injection.[4] The EAG experts noted that the population on PD tended to be younger and more able to administer the medication themselves. In the expert's experience 98% of people either self-administer or have a family member administer. Therefore, the EAG do not consider that there would be any significant saving of qualified nurse time (from not having to undertake ESA injections) if an increased use of HIF-PHIs led to a reduction in use of injectable ESAs.

The EAG's clinical experts were also concerned that people who previously received injectable ESAs through HD would not welcome a change to an oral medication. As noted in Section 2.2, a systematic review found that people with DD-CKD had a mean intake of 15 pills per day. People with such a high bill burden may not welcome an additional daily oral medication.

Vadadustat may also be an important treatment option for people resistant to injectable ESAs

Section B.1.3.3 of the CS highlighted a need for alternative treatment for people who were resistant to injectable ESAs. The EAG's clinical experts understood that HIF-PHIs, such as vadadustat and roxadustat, utilised iron through different mechanisms to injectable ESAs. As such, they may be a treatment option in people who are resistant to injectable ESAs. The UK Kidney Association (UKKA) 2024 Clinical Practice Guideline[5] made a recommendation to consider use of HIF-PHIs in people with hyporesponsiveness (resistance) to injectable ESA therapy or underlying inflammation (recommendation 4.7.5). Therefore, the EAG considered this to be a relevant group who may benefit from vadadustat therapy.

However, the INNO$_2$VATE – incident trial excluded people who met the criteria of injectable ESA resistance within eight weeks prior to or during screening. Similarly, the INNO$_2$VATE – prevalent trial only included people who were currently maintained on ESA therapy and excluded people with hypersensitivity to darbepoetin alfa. Given these criteria, the EAG considered people with resistance to injectable ESAs were excluded from the trials and hence there is no evidence for this population in the CS.

Home therapies

The company stated that despite NICE recommending that all patients who were suitable for home therapies were offered the choice, fewer than 10% of the UK's Kidney Replacement Therapy patient population were on home therapies. They posited that an oral medication may encourage more people to choose home therapies. The EAG's clinical experts did not expect this to be the case. They reasoned that the main barrier to home therapies was the confidence of the person using the dialysis equipment, and in particular, using it unsupervised. If a person were comfortable using the equipment, then whether their therapy was oral rather injectable would not play a role in their decision to use home therapies. Also, if a person decided to switch to home HD, then their injectable ESA would be administered IV into the dialysis lines, rather than as a separate injection.

Delivering injections

The EAG's clinical experts noted that there was an infrastructure built around injectable delivery resources. This included the people who work in the marshalling, provision, and delivery of ESA injections. In Section B.1.3.1.5 of the CS, the company expanded on the healthcare resources involved in DD-CKD care, including storage and delivery of ESA injections. The EAG agreed that a move to an oral therapy does not require cold-chain storage, with its associated risks of wastage and quality degradation.

2.4. Critique of company's definition of decision problem

A summary of the decision problem for this appraisal, and the EAG's appraisal of how the CS addresses it, is shown in Table 4.

The population in the final scope issued by NICE was adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis. The company

defined the population differently in the decision problem table in the CS (see Table 1, Doc B). However, at the clarification stage the company agreed the population could be defined as 'Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis' to align with the MHRA marketing authorisation.[6]

The intervention in the final scope[7] was vadadustat, an HIF-PHI, and this was the intervention addressed in the CS. Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor and is a film-coated tablet for oral administration. The starting dosage used in the pivotal trials, $INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent, was 300 mg once daily. Dose increases of 150 mg were permitted once every four weeks up to a maximum of 600 mg, and dose decreases of 150 mg could occur more frequently. The regimen was in line with the marketing authorisation granted by the MHRA.[6]

The comparators in the final scope were injectable ESAs. Epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta were used in the UK for treatment of people with DD-CKD. The injectable ESA used in the $INNO_2VATE$ trials was darbepoetin alfa, which was administered IV into the dialysis lines as part of HD, or subcutaneously (SC) / IV for people using PD.

In the pivotal trials, all the outcome measures specified in the scope were measured, except for health-related quality of life (HRQoL). The company stated that HRQoL data were not collected for the $INNO_2VATE$ trials. Instead, the company assumed that the HRQoL associated with the use of vadadustat was at least the same as observed for injectable ESAs. This is further explored in Section 4.2.7. Outcomes were often not reported clearly or consistently. For example, the additional therapy through IV iron outcome analysis was not presented in the clinical section of the report, and major adverse cardiovascular events (MACE) and hospitalisation outcomes were not reported separately for each trial. However, the company did present MACE and hospitalisation outcomes separately for each pivotal trial at the clarification stage (Question A7). This is discussed in relation to the economic model in Section 4.2.6.3.

The final scope issued by NICE requested subgroup analysis according to previous exposure to ESAs, if the evidence allowed. The two pivotal trials presented data in people at different stages of the treatment pathway, with differing exposure to ESA therapy. Subgroup data were reported for 192 (52.0%) people in the $INNO_2VATE$ - incident trial who were naïve to ESA treatment at baseline. At the clarification stage (Question A4), the EAG requested data on this subgroup to allow their assessment through the economic model. However, these data were not provided

and the EAG's attempts to provide cost-effectiveness for the different trials separately was subject to limitations as not all the inputs were included in the model by trial. See Section 6.2.7 for further details.

Special considerations, including issues related to equity or equality, were noted in the CS. The company stated that self-administration of an injectable ESA posed a challenge to people and that the NHS was experiencing a severe shortage of medical staff, including for the qualified nurses required to administer injectable ESAs. As addressed in Section 2.3.2, the EAG's clinical experts explained that, while self-administration of injectable ESAs could be a challenge, 98% of people either self-administer or have a family member administer. However, they also agreed that an HIF-PHI, which could be easily stored, may be preferred to an injectable ESA by people on PD who cannot receive the injectable ESA administered IV into the dialysis lines.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with symptomatic anaemia associated with chronic kidney disease (CKD) on chronic maintenance dialysis	Adult patients with anaemia in chronic kidney disease (CKD) who are on dialysis	Population is aligned with the NICE scope	The company confirmed at the clarification stage (Question A1) that the difference in phrasing was an oversight, and the CS was submitted in line with the population detailed in the final scope issued by NICE.
Intervention	Vadadustat	Vadadustat	N/A	The intervention in the pivotal trials was vadadustat, an HIF-PHI. The dose used in both $INNO_2VATE$ trials was in line with the marketing authorisation granted by the MHRA.
Comparator(s)	Erythropoiesis stimulating agents (ESAs)	Erythropoiesis stimulating agents (ESAs)	N/A	The EAG understood these to be “injectable” ESAs. The injectable ESA used in the pivotal trials was darbepoetin alfa and the initial dose given was based on the previous dose or, in the case of people who had not received darbepoetin alfa before, on information on the product label.
Outcomes	The outcome measures to be considered include:	The outcome measures include: • Haemoglobin response	The clinical trial programme of vadadustat did not collect health-	The EAG further explore the assumptions linked to HRQoL outcome data in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Haemoglobin (Hb) response • Maintenance of haemoglobin levels • Use of additional therapy (including blood transfusion and intravenous iron) • Hospitalisation • Mortality • Adverse effects of treatment including major adverse cardiovascular events • Health-related quality of life (HRQoL)	• Maintenance of haemoglobin levels • Use of additional therapy (including blood transfusion and intravenous iron) • Hospitalisation • Mortality • Adverse effects of treatment including major adverse cardiovascular events	related quality of life (HRQoL) data. However, published literature has been used to support the input of EQ-5D data into the economic model. MEDICE assumes that the HRQoL associated with the use of vadadustat is at least the same as observed for ESAs, with potential additional benefits expected for vadadustat due to oral administration route.	Section 4.2.7. The EAG recognised that data were collected for all of the other outcome measures in the two pivotal trials. However, these data were not always reported clearly and consistently, and this is discussed in Section 3.2.2.6.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	As per NICE scope	N/A	As per the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account			
Subgroups	If the evidence allows subgroups according to previous exposure to erythropoiesis stimulating agents will be considered	The following subgroups are presented: • Hb stratification level at baseline • Geographical region • New York Heart Association (NYHA) Congestive Heart Failure (CHF) stratification level • Target Hb level • Demographics and medical history (age, sex, race, presence of diabetes mellitus and hypertension) • Baseline laboratory measurements (C-reactive protein, baseline TSAT and baseline ferritin)	The pivotal trial programme for vadadustat was designed as two separate non-inferiority open-label randomised controlled trials (RCTs) to support the broader target population approved in its label for dialysis-dependent patients requiring correction and maintenance of Hb levels (limited exposure to ESAs) as well as maintenance of Hb levels (already receiving ESAs). Based on data available from the pivotal trials, no clinically meaningful differences between ESA and vadadustat are	More than half of the participants in the $INNO_2VATE$ – incident trial were not on an injectable ESA at baseline. The EAG understood this subgroup to be naïve to ESA therapy. The company presented outcome data for this subgroup in the CS and further safety data at the clarification stage (Question A4).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			anticipated and MEDICE do not expect the available evidence to substantiate subgroup analyses	
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	MEDICE believe that access to an oral option could reduce inequalities in access to care for dialysis-dependent (DD) CKD patients given that: • This disease is multi-comorbid in nature and its severity may vary among patients, thereby limiting their ability to access optimal anaemia care required for ESA administration. Although home haemodialysis (in possible cases) offers many advantages to patients in terms of convenience, self-administration of an injectable ESA may pose as an additional challenge for many patients. • Patients opting for peritoneal dialysis can be anxious and have a great deal of information and equipment to manage. An oral option would be preferable to many patients. Patient choice, patient empowerment and treatment delivery are crucial for equity and equality.	MEDICE believes NHS patient access to vadadustat is of reasonable urgency as it will offer benefits to both patients and the NHS that are tangible in nature in terms of convenience and cost-savings via averted resource use	The EAG's clinical experts explained that in the majority of people (those on HD) injectable ESAs were administered IV into the dialysis lines rather than as a separate injection. However, they also noted that an oral medication that can be easily stored would benefit those who are on PD and cannot receive an injectable ESA as part of their dialysis. They further clarified that there was a lot of infrastructure in place to deliver injections and many people were involved in marshalling, delivering, and nursing the service.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		• NHS is currently experiencing a severe shortage of medical staff (1, 2), including qualified nurses required to administer ESAs. • Vadadustat may also be an important treatment option for patients resistant to ESAs. The new UKKA Guidelines 2024 recommend starting a HIF-PHI in patients with inadequate response to high, escalating doses of ESAs (3). • Despite NICE recommending that all patients who are suitable for home therapies are offered the choice (4), less than 10% of the UK's Kidney Replacement Therapy patient population are on home therapies (5), and there is a lack of equity in which patients are offered them (6).		

Abbreviations: CKD, chronic kidney disease; DD, dialysis-dependent; EAG, External Assessment Group; ESA, erythropoiesis-Stimulating Agents; HD, haemodialysis; HIF-PHI, Hypoxia-inducible factor–prolyl hydroxylase inhibitors; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence MHRA; PD, peritoneal dialysis; RCT, randomised controlled trial; TSAT, Transferrin saturation.

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify RCTs that have measured the efficacy and safety of vadadustat and injectable ESAs for treatment of adults with anaemia in chronic kidney disease who are dialysis dependant (DD-CKD).

The EAG found the company's SLR to use appropriate searches (while noting some weakness with the study-type filters used – see Table 5), inclusion criteria and screening to identify relevant studies. In Section D.7.1 of the CS, the company stated that six relevant clinical trials were included in the review. However, the company hand selected two eligible trials to be included and excluded four trials using unknown criteria.

Two of the excluded trials, FO_2CUS (NCT04707768)[8] and MT-6548-J03 (NCT03439137),[9-11] were excluded as they were "conducted in different geographies (namely the US and Japan, respectively)". However, this was not an exclusion criterion in the protocol and the EAG's clinical experts were not aware of any reason why trials conducted in the US or Japan would not be relevant to the UK. They were also not aware of any differences in efficacy of treatment for anaemia in CKD related to a person's ethnic background.

At the clarification stage, the company explained that the dosing regimen used in the FO_2CUS trial was different to the dosing regimen specified in the SmPC. The EAG considered this to be a valid reason to exclude the trial from the SLR. The company reiterated at the clarification stage that MT-6548-J03 was excluded because there were differences in 1) subject characteristics and 2) the different endpoints it analysed compared to those analysed in the pivotal global studies. They also correctly noted that the MHRA did not discuss MT-6548-J03 in full in the summary of product characteristics (SCE) "due to differences in subject characteristics and endpoints analysed".[12] However, the EAG understood the population to be relevant to the decision problem and, in the opinion of the EAG, the efficacy endpoints were aligned with the pivotal trials.

Two further excluded trials, FO_2RWARD-2 (NCT03799627)[13] and AKB-6548-CI-0018 (NCT03140722),[14] were excluded because they were phase II trials and so "superseded" by the $INNO_2$VATE trials. However, phase II trial were not an exclusion criterion in the protocol. At the clarification stage, the company noted that the AKB-6548-CI-0018 trial enrolled two people and

was terminated. It was unclear why the trial was terminated but the EAG consider this was a valid reason for excluding the trial from the SLR. The company continued to exclude the FO_2RWARD-2 trial at the clarification stage and noted that it was conducted in the US and there were "potentially significant patient demographic and healthcare system disparities versus the European or English setting". As noted above, the EAG's clinical experts were not aware of any reason why RCTs conducted in the US would not be relevant to UK care. However, the company trial was not published at the time of writing and the company did not have access to the results. The EAG accepted that it was reasonable to exclude the trial given it could not be accessed.

Therefore, the EAG considered that the MT-6548-J03 trial were incorrectly excluded from the SLR, for reasons not stated in the protocol. The EAG consequently considered there to be a risk of bias in the SLR as a relevant trial was incorrectly excluded from the analyses.

The two trials the company selected for the submission were $INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent. The EAG considered the data extraction methods and tool for quality assessment used in the SLR to be appropriate. However, the company did not report any methods for the evidence synthesis used, either in Appendix D or Section B.2.8 (Meta-analysis) of the CS. The EAG understood, after interrogating how the efficacy data was used in the model, that the two trials were pooled as if these data came from a single trial. It is understood that compared to standard meta-analysis, the treat-as-one-trial method disregards between-study variation. This leads to estimation of narrower confidence intervals than may be warranted. The EAG did not consider it was appropriate to treat the $INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent as a single trial as they had different eligibility criteria and did not share the same trial locations. It is best practice to employ a meta-analytic approach that takes into account between-study variability, given the differences in the people recruited into each trial.

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	D.1	The company conducted an SLR for clinical evidence in MEDLINE, Embase, and Cochrane (all through OvidSP), and from five conference series (ASN, ERA/EDTA, NKF, ISPD, ISPOR and UKKW). There were complemented by hand searches and searches of clinical trial registries. The search terms used for the population and intervention were reasonable. However, it was unclear if any study

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		type filters were used. While the search filter for RCTs was probably adequate, the search terms used for prospective and controlled clinical studies were insufficient. Therefore, relevant cohort or controlled studies were likely to have been missed. The EAG also noted some inconsistencies in the PRISMA diagrams, although these were corrected post clarification.
Inclusion criteria	D.1.5.1	The inclusion criteria were appropriate for the decision problem
Screening	D.1.5.2	Appropriate: the publications were screened by two reviewers, with conflicts resolved by a third independent reviewer
Selection of included trials	D.1.7	The company found six relevant clinical trials met the inclusion criteria. However, the company hand selected two eligible trials to be included and excluded four using unknown criteria. At clarification, the EAG established that two trials could be excluded for a valid reason but considered the MT-6548-J03 and FO2RWARD-2 trials were incorrectly excluded from the SLR.
Data extraction	D.1.6	Appropriate: data extraction was performed by a single reviewer and quality checked by a second reviewer to ensure accuracy
Tool for quality assessment of included study or studies	D.1.7.3	Appropriate: the quality assessment of the included RCTs was performed using the Cochrane Risk of Bias tool (RoB 2) for RCTs.[15]
Evidence synthesis	NR	Evidence synthesis methods were not reported in Appendix D with the other SLR methods and in "Meta-analysis" (Section B.2.8), the company do not address how data in the two included trials were pooled. The EAG were aware from the model that the data were pooled using the treat-as-one-trial method. The EAG considered this method was inappropriate. It disregarded study-to-study variation leading to narrower confidence intervals.

Abbreviations: CS, Company submission; EAG, External Assessment Group; RCT, randomised controlled trial; SLR, systematic literature review.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described two trials (Table 6) of vadadustat versus injectable ESAs:

- $INNO_2VATE$- incident[16,17]
- $INNO_2VATE$ - prevalent[16,18]

As noted in Section 3.1, the company identified four other trials that met the inclusion criteria, and that the EAG considered that one of these trials (MT-6548-J03[9]) was inappropriately excluded from the SLR. MT-6548-J03 was a phase III, randomised trial that recruited 323 people and concluded that vadadustat was as effective as darbepoetin alfa in maintaining mean Hb levels within the target range for up to 52 weeks, and that it was well tolerated with no new safety concerns identified.

The EAG noted that the conclusions of the MT-6548-J03 matched those of the $INNO_2VATE$ trials, indicating similar results. Therefore, while the EAG had some concerns over the risk of bias of the SLR due to excluding a relevant RCT, it was not expected to have a meaningful impact on the efficacy and safety results.

Table 6: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator
INNO2VATE – incident (NCT02865850)	Phase III, randomised, open-label, sponsor-blinded, active-controlled, multicentre, non-inferiority study	Patients with anaemia who have recently initiated dialysis treatment for DD-CKD	Vadadustat	Darbepoetin alfa
INNO2VATE – prevalent (NCT02892149)	Phase III, randomised, open-label, sponsor-blinded, active-controlled, multicentre, non-inferiority study	Patients with anaemia who have dialysis treatment for DD-CKD	Vadadustat	Darbepoetin alfa

Abbreviations: RCT, randomised controlled trial; DD-CKD, dialysis-dependent chronic kidney failure.

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

$INNO_2VATE$- incident and $INNO_2VATE$ - prevalent were both phase III, randomised, open-label, sponsor-blinded, active-controlled, multicentre, non-inferiority trials. $INNO_2VATE$- incident had centres in North America, South America, Europe and Asia, but no centres in the UK. $INNO_2VATE$- prevalent had centres in North America, South America, Europe, Asia, and Australasia, with five centres in the UK.

People were randomised to treatment or control, stratified according to geographic region (United States versus Europe versus other regions), New York Heart Association (NYHA) heart failure classification (class 0 or I versus class II or III), and Hb concentration at trial entry ($INNO_2VATE$- incident trial: <95 versus ≥95 g/L; $INNO_2VATE$- prevalent trial: <100 vs. ≥100 g/L). Following randomisation, the company noted four periods during each of the trials:

- Correction/Conversion Period (Weeks 0 to 23): initial period on study medication.
- Maintenance Period (Weeks 24 to 52): period on study medication during which efficacy was be assessed (primary evaluation period: Weeks 24 to 36; secondary evaluation period: Weeks 40 to 52).
- Long-term Treatment Period (Week 53 to until week 182 / EOT): continued study medication to assess long-term safety.
- Follow-up Period (EOT + 4 weeks): post-treatment visits for safety (either in person or via telephone).

A point of care device (HemoCue) was used throughout the studies to monitor Hb. Hb levels were used to determine if the dose of study medication (vadadustat or darbepoetin alfa) would need to be adjusted or interrupted. From weeks 0 to 12, Hb was monitored every two weeks. From Week 12 to Week 52, Hb was monitored every four weeks. Monitoring of Hb continued from Week 53 through to the end of the study. Haemoglobin was also assessed via a complete blood count through the central laboratory for efficacy and safety evaluations (although dose adjustments were based on the point of care device Hb value).

3.2.2.2. Population

Trial eligibility criteria

The people recruited to INNO$_2$VATE- incident were adults with anaemia who had initiated chronic maintenance dialysis (either peritoneal dialysis (PD) or haemodialysis (HD)) for CKD within 16 weeks prior to screening. They were required to have a mean screening Hb between 80 and 110 g/L. The EAG's clinical experts explained that the people recruited to INNO$_2$VATE- incident were at an early phase of treatment, at a time when most would need a correction of their Hb levels to the recommended target range. This target range was "geography specific" and was a Hb level of 100 g/L to 110 g/L in the United States (US) and 100 g/L to 120 g/L outside of the US. Once their Hb was corrected then the aim of treatment was maintenance within the geography specific recommended target range.

The people recruited to INNO$_2$VATE- prevalent were people with anaemia who had received chronic maintenance dialysis (either PD or HD) for CKD for at least 12 weeks prior to screening, and were currently maintained on ESA therapy with a dose received within six weeks prior to or during screening. Similar to INNO$_2$VATE- incident, they were required to have a mean screening Hb between 80 and 110 g/L. The EAG's clinical experts explained that the people recruited to the INNO$_2$VATE – prevalent trial would be on a stable dose of injectable ESA treatment and the majority of people recruited would already be within, or close to, the geography specific target range. Therefore, the aim of treatment in this population was maintenance of Hb levels, rather than their correction.

The company claimed at the clarification stage (Question A3) that the two trials, when combined, would be reflective of the real-world target population eligible for vadadustat. This would equate to 10% of people at an early stage of ESA treatment who require correction of their Hb levels and 90% who require maintenance of their Hb levels. It was unclear to the EAG whether these proportions accurately reflected the DD-CKD population in the UK.

Baseline characteristics

The baseline characteristics of people recruited to INNO$_2$VATE – incident were presented in Table 6 (Document B), and for INNO$_2$VATE – prevalent in Table 9 (Document B).

In the INNO$_2$VATE- incident trial, there were no notable differences between the baseline characteristics of people randomised to vadadustat compared to those randomised to

darbepoetin alfa. In line with the expectations of the EAG's clinical experts, the mean (SD) baseline Hb was 92.8 g/L (11.1), which was below the recommended target range and required correction. Prior to the trial beginning, 92 (50.8%) of people in the vadadustat arm and 85 (45.2%) of people in the darbepoetin alfa arm, were using injectable ESAs, and the mean (SD) time since diagnosis with CKD was 4.5 (6.9) years. Most people (327, 88.6%) were on in-centre HD, 38 (10.2%) people were on PD, and 4 (1.1%) were unknown or had used both. The time (SD) since dialysis was initiated was 0.14 (0.09) years in the vadadustat arm and 0.15 (0.28) in the darbepoetin alfa arm.

In the INNO$_2$VATE – prevalent trial, there were no notable differences between the baseline characteristics of people randomised to vadadustat compared to those randomised to darbepoetin alfa. The mean (SD) baseline Hb was 102.4 g/L, which was within the recommended target range and required maintenance rather than correction. Prior to the trial, all participants were using injectable ESAs, and the mean (SD) time since diagnosis with CKD was 6.8 (6.5) years. Most people (3,285, 92.4%) were on in-centre HD, 280 (7.9%) people were on PD, and 35 (1.0%) were unknown or using a combination. The mean (SD) time since dialysis was initiated was 4.0 (4.0) years in the vadadustat arm and 3.9 (4.0) in the darbepoetin alfa arm.

Dropouts

The company presented the CONSORT flow diagrams for the two pivotal trials in Figures 3 and 4 in Section D.2 of the CS.

INNO$_2$VATE – incident trial

In the INNO$_2$VATE – incident trial, 21 (11.6%) of the participants in the vadadustat arm discontinued from the study, 15 due to death, three withdrew informed consent, and three were lost to follow-up. In the darbepoetin alfa arm 23 (12.2%) discontinued from the study, 19 people due to death, two withdrew informed consent, and two were lost to follow-up. By the end of study (182 weeks), 60 (33.1%) people in the vadadustat arm and 49 (26.1%) in the darbepoetin alfa arm had discontinued treatment.

The reasons for discontinuing treatment were presented in Section D.2 of the CS. Fifteen people in the vadadustat arm discontinued due to unacceptable toxicity compared to six people in the darbepoetin alfa arm. One person in the vadadustat arm discontinued due to lack of efficacy and zero people in the darbepoetin alfa arm. A notable difference in reasons for

discontinuation between treatment arms was “subject no longer wishes to receive study drug”. Twenty people discontinued for this reason in the vadadustat arm and ten in the darbepoetin alfa arm. It was not clear to the EAG why people would no longer wish to receive a study drug when, for them, it was effective and did not offer unacceptable toxicity. The EAG requested clarification on this (Question A9). The company stated that the most frequent reasons for discontinuations suggested that people preferred to switch to a drug for which effect and dosing were well known. The EAG understood this to mean people switching from vadadustat, or less commonly darbepoetin alfa, back to the injectable ESA they were using prior to the trial.

INNO$_2$VATE – prevalent trial

In the INNO$_2$VATE – prevalent trial, 352 (19.8%) of the people in the vadadustat arm discontinued from the study, 262 due to death, 53 withdrew informed consent, and 37 were lost to follow-up. In the darbepoetin alfa arm 356 (20.0%) people discontinued from the study, 278 due to death, 47 withdrew informed consent, and 31 were lost to follow-up.

By the end of the study (182 weeks), the EAG noted that overall study drug discontinuations were substantially higher in the vadadustat arm than the darbepoetin alfa arm. In the vadadustat arm, 899 (50.6%) people discontinued the study drug treatment, while in the darbepoetin alfa arm, 653 (36.7%) discontinued the study drug treatment. Ninety-nine people discontinued in the vadadustat arm due to unacceptable toxicity compared to 55 people in the darbepoetin alfa arm. Sixty-three people in the vadadustat arm discontinued due to lack of efficacy compared to five people in the darbepoetin alfa arm. A notable difference in reasons for discontinuation between treatment arms was “subject no longer wishes to receive study drug”. In the vadadustat arm, [redacted] people discontinued for this reason compared to [redacted] in the darbepoetin alfa arm. The EAG likewise requested clarification on this (Question A10), and again, the company stated that the most frequent reasons for discontinuations suggested that people preferred to switch to a drug for which effect and dosing were well known. The EAG understood this to mean people switched from vadadustat, or less commonly from darbepoetin alfa, back to the injectable ESA they were using prior to the trial.

The EAG’s clinical experts reasoned that for both trials, vadadustat discontinuations may be linked to the additional pill burden of a daily oral drug. Prior to the trial more than 90% of participants were on HD and their injectable ESA was administered IV into the dialysis lines, and as such, was not associated with increased medication burden. As noted in Section 2.2, a systematic review found that the mean pill burden of people with DD-CKD was 15 pills per day.

People who were randomised to vadadustat had an additional daily pill on top of the pills they were already taking. The review also found that excessive medication burden led to poorer medication adherence, and reduced quality of life.

3.2.2.3. Intervention

People randomised to vadadustat initiated dosing at two tablets (300 mg) once daily at the baseline visit. The dose levels of vadadustat utilised in the studies were 150, 300, 450, and 600 mg (available tablet strength was 150 mg). A person's dose was adjusted or interrupted based on regular monitoring using a point of care device. The EAG noted that the investigator was able to dose outside the Interactive Web Response (IWR) system dosing recommendation at their discretion.

3.2.2.4. Comparator

The ESA used in the $INNO_2VATE$ trials was darbepoetin alfa, which was administered subcutaneously (SC) or intravenously (IV). The EAG understood it was either administered during HD (at home or hospital) or self-administered by people using PD. Sixteen (8.6%) of people in the darbepoetin alfa arm of the $INNO_2VATE$- incident trial, and 143 (8.0%) of people in the darbepoetin alfa arm of the $INNO_2VATE$ – prevalent trial, were using PD during the trial.

The company stated that the initial dose was based on the previous dose or, in the case of people who had not received darbepoetin alfa before randomisation, on information in the product label. Hb was monitored via a point of care device throughout the study to determine if the dose of darbepoetin alfa would be adjusted or interrupted. Adjustments to doses of darbepoetin alfa were guided by an IWR system based on Hb concentration and a programmed dose adjustment algorithm based on the approved local product label for adult patients with CKD on dialysis. Details of the algorithm could be found in the protocol for the $INNO_2VATE$ trials.[19] The EAG noted that the investigator was able to dose outside the IWR system dosing recommendation at their discretion.

3.2.2.5. Outcomes

The outcomes reported in the pivotal trials with respect to the NICE final scope are summarised in Table 7. The EAG noted that the trial collected data on people for 182 weeks (3.5 years) from baseline, but limited data were available after the secondary efficacy period (weeks 40 to 52).

Table 7: Outcomes reported in the included trials of the technology

	INNO$_2$VATE- incident	**INNO$_2$VATE – prevalent**
Haemoglobin response	✓	✓
Maintenance of haemoglobin levels	✓	✓
Use of additional therapy (including blood transfusion and intravenous iron)	✓ RBC transfusion × IV iron*	✓ RBC transfusion × IV iron*
Hospitalisation	✓	✓
Mortality	✓	✓
Adverse effects of treatment including major adverse cardiovascular events	✓	✓
Health-related quality of life	×	×
Additional outcomes	✓ Change from baseline in iron-related parameters ✓ Change from baseline in serum glucose and lipid parameters	✓ Change from baseline in iron-related parameters ✓ Change from baseline in serum glucose and lipid parameters

Abbreviations: IV, intravenous; RBC, red blood cells.

* IV iron rescue therapy in each arm of the trial at five timepoints as a clinical parameter and variable for the economic model in Section B.3.3.5 of the CS. However, this outcome was not detailed in the clinical section of the report and no formal analysis was presented.

Haemoglobin response / maintenance of haemoglobin levels

Outcome measures were reported in the CS that assessed the Hb response to treatment and the maintenance of a person's Hb levels. The company reported change from baseline in Hb and the number of people who were within the recommended target range. These outcomes were reported at 24 to 36 weeks and 40 to 52 weeks.

In Table 10 (Document B), the company prespecified a non-inferiority margin for the mean Hb change from baseline in the INNO$_2$VATE trials. Non-inferiority was established based on a 95% confidence interval (CI) for the difference between the vadadustat group and darbepoetin alfa and using a noninferiority margin of -7.5 to 7.5 g/L. The EAG considered this to be reasonable for analysis of the INNO$_2$VATE trials if the company were unable to source a validated minimum clinically important difference.

In Appendix M of the CS, the company quoted a non-inferiority margin of -15% to 15% in for the proportion of patients with average Hb value within geography-specific target range. The EAG was unable to critique this methodology because no details of how this non-inferiority margin was formulated were presented in the CS. The EAG was also concerned that this non-inferiority margin was not prespecified in the trial protocols. Use of additional therapy (including blood transfusion and intravenous iron)

The company presented outcomes assessing use of additional therapy during the trial. People were given what the company has termed "rescue therapy" – using injectable ESAs or red blood cell (RBC) transfusion – based on guidelines provided in the trial protocol.[19] The company categorised rescue therapy as "narrow rescue therapy" and "broad-on-treatment rescue therapy". The EAG requested clarification on the definitions of narrow rescue therapy and broad-on-treatment rescue therapy at the clarification stage (Question A8).

ESA rescue therapy: ESA narrow rescue therapy was given due to low Hb (<95 g/L) and/or worsening of symptoms of anaemia (i.e. shortness of breath, fatigue, weakness, headaches, and dizziness). The EAG understood broad-on-treatment rescue therapy with ESAs to be any use of ESAs, outside of the trial comparator dose.

RBC transfusion: The company did not clearly define narrow rescue therapy or broad-on-treatment rescue with RBC transfusions. However, the EAG understood from the response to clarification question A8 that narrow rescue therapy were instances where there were either worsening of anaemia (low Hb) or moderate to severe symptoms of anaemia. Broad rescue therapy also included instances where in the event of an acute or severe loss of blood, an RBC transfusion was administered as clinically indicated using their local institution's transfusion guidelines.

Intravenous iron: The company reported the proportion of patients receiving IV iron rescue therapy in each arm of the trial at five timepoints as a clinical parameter and variable for the economic model in Section B.3.3.5 of the CS. However, this outcome was not detailed in the clinical section of the report and no formal analysis was presented.

Hospitalisation: The company provided hospitalisations for heart failure in in each treatment arm in each pivotal trial at the clarification stage (Question A7).

Mortality: The company provided the mortality outcomes in each treatment arm in each pivotal trial at the clarification stage (Question A7).

Adverse effects of treatment including major adverse cardiovascular events

The company collected safety data, including major adverse cardiovascular events (MACE), during the $INNO_2VATE$ trials. Summaries of TEAEs in each trial were presented in Section B.2.10 of the CS. In Table 13 in Appendix F of the CS, the company also presented detailed summaries of TEAEs, MACE, and TEAEs linked to mortality, in a combined summary of both pivotal trials. At the clarification stage (Question 7), the company presented these data separately for each $INNO_2VATE$ trial.

Health-related quality of life

No health-related quality of life (HRQoL) data were collected in the $INNO_2VATE$ trials.

Additional outcomes

The company presented change from baseline in iron-related parameters. These included hepcidin, ferritin, total iron-binding capacity, serum iron, and transferrin saturation. The EAG's clinical experts said that ferritin, serum iron, and transferrin saturation were commonly measured. The company also presented change from baseline in serum glucose and the following lipid parameters: glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The EAG's clinical experts indicated that these factors were useful for assessing CV risk, and while this was relevant to the DD-CKD population given the number of people with hypertension and type 2 diabetes, it was not directly related to their anaemia.

Statistical analysis

In Table 10 (Document B), the company defined the analysis sets used in the CS:

- Randomised population: all patients randomised. Analyses of this population was based on the randomised treatment.
- Full analysis set (FAS) population: all people in the randomised population who received at least one dose of study drug and had at least one post-dose Hb measurement. Analyses of this population was based on the randomised treatment.

- Per protocol (PP) population: all randomised people who received study drug during the primary efficacy period (weeks 24 to 36), had at least one Hb assessment during the primary efficacy period (weeks 24 to 36), and had no critical or major protocol deviation affecting the primary endpoint analyses, i.e., prior to week 36. Analyses of this population was based on actual treatment received.

- Safety population: all people in the randomised population who received at least one dose of study drug. Analysis of this population was based on the actual treatment received. Patients who received in error both vadadustat and darbepoetin alfa (excluding rescue therapy) were classified by the more frequently received study drug.

Efficacy analyses utilised the randomised, FAS population, and PP populations while safety analyses (including MACE) utilised the safety population.

In Table 10 (Document B), the company stated that the assessment of the primary outcome and secondary outcomes involved analysis of covariance (ANCOVA) with multiple imputation for missing data. Further details of this analysis were presented in Appendix B of the $INNO_2VATE$ trials protocols.[19] Standard multiple imputation was used, where imputation of missing values was based on the group to which the patient was randomized. The EAG understood the analysis used to be appropriate but noted that the analysis did not address underpinning issues in the trials about attrition.

3.2.2.6. Critical appraisal of the design of the studies

The company presented a quality assessment of the two $INNO_2VATE$ trials in Section D.1.7.4 of the CS using the Cochrane Risk of Bias tool (RoB 2).[15] The company had some concerns over the quality of the studies, due to unclear allocation concealment. All other domains were determined to be at low risk.

Table 8: Risk of bias summary for individual studies presented in studies (reproduced from Table 12, Appendix D)

Trial ID	Was the randomisation method adequate?	Was the allocation adequately concealed?	Were participants and investigators blind to exposure and comparison?	Were outcomes assessors blinded?	Were drop-outs between groups adequately explained? Were unexpected imbalances adjusted for?	Were all outcomes adequately reported?	Did study appear free from other sources of bias?
$INNO_2VATE$ 2021 (incident and prevalent trial)	Yes	Unclear	No	Yes	Yes	Yes	Yes

The EAG assessed the risk of bias of the $INNO_2VATE$ trials and presents a summary below.

Domain 1: Risk of bias arising from the randomization process: The trial protocol stated that randomisation and allocation were undertaken using an Interactive Web Response (IWR) system. The EAG understood this to be an appropriate random sequence generation process and the allocation sequence was concealed. The baseline characteristics of participants did not suggest a problem with the randomisation process.

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

The trials were open label and the people in the trial and the treating physicians were aware of the treatment they were receiving or administering. The participants were at risk of altered health-related behaviours based on the treatment they were receiving. In addition, the carers and people delivering the interventions were aware of the assigned intervention and they were at risk of altering administration of non-protocol interventions based on the assigned intervention. Therefore, the EAG had some concerns for risk of bias due to deviations from the intended interventions.

Domain 3: Missing outcome data

Five (1.4%) participants in the $INNO_2VATE$ – incident trial and 68 (1.9%) of participants in the $INNO_2VATE$ – prevalent trial were lost to follow-up. The proportions were very similar between

treatment arms. The EAG considered the trials to be at low risk of bias due to missing outcome data.

Domain 4: Risk of bias in measurement of the outcome

The EAG understood the methods of outcome measurement were suitable. While the trial was open-label, the protocol stated that the study involved blinded adjudication of MACE, the use of an independent data monitoring committee (IDMC), and an identical schedule of visits, procedures, and assessments for both treatment groups. In order to reduce subjectivity of dose adjustment, the adjustments to doses for vadadustat and darbepoetin alfa were guided by Hb concentration and dose adjustment algorithms. However, investigators were able to make dose adjustments at their discretion and this will have been influenced by the knowledge of the person's treatment. In sum, the EAG recognised the trials put in place systems to reduce bias but have some concerns over risk of bias in measurement in the use of rescue therapy. The EAG considered investigators may be more likely to have offered rescue therapy, at their discretion, to people on the new treatment (vadadustat).

Domain 5: Risk of bias in selection of the reported result

The efficacy outcomes collected in the INNO$_2$VATE trials were detailed in the trial's protocol.[19] While the company reported the majority of these outcomes in the CS, they did not report the following:

- Mean weekly dose of IV elemental iron administered from baseline to week 52.
- Hb increase of >10 g/L from baseline.
- Maintenance of iron sufficiency (defined as ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20%).
- Receiving IV iron therapy.
- Hb >120 g/L, >130 g/L, or >140 g/L.
- Hb increase >10 g/L within any 2-week interval or >20 g/L within any 4-week interval.

The EAG was therefore concerned that relevant outcomes stated in the NICE final scope, such as use of additional IV iron, were not reported as clinical outcomes in the CS. The EAG considered the Hb response and maintenance outcomes reported in the CS to be the most

relevant outcomes collected in the trial. However, the Hb increase of >10 g/L from baseline outcome would have provided further evidence linked to the correction of Hb in the PEP of the $INNO_2VATE$ – incident trial.

The reporting of MACE events in the CS was combined for both trials. It was unclear why these outcomes were reported together when the efficacy outcomes and other AE outcomes were reported separately for each trial. However, the company provided these data separated by trial at the clarification stage.

Therefore, the EAG had concerns over the selection of the reported results for the $INNO_2VATE$ trials because there were relevant outcomes collected that were not reported.

Overall risk of bias

Overall, the EAG had some concerns over the risk of bias for the $INNO_2VATE$ trials. This was primarily due to the open label design that may have led to deviations from the intended interventions and potentially a risk of bias in measurement of the rescue therapy outcomes. The company also did not report all the outcomes collected in the trial. A number of these unreported outcomes, such as details of iron therapy received during the trial, were relevant to the decision problem.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

The EAG selected the outcomes most relevant to the decision problem and economic modelling for critique in this section. The $INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent data have been presented side by side, to highlight similarities and differences between the trial results. The company provided a meta-analysis at the clarification stage (Question A3) and that is presented in this section.

Haemoglobin response / maintenance of haemoglobin levels

The EAG did not consider it possible to disambiguate Hb response from maintenance of Hb levels and presents these outcomes with reference to the treatment aim. The aim of treatment in the primary efficacy period (PEP) of the $INNO_2VATE$ – incident trial was correction of low Hb levels (haemoglobin response), but the aim in the secondary efficacy period (SEP) was

maintenance of Hb levels. The aim of treatment in the $INNO_2VATE$ prevalent trial was primarily maintenance of Hb in both the PEP and the SEP.

Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)

The $INNO_2VATE$ – incident trial found darbepoetin alfa offered a statistically significant increase (LSM: 3.1 g/L; 95% CI: 1.0, 5.3) in Hb over vadadustat at the PEP (24 to 36 weeks; Table 9). However, this change was within the non-inferiority margin (-7.5 to 7.5 g/L) pre-specified by the company. Given the aim of treatment was to correct Hb, the EAG considered this may be a meaningful limitation of vadadustat treatment. The EAG noted that the mean (SD) baseline Hb (g/L) in the vadadustat arm was 93.69 (10.70) and the least squared mean (LSM) increase in Hb was 12.6 (1.09). This meant that, even in the vadadustat arm, most people were above Hb 100 g/L (i.e. within the recommended target range) after the PEP (24 to 36 weeks).

The $INNO_2VATE$ – prevalent trial found darbepoetin alfa offered a statistically significant (LSM: 1.7 g/L; 95% CI: 1.0, 2.3) increase in Hb over vadadustat at the PEP (24 to 36 weeks; Table 9). However, this met the company's non-inferiority margin, and the aim of treatment in the $INNO_2VATE$ – prevalent trial was maintenance of Hb levels in the recommended target range. Given the aim of treatment, the EAG's clinical experts stated that maintenance of Hb was achieved by a treatment that offered a small increase in Hb (i.e. a treatment effect and 95% confidence interval above zero). Darbepoetin alfa and vadadustat both demonstrated a treatment effect and 95% confidence interval above zero, and on the advice of their clinical experts, the EAG understood both medications to be equally effective in the maintenance context.

At the clarification stage (Question A3), the company provided a fixed effect meta-analysis for this outcome, alongside the pooled individual patient data (IPD) results. However, given the heterogeneity of results from the two trials, the EAG considered a random effects meta-analysis to be a more appropriate model for this analysis. The fixed effect meta-analysis found a statistically significant benefit for darbepoetin alfa over vadadustat in increasing a person's Hb.The EAG noted that this increase lay within the -7.5 to 7.5 g/L inferiority margin pre-specified by the company. Although it was clear from the point estimate that $INNO_2VATE$ – prevalent, the larger trial, dominated the meta-analysis. Also, the treatment aims of the two trials were different at the PEP and the EAG cautions against drawing strong conclusion from any pooled analysis of this outcome.

The point estimate of the fixed effect meta-analysis reflected the point estimate of the pooled IPD. However, the pooled IPD (treat-as-one-trial method) disregarded study-to-study variation, which led to narrower confidence intervals.

Table 9: Change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)

$INNO_2VATE$ - incident	**Vadadustat (N=181)**	**Darbepoetin alfa (N=188)**	**Treatment comparison vadadustat versus darbepoetin alfa**
Change from baseline (g/L)			
Mean (SD)	9.9 (12.76)	14.2 (14.14)	-
Least squares mean (SEM)	12.6 (1.09)	15.8 (1.08)	-3.1 (1.10)
95% CI	10.5, 14.8	13.7, 17.9	-5.3, -1.0
$INNO_2VATE$ – prevalent	**Vadadustat (N=1,777)**	**Darbepoetin alfa (N=1,777)**	**Treatment comparison vadadustat versus darbepoetin alfa**
Change from baseline (g/L)			
Mean (SD)	1.1 (11.08)	3.0 (11.03)	-
Least squares mean (SEM)	1.9 (0.32)	3.6 (0.32)	-1.7 (0.33)
95% CI	1.2, 2.5	2.9, 4.2	-2.3, -1.0

Efficacy outcomes for vadadustat (N=1,958) vs darbepoetin alfa (N=1,965) from $INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent trials		
	Fixed effects meta-analysis[a]	**Pooled IPD results from EPAR**
Mean difference (g/L)	-1.8	NR
Least squares mean difference (g/L)	NR	-1.8
95% CI	-2.7, -1.0	-2.4, -1.2
p-value	<0.0001	NR

Abbreviations: CI: confidence interval; Hb, haemoglobin; IPD, individual patient data; N: number of patients; NR, not reported; SD: standard deviation; SEM: standard error of mean.

Note: [a] Analyses were performed in R version 4.3.2 on published aggregate data. The inverse variance method was used for estimation of weights and a restricted maximum-likelihood estimator was applied for tau2. Meta-analyses of binary outcomes and count outcomes used the respective relative effects estimates (i.e., odds ratios or rate ratios, respectively) as data inputs. In that case, outcome measures are log-transformed in order to be able to use the assumption that the effects are normally distributed. Test of heterogeneity was met for all analyses performed.

Change in average Hb between baseline and the secondary efficacy period (weeks 40 to 52)

The $INNO_2VATE$ – incident trial found darbepoetin alfa and vadadustat equally effective at the SEP (weeks 40 to 52). However, as noted above, the mean Hb of people in the $INNO_2VATE$ – incident trial was more than 100 g/L after the PEP, and so most people were inside the

recommended target range (100 to 120 g/L). Once a person's Hb was inside the recommended target range the treatment aim changed from correction to maintenance, and their dose adjusted on that basis. Given the change in treatment aim for a substantial proportion of participants after the PEP, the EAG cautions against drawing conclusions from change in average Hb between baseline and the SEP outcome.

The aim of treatment in the $INNO_2VATE$ – prevalent trial continued to be maintenance of Hb through both the PEP and SEP. In line with the PEP results, darbepoetin alfa offered a statistically significant increase in Hb over vadadustat at 40 to 52 weeks though the company noted that the result was non-inferior based on their pre-specified non-inferiority margin (-7.5 to 7.5 g/L). However, given both treatments were effective in a maintaining a person's change in Hb above zero by the SEP, the EAG considered them equally effective in the maintenance context.

At the clarification stage (Question A3), the company provided a fixed effect meta-analysis for this outcome, alongside the pooled IPD results. However, given the heterogeneity of results from the two trials, the EAG considered a random effects meta-analysis to be a more appropriate model for this analysis. The fixed effect meta-analysis found a statistically significant benefit for darbepoetin alfa over vadadustat in increasing a person's Hb but the company noted that the result was non-inferior based on their pre-specified non-inferiority margin (-7.5 to 7.5 g/L). Although it was clear from the point estimate that $INNO_2VATE$ – prevalent, the larger trial, dominated the meta-analysis. Also, the treatment aims of the two trials were different at the PEP and the EAG cautions against drawing strong conclusion from any pooled analysis of this outcome.

The point estimate of the fixed effect meta-analysis reflected the point estimate of the pooled IPD. However, the pooled IPD (treat-as-one-trial method) disregarded study-to-study variation and led to narrower confidence intervals.

Table 10: Change in average Hb between baseline and the secondary efficacy period (weeks 40 to 52)

$INNO_2VATE$ - incident	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Treatment comparison vadadustat versus darbepoetin alfa
Change from baseline			
Mean (SD)	11.5 (13.45)	13.6 (15.68)	-
Least squared mean (SEM)	14.2 (1.32)	15.0 (1.36)	-0.7 (1.34)

95% CI	11.7, 16.8	12.3, 17.6	-3.4, 1.9
INNO$_2$VATE – prevalent	**Vadadustat (N=1,777)**	**Darbepoetin alfa (N=1,777)**	**Treatment comparison vadadustat versus darbepoetin alfa**
Change from baseline			
Mean (SD)	1.5 (11.78)	3.5 (11.31)	-
Least squared mean (SEM)	2.3 (3.5)	4.1 (3.3)	-1.8 (0.35)
95% CI	1.6, 2.9	3.4, 4.8	-2.5, -1.2

Efficacy outcomes for vadadustat (N=1,958) vs darbepoetin alfa (N=1,965) from INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials

	Fixed effects meta-analysis[a]	**Pooled IPD results from EPAR**
Mean difference (g/L)	-1.7	NR
Least squares mean difference (g/L)	NR	-1.7
95% CI	-2.7, -0.8	-2.4, -1.1
p-value	0.0002	NR

Abbreviations: CI: confidence interval; Hb, haemoglobin; IPD, individual patient data; N: number of patients; NR, not reported; SD: standard deviation; SEM: standard error of mean.

Note: [a] Analyses were performed in R version 4.3.2 on published aggregate data. The inverse variance method was used for estimation of weights and a restricted maximum-likelihood estimator was applied for tau2. Meta-analyses of binary outcomes and count outcomes used the respective relative effects estimates (i.e., odds ratios or rate ratios, respectively) as data inputs. In that case, outcome measures are log-transformed in order to be able to use the assumption that the effects are normally distributed. Test of heterogeneity was met for all analyses performed.

Proportion of patients with average Hb value within geography-specific target range (PEP / SEP)

Outcomes assessing the proportion of people with average Hb value within geography-specific target range were presented in Section M.1.2 (INNO$_2$VATE – incident) and Section M.2.2 (INNO$_2$VATE – prevalent) of the CS and reproduced below in Table 11.

The INNO$_2$VATE – incident trial found darbepoetin alfa to have a statistically significant benefit (OR: 0.6; 95% CI: 0.40, 0.96) over vadadustat in the proportion of people with average Hb value within geography-specific target range in the PEP. However, the drugs were equally effective during the SEP.

The INNO$_2$VATE – prevalent trial found darbepoetin alfa to have a statistically significant benefit over vadadustat in the proportion of people with average Hb value within geography-specific target range at both the PEP (OR: 0.9; 95% CI: 0.76, 1.00) and the SEP (OR: 0.8; 95% CI: 0.68, 0.91).

At the clarification stage (Question A3), the company provided a fixed effect meta-analysis for the proportion of patients with average haemoglobin value within geography-specific target range at the PEP and the SEP. However, given the heterogeneity of results from the two trials, the EAG considered a random effects meta-analysis to be a more appropriate model for this analysis. In both the PEP and the SEP, the fixed effect meta-analysis found a statistically significant benefit for darbepoetin alfa over vadadustat. The EAG considered this to be convincing evidence that darbepoetin alfa is more effective than vadadustat in maintaining people in the recommended target range. Although it was clear from the point estimates that $INNO_2VATE$ – prevalent, the larger trial, dominated the meta-analysis.

Table 11: Proportion of patients with average Hb value within geography-specific target range (stratified Mantel-Haenszel method with multiple imputations; randomised population; adapted from Tables 2 and 14 in Appendix M)

$INNO_2VATE$ - incident	**Vadadustat (N=181)**	**Darbepoetin alfa (N=188)**	**Treatment comparison vadadustat – darbepoetin alfa**
Weeks 24 to 36			
n (%) of responders based on the observed data	79 (43.6)	107 (56.9)	-
95% CI	36.3, 51.2	49.5, 64.1	-
n (%) of responders based on the observed + imputed data[a]	89 (49.0)	114 (60.8)	-
95% CI[a]	47.0, 51.4	59.0, 62.8	-
Proportion difference (vadadustat – darbepoetin alfa) (95% CI)[b]	-	-	-0.12 (-0.22, -0.01)
Odds ratio (vadadustat/darbepoetin alfa) (95% CI)[b]	-	-	0.6 (0.40, 0.96)
Weeks 40 to 52			
n (%) of responders based on the observed data	72 (39.8)	77 (41.0)	-
95% CI	32.6, 47.3	33.9, 48.4	-
n (%) of responders based on the observed + imputed data[a]	91 (50.1)	94 (49.9)	-
95% CI[a]	47.0, 53.6	46.8, 53.7	-
Proportion difference (vadadustat – darbepoetin alfa) (95% CI)[b]	-	-	0.00 (-0.11, 0.11)
Odds ratio (vadadustat/darbepoetin alfa) (95% CI)[b]	-	-	1.0 (0.64, 1.59)

INNO$_2$VATE – prevalent	**Vadadustat (N=1,777)**	**Darbepoetin alfa (N=1,777)**	**Treatment comparison vadadustat versus darbepoetin alfa**
Weeks 24 to 36			
n (%) of responders based on the observed data	874 (49.2)	946 (53.2)	-
95% CI	46.8, 51.5	50.9, 55.6	-
n (%) of responders based on the observed + imputed data[a]	956 (53.8)	1,016 (57.2)	-
95% CI[a]	53.1, 54.4	56.6, 58.0	-
Proportion difference, vadadustat – darbepoetin alfa (95% CI)[b]	-	-	-0.03 (-0.07, 0.00)
Odds ratio (vadadustat/darbepoetin alfa) (95% CI)[b]	-	-	0.9 (0.76, 1.00)
Weeks 40 to 52			
n (%) of responders based on the observed data	787 (44.3)	905 (50.9)	-
95% CI	42.0, 46.6	48.6, 53.3	-
n (%) of responders based on the observed + imputed data[a]	926 (52.1)	1,029 (57.9)	-
95% CI[a]	51.2, 53.1	57.1, 58.7	-
Proportion difference, vadadustat – darbepoetin alfa (95% CI)[b]	-	-	-0.06 (-0.09, -0.02)
Odds ratio, vadadustat/darbepoetin alfa (95% CI)[b]	-	-	0.8 (0.68, 0.91)
Efficacy outcomes from INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials			
	Vadadustat (N=1,958)	**Darbepoetin alfa (N=1,965)**	**Fixed effects meta-analysis[c]**
Weeks 24 to 36			
Odds ratio (95% CI)	-	-	0.87 (0.76, 0.99)
p-value	-	-	0.034
Weeks 40 to 52			
Odds ratio (95% CI)	-	-	0.82 (0.71, 0.94)
p-value	-	-	0.0042

Abbreviations: CI, confidence interval; Hb, haemoglobin; N, number of people; n, number of people within specific category.

Notes:

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

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

[c] Analyses were performed in R version 4.3.2 on published aggregate data. The inverse variance method was used for estimation of weights and a restricted maximum-likelihood estimator was applied for tau2. Meta-analyses of binary outcomes and count outcomes used the respective relative effects estimates (i.e., odds ratios or rate ratios, respectively) as data inputs. In that case, outcome measures are log-transformed in order to be able to use the assumption that the effects are normally distributed. Test of heterogeneity was met for all analyses performed.

Use of additional therapy (including blood transfusion and intravenous iron)

The company reported additional therapy categorized as "narrow rescue therapy" and "broad-on-treatment rescue therapy". As discussed in Section 3.2.2.5, narrow rescue therapy was therapy attributable to a low Hb (<95 g/L) and/or worsening of symptoms of anaemia. Broad-on treatment rescue therapy was all the rescue therapy received by a trial participant. The company have used narrow rescue therapy in the economic model, but the EAG prefer broad-on-treatment rescue therapy as it better represented the rescue therapy received by people with DD-CKD in the INNO$_2$VATE trials.

Number of red blood cell transfusion episodes received

Both treatments resulted in a similar rate of broad-on-treatment RBC transfusion episodes at 52 weeks in the INNO$_2$VATE – incident trial (rate ratio: 0.9; 95% CI: 0.50, 1.67; Table 11) and the INNO$_2$VATE – prevalent trial (rate ratio: 1.0; 95% CI: 0.86, 1.19). It was unclear why the company did not present a meta-analysis for this outcome alongside the ESA rescue therapy meta-analysis at the clarification stage. However, the EAG understood the data presented to be evidence of no difference between the trial arms for broad-on-treatment RBC transfusion episodes.

Table 12: Number of red blood cell transfusion episodes received (zero-inflated Poisson regression model) broad-on-treatment rescue therapy (randomised population; adapted from Tables 6 and 18 in Appendix M)

INNO$_2$VATE – incident	**Vadadustat (N=181)**	**Darbepoetin alfa (N=188)**	**Treatment comparison vadadustat – darbepoetin alfa**
Number of RBC transfusion episodes	34	35	-
Rate ratio (95% CI)	-	-	0.9 (0.50, 1.67)
p-value[a]	-	-	0.7785
Number (%) of patients without any episodes	159 (88.8)	169 (90.9)	-
INNO$_2$VATE – prevalent	**Vadadustat (N=1,777)**	**Darbepoetin alfa (N=1,777)**	**Treatment comparison vadadustat versus darbepoetin alfa**

Number of RBC transfusion episodes	379	432	-
Rate ratio (95% CI)	-	-	1.0 (0.86, 1.19)
p-value[a]	-	-	0.9025
Number (%) of patients without any episodes	1,519 (85.9)	1,518 (85.8)	-

Abbreviations: CI, confidence interval; N, number of people; n, number of people within specific category; SD, standard deviation.

Note:

[a] From a zero-inflated Poisson regression model with treatment group, baseline Hb and the two randomisation stratification factors, geographic region and New York Heart Association (NYHA) HF class (0 or I versus II or III) as covariates, adjusting for patient's exposure duration.

People on vadadustat received a higher number of narrow RBC transfusion episodes in both INNO$_2$VATE trials. The INNO$_2$VATE – incident trial had relatively few events and found a numerical benefit for darbepoetin alfa over vadadustat (rate ratio: 1.7; 95% CI: 0.71, 4.10). The INNO$_2$VATE – prevalent trial found a statistically significant benefit for darbepoetin alfa over vadadustat (rate ratio: 1.4; 95% CI: 1.05, 1.74).

Table 13: Number of red blood cell transfusion episodes received (zero-inflated Poisson regression model) narrow rescue therapy (randomised population; adapted from Tables 5 and 17 in Appendix M)

INNO$_2$VATE – incident	**Vadadustat (N=181)**	**Darbepoetin alfa (N=188)**	**Treatment comparison vadadustat – darbepoetin alfa**
Number of RBC transfusion episodes	23	15	-
Rate ratio (95% CI)	-	-	1.7 (0.71, 4.10)
p-value[a]	-	-	0.2316
Number (%) of patients without any episodes	166 (92.7)	178 (95.7)	-
INNO$_2$VATE – prevalent	**Vadadustat (N=1,777)**	**Darbepoetin alfa (N=1,777)**	**Treatment comparison vadadustat versus darbepoetin alfa**
Number of RBC transfusion episodes	187	160	-
Rate ratio (95% CI)	-	-	1.4 (1.05, 1.74)
p-value[a]	-	-	0.0178
Number (%) of patients without any episodes	1,636 (92.5)	1,657 (93.7)	-

Abbreviations: CI, confidence interval; N, number of people; n, number of people within specific category; SD, standard deviation.

Note:

[a] From a zero-inflated Poisson regression model with treatment group, baseline Hb and the two randomisation stratification factors, geographic region and New York Heart Association (NYHA) HF class (0 or I versus II or III) as covariates, adjusting for patient's exposure duration.

Number of ESA rescue therapy episodes received

Both trials found people on vadadustat had a statistically significant higher rate of broad-on-treatment ESA rescue therapy episodes at 52 weeks over people on darbepoetin alfa. The $INNO_2VATE$ – incident trial found a rate ratio (95% CI) of 3.3 (2.02, 5.24) and the $INNO_2VATE$ – prevalent trial 2.8 (2.48, 3.10). At the clarification stage (Question A3), the company presented a fixed effect meta-analysis. The fixed effect meta-analysis found people on vadadustat were 2.8 (2.5 to 3.1) times more likely to have ESA rescue therapy than people on darbepoetin alfa. Although it was clear from the point estimate that $INNO_2VATE$ – prevalent, the larger trial, dominated the meta-analysis.

At the clarification stage (Question A8), the company also noted some uncertainty around the measurement of this outcome. Any ESA therapy given to a person in the vadadustat arm was considered broad-on-treatment rescue therapy. When people in the darbepoetin alfa arm were given a different injectable ESA, this was also considered broad-on-treatment rescue therapy. However, when people in darbepoetin alfa arm received large dose adjustments (≥50% or ≥100%) it was only assigned as rescue therapy if the investigator designated it thus. The company noted that the SmPC states that "If a dose adjustment is required to maintain Hb at the desired level, it is recommended that the dose is adjusted by approximately 25%". Therefore, they considered whether larger increases in dose could be automatically considered rescue therapy. The company undertook post-hoc analysis to explore a wider definition of rescue therapy. In this analysis they found that 25% of people in the darbepoetin alfa arm had rescue therapy using the 50% or more criterion and approximately 10% using the 100% or more criterion, compared with subjects who received vadadustat (which they say was approximately 5% to 8%). However, the EAG considered the ESA rescue therapy as recorded by the trial investigators to be the most robust estimate.

Table 14: Number of ESA rescue therapy episodes received (zero-inflated Poisson regression model) broad-on-treatment rescue therapy (randomised population; adapted from Tables 10 and 22 in Appendix M)

$INNO_2VATE$ – incident	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Treatment comparison vadadustat – darbepoetin alfa
Number of ESA rescue therapy episodes	101	31	-

Rate ratio (95% CI)	-	-	3.3 (2.02, 5.24)
p-value[a]	-	-	<0.0001
Number (%) of patients without any episodes	128 (71.5)	162 (87.1)	-
$INNO_2VATE$ – prevalent	**Vadadustat (N=1,777)**	**Darbepoetin alfa (N=1,777)**	**Treatment comparison vadadustat versus darbepoetin alfa**
Number of ESA rescue therapy episodes	1,402	571	-
Rate ratio (95% CI)	-	-	2.8 (2.48, 3.10)
p-value[a]	-	-	<0.0001
Number (%) of patients without any episodes	1,000 (56.6)	1,396 (78.9)	-
Efficacy outcomes from $INNO_2VATE$ – incident and $INNO_2VATE$ – prevalent trials			
	Vadadustat (N=1,958)	**Darbepoetin alfa (N=1,965)**	**Fixed effects meta-analysis[b]**
ESA rescue episodes, broad-on rescue definition			
Incident rate ratio (95% CI)	-	-	2.8 (2.53, 3.15)
p-value	-	-	<0.0001

Abbreviations: CI, confidence interval; ESA, erythropoietin stimulating agents; N, number of people; n, number of people within specific category; SD, standard deviation.

Notes:

[a] From a zero-inflated Poisson regression model with treatment group, baseline Hb and the two randomisation stratification factors, geographic region and New York Heart Association (NYHA) HF class (0 or I versus II or III) as covariates, adjusting for patient's exposure duration.

[b] Analyses were performed in R version 4.3.2 on published aggregate data. The inverse variance method was used for estimation of weights and a restricted maximum-likelihood estimator was applied for tau2. Meta-analyses of binary outcomes and count outcomes used the respective relative effects estimates (i.e., odds ratios or rate ratios, respectively) as data inputs. In that case, outcome measures are log-transformed in order to be able to use the assumption that the effects are normally distributed. Test of heterogeneity was met for all analyses performed.

Both trials found people on vadadustat had a statistically significant increase in rate of narrow ESA rescue therapy episodes at 52 weeks over people on darbepoetin alfa. The $INNO_2VATE$ – incident trial found a rate ratio (95% CI) of 7.0 (3.47, 14.13) and the $INNO_2VATE$ – prevalent trial 3.5 (3.08, 4.04). At the clarification stage (Question A3), the company presented a fixed effect meta-analysis. However, given the heterogeneity of results from the two trials, the EAG considered a random effects meta-analysis to be a more appropriate model for this analysis. The fixed effect meta-analysis found people on vadadustat were 3.6 (3.1 to 4.1) times more likely to have ESA rescue therapy than people on darbepoetin alfa. Although it was clear from the point estimate that $INNO_2VATE$ – prevalent, the larger trial, dominated the meta-analysis.

Table 15: Number of ESA rescue therapy episodes received (zero-inflated Poisson regression model) narrow rescue therapy (randomised population; adapted from Tables 9 and 21 in Appendix M)

INNO$_2$VATE – incident	**Vadadustat (N=181)**	**Darbepoetin alfa (N=188)**	**Treatment comparison vadadustat – darbepoetin alfa**
Number of ESA rescue therapy episodes	88	12	-
Rate ratio (95% CI)	-	-	7.0 (3.47, 14.13)
p-value[a]	-	-	<0.0001
Number (%) of patients without any episodes	139 (77.7)	176 (94.6)	-
INNO$_2$VATE – prevalent	**Vadadustat (N=1,777)**	**Darbepoetin alfa (N=1,777)**	**Treatment comparison vadadustat versus darbepoetin alfa**
Number of ESA rescue therapy episodes	1116	362	-
Rate ratio (95% CI)	-	-	3.5 (3.08, 4.04)
p-value[a]	-	-	<0.0001
Number (%) of patients without any episodes	1,148 (64.9)	1,520 (85.9)	-
Efficacy outcomes from INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials			
	Vadadustat (N=1,958)	**Darbepoetin alfa (N=1,965)**	**Fixed effects meta-analysis[b]**
ESA rescue episodes, narrow rescue definition			
Incident rate ratio (95% CI)	-	-	3.59 (3.14, 4.10)
p-value	-	-	<0.0001

Abbreviations: CI, confidence interval; ESA, erythropoietin stimulating agents; N, number of people; n, number of people within specific category; SD, standard deviation.

Notes:

[a] From a zero-inflated Poisson regression model with treatment group, baseline Hb and the two randomisation stratification factors, geographic region and New York Heart Association (NYHA) HF class (0 or I versus II or III) as covariates, adjusting for patient's exposure duration

[b] Analyses were performed in R version 4.3.2 on published aggregate data. The inverse variance method was used for estimation of weights and a restricted maximum-likelihood estimator was applied for tau2. Meta-analyses of binary outcomes and count outcomes used the respective relative effects estimates (i.e., odds ratios or rate ratios, respectively) as data inputs. In that case, outcome measures are log-transformed in order to be able to use the assumption that the effects are normally distributed. Test of heterogeneity was met for all analyses performed.

IV iron therapy

No outcomes assessing use of IV iron therapy during the trial were presented in the clinical sections of the CS. The company did present the proportion of people receiving IV iron rescue

therapy in B.3.3.5 of the report as clinical parameters and variables for the economic model (Table 16). The EAG interpret these data as a signal that people with DD-CKD on vadadustat or darbepoetin alfa require similar IV iron therapy. However, the company did note a limitation of these data was that the frequency of IV iron administration was not recorded, and thus it was not clear from these data how often people received IV iron. The company also presented iron-related parameters in Tables 11 and 23 in Appendix M of the CS.

Table 16: Proportion of patients receiving IV iron rescue therapy (reproduced from Table 26 in Document B)

Type of rescue therapy	Week	Cycle	Vadadustat	ESA
IV iron rescue therapy (%)	Week 2-8	1	50.8	53.0
	Week 10-20	2	55.6	55.6
	Week 24-36	3	57.3	56.8
	Week 40-52	4	58.9	59.2
	Week 64+	5+	63.0	65.0

Abbreviations: ESA, erythropoietin stimulating agent; IV, intravenous.

Hospitalisation

The company presented hospitalisation outcomes as an adverse event for each trial at the clarification stage (Question A7). The EAG understood from these data that there was no evidence that people with DD-CKD treated with vadadustat had different hospitalisations due to heart failure to those treated with darbepoetin alfa (Table 17).

Table 17: Summary of hospitalization adverse events in the INNO$_2$VATE trials

INNO2VATE - incident			
Event, n (%)	Vadadustat (N=179)	Darbepoetin Alfa (N=186)	Total (N=365)
People with Any Hospitalisations for Heart Failure	[redacted]	7 (3.8)	[redacted]
Any MACE plus Hospitalisations for Heart Failure	[redacted]	28 (15.1)	[redacted]
INNO2VATE - prevalent			
Event, n (%)	Vadadustat (N=1,768)	Darbepoetin Alfa (N=1,769)	Total (N=3,537)
People with Any Hospitalisations for Heart Failure	[redacted]	82 (4.6)	[redacted]

INNO2VATE - incident			
Any MACE plus Hospitalisations for Heart Failure	[redacted]	405 (22.9)	[redacted]

Abbreviations: MACE, Major Adverse Cardiovascular Events; N, number of people; n, number of people within specific category.

Mortality

The company presented mortality outcomes as an adverse event for each trial at the clarification stage (Question A7). The EAG understood from these data that there was no evidence that people with DD-CKD treated with vadadustat had different mortality outcomes to those treated with darbepoetin alfa (Table 18).

Table 18: Summary of mortality outcomes in the INNO$_2$VATE trials

INNO$_2$VATE - incident			
Event, n (%)	Vadadustat (N=179)	Darbepoetin Alfa (N=186)	Total (N=365)
All-cause Mortality	[redacted]	20 (10.8)	[redacted]
CV Deaths	[redacted]	10 (5.4)	[redacted]
Non-CV Deaths	[redacted]	8 (4.3)	[redacted]
Unknown Deaths	[redacted]	2 (1.1)	[redacted]
INNO$_2$VATE - prevalent			
Event, n (%)	Vadadustat (N=1,768)	Darbepoetin Alfa (N=1,769)	Total (N=3,537)
All-cause Mortality	[redacted]	290 (16.4)	[redacted]
CV Deaths	[redacted]	150 (8.5)	[redacted]
Non-CV Deaths	[redacted]	108 (6.1)	[redacted]
Unknown Deaths	[redacted]	32 (1.8)	[redacted]

Abbreviations: MACE, Major Adverse Cardiovascular Events; N, number of people; n, number of people within specific category.

Health-related quality of life

No health-related quality of life data were collected in the two pivotal trials.

3.2.3.2. Subgroup analyses

The company presented forest plots for prespecified subgroup analysis in Appendix E of the CS. The outcomes analysed were:

- Change from baseline in haemoglobin to the average over the PEP (weeks 24 to 36);
- Change from baseline in haemoglobin to the average over the SEP (weeks 40 to 52);
- Proportion of people with average haemoglobin values within geography-specific target range during the PEP (weeks 24 to 36);
- Proportion of people with average haemoglobin values within geography-specific target range during the SEP (weeks 40 to 52).

INNO$_2$VATE – incident trial

There were no significant differences between the effectiveness estimates of vadadustat versus darbepoetin alfa in the any of the subgroups analysed in the INNO2VATE – incident trial. The EAG noted that there was an increased numerical benefit for darbepoetin alfa over vadadustat in people with an Hb less than 95 g/L compared to people with 95 g/L or more for the change from baseline in haemoglobin outcomes (PEP and SEP). The EAG interpreted this to be the result of darbepoetin alfa's statistically significant benefit over vadadustat at correcting people's Hb in the PEP of treatment. People with an Hb of 95 g/L or more did not require substantial correction of their Hb and the advantage of darbepoetin alfa over vadadustat was reduced.

Another subgroup of interest to the in the NICE final scope were people with no prior ESA use i.e. people who have recently been diagnosed with anaemia in DD-CKD and require ESA therapy. The subgroup analysis in this population was inconsistent but the EAG noted that in people with no prior ESA use, vadadustat showed a small numerical benefit over darbepoetin alfa for two outcomes:

- Change from baseline in haemoglobin to the average over the SEP (weeks 40 to 52)
- Proportion of people with average haemoglobin values within geography-specific target range during the SEP (weeks 40 to 52).

INNO$_2$VATE – prevalent trial

Given the treatment aim was maintenance of Hb rather than correction, the EAG focused their analysis on the proportion of people with average Hb values within the relevant geography-specific target range at the PEP and SEP. The forest plots presented in Appendix E did not indicate any subgroups for whom the effectiveness of vadadustat versus darbepoetin alfa substantially varied from the overall effect. The EAG did not consider any of the small differences in efficacy within the subgroups to be notable.

3.2.3.3. Adverse effects

Adverse effects outcomes were presented in Section B.2.10. and Appendix F of the CS.

INNO$_2$VATE – incident trial

A summary of INNO$_2$VATE – incident adverse events was presented in Table 15 of Document B. Treatment-emergent serious adverse events (TE-SAEs) were experienced by 89 (49.7%) people in the vadadustat arm and 105 (56.5%) people in the darbepoetin alfa arm. Five (2.8%) people in the vadadustat arm and two (1.1%) people in the darbepoetin alfa arm sustained a treatment-emergent adverse event (TEAE) leading to study treatment discontinuation. The specific TE-SAEs, presented in Table 2 in Document F, were well matched between treatment arms. The only notable difference was 11 (6.1%) people in the vadadustat arm, and 22 (11.8%) of people in the darbepoetin alfa arm, experienced gastrointestinal disorders. However, the EAG noted that gastrointestinal disorders were not noted as important adverse events in the SmPC for darbepoetin alfa.[20]

INNO$_2$VATE – prevalent trial

A summary of INNO$_2$VATE – prevalent adverse events was presented in Table 16 of Document B. TE-SAEs were experienced by 973 (55.0%) people in the vadadustat arm and 1,032 (58.3%) people in the darbepoetin alfa arm. The specific TE-SAEs, presented in Table 6 in Document F, were well matched between treatment arms. However, 91 (5.1%) people vadadustat arm and 20 (1.1%) people in darbepoetin alfa arm sustained a TEAE leading to study treatment discontinuation. It was unclear to the EAG why nearly five times as many people discontinued treatment due to TEAEs in the vadadustat arm in comparison to the darbepoetin alfa arm, given the similarity in the number of treatment-emergent SAEs and the specific TE-SAEs that occurred.

Major adverse cardiovascular events

The company presented a summary of major adverse cardiovascular events (MACE) in the combined safety population in Appendix F. The EAG has summarised this in Table 19, below. The company also presented a summary of MACE for each trial at the clarification stage (Question A7).

In the combined safety population, 355 (18.2%) people in the vadadustat arms, and 377 (19.3%) people in the darbepoetin alfa arms, experienced a MACE. The EAG's clinical experts

were not aware of any plausible mechanism driving a difference in MACE outcomes between treatment arms and the EAG considered it reasonable to assume no difference in MACE between the treatment arms.

The company also reported cardiovascular (CV) MACE (including individual components of CV death, non-fatal MI, and non-fatal stroke), any thromboembolic events (including vascular access thrombosis, arterial thrombosis, deep vein thrombosis, and pulmonary embolism), as well as any hospitalisation for heart failure. The company concluded they were all similar between the vadadustat and darbepoetin alfa treatment groups. The EAG agreed with the company that the evidence supported a conclusion that there were no differences between the treatments for MACE and MACE-related outcomes.

Table 19: Summary of patients with any events (first and subsequent MACE) – overall (safety population; adapted from Table 13, Appendix F)

Event, n (%)	Vadadustat (N=1,947)	Darbepoetin Alfa (N=1,955)	Total (N=3,902)
Patients with Any MACE	355 (18.2)	377 (19.3)	732 (18.8)
Patients with Any CV MACE	[redacted]	242 (12.4)	[redacted]
Patients with Any Thromboembolic Events	[redacted]	148 (7.6)	[redacted]
Vascular Access Thrombosis	[redacted]	120 (6.1)	[redacted]
Arterial Thrombosis	[redacted]	4 (0.2)	[redacted]
Deep Vein Thrombosis	[redacted]	20 (1.0)	[redacted]
Pulmonary Embolism	[redacted]	9 (0.5)	[redacted]
Patients with Any Hospitalisations for Heart Failure	[redacted]	89 (4.6)	[redacted]
Patients with Any Expanded MACE	[redacted]		[redacted]
Any MACE plus Thromboembolic Events	[redacted]	490 (25.1)	[redacted]
Any MACE plus Thromboembolic Events Excluding Vascular Access Thrombosis	[redacted]	397 (20.3)	[redacted]
Any MACE plus Hospitalisations for Heart Failure	[redacted]	433 (22.1)	[redacted]
Any MACE plus Hospitalisations for Heart Failure or Thromboembolic Events	[redacted]	539 (27.6)	[redacted]
Any MACE plus Hospitalisations for Heart Failure or Thromboembolic Events Excluding Vascular Access Thrombosis	[redacted]	449 (23.0)	[redacted]

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event; n, number

Source: Appendix F, CS

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company did not conduct an indirect treatment comparison (ITC) for this submission. The EAG was concerned that there were six injectable ESAs (erythropoietin, epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta) that may have been used for this population but only darbepoetin alfa was evaluated in the two pivotal trials. A recent Cochrane review by Chung et al. (2023)[21] on injectable ESAs for anaemia in adults with CKD concluded that the authors were not confident that different epoetin drugs were better or worse than each other for chances of needing a blood transfusion, death, a heart attack or stroke, having a clot in a fistula or dialysis vascular catheter, or the chances of needing dialysis for people with milder kidney disease. However, the EAG's clinical experts stated that they considered all injectable ESAs to be equally effective and safe, and that NHS trusts undertook a bidding process with manufacturers to acquire an injectable ESA supply at the lowest cost. Therefore, the EAG accepted that an ITC was not required for this submission and that the efficacy and safety of ESA treatment could be modelled on the darbepoetin alfa data taken from the pivotal trials. However, given this circumstance, the EAG also considered that the appropriate cost of comparator medication would therefore be the lowest priced ESA (see Section 4.2.8.1).

3.4. Conclusions of the clinical effectiveness section

The two INNO$_2$VATE clinical trials presented in the CS recruited people at different stages of treatment for anaemia in DD-CKD and both the baseline characteristics of the trial participants and the treatment aims in the trials primary efficacy periods were not well aligned. This clinical diversity led to inconsistency between the trials in the results in the majority of the efficacy outcomes reported.

However, the company pooled the inconsistent efficacy outcome data for use in the economic model. In pooling the efficacy data, the estimates were weighted heavily in favour of the substantially larger INNO$_2$VATE – prevalent trial. Therefore, the pooled estimates represented the population recruited to the INNO$_2$VATE – prevalent trial, who were people with longer-standing DD-CKD who had been on long-term ESA treatment. The population recruited to INNO$_2$VATE – incident who had been diagnosed more recently and were new, or entirely naïve, to ESA treatment were not well represented by the economic model (Key Issue 1).

The results of the two clinical trials showed that vadadustat was non-inferior to darbepoetin alfa in correcting a person's Hb by the pre-specified non-inferiority margin. However, darbepoetin alfa had a statistically significant benefit over vadadustat in maintaining a person's Hb within the recommended target range. The company reported efficacy data up to 52 weeks, but the EAG has no reason to believe ESA treatment efficacy wains. Rescue therapy through RBC transfusion episodes were similar between treatment arms. However, people on vadadustat arms had substantially higher rates of ESA rescue therapy episodes. The trials found there was no difference between people treated with vadadustat or darbepoetin alfa for any safety outcomes reported, including MACE.

Given the benefit in efficacy of darbepoetin alfa over vadadustat, and the similar safety profiles, the company emphasised the benefits of an HIF-PHI (vadadustat) over injectable ESAs in administration, and also in support of home therapies. However, the EAG were aware that the great majority of people's injectable ESA was administered IV into the dialysis lines rather than as a separate injection, and the people who would be required to inject themselves were those on PD, who tended to be younger and very able to administer the medication themselves. Therefore, the EAG did not accept that injectable ESAs provided a challenge for self-administration, and understood that the principal barrier to home therapies was undertaking dialysis unsupervised not administration of ESAs. However, the EAG's did accept there was an infrastructure built around injectable delivery resources and a move to an oral therapy does not require cold-chain storage, with its associated risks of wastage and quality degradation.

The EAG was concerned that the company did not address the pill/medication burden of people with DD-CKD (Key Issue 2). Prior to the trial, over 90% of people received their injectable ESA through administered IV into the dialysis lines, and the EAG understood this did not present a medication burden. However, people randomised to vadadustat then had another daily medication to take on top of an average of 15 pills per day. Excessive medication burden can lead to poorer medication adherence, and reduced quality of life. The EAG considered the substantially higher attrition in the vadadustat arms in the $INNO_2VATE$ trials to be related to the increased pill burden imposed by the use of an additional daily oral medication. No HRQoL data were collected during the $INNO_2VATE$ trials and it was unclear to what extent the extra pill burden of vadadustat affected people's quality of life. However, the EAG ran a scenario in the economic model where a published disutility for increased pill burden was applied.

On the basis of the above conclusions, the EAG considered that, despite its reduced efficacy in maintaining a person's Hb within the recommended target range, vadadustat may be a preferred treatment option for people on PD who value the flexibility afforded them by an oral treatment that does not require cold-chain storage. It may potentially be a useful treatment for people who are resistant (hyporesponsive) to ESAs but this population was not addressed in the $INNO_2VATE$ trials and the efficacy and safety of vadadustat in that population is unclear.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted a SLR of previous economic evaluations, health related quality of life and utilities, and healthcare resource use and costs. The EAG found the searches to be adequately structured, though not as comprehensive as those used for the clinical SLR. There were a number of inconsistencies in the PRISMA diagrams, although these were corrected at the clarification stage. The inclusion criteria, screening methods, and data extraction process were adequate for each of the reviews. The company undertook quality assessment of the included studies for the previous economic evaluations included in the review. However, it was unclear what quality assessment tool was used and the EAG considered that to be a limitation and a risk of bias of the SLR. The EAG also noted that various sources are used to populate the model that were not identified from the SLR, mainly reflecting inputs used in the prior roxadustat submission (TA807). Individual assessment and critique of the inputs used in the model are discussed in turn in the relevant sub-sections of this report.

Table 20. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	G.1.1, G.1.2, G.1.3, G.1.4	The company conducted an SLR for economic evaluations in MEDLINE, Embase, EconLit, DARE, NHS EED, CENTRAL, and CDSR (all through OvidSP), and from five conference series (ASN, EN, ERA/EDTA, ISPD and ISPOR). There were complemented by searches of previous submissions to CADTH, IQWiG, HAS, ICER, NICE and SMC. The search terms used for the population and intervention were briefer than in the clinical search, running the risk of missing relevant articles. It was unclear if any study type filters were used, but the terms looked reasonable. The EAG also noted some inconsistencies in the PRISMA diagrams, although these were corrected post clarification.
Inclusion criteria	Table 13, Appendix G	The inclusion PICO criteria were suitable for the decision problem. The

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		company included cost-benefit analyses, cost-minimization analyses, cost-effectiveness analyses, cost-utility analyses, and budget impact models.
Screening	G.1.5.2	The EAG considered the methods for screening to be adequate.
Data extraction	G.1.6	The EAG was satisfied with the data extraction process.
QA of included studies	G.1.7.4, Table 15	Quality assessment of the included studies was presented but it was unclear what tool was used to make the assessment.

Abbreviations: ASN, American Society of Nephrology; CADTH, Canadian Agency for Drugs and Technologies in Health; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CS, Company Submission; DARE, Database of Abstracts of Reviews of Effects; EAG, External Assessment Group; EN, European Nephrology conference; ERA/EDTA, European Renal Association: European Dialysis and Transplant Association Congress; HAS, Haute Autorité de Santé; HRQoL, health-related quality of life; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; ICER, Institute for Clinical and Economic Review; ISPD, International Society for Peritoneal Dialysis meetings; NHS EED, NHS Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; PICO, patient/population, intervention, comparison and outcomes; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; QA, quality assessment; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

Table 21. Summary of EAG's critique of the methods implemented by the company to identify health related quality of life and utilities

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	H.1.1, H.1.2, H.1.3, H.1.4	The company conducted an SLR for economic evaluations in MEDLINE, Embase, CENTRAL, and CDSR (all through OvidSP), and from five conference series (ASN, EN, ERA/EDTA, ISPD and ISPOR). There were complemented by searches of previous submissions to CADTH, IQWiG, HAS, ICER, NICE and SMC. The search terms used for the population and intervention were briefer than in the clinical search, running the risk of missing relevant articles. It was unclear if any study type filters were used, but the terms looked reasonable. The EAG also noted some inconsistencies in the PRISMA diagrams, although these were corrected post clarification.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Inclusion criteria	Table 9, Appendix H	The inclusion PICO criteria were suitable for the decision problem. The company included economic evaluations reporting utility/disutility data (model-, or not model-based), patient surveys/interviews, clinical trials, real-world observational studies (prospective and retrospective), utility elicitation/validation studies.
Screening	H.1.5.2	The EAG considered the methods for screening to be adequate.
Data extraction	H.1.6	The EAG was satisfied with the data extraction process.
QA of included studies	N/A	No quality assessment was performed.

Abbreviations: ASN, American Society of Nephrology; CADTH, Canadian Agency for Drugs and Technologies in Health; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CS, Company Submission; DARE, Database of Abstracts of Reviews of Effects; EAG, External Assessment Group; EN, European Nephrology conference; ERA/EDTA, European Renal Association: European Dialysis and Transplant Association Congress; HAS, Haute Autorité de Santé; HRQoL, health-related quality of life; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; ICER, Institute for Clinical and Economic Review; ISPD, International Society for Peritoneal Dialysis meetings; NHS EED, NHS Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; PICO, patient/population, intervention, comparison and outcomes; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; QA, quality assessment; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

Table 22. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	I.1.1, I.1.2, I.1.3, I.1.4	The company conducted an SLR for economic evaluations in MEDLINE, Embase, EconLit, DARE, NHS EED, CENTRAL and CDSR (all through OvidSP), and from five conference series (ASN, EN, ERA/EDTA, ISPD and ISPOR). There were complemented by searches of previous submissions to CADTH, IQWiG, HAS, ICER, NICE and SMC. The search terms used for the population and intervention were briefer than in the clinical search, running the risk of missing relevant articles. It was unclear if any study type filters were used, but the terms looked reasonable.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		The EAG also noted some inconsistencies in the PRISMA diagrams, although these were corrected post clarification.
Inclusion criteria	Table 13, Appendix I	The inclusion PICO criteria were suitable for the decision problem. The company included cost studies, burden/cost of illness studies, clinical trials, real-world observational studies (prospective and retrospective).
Screening	I.1.5.2	The EAG considered the methods for screening to be adequate.
Data extraction	I.1.6	The EAG was satisfied with the data extraction process.
QA of included studies	N/A	No quality assessment was performed.

Abbreviations: ASN, American Society of Nephrology; CADTH, Canadian Agency for Drugs and Technologies in Health; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CS, Company Submission; DARE, Database of Abstracts of Reviews of Effects; EAG, External Assessment Group; EN, European Nephrology conference; ERA/EDTA, European Renal Association: European Dialysis and Transplant Association Congress; HAS, Haute Autorité de Santé; HRQoL, health-related quality of life; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; ICER, Institute for Clinical and Economic Review; ISPD, International Society for Peritoneal Dialysis meetings; NHS EED, NHS Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; PICO, patient/population, intervention, comparison and outcomes; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; QA, quality assessment; SLR, systematic literature review; SMC, Scottish Medicines Consortium.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

The reference case for each attribute, along with EAG commentary, is shown in Table 23.

Table 23: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓ No comments
Perspective on costs	NHS and PSS	✓ No comments

Attribute	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	× The model compares to one comparator therefore fully incremental analysis is not provided. The EAG has concerns with the model structure presented by the company.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓ No comments
Synthesis of evidence on health effects	Based on systematic review	× Utility sources based on a prior submission in a similar disease area TA807.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	✓ No comments
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	✓ Based on a published systematic literature review
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	✓ No comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓ No comments
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✓ Costs are based on NHS and PSS resources
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓ No comments

Abbreviations: EQ-5D, EuroQol 5 dimension; HRQoL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY, quality adjusted life year; TA, technology appraisal

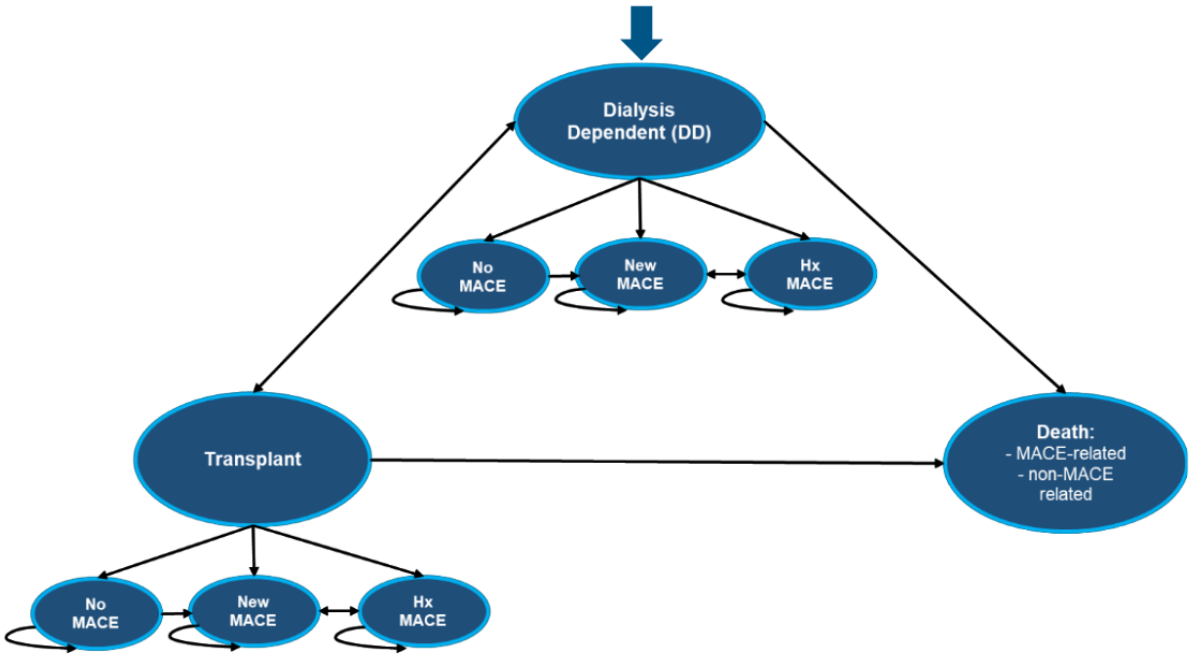
4.2.2. Model structure

The company developed a *de novo* Markov cohort model consisting of three mutually exclusive health states: dialysis dependent (DD), transplant, and death. These health states are further subdivided into sub-states based on MACE events. The DD and transplant health states are subdivided into three sub-states: no history of MACE ('No MACE'), history of MACE ('Hx MACE'), and new non-fatal MACE ('new MACE'). The death health state is subdivided into two sub-states: MACE-related deaths and non-MACE related deaths.

Hb levels were also accounted for and split into three categories: <100 g/L, 100 – 120 g/L, and ≥120 g/L, in addition to patients who are on and off vadadustat or injectable ESA treatment. However, the overarching model structure presented by the company does not consider these as formalized health states, and the consideration of Hb levels only impact HRQoL.

A schematic of the submitted model is provided in Figure 2 (based on Figure 8 in the CS).

Figure 2: Cost-effectiveness model structure (company base case)



Abbreviations: DD, dialysis-dependent; Hx, history; MACE, major adverse cardiovascular event

The company stated that this model structure is simpler than the previously submitted roxadustat model in TA807, which included eight health states based on different Hb levels (the TA807 model was criticised by the EAG and committee for being overly complex, due to the

number of different Hb levels modelled). The company also stated that this model structure is advantageous over other structures identified in the SLR as it reflects the clinical course of CKD patients with anaemia, which can be modelled directly using the INNO$_2$VATE trial results. The EAG noted, however, that not all transitions are modelled using the INNO$_2$VATE trials. The model also relies on the use of external sources to inform health state transitions. The company confirmed at clarification that the justification of the model structure should be amended to "*can be predominantly modelled directly using the INNO$_2$VATE trials".*

Patients enter the model in either the 'No MACE DD' or 'Hx MACE DD' health states. In each model cycle (3-months), patients can transition to transplant, death or remain in the DD health state. Patients with no history of MACE who experience a non-fatal MACE event will transition to the 'New MACE' sub-state of their respective health state for one cycle, then transition to the 'Hx MACE' sub-state after one cycle. Those with a history of MACE who experience a new non-fatal MACE event transition to the 'New MACE' sub-state of their respective health state for one cycle and return to 'Hx MACE'. Patients can experience a new MACE several times during the model time horizon (though the model structure does not allow tracking of this). From the 'Transplant' health state, patients can also transition back to the 'DD' health state, if the transplant fails.

The EAG did not agree that this model structure is simpler than the roxadustat model and consider the structure to be overly complex for the decision problem and the purpose of treatment with vadadustat. The EAG had three main concerns with the model structure, which are discussed in detail below:

- Disassociating Hb levels from the model structure
- Use of sub-states for MACE
- Application of clinical efficacy data from both external sources and trial data

Based on these concerns, the EAG has developed a modified model structure which formally incorporates Hb levels within the health states, removes MACE sub-states, and appropriately adjusts data from the UKRR report before incorporating INNO$_2$VATE data. The EAG considered this model structure to be simpler than the company's and include relevant health states based on the value of the treatments being considered (to appropriately compare costs and outcomes). Further details of the changes made by the EAG can be found in Section 6.2.

4.2.2.1. Hb levels

The EAG noted that the primary efficacy endpoint and the key secondary efficacy endpoint of the $INNO_2VATE$ trial (change in Hb from baseline to weeks 24 to 36 and weeks 40 to 52) are not used as part of the model structure presented (and instead used to inform HRQoL only). Given the intention of vadadustat is to treat the symptoms of anaemia caused by chronic kidney disease, the EAG considers the omission of Hb levels from the model health states a substantial limitation/omission in the company's chosen structure.

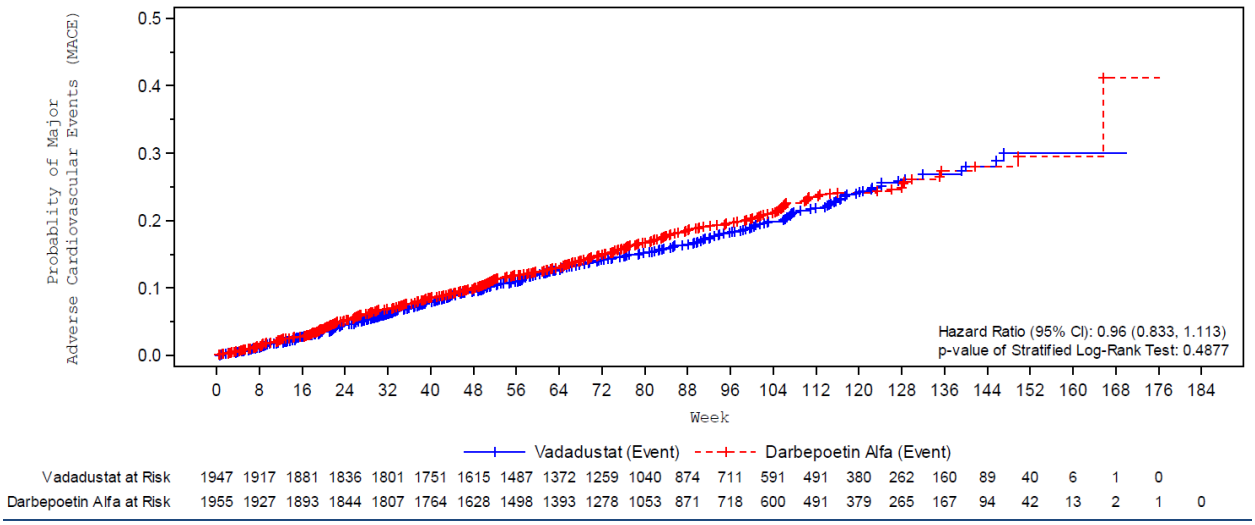
Although the company included Hb levels to inform health-related quality of life, these did not interact with any other aspect such as mortality, costs, and treatment discontinuation. Clinical experts consulted by the EAG indicated that Hb levels impact a patient's quality-of-life and that the Hb thresholds are chosen not on costs or mortality differences. However, patients with a lower Hb level can have an increased risk of stroke or heart attack and patients with >120 d/L may have a higher mortality rate. However, the EAG considered that the incremental differences in these factors for patients on vadadustat and injectable ESAs would be minimal and therefore are content with only considering the implications on quality-of-life.

4.2.2.2. Sub-states for MACE

The EAG considered the use of sub-states to factor in MACE creates complexities that are not required, given there is no evidence to substantiate a difference in MACE events. As discussed in Section 3.2.3.3, the EAG considered it reasonable to assume that there were no differences between people treated with vadadustat or injectable ESAs for MACE and MACE-related outcomes. Based on the results of the $INNO_2VATE$ trials, the primary safety outcome of time to first MACE event results in a hazard ratio of 0.96 (95% CI: 0.83 – 1.11). Also, the conclusion in Appendix F of the CS stated that *"there was no difference between vadadustat and darbepoetin alfa treatment groups for the time to first MACE".* This was further demonstrated by the Kaplan-Meier curves in

Figure 3, which shows continuous cross-over of the curves. The company were unable to provide any further evidence to support any differences in MACE when asked at clarification stage.

Figure 3: Kaplan-Meier curves of time to first MACE



Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events

Although the EAG agreed with the company that MACE can have a large impact on costs and quality of life, the incremental difference between vadadustat and injectable ESAs is expected to be zero. Therefore, the EAG considered there was no need to include MACE sub-states within the model.

4.2.2.3. Application of clinical data

The model structure uses external data from the UKRR to inform transitions between the 'DD' and transplant states, as well as long-term mortality assumptions. As the UKRR data are based on patients from start of kidney replacement therapy, the company adjust the starting transition matrix to align with the median time since dialysis from the INNO$_2$VATE trials of 2.4 years (cycle 10). Although the EAG could see the reasoning for the adjustment, it has been applied to data involving the INNO$_2$VATE trials (i.e., MACE transitions) and therefore does not appear to be correctly accounted for within the economic model. The resulting transition matrices, calculated for cycles 5-12, are used from the start of the model to account for the 2.4-year adjustment. However, the matrices for cycle 5-12 incorporates MACE data from Q4 of the INNO$_2$VATE trials (instead of Q1). This is because the company have not time-adjusted the UKRR data before applying the data from the INNO$_2$VATE trials.

The EAG believed that the adjustment should be made only to the UKRR data to align the baseline median time since dialysis between the two sources. The incorporation of the

INNO$_2$VATE trial data could then be used to inform the sub-states after the adjustment to the UKRR data. The EAG considered the misalignment in the application of clinical data a key limitation of the model.

In addition, the patient characteristics used to inform the model were based on the pooled INNO$_2$VATE trials and not the UKRR cohort used to inform the transitions. It was unclear what might have been the limitations of this or whether any potential bias had been introduced.

4.2.3. Population

In line with the NICE final scope, the modelled patient population reflected DD-CKD patients with anaemia. Two patient populations were pooled together in the company analysis, which reflected the two populations of the INNO$_2$VATE trials:

- INNO$_2$VATE – incident (n = 369)
- INNO$_2$VATE – prevalent (n = 3554)

Although the NICE final scope requested subgroup analysis according to previous exposure to ESAs if evidence allowed, the company did not provide any further analysis beyond the pooled INNO$_2$VATE data. When asked to provide a subgroup with this population, the company provided further data tables from this subgroup but did not incorporate them into the cost-effectiveness model, therefore a cost-effectiveness analysis of this subgroup was not possible. In Section 3.2.3.3, the EAG noted the subgroup analysis in this population was inconsistent, although vadadustat showed a small numerical benefit over darbepoetin alfa for two clinical outcomes.

A summary of baseline characteristics used to inform the model are provided below in Table 24. The method of pooling used by the company involved calculating averages weighted by the size of the study for categorical covariates and calculating overall proportions of the pooled sample size in each category for categorical covariates. The proportions of patients on each type of dialysis were calculated based on the safety analysis set of the pooled trials (n = 3902), whereas the other baseline characteristics were calculated based on the randomized pooled population (n = 3923). The rationale for this was not provided by the company.

Table 24: Population settings used in the base case of the cost-effectiveness model, based on the pooled INNO2VATE trials baseline characteristics

Characteristic	INNO2VATE trials - pooled (n = 3923)
Age - mean	57.9
Proportion female – %	43.6%
History of CVD – %	49.5%
History of CVD, type	
MI	48.9%
Stroke	51.1%
Thromboembolic events	0 %
Hospitalisation	0 %
Method of dialysis	
Peritoneal dialysis - %	7.9%
Haemodialysis - %	92.1%
Median time since dialysis initiation, years	2.4

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction

As discussed in Section 3.2.3.1, the EAG noted that the pooling of the trials applied a much larger weight to the characteristics from the prevalent trial given the larger sample size, which means that the model efficacy is primarily informed by patients who had been dialysis dependent for at least 16 weeks before treatment with vadadustat (the $INNO_2VATE$ – prevalent trial population). The EAG also noted that there was a larger proportion of patients with a history of CVD in the $INNO_2VATE$ – prevalent trial which would be expected to have an impact on the number of further MACE events observed in the trial. At clarification stage, the EAG requested the company provide subgroup analyses for the two separate populations using the $INNO_2VATE$ trials in the cost-effectiveness model. However, the company stated that as MACE outcomes are a key part of the model and are only available for the pooled population, the company were unable to provide the requested subgroup analyses.

Given the imbalance in the sample sizes, and without subgroup analyses, it was not possible for the EAG to fully consider the efficacy and cost-effectiveness outcomes of the incident and prevalent populations independently. This limited the extent to which the EAG could fully interpret outcomes in a real-world setting, where both incident and prevalent patients may be treated. This was relevant to not only the MACE events, but other outcomes considered within the model (e.g., Hb levels). As the EAG's modified model structure removed MACE (discussed in Section 4.2.2 and 6.2), and the majority of inputs for the model were provided separately in

the original model submitted, the EAG has explored subgroup analyses for the incidence and prevalent patients separately. However, this was subject to some limitations. Further details of this analyses are found in Section 6.2.

4.2.4. Interventions and comparators

In the INNO$_2$VATE trials, vadadustat was dosed at 300mg per day (2 x 150 mg tablets) with appropriate titration to between 150mg and 600mg. Dose changes were made with the intention of maintaining or achieving target Hb levels of 100-120g/L. The company calculated mean weekly doses between week 2 to 52, week 64 to 104, and week 116 to 156 from the INNO$_2$VATE trials to inform mean weekly dose inputs for years 1, 2, and 3 in the model. The mean weekly dose for year 3 was also used for the remaining years in the model time horizon.

The company's base case included darbepoetin alfa as the main comparator, with scenario analyses that compared vadadustat to other injectable ESAs currently available in UK practice. Dosing for darbepoetin alfa for the base case of the model was carried out in the same manner to vadadustat, i.e., calculating mean weekly doses for years 1, 2, and 3+ from the pooled INNO$_2$VATE trial data. The company sourced the doses for other ESAs included in the model using ESAs conversion factors from a study on dose conversion ratios in ESAs for patients on haemodialysis.[22]

The average doses per week (without wastage) for years 1, 2, and 3+ for vadadustat and darbepoetin alfa applied in the company's base case are presented in Table 25.

Table 25: Weekly doses of vadadustat and darbepoetin alfa used in the model base case, as calculated from the INNO2VATE trials

	Vadadustat (mg)	Darbepoetin alfa (mcg)
Year 1	[redacted]	32
Year 2	[redacted]	37
Year 3+	[redacted]	40

The company justified choosing darbepoetin alfa as the main comparator to be in line with the INNO$_2$VATE trials. Clinical opinion sought by the EAG noted that the choice of injectable ESAs varies by region. Therefore, darbepoetin alfa may not be used throughout the UK. Despite this variation, the EAG agreed that darbepoetin alfa is likely to be the most appropriate comparator in the base case. This was primarily driven by: the acceptance of the class effect between injectable ESAs (discussed in Section 3.3, darbepoetin alfa being the comparator in the pivotal

$INNO_2VATE$ trials, and darbepoetin alfa resulting in the lowest cost per week compared to the other injectable ESAs. Given this reasoning, the EAG focuses its critique on the comparison between vadadustat and darbepoetin alfa.

4.2.5. Perspective, time horizon and discounting

In line with NICE methods guidance, economic analyses were undertaken from an NHS and PSS payer perspective. Discount rates for costs and outcomes were chosen to be 3.5% per annum as per NICE methods guidance. Overall, the EAG were satisfied that the perspective adopted, and discounting applied are aligned with the NICE reference case.

The time horizon for the trial was chosen to be 42 years. The justification from the company was that all patients had died within the model after around year 41 (a typographical error in the company submission previously stated this as 13), indicating that 42 years is more than ample to cover the lifespan of the patients.

The company applied a 3-month cycle length (with half cycle correction), justified based on the recommended frequency of monitoring iron deficiency in the NICE guideline on managing CKD. The company also stated that three months was considered appropriate to monitor changes in Hb levels alongside results of the therapy used. The EAG agreed that three months is appropriate regarding Hb levels. However, the company's model focuses on transitions between MACE events and transplant, with Hb levels considered separately as a component to HRQoL only.

The EAG therefore asked the company to justify its three-monthly cycle length for MACE. The company confirmed that within the $INNO_2VATE$ trials, most patients only experienced one MACE, with subsequent MACE happening on average 97.3 days after the first, and 91.3 days after the second. As such the company believe that multiple events are unlikely to occur within the 3-month cycle length. The company also stated that they believed that a 3-month cycle length is conservative as the treatment effect is likely to be underestimated if multiple transitions occur within a cycle. This is because the modelling of vadadustat lowers progression events, and additional time spent in active treatment health states is likely to over-estimate treatment costs. This contradicts the company's justification for the appropriateness of the cycle length if this statement were true, however, and the EAG saw no evidence that the 3-month cycle length could be conservative to vadadustat.

Overall, the EAG were satisfied that a 3-month cycle length is appropriate for decision making and is aligned with the EAG model changes. Justification for the 3-months is based on the availability of evidence to inform model health state transitions between DD and transplant and information available to inform Hb levels. Section 6.2 provides further details on changes the EAG has made to the company model.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Overview of treatment effectiveness reflected within the model

The company's model captures the impact of treatment through transitions between MACE events and mortality, which impact the resulting transitions between the 'DD' and 'Transplant' health states. Quality-of-life impacts are modelled through Hb levels. The pooled INNO$_2$VATE trials have been used to derive the transitions between the MACE events and Hb levels. External literature sources have been used to model the transitions between the 'DD', 'Transplant' and 'Death' health states.

A summary of data sources used for each transition and time points are provided in Table 26, provided by the company in response to clarification questions.

Table 26: Summary of data used for each health-state and transitions

Modelling feature	Data source
Main health state	25th UKRR report[4] for baseline transitions between dialysis, transplant and death in DD CKD patients is applied through model time horizon except for mortality Long-term mortality data (beyond cycle 20) is based on linear regression estimates of survival since kidney replacement therapy start in line with 25th UKRR report[4]
Treatment status	Discontinuation rates from INNO$_2$VATE trials for Cycles 0-2, Cycles 3-4, Cycles 5-20 Discontinuation rates were assumed to be constant beyond cycle 20 All transplant patients discontinued vadadustat in line with INNO$_2$VATE trials' design In cycle 1 in vadadustat arm, proportion of patients with Hb level <10 g/dL in line with the stopping rule was used to estimate rate of discontinuation
MACE substate	INNO$_2$VATE trial IPD data for estimating risk of MACE and death in anaemia DD CKD patients with and without prior history of MACE is applied through model horizon for the ESA arm and for vadadustat arm beyond treatment waning timepoint HR of MACE risk for vadadustat relative to darbepoetin alfa from INNO$_2$VATE trials is applied up to a point of treatment waning of vadadustat
Haemoglobin substate	Proportion of patients falling into different Hb level cut-offs from INNO$_2$VATE trials' IPD data was applied for Cycles 0-2, Cycles 3-4, Cycles 5-20

Modelling feature	Data source
	Distribution of patients between Hb level cut-offs was assumed to be constant beyond cycle 20 (5 years)

Abbreviations: CKD, chronic kidney disease; DD, dialysis dependent; Hb, haemoglobin; HR, hazard ratio; IPD, individual patient-data; MACE, major cardiovascular event

Source: Company clarification response

The following sub-sections consider the transition elements separately and contain the EAG's critique of these aspects of the company's model.

4.2.6.2. Transition probabilities: DD → Transplant → Death

The transitions between the 'DD', and 'Transplant' health states were estimated from the 25th UKRR Annual Report.[4] The start and subsequent kidney replacement therapy (KRT) modalities for adult patients incident to KRT in 2016 at 90 days, 1 year, 3 years and 5 years, were used to establish the proportion of patients in each health state at each time point. HD and PD modalities were combined to inform the proportion of patients in the 'DD' state (Table 27). Linear extrapolation was then used to estimate the proportions in each health state per model cycle between the above time points. The probabilities of moving between health states per model cycle were calculated from the proportions in each health state per cycle. The EAG considered the use of the UKRR annual report to be appropriate.

Table 27: Proportion of patients in each health state

Starting health state at time 0	**DD**			**Transplant**		
Resulting health state	**DD**	**Transplant**	**Death**	**DD**	**Transplant**	**Death**
90 days	94.0%	1.6%	4.4%	0.5%	99.3%	0.2%
1 year	77.3%	8.4%	14.3%	1.1%	97.7%	1.2%
3 years	44.9%	20.4%	34.7%	1.5%	94.6%	3.9%
5 years	24.6%	23.4%	51.9%	1.9%	89.5%	8.6%

Abbreviation: DD, dialysis-dependent

Source: Company's economic model

4.2.6.3. MACE events

To determine the occurrence of MACE events, data from the pooled INNO$_2$VATE trials were utilised. MACE was defined as non-fatal myocardial infarction (MI) and non-fatal stroke. The company used this MACE definition as the base case as it was the primary safety endpoint in the INNO$_2$VATE trials. An alternative MACE definition was also provided, which included

hospitalisation for heart failure and thromboembolic events excluding vascular access thrombosis. This was labelled 'expanded MACE' and tested in a scenario analysis.

For the comparator arm, the IPD from the pooled INNO$_2$VATE trials was used to estimate the probability of a MACE event per cycle for the first four model cycles. For vadadustat, the probability of a MACE event per cycle was derived using a HR of 0.96 (95% CI 0.833 – 1.113), estimated from the INNO$_2$VATE trials of time to first MACE event, applied to the darbepoetin alfa MACE probabilities.

These probabilities were used to derive the transition matrices for cycle 1, cycles 2-4, cycles 5-12 and cycles 13-20+, combined with the probabilities of moving between the 'DD' and 'Transplant' health states described in Section 4.2.6.2. Due to the adjustment to account for median time on dialysis at 2.4 years, the transition matrix for cycle 5-12 was used at baseline. The death events from the IPD were used to inform the transitions to death which were proportionally split by MACE and non-MACE related deaths using data from the 25th UKRR Annual Report.[4]

In the company's base case, a treatment waning effect was applied at 5 years to account for a potential reduction in the vadadustat treatment effect on MACE events. After this time point, the vadadustat treatment arm use the transition probabilities of the darbepoetin alfa arm.

The EAG had concerns with the appropriateness of including MACE in the model structure and the application of the data within the model. These are discussed in Sections 4.2.2.2 and 4.2.2.3. As part of clarification questions, the company were asked to provide justification for assuming a treatment effect for vadadustat, given the point estimate of the HR is close to 1 and the 95% CI crosses 1. However, the company provided no further evidence. The EAG also requested the company justify the appropriateness to apply a HR, instead of using the same approach to estimate MACE as per the injectable ESA arm. The company provided evidence to support the proportional hazard assumption and provided a scenario using the same approach as the comparator to calculate the MACE transitions using IPD. Due to the company's approach of adjusting for median dialysis (see Section 4.2.2)., this scenario only used data from Q3 of the INNO$_2$VATE MACE data, which demonstrates worse MACE point estimates for vadadustat compared to darbepoetin alfa. It therefore resulted in an overall life-year and QALY loss for vadadustat (-0.05 and -0.04 for LY and QALYs, respectively). The EAG consider this to support the conclusion that, overall, there is no evidence of a difference in MACE between vadadustat and injectable ESAs (given the HR approach gives a slight incremental LY and QALY benefit vs

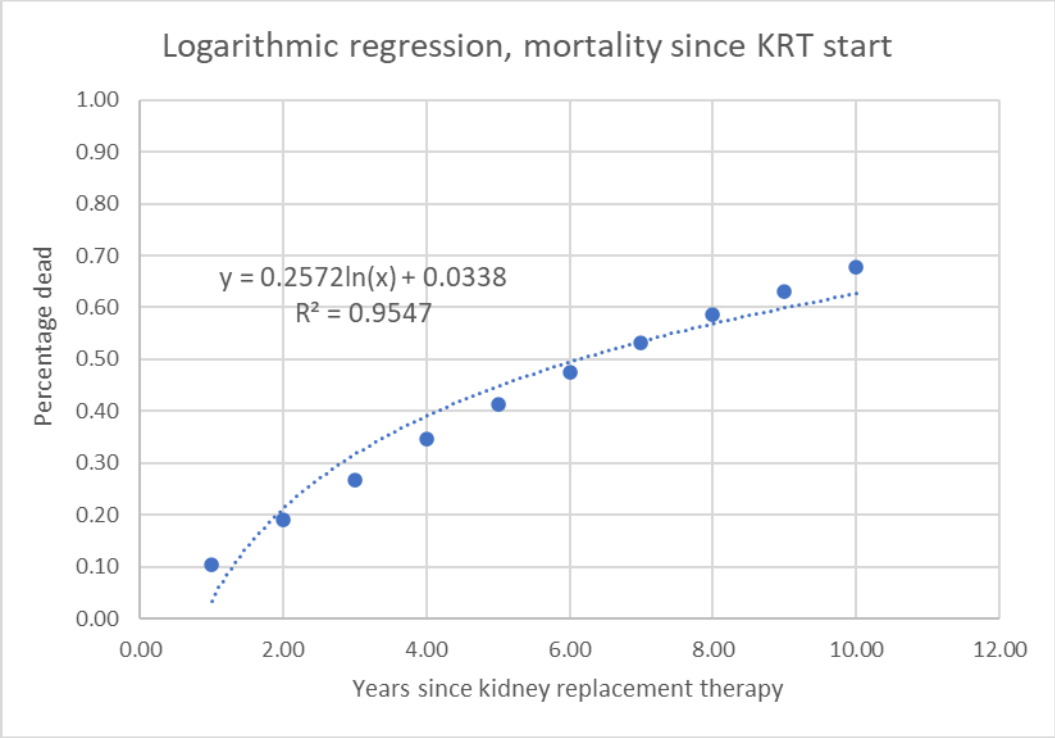
using the IPD approach). The EAG therefore believes that the company's approach to adjust the INNO$_2$VATE data for median time to dialysis is incorrect (see Section 4.2.2).

4.2.6.4. Long-term mortality

Transition probabilities from cycle 20 were adjusted for probability of death informed by long-term survival data reported in the 25th UKRR annual report.[4] The UKRR 25th annual report presents a 10-year rolling cohort of incidence patients from start of KRT according to age at KRT start. The age group 55-64 was used for the economic model as this aligned with the model's patient population. The survival data was digitized, with the proportion surviving at each time point subtracted from 100% to estimate mortality. The company used this data to derive a regression model to derive long-term mortality estimates. Both linear and logarithmic regression models were derived.

Based on clinical opinion that after 10 years a plateau in mortality is expected, the company chose the logarithmic regression model to inform long-term mortality (Figure 4). The logarithmic regression model was used to adjust the transition probabilities from cycle 20 onwards for the darbepoetin alfa arm (assuming the same split of MACE and non-MACE fatalities). For vadadustat, the long-term survival was adjusted for the time since first MACE HR and used to adjust the transition probabilities from cycle 20. Mortality estimates in both arms were adjusted for age-sex matched general population if mortality was estimated to go below general population.

Figure 4: Logarithmic regression model for mortality



Key: KRT, kidney replacement therapy

Source: CS Figure 9

The EAG was unclear why the company decided to extrapolate the mortality data using a logarithmic regression model, instead of using parametric survival models as outlined in NICE TSD 14,[23] and asked the company to provide these at clarification stage. The company created pseudo patient-level data using the Guyot algorithm and fitted parametric models to the UKRR data using the *flexsurv* package in R. The statistical and visual fits are provided in Table 28 and Figure 5, respectively.

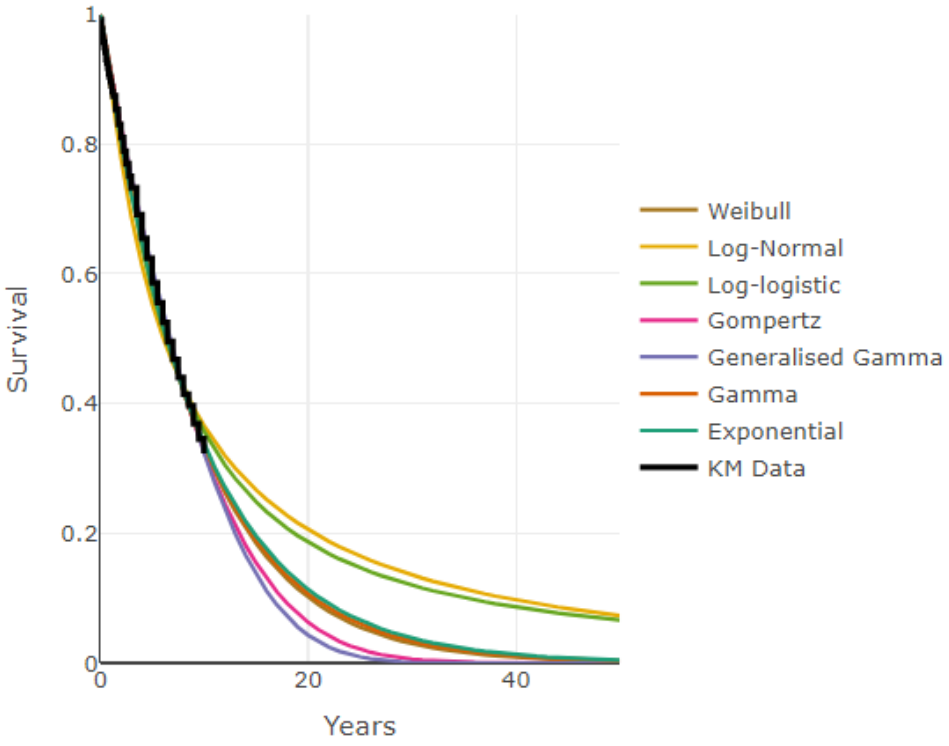
Table 28: Statistical fits for UKRR survival data

Model	AIC	AIC Rank	BIC	BIC Rank
Generalised Gamma	150,505	1	150,530	1
Gamma	150,815	4	150,832	4
Log-logistic	152,083	6	152,100	6
Log-Normal	153,683	7	153,700	7
Gompertz	150,588	2	150,604	2
Weibull	150,780	3	150,797	3
Exponential	150,855	5	150,863	5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; UKRR, United Kingdom renal registry

Source: Company response to clarification questions Table 13

Figure 5: Parametric models fit to UKRR survival data



Abbreviations: KM, Kaplan-Meier; UKRR, United Kingdom renal registry

Source: Company response to clarification questions Figure 2

The company felt that log-logistic and log-normal provided long-term outcomes which were too optimistic at 40 years (10% alive). For the company's scenario, therefore, the Gompertz curve was chosen, as it was the best fitting model most compatible with proportional hazards. The EAG agreed that log-logistic and log-normal appear too optimistic in the long-term. Generalised gamma is statistically the best fitting but has the most pessimistic outcomes. Given that the EAG don't consider MACE in their modified model structure – and therefore do not apply a MACE HR – the choice of curve is not impacted by the proportional hazard properties (as HRs should only be applied to curves which support the proportional hazard assumption).

The clinical expert consulted by the EAG suggested that 3% survival at 40 years would be fairly optimistic but not overly so for patients starting dialysis and suggested that gamma or exponential might be plausible curves. As gamma yields slightly better AIC and BIC fit statistics,

this has been chosen to inform the EAG's base case. Generalised gamma, exponential, and Gompertz are tested in scenario analysis (see Section 6.2).

4.2.6.5. Haemoglobin levels

Haemoglobin was split into three categories (regardless of health state occupancy); 1) <10 g/dL, 2) ≥10 - <12 g/dL, and 3) ≥12 g/dL. The proportion of patients in each Hb level was informed by the pooled INNO$_2$VATE trials for the first five model cycles (0-4). After cycle 4 (week 52), the distribution of patients in each Hb category was assumed constant. The proportion of patients in each haemoglobin health state were used to determine quality of life impacts for patients in the "DD" health state.

The company used the treatment specific data from the INNO$_2$VATE trials, which aggregated patients into respective Hb categories at the different timepoints. The EAG considered there were several limitations with this:

- The approach resulted in the baseline distribution of haemoglobin levels to differ between the vadadustat arm and the injectable ESAs arm, as shown in Table 29.
- An extension to this was that the distribution of Hb levels was based on aggregate outcomes and not relative differences based on the same initial starting point. This was a limitation in the analysis as the starting points for the two arms are different, which limited the ability to understand the impact that the treatment had over time.
- A further limitation in the approach was that by using aggregate outcomes, transparency was lost in the process as it's not possible to understand the proportion of patients on each treatment arm moving between all the possible Hb states. That is:
  - The % of patients with <100 g/L who stay in <100 g/L
  - The % of patients with < 100 g/L who move transition to ≥100-<120 g/L
  - The % of patients in with < 100 g/L who move transition to ≥120 g/L
  - The % of patients with ≥100-<120 g/L who transition to <100 g/L
  - The % of patients with ≥100-<120 g/L who remain in ≥100-<120 g/L
  - The % of patients with ≥100-<120 g/L who move transition to ≥120 g/L

  - The % of patients with ≥120 g/dL who transition to <100 g/L
  - The % of patients with ≥120 g/L who transition to ≥100-<120 g/L
  - The % of patients with ≥120 g/L who remain in to ≥120 g/L
- This was important not only to understand the relative effectiveness of vadadustat versus darbepoetin alfa, but crucially to understand the proportion of patients not benefitting from treatment with vadadustat. These patients, in line with the SmPC guidance, would be expected to discontinue treatment.

Given the limitations, the EAG requested the company to provide a scenario using the same baseline haemoglobin distribution and using transitions between the haemoglobin categories using the count methodology. This was subsequently provided by the company as an option in the economic model. The distribution of patients between each Hb level using the original estimates and revised approach are presented in Table 29.

Table 29: Cohort distribution by Hb level

Treatment/ Hb level		Week 1	Week 12	Week 24	Week 36	Week 52
		Cycle 0	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Original distributions	**Vadadustat**					
	<100 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥100-<120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ESA					
	<100 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥100-<120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised distributions	**Vadadustat**					
	<100 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥100-<120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ESA					
	<100 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥100-<120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥120 g/L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: Hb, haemoglobin

Source: CS Table 48

The granularity in the revised approach allowed the EAG to better understand the efficacy of treatment and apply an appropriate discontinuation based on the SmPC guidance. The EAG used the same distribution of Hb levels at baseline and used this revised approach in the EAG base case (see Section 6.3).

4.2.6.6. Treatment discontinuation

The proportion of patients on treatment per model cycle was informed by data from the pooled INNO$_2$VATE trials. The trial data was available for the first 52 weeks. After this, the company assumed within the model that there was no further treatment discontinuation on either treatment arm.

The company also applied a treatment stopping rule for patients on vadadustat at 24-weeks for those who had Hb level under 100 g/L. Patients are discontinued treatment from model cycle 1 (week 13) and are assumed to receive darbepoetin alfa treatment, and thereafter have the discontinuation rates and transition probabilities from the darbepoetin alfa arm applied. The proportion of patients discontinuing vadadustat due to the stopping rule was based on the maximum value between the proportion with Hb level < 100g/L in cycle 2 ([redacted]) or the proportion not on treatment in cycle 2 (16.3%).

This proportion does not align with the proportion of patients in the '<100g/L' category in the model at cycle 1 (42.0%), which is calculated from the proportion of patients in the INNO$_2$VATE trials in cycle 1. The EAG was concerned that the misalignment of the timing of this discontinuation (i.e., 13 weeks versus 24 weeks) may underestimate the proportion of patients still on treatment between these time points by discontinuing them too soon. When asked to clarify the difference in these timings, the company justified it as cycle 2 starts at week 26, which is beyond the 24-week stopping rule, so instead they discontinued patients at cycle 1 (week 13). However, the EAG noted that when you factor in half cycle correction, cycle 1 translates to week 7, whereas cycle 2 translates to week 20.

The company were asked to provide justification for assuming no further treatment discontinuations occur after one year. The company assumed that discontinuations happened within the first year, as this was sufficient for patients to discontinue due to adverse events or suboptimal Hb levels. However, most of the discontinuations which happened in the INNO$_2$VATE trials in the first year were classed as "subject no longer wants to receive study drug". While the company could not provide any further granularity, they informed the EAG that they had assumed it was 1) due to the open-label design of the trial and 2) patients preferring to

use a drug where the efficacy and dose of the drug is well-known. As such, there appears no reason to assume that these types of discontinuations did not still occur after the first year of treatment. Longer follow-up data of the INNO$_2$VATE trial data is available, and the Kaplan-Meier plots provided by the company at clarification stage show treatment discontinuations occurring after 52 weeks (Figure 6).

Figure 6: Kaplan-Meier plot of treatment discontinuations in the INNO$_2$VATE trials

At clarification stage, the company also provided an alternative way of estimating the proportion of patients on treatment per cycle using parametric survival models fitted to the treatment discontinuation data. Transplant and death were classed as censored events in order to estimate the proportion of patients on treatment within the 'DD' health state as it is applied in the

economic model however the company also provided an analysis where they were classed as events. Statistical goodness of fits are presented in Table 30 and visual fits in

Figure 7 and

Figure 8. The company considered the Weibull model to be the best fitting model as it was less than 3 difference in AIC and BIC statistic. However, they did not provide any further justification for this choice.

Table 30: Statistical fits for parametric models fit to time to treatment discontinuation data from INNO$_2$VATE trials (censored analysis)

Model	Vadadustat				Darbepoetin alfa			
	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Generalised Gamma	10,972	1	10,989	5	6,977	2	6,994	5
Gamma	10,974	4	10,985	3	6,978	4	6,989	4
Log-logistic	10,972	2	10,983	1	6,983	6	6,994	6
Log-Normal	10,990	6	11,001	7	7,011	7	7,022	7
Gompertz	10,976	5	10,987	4	6,975	1	6,986	2
Weibull	10,973	3	10,984	2	6,978	3	6,989	3
Exponential	10,995	7	11,000	6	6,979	5	6,984	1

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

Source: Company response to clarification questions Table 23 & Table 24

Figure 7. Parametric curves fitted to the treatment discontinuation data for each arm of the INNO$_2$VATE trials for vadadustat arm (censored analysis)

Abbreviations: KM, Kaplan-Meier

Source: Company response to clarification questions Figure 5

Figure 8. Parametric curves fitted to the treatment discontinuation data for each arm of the INNO$_2$VATE trials for darbepoetin alfa arm (censored analysis)

Abbreviations: KM, Kaplan-Meier

Source: Company response to clarification questions Figure 6

The EAG's preferred approach was the application of parametric distributions to the time to discontinuation data from the INNO$_2$VATE trials classing transplant and death as events instead of being censored. This, therefore, informs the EAG base case (see Section 6.2.2 and 6.3). In addition to this, the EAG chose to remove the proportion of patients who have not experienced an adequate response to treatment with vadadustat in Cycle 2 of the model, to align with the SmPC and how vadadustat will be used in practice.

The limitation associated with the stopping rule for vadadustat is that the efficacy of the treatment is based on patients remaining on treatment, and therefore maintaining Hb levels. This adds an element of bias towards darbepoetin alfa given the lack of a stopping rule for this treatment. However, in the absence of data from INNO$_2$VATE that consider the stopping rule for vadadustat, it is not possible to account for this in the model. Application of a treatment waning effect would be a possibility for those patients discontinuing treatment. However, this does not

address this limitation, given that there was not much difference in Hb response between arms in the INNO$_2$VATE trials – any differences that were witnessed favoured the darbepoetin alfa arms.

4.2.6.7. Adverse events (other than MACE)

The company incorporated adverse events (AEs) which were not considered to be MACE (see Section 3.2.3.3) within the cost-effectiveness model. AEs were informed from the pooled INNO$_2$VATE trials and were based on severe TEAEs which occurred in at least 2% of patients on either treatment arm. This resulted in the consideration of pneumonia, sepsis, fluid overload, and hyperkalaemia (Table 31). The cost-effectiveness model assumed that the darbepoetin alfa arm in the INNO$_2$VATE trials was reflective of other ESAs.

The health-related impact and corresponding costs of treating the AEs were incorporated within the cost-effectiveness analysis and are reported in Sections 4.2.7.4 and 4.2.8.7, respectively.

Table 31: Proportion of patients experiencing severe TEAEs excluding MACE

Adverse event	Vadadustat		ESA	
	Percentage of patients (%)	SE	Percentage of patients (%)	SE
Pneumonia	4.4%	0.4%	3.9%	0.4%
Sepsis	3.2%	0.3%	3.3%	0.3%
Fluid overload	3.6%	0.4%	2.3%	0.2%
Hyperkalaemia	0.2%[a]	0.0%	0.2%*	0.0%

Abbreviations: ESA, erythropoietin stimulating agent; SE, standard error; TEAE, treatment-emergent adverse event

Note:

[a] The percentage of patients experiencing hyperkalaemia was >2% in INNO$_2$VATE – incident. However, when a weighted average of the percentage of patients experiencing hyperkalaemia in INNO$_2$VATE – incident and INNO$_2$VATE – prevalent was calculated, it was 0.2% for both the treatment arms, as the sample size of INNO$_2$VATE – incident is much lower than the sample size of INNO$_2$VATE – prevalent.

Source: CS, Table 52

4.2.7. Health-related quality of life

4.2.7.1. Impact of health state

HRQoL data were not reported in the INNO$_2$VATE trials. Therefore, the health state utilities for the dialysis dependent and transplant health states were derived from Liem et al., 2008[24] which was a meta-analysis of utility values for patients on either HD, PD, or those who had a renal transplant. These patients had end-stage renal disease but were not necessarily anaemic. The company considered Liem et al. as the most appropriate source as it was previously used to inform TA807 for roxadustat in CKD.

The utilities from Liem et al.[24] were used to inform the utilities of the 'no MACE' substates, with additional disutilities for MACE events applied. The disutilities associated with each of the MACE events were derived from a catalogue of EQ-5D scores for the UK (Sullivan et al., 2011[25]) as reported in Table 32. The total disutility applied was based on the type of MACE event and the corresponding frequency, as observed in the INNO$_2$VATE trials (see Section 4.2.6.3). The company base case assumed that a patient having a history of thromboembolic events, or a history of heart failure, carried no additional deficit to subsequent quality of life. The CS did not explicitly outline the method used to calculate the annual disutility estimates for the 'new MACE' and 'history of MACE' health states using the frequencies and MACE type-specific disutilities within the submission. Both of the studies used to inform health state utility values (Liem et al.[24] and Sullivan et al.[25]) used EQ-5D to estimate index scores.

The utilities for the 'DD' and 'Transplant' health states and associated disutilities for MACE and events are presented in Table 32.

Table 32: Health state utilities and disutilities associated with MACE events in the company's base case

	Utility	**Source**
Health state		
Dialysis dependent, no MACE	0.56	Liem et al., 2008[24]
Transplant, no MACE	0.81	
Type of MACE		
MI	-0.0626	Sullivan et al., 2011[25]
Acute stroke	-0.1171	
Acute thromboembolic event	-0.0646	
Acute (sustained) HF	-0.1167	
Resulting disutility for new MACE events		Average disutility weighted by frequency of each MACE event observed in INNO$_2$VATE trials
Vadadustat	-0.075	
Darbepoetin alfa	-0.076	
History of MACE event		
History of MI	-0.0368	Sullivan et al., 2011[25]
History of stroke	-0.0349	
History of thromboembolic event	0 (assumed)	
History of HF	0 (assumed)	

	Utility	Source
Resulting disutility for history of MACE events		Average disutility weighted by frequency of history of each MACE event observed in INNO2VATE trials
Vadadustat	-0.036	
Darbepoetin alfa	-0.036	

Abbreviations: HF, heart failure; MACE, major adverse cardiac event; MI, myocardial infarction

Following review of the sources used by the company to inform health state utility values, the EAG identified a more recent and potentially more relevant source from Cooper et al., 2020.[26] This is a systematic review of CKD patients' HRQoL scores and detailed utility values for both dialysis-dependent and post-transplant patients. The company added this source as a scenario following clarification questions, from which they derived the HSUs shown in Table 33.

Table 33: Health state utility values derived from Cooper et al. (2020)[26]

Health state	Utility value
Dialysis-dependent (calculated as a weighted average using proportions on each dialysis type in INNO$_2$VATE trial)	0.66
Renal transplant	0.83

Although neither Liem et al. nor Cooper et al. included anaemia-specific values, both reported outcomes associated with CKD stage and are therefore considered justifiable as anaemia-related disutilities were applied separately (i.e. Hb levels). The EAG used the more recent study (Cooper et al., 2020[26]) to inform it's preferred base case (see Section 6.3).

The EAG agreed with the use of Sullivan et al., 2011[25] to inform disutilities associated with MACE events. However, given the large decrement associated with the incidence of thromboembolic events, it was unclear why this was assumed to have no long-term effect.

4.2.7.2. Impact of Hb

Hb levels, although not explicitly captured in the health states in the model, were associated with additional utility adjustments in the company base case. These adjustments were made based on a cost-effectiveness analysis for anaemia treatment in patients with chronic kidney disease from Yarnoff et al. (2016),[27] which gave a utility decrement of -0.0114 for a 1 g/dL (10 g/L) decrease in Hb from the reference of 13 g/dL (130 g/L). The company used this estimate to calculate utility decrements for each of the Hb categories described in the model. This was applied by first calculating the additive disutilities for each 10g/L (1g/dL) decrease in Hb level

(with a Hb level of <70g/L having a fixed utility), and then estimating the mean distutility for each of the defined categories. The decrements calculated and used in the company's base case are presented in Table 34.

Table 34: Disutilities associated with Hb categories in the company's base case

Hb level	Utility decrement
<100 g/L	-0.0627
≥100 g/L - < 120g/L	-0.0285
≥120 g/L	-0.0057

Abbreviations: Hb, haemoglobin

The EAG believed that the use of the utility decrement per 10 g/L from the cost-effectiveness analysis by Yarnoff et al. (2016)[27] is appropriate, given that this analysis was also conducted in anaemia patients with CKD. The EAG also noted that the additive disutility approach was applied in the same way in TA807[28] for roxadustat, and therefore agreed with the inclusion and methodology.

4.2.7.3. Impact of treatment

In the cost-effectiveness model, the only treatment-specific increments in utility were due to the method of administration, which is explored in the company's scenario analysis. The utility increments were derived from a study which assessed a cost-effectiveness model evaluating roxadustat for the treatment of anaemia in non-dialysis-dependent CKD patients (Lorenzo et al., 2023[29]). In the paper, the utility increment for receiving oral administration of roxadustat three times weekly was estimated to be 0.041 per year. For injectable ESAs, the utility increment for receiving subcutaneous injection once every four weeks compared to every two weeks was 0.017 per year, but it was expected that only 35% of patients would receive an injection once every four weeks. The proportion of patients on each injection frequency was then multiplied by the corresponding utility increment (0.017 for every four weeks and 0 for every two weeks as this was the reference) to calculate a weighted mean increment to be applied to the darbepoetin alfa group. The company applied by-cycle utility increments by dividing these yearly increments by 4 (the number of cycles per year). The company acknowledged that this increment would only affect patients on peritoneal dialysis. It was therefore only applied on those patients in the model.

The EAG noted that the utility increments associated with the mode of administration of treatment differed between the model and the CS, and that the inputs in the model are the correctly applied utilities from Lorenzo et al. (2023).[29] The EAG believed that this source was appropriate to inform the utility increments associated with the mode of administration.

After consultation with clinical experts, it was apparent that some patients may find taking an oral treatment instead of injectable ESAs more of a burden, given the amount of other oral treatments most patients are likely to have (discussed in Sections 2.2 and 3.2.2.2 relating to Key Issue 2). This may incur a decrement to a patient's quality of life. The EAG agreed with the company that any benefit of an oral treatment would be to those patients on PD. However, for those on HD, a utility decrement may also be appropriate to account for the additional 'pill burden'. The EAG has explored a scenario applying a decrement to those patients on HD. Further details can be found in Section 6.2.

4.2.7.4. Impact of adverse events (other than MACE)

Non-MACE adverse event disutilities for pneumonia and sepsis were also derived from the catalogue of EQ-5D scores for the UK (Sullivan et al., 2011[25]). Prior NICE technology appraisals (TA599[30] and TA807[28]) were utilised to derive disutility values for fluid overload and hyperkalaemia. The disutility values and sources are presented in Table 35.

Table 35: Non-MACE related disutilities

	Utility decrement	Stated source
Non-MACE related		
Pneumonia	-0.0776	Sullivan et al. 2011[25]
Sepsis	-0.0559	Sullivan et al. 2011[25]
Fluid overload	-0.0029	TA599[30]
Hyperkalaemia	-0.0300	TA807[28]
Duration of non-MACE related disutilities, cycles	0.1533 (equivalent to two weeks)	Assumed

Abbreviations: MACE, major adverse cardiac event

The EAG considered the source from Sullivan et al., 2011[25] to be appropriate in informing the disutility associated with pneumonia. However, the company also used the disutility associated with HIV infection in Sullivan et al.[25] as its source for a disutility associated with sepsis. The appropriateness of this disutility was unclear to the EAG, and the reason why it was used as a proxy was not provided by the company.

The source for the disutility associated with fluid overload was deemed to be appropriate by the EAG. The disutility associated with hyperkalaemia could not be found in the source stated by the company, however this disutility was used in other appraisals (TA877).[31]

The company assumed that the disutility for each of the non-MACE related adverse events would last for two weeks (0.1533 cycles) in the model. Their justification was that they expected that adverse events associated with vadadustat would arise shortly after treatment initiation. The EAG agreed that this assumption was broadly appropriate.

4.2.8. Resources and costs

4.2.8.1. Treatment costs

Treatment pricing

Prices for each injectable ESA were based on list prices on the British National Formulary (BNF).[32] The price per unit of each treatment used in the model was calculated by averaging the cost per unit (mcg/mg/IU) across all formulations of each treatment, as opposed to selecting the cheapest formulation.

The price of vadadustat was similarly calculated by taking an average unit price across all variations in pack size and dosage, though all formulations resulted in the same price per unit. The resulting costs per unit are presented in Table 36.

Table 36: Cost per unit for each treatment

Regimen	Cost per unit	Source
Vadadustat	[redacted] mg [redacted] mg with discount	MEDICE
Darbepoetin alfa (base case)	£1.47 mcg	BNF[32]
Epoetin alfa	£0.01 IU	
Epoetin beta	£0.01 IU	
Epoetin zeta	£0.00 IU	
CERA	£1.47 mcg	

Abbreviations: CERA, Continuous erythropoietin receptor activator; IU, international units; mg, milligrams; mcg, micrograms

The EAG believed that, while the unit costs of darbepoetin alfa (which informed the company's base case) were consistent across all treatment formulations, in general the model should select the formulation with the lowest price per unit from BNF instead of averaging across all

formulations for each treatment. This ensures that pricing of a new treatment represents at least a zero net health benefit to NHS patients as a whole, rather than a negative. This would have a minor impact on the costs of CERA and epoetin-A, -B and -Z.

Treatment dosing

The weekly dose of vadadustat and darbepoetin alfa in years 1-3 was based on the average dose received by patients in the pooled INNO$_2$VATE trials at the study timepoints between week 2 – 52; 64 – 104; and 116 – 156, respectively (see Table 25 for dosing at these timepoints). Though not included in the model base case, weekly doses of all other injectable ESAs were calculated using conversion factors relative to darbepoetin alfa (Table 37). Table 37: Treatment dosing in Year 1 and conversion factors used in the Company's modelDose conversions were also applied in the TA807 NICE submission for roxadustat,[28] which was approved. However, the EAG noted that TA807 employed different methodology by first converting all regimens from international units to micrograms for comparability, before deriving a conversion factor based on the weekly dose for each regimen as stated on the BNF. The company's base case did not apply any wastage to treatment costs. This was based on clinical opinion.

Table 37: Treatment dosing in Year 1 and conversion factors used in the Company's model

Regimen	Dose per Week (Without Wastage)	Dose Unit	Conversion Factor	Source
Vadadustat	[redacted]	mg	-	Pooled INNO2VATE trials
Darbepoetin alfa (base case)	32	mcg	-	Pooled INNO2VATE trials
Epoetin alfa	11,758	IU	362.5	FDA Prescribing Information for Aranesp[33]
Epoetin beta	11,758	IU	362.5	Assumed same as above
Epoetin zeta	11,758	IU	362.5	Assumed same as above
CERA	39	mcg	1.21	Choi et al. (2013)[22]

Abbreviations: CERA, Continuous erythropoietin receptor activator; FDA, U.S. Food and Drug Administration; IU, international units; mcg, micrograms; mg, milligrams.

The clinical experts consulted by the EAG agreed with the company that not including wastage was appropriate. There is vast experience in using these treatments, such that any wastage is minimal, if any.

The EAG noted that the dosing used in the model for injectable ESAs did not appear to be fully in line with BNF or the relevant SmPCs, specifically regarding epoetin-A, -B and -Z, and CERA, (Table 38). The model dosing frequency for darbepoetin alfa was aligned with BNF as being administered once weekly, so these discrepancies would not affect the model base case.

Table 38: Treatment doses in Company's model compared with the SmPCs

Regimen	Model Dosing (Per fortnight)[a]	SmPC Dosing (Per Fortnight)		
		Initial	Maintenance	Source
Vadadustat	14	-	-	-
Darbepoetin alfa (base case)	2	2	1-2	EMA (Aranesp)[34]
Epoetin alfa	4	6	4-6[b]	MHRA (EPREX)[35]
Epoetin beta	4	6	1-2[b]	EMA (NeoRecormon)[36]
Epoetin zeta	4	4-6[b]	4-6[b]	EMA (Retacrit[37] & Silapo[38])
CERA	2	0.5[c]-1	0.5[c]	EMA (Mircera)[39]

Abbreviations: BNF, British National Formulary; CERA, Continuous erythropoietin receptor activator; EMA, European Medicines Agency; HD, haemodialysis; MHRA, Medicines and Healthcare products Regulatory Authority; PD, peritoneal dialysis; SmPCs, Summaries of Product Characteristics.

[a] Note that doses in the Company's model were specified per week, not per fortnight. Weekly doses have been doubled to represent dosing per fortnight to align with treatments stated on the BNF that were administered less frequently (e.g., CERA).

[b] Value depends on dialysis type, i.e., HD or PD

[c] A dose of 0.5 signifies that treatment was administered once per month.

Furthermore, the EAG preferred the approach taken in TA807 for roxadustat regarding calculation of conversion factors by first converting all regimens into micrograms and then using dose information from the BNF. The TA807 approach resulted in a conversion factor for each individual regimen using the same source, as opposed to assuming the same conversion factor for epoetin-A, -B and -Z and using a different source to calculate a conversion factor for CERA, as in the company's approach. However, as only darbepoetin alfa was considered as a comparator in the company's base case, this change would not influence the model outcomes and therefore is not discussed further.

4.2.8.2. Administration costs

The proportion of patients receiving each treatment via intravenous, assisted subcutaneous or independent subcutaneous modes of administration in the model were based on several assumptions (Table 39).

Table 39: Company model assumptions related to treatment modes of administration

Patient Type	Company Assumptions	Source
Haemodialysis	Only HD patients received intravenous treatment	Assumption
	81% of HD patients required hospital admission to administer ESAs	Michalopoulos et al., 2022[40] supplementary materials table S1
	Some HD patients received treatment via independent subcutaneous injection	Calculation of HD patients *not* requiring hospital admission based on Michalopoulos et al., 2022[40]
Peritoneal dialysis	Only PD patients received treatment via assisted subcutaneous injection	Assumption
	15% of PD patients required nurse assistance to administer ESAs	TA807 (Section 4.2.9.1)[41], 15% of patients *not* receiving dialysis may require a home district nurse, and an additional 5% of patients may require hospital administration
	Some PD patients received treatment via independent subcutaneous injection	Calculation of PD patients *not* requiring nurse assistance based on TA807[41]

Abbreviations: ESAs, erythropoiesis-stimulating agents; HD, haemodialysis; PD, peritoneal dialysis.

The proportions of patients receiving each mode of administration were weighted in the model according to the UK population of dialysis-dependent CKD patients receiving HD and PD, (which in the model base case was 92.1% and 7.9%, respectively) based on the proportion of patients receiving each form of dialysis in the INNO$_2$VATE trials. The resulting weighted proportions of patients receiving each mode of administration, and associated costs, are shown in Table 40. As an oral treatment, vadadustat was assumed to have no administration cost.

Table 40: Administration costs of injectable ESAs in Company's model

Mode of administration	Weighted proportion of patients	Description	Price (£)	Cost Source
Intravenous	75%	Hospital administration (Band 6, per hour of patient related nurse work [15- minute appointment])	30.88	PSSRU (2019)[42] inflated to 2022/23 costs[43]
Independent subcutaneous injection	24%	-	0	Assumption
Assisted subcutaneous injection	1%	Home district nurse appointment (Band 6, per hour of patient related work [15-minute appointment])	22.95	PSSRU (2019)[42] inflated to 2022/23 costs[43]

Abbreviations: ESAs, erythropoiesis-stimulating agents; GBP, Great British Pounds; PSSRU, Personal Social Services Research Unit.

Overall, the EAG agreed with the approach used to inform administration costs. However, the EAG noted that the company's assumption that 15% of PD patients required nurse assistance was based on non-dialysis-dependent CKD patients, meaning this assumption may not hold when applied to DD patients. The costs of a nurse appointment were derived from an older version of the PSSRU (2019) and inflated, instead of using a more recent version of the PSSRU. However, it appears that more recent versions do not contain the exact same cost, specifically that of *patient-facing* nurse appointments. Therefore, the EAG considered the approach taken by the company to be appropriate. However, a scenario employing an updated, though not identical, costs using available information from the PSSRU (2022) was considered by the EAG in Section 6.2.

4.2.8.3. Rescue therapy costs

Additional therapies termed 'rescue therapies' were also costed for in the model. The aim of these therapies was to address rapid changes in Hb levels of patients in the short term. The therapies used were IV iron, RBC transfusion, and additional treatment with an ESA. The company assumed that these therapies only had an impact on costs, with no effect on efficacy of primary treatment or HRQoL.

IV iron rescue therapy

To calculate the costs of IV iron rescue therapy, the company used data from the INNO$_2$VATE trials on average weekly dose, unit cost of IV iron, administration costs and proportion of patients requiring IV iron rescue therapy. A summary of IV iron costs in the company's model is provided in Table 41.

Table 41: Summary of costs used for IV iron rescue

Category	Cost (£)	Source
Cost per 1mg of IV iron	0.09	BNF[32] (weighted by iron dextrose, iron sucrose, ferric carboxymaltose and NHS 2022-2023 financial year PCA database market shares[44])
IV iron administration	£356.38	National Cost Collection[45] (SA04G-L)

Abbreviations: IV, intravenous; NHS, National Health Service

The frequency of IV iron administration was not reported explicitly in the INNO$_2$VATE trials, so the company assumed that this was once weekly (i.e., 13.04 times per model cycle). The proportion of patients receiving IV iron rescue therapy was taken from the INNO$_2$VATE trials, and the company used these estimates at different timepoints to inform the proportion of patients on IV iron rescue therapy in specific cycles in the model (Table 42). The proportion of patients receiving iron rescue therapy at cycle 5 was applied for the remainder of the model time horizon of 42 years.

Table 42: Proportion of patients receiving IV iron rescue therapy at specific cycles in the model

Cycle	Weeks in INNO$_2$VATE trials	Proportion receiving IV iron rescue therapy	
		Vadadustat	ESAs
1	2-8	50.8%	53.0%
2	10-20	55.6%	55.6%
3	24-36	57.3%	56.8%
4	40-52	58.9%	59.2%
5+	64+	63.0%	65.0%

Abbreviations: ESA, erythropoietin-stimulating agents; IV, intravenous

RBC transfusion and ESA rescue therapy

For RBC transfusions and ESA rescue therapies, the company calculated rates per 100 patient-years (i.e., the number of events that would be expected to occur in 100 years of a patient's life) from the INNO$_2$VATE trials. These rates were then transformed into probabilities per cycle that were subsequently used in the model. The rates per 100 patient-years and probabilities per cycle for RBC transfusions are shown in Table 43. Both the rates of RBC transfusions and ESA rescue therapy were higher in the vadadustat arm and subsequently led to a higher probability of receiving these treatments per cycle in this arm.

Table 43. Rates of RBC and ESA rescue therapy in Company's model

Type of rescue therapy	Vadadustat	ESA
RBC transfusion (rate per 100 PY)	9.43	6.84
ESA (rate per 100 PY)	30.47	8.29
RBC transfusion (probability per cycle)	0.023	0.017
ESA rescue (probability per cycle)	0.073	0.021

Abbreviations: ESA, erythropoiesis-stimulating agent; PY, patient-years; RBC, red blood cell.
Source: Data was sourced from the pooled INNO$_2$VATE trials

The cost per episode of RBC transfusion was derived from the National Cost Collection 2021/2022.[45] For ESA rescue therapy, the company assumed that only darbepoetin alfa would be given. The dose of darbepoetin alfa applied per episode requiring ESA rescue therapy was assumed to be 75% higher than the overall average weekly dose for the patients treated with darbepoetin alfa. The mean weekly dose applied for ESA rescue therapy was 63.86 mcg of darbepoetin alfa. This mean weekly dose, and the corresponding cost, were applied in both the vadadustat and darbepoetin alfa arms in the model when patients required ESA rescue therapy.

The EAG believed that the approaches taken by the company in the application of IV iron and RBC infusion rescue therapies were appropriate, and accurately reflected the proportion of patients receiving these rescue therapies in the INNO$_2$VATE trials. The company sought clinical opinion on dosing for ESA rescue therapy, with the clinical expert suggesting that a 75% increase in the regular dose was appropriate. The EAG therefore agreed with the approach taken by the company.

However, the EAG noted that the treatment specific rescue rates were applied throughout the entire time horizon for each treatment. This does not align with the model assumptions for the

vadadustat arm for those patients who come off vadadustat treatment and go on to receive injectable ESAs after the stopping rule. The EAG has therefore explored using ESA rescue rates for those patients who come off vadadustat treatment due to the stopping rule (see Section 6.2).

4.2.8.4. Monitoring costs

Monitoring costs were informed by TA807 for roxadustat (committee papers, Section 4.2.9.2)[41] and were based on the number of 15-minute appointments with a hospital-based medical consultant. It was assumed that patients would require four consultant visits in the first model cycle, followed by 1.5 visits per cycle thereafter. TA807 stated that these assumptions were based on a combination of clinical advice, the draft roxadustat SmPC (TA807 Committee papers[41] ACM1, appendix C), and NICE guidance (NG8;[46] which has since been updated and replaced by NG203[47]). The EAG considered this monitoring frequency to be appropriate.

The company used a consultant based cost taken from the PSSRU (2021)[48] and inflated this to 2021/2022 costs. The EAG considered that a more appropriate monitoring cost could be informed by the PSSRU (2022),[43] which resulted in an updated cost of £36.25 per monitoring appointment. This alternative cost was applied in the EAG's base case settings (see Section 6.2).

4.2.8.5. Disease management costs

Disease management costs in the company's model included costs for dialysis, insertion procedures, and transplant (Table 44).

The number of live, after brain death, and after circulatory death donors were taken from the NHS Organ Donation and Transplant Activity Report 2022/23[49] and used to generate a percentage of live donor transplants. Dialysis and transplant costs were applied to the respective health state occupancy per model cycle.

Table 44: Disease management costs

Model Input	Source	HRG Code	Weighted Average Yearly Cost (£)	Weighted Average Cost Per Cycle (£)
Dialysis				
Hospital-based HD		LD01A-LD04A	21,585.31	5,396.33

Model Input	Source	HRG Code	Weighted Average Yearly Cost (£)	Weighted Average Cost Per Cycle (£)
Satellite-based HD	NHS Cost Collection 2021/22[45]	LD05A-LD08A		
Home-based HD		LD09A-LD10A		
CAPD		LD11A	25,089.70	6,920.58
APD		LD12A-LD13A		
Insertion Procedure				
Insertion for HD	NHS Cost Collection 2021/22[45]	YR41A	1,012.73	-
Insertion for PD		LA05Z	1,201.69	-
Transplantation: Recipient Costs				
Transplant procedure	NHS Cost Collection 2021/22[45]	LA01A-LA03A	18,503.60	-
Pre-screening appointment		LA12A		-
Follow-up appointment		LA13A		-
Transplantation: Donor Costs				
Pre-screening appointment	NHS Cost Collection 2021/22[45]	LA10Z	394.92	-
Follow-up appointment		LA13A		-
Examination post-transplantation		LA14Z		-
Long-Term Transplant Costs				
Annual maintenance	Kerr et al. (2012),[50] using NHS Cost Collection 2009/10. Inflated to 2022/23 costs	-	9,135.03	2,283.76

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; HD, haemodialysis; HRG, Healthcare Resource Group.

The number of patients receiving in-centre HD, home-based HD, and PD were taken from the 25th annual report of the UK Kidney Association.[4] The proportions of patients receiving each type of dialysis (Table 45) were also taken from the same report, though it is worth noting that these data were only for patients *prevalent* to dialysis, so it is unclear whether similar proportions would apply to the incident patient population.

Table 45. Unweighted proportion of patients receiving each dialysis type in the model

Dialysis Type	Dialysis Subgroup	Proportion of Patients	Source
Haemodialysis	Hospital	0.317	25th annual report of the UK Kidney Association[4]
	Satellite	0.502	
	Home	0.047	
	Total	0.866[a]	
Peritoneal dialysis	Continuous ambulatory	0.054	
	Automated	0.078	
	Total	0.132[a]	

Note:

[a] Totals for haemodialysis and peritoneal dialysis are the sum of all proportions of the same dialysis type.

The EAG considered the costs selected for disease management in the model (see Table) to be appropriate. Though the proportions of patients receiving each form of HD and PD used in the model did not include incident patients, this information was not available in the 25th annual report from the UK Kidney Association, and the EAG was unaware of any reason the proportion of incident patients receiving each form of dialysis would differ from prevalent patients. Additionally, due to the small number of patients in the INNO$_2$VATE – Incident trial, differing proportions between incident and prevalent patients would likely not have a large impact on the model.

4.2.8.6. MACE costs

The company's definition of MACE included fatal and non-fatal myocardial infarction (MI) and stroke, while expanded MACE additionally included hospitalisation for thromboembolic events or heart failure. The model assumed that 100% of patients would require hospitalisation after a MACE regardless of the regimen received by patients. Therefore, MACE costs were based on hospital-based treatment in line with the National Cost Collection 2021/2022 (Table 46).[45] The company base case only included costs for MACE and not expanded MACE.

Table 46: Hospitalisation costs for MACE and expanded MACE

MACE	Cost (£)	HRG code
MI	2,084	EB10A-E
MI rehabilitation	484	VC38Z
Stroke	4,409	AA35A-F
Stroke rehabilitation	533	VC04Z
Thromboembolic events	1,095	YQ51A-E
Hospitalisation for HF	2,542	EB03A-E

Abbreviations: HF, heart failure; HRG, Healthcare Resource Group; MACE, major adverse cardiovascular event; MI, myocardial infarction

Source: National Cost Collection 2021–22[45]

The frequencies of MACE events were separated by treatment arms and based on the proportion of each type of MACE event occurring in the $INNO_2VATE$ trials. An error was noted in the model whereby the proportions of all-cause mortality, non-fatal MI and non-fatal stroke used event data from the vadadustat $INNO_2VATE$ trial arm instead of darbepoetin alfa for the latter treatment arm. This was corrected by the EAG (see Section 6.1).

Long-term maintenance costs of MACE events were also included in the model. An annual cost of MI was taken from the assessment report of TA182 in Table 33 from 2013,[51] which was then inflated from 2021/2022 costs. The cost of stroke was taken from Xu et al., 2018[52] who reported a cost per patient in the first year and over five years. This cost was inflated from 2014/2015 prices, though the EAG note that the source, Xu et al., 2018,[53] appeared to rely on NHS reference costs from 2013/2014[54] and the PSSRU (2014),[55] so inflation from 2013/2014 costs may have been more appropriate. The EAG identified Patel et al., 2020[56] as a more recent source of long-term stroke maintenance costs (i.e., after Year 1), which used NHS figures from 2014/2015. The EAG believed Patel et al., 2020 was a more suitable source once values were inflated, resulting in a long-term annual maintenance cost of stroke of £8,875.92. These changes have been explored as scenarios and applied in the EAG's base case (described in Section 6.2.6).

4.2.8.7. Non-MACE adverse event costs

Adverse events included in the model were based on the occurrence of severe TEAEs in at least 2% of patients in either treatment arm in the $INNO_2VATE$ trials. This led to four adverse events being costed in the model: pneumonia, sepsis, fluid overload, and hyperkalaemia. All adverse events were costed using the NHS 2021/2022 Cost Collection.[45] Adverse events experienced in the darbepoetin alfa arm of the $INNO_2VATE$ trials were assumed to reflect those

of all injectable ESAs. The proportion of patients experiencing each adverse event (Table 31) were multiplied by the adverse event costs and applied as a one-off cost at the start of the model, resulting in a cost of £55 for vadadustat and £45 for darbepoetin alfa. Costs of each adverse event are shown in Table 47 and costs specific to hyperkalaemia are shown in Table 48.

Table 47. Costs and proportions of adverse events included in the model

Adverse event	Cost per event episode (£)	Source
Pneumonia	385.19	National Cost Collection 2021–22[45] (DZ11R-V)
Sepsis	456.64	National Cost Collection 2021–22[45] (WJ06G-J)
Fluid overload	640.54	National Cost Collection 2021–22[45] (DZ20F)
Hyperkalaemia	85.66	TA877[57]

Table 48: Costs associated with hyperkalaemia adverse event included in the model

Cost	Unit Price (GBP, £)	Source
Integrated blood services	2.39	NHS 2021/2022 Cost Collection[53]
GP visit: per patient contact lasting 9.22 minutes, including direct care staff costs, w/o qualification costs	34.67	PSSRU (2022)[43]
Dietitian visit: 15-minute appointment (band 4)	9.25	PSSRU (2020)[58]
Potassium binders (45g per day of Calcium Resonium)	36.97	BNF (calcium polystyrene sulfonate powder)[32]

Source: TA877 of finerenone for treating chronic kidney disease in people with type 2 diabetes.[57]
Abbreviations: BNF; British National Formulary; GBP, Great British Pounds; GP, General Practitioner; PSSRU, Personal Social Services Research Unit; w/o, without.

The EAG noted that an NHS indicative price on BNF[32] for the Sovereign Medical Ltd formulation of calcium polystyrene sulfonate powder was listed at £77.58 per 300g. As this was cheaper than the formulation used in the company's model the EAG believed this cost would have been more appropriate, resulting in a price of £11.64 per 45mg.

The EAG could not align the cost of a dietitian appointment used in the model with values in TA877,[52] the PSSRU (2020),[58] nor any more recent versions of the PSSRU. It was therefore unclear how this cost was derived. Therefore, the EAG proposed that a dietitian visit should be costed using the PSSRU (2022) prices of hospital-based Band 4 scientific and professional staff, resulting in a cost of £8.50 per 15-minute appointment.

In relation to the cost of fluid overload, the EAG are unsure why a single cost of pulmonary oedema day case treatment was used instead of taking an average of all oedema-related costs in the NHS Cost Collection 2021/2022.

4.2.9. Uncertainty

The company provided the relevant sensitivity analyses to quantify the model uncertainty: probabilistic sensitivity analysis (PSA), one-way sensitivity analysis (OWSA), and scenario analysis. There were several instances where model parameters were either missed from the sensitivity analysis or did not feed through the parameters sheet as expected. In addition, the EAG considered that some parameters could have had a more appropriate distribution applied to estimate the uncertainty distribution. The EAG has corrected these in their base case. Details of the EAG's model review findings can be found in Appendix B.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The results presented in this report incorporate the company's proposed PAS discount for the technology of interest and list prices for all comparator treatments. This report is accompanied by a confidential appendix that reports the results of the analyses when confidential prices for comparator treatments are included.

5.1.1. Base case results

The company provided an updated model at clarification stage with corrections applied as requested by the EAG. These corrections were related to technical errors in the calculation of:

- The proportion of patients receiving rescue therapy in each cycle.
- The calculation of the proportion of patients still on treatment per cycle in the darbepoetin alfa arm.
- Using the same baseline distribution of Hb levels between vadadustat and darbepoetin alfa.

The updated results reported by the company are shown in Table 49. At the discounted price for vadadustat, the deterministic and probabilistic results show the incremental cost-effectiveness ratio (ICER) to be dominant with a small QALY benefit at a lower incremental cost for vadadustat.

Table 49: Company's base case results – at discounted price

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Vadadustat	[redacted]	4.94	-	-	-
Darbepoetin alfa	£313,510	4.91	[redacted]	0.02	Dominant
*Company probabilistic base case**					
Vadadustat	[redacted]	4.93	-	-	-
Darbepoetin alfa	£313,730	4.92	[redacted]	0.01	Dominant

Abbreviations: QALYs, quality-adjusted life-years

Notes: * Produced by the EAG on the company's model post clarification questions

5.2. Company's sensitivity analyses

5.2.1. Deterministic sensitivity analyses

The company presented the results of a OWSA to explore the sensitivity of base case results to the variation of isolated parameters within a 95% confidence interval. The company did not provide an updated OWSA at the clarification stage, and therefore the EAG re-ran the analysis with the corrections outlined in Section 5.1.1. As additional inputs had been added to the model, the EAG also corrected the OWSA model sheets to ensure the correct ranges were being taken for the results tables. The results of the updated OWSA are presented in Table 50, Figure 9 and

Figure 10.

Table 50: OWSA: Incremental net-monetary benefit from company's model (analysis ran by EAG on the updated company CEM provided at clarification stage) – discounted price

Parameter	iNMB (WTP = £20,000)		iNMB (WTP £30,000)	
	Lower bound of parameter (£)	Upper bound of parameter (£)	Lower bound of parameter (£)	Upper bound of parameter (£)
Utility, DD, No MACE, vadadustat	[redacted]	[redacted]	[redacted]	[redacted]
Utility, DD, No MACE, ESA	[redacted]	[redacted]	[redacted]	[redacted]
Utility, Transplant, No MACE, vadadustat	[redacted]	[redacted]	[redacted]	[redacted]
Utility, Transplant, No MACE, ESA	[redacted]	[redacted]	[redacted]	[redacted]
Vadadustat efficacy, HR of MACE, no history of MACE	[redacted]	[redacted]	[redacted]	[redacted]
Vadadustat efficacy, HR of MACE, history of MACE	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate - Outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Disutility, Hb level, <10 g/dL	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis service cost	[redacted]	[redacted]	[redacted]	[redacted]
Cost of stroke, non-fatal, long term	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DD, dialysis-dependent; ESA, erythropoietin stimulating agents; HR, hazard ratio; iNMB, incremental net-monetary benefit; IV, intravenous; MACE, major adverse cardiac events; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year

Figure 9: DSA: Tornado diagram for iNMB results on company revised base case post clarification stage (WTP = £20,000) – discounted price

Abbreviations: DD, dialysis-dependent; ESA, Erythropoietin stimulating agents; HR, hazard ratio; iNMB, incremental net monetary benefit; MACE, major cardiac adverse event

Figure 10: DSA: Tornado diagram for iNMB results on company revised base case post clarification stage (WTP = £30,000) – discounted price

Abbreviations: DD, dialysis-dependent; ESA, Erythropoietin stimulating agents; HR, hazard ratio; iNMB, incremental net monetary benefit; MACE, major cardiac adverse event

The EAG noticed several instances where some inputs were not included within the OWSA to assess the uncertainty. In addition, the lower and upper bounds for each variable were derived assuming a normal distribution instead of the input specific distribution (e.g., beta for percentages). These include:

- Median time since dialysis
- Patient characteristics for history of MACE
- Adverse events
- IV iron weekly dose
- Average ESA dose per week
- ESA rescue dose
- Monitoring frequencies
- IV iron usage

A list of inputs and changes made in the EAG's sensitivity analysis is presented in Appendix B.

5.2.2. Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to explore parameter uncertainty with 10,000 iterations, which the company stated was when the PSA started to converge. This PSA was updated following the clarification stage and re-run by the EAG. In line with the format presented in the CS, the updated PSA results using the discounted price of vadadustat are shown in Figure 11 (scatterplot for incremental discounted costs and QALYs) and Figure 12 (cost-effectiveness acceptability curve (CEAC)).

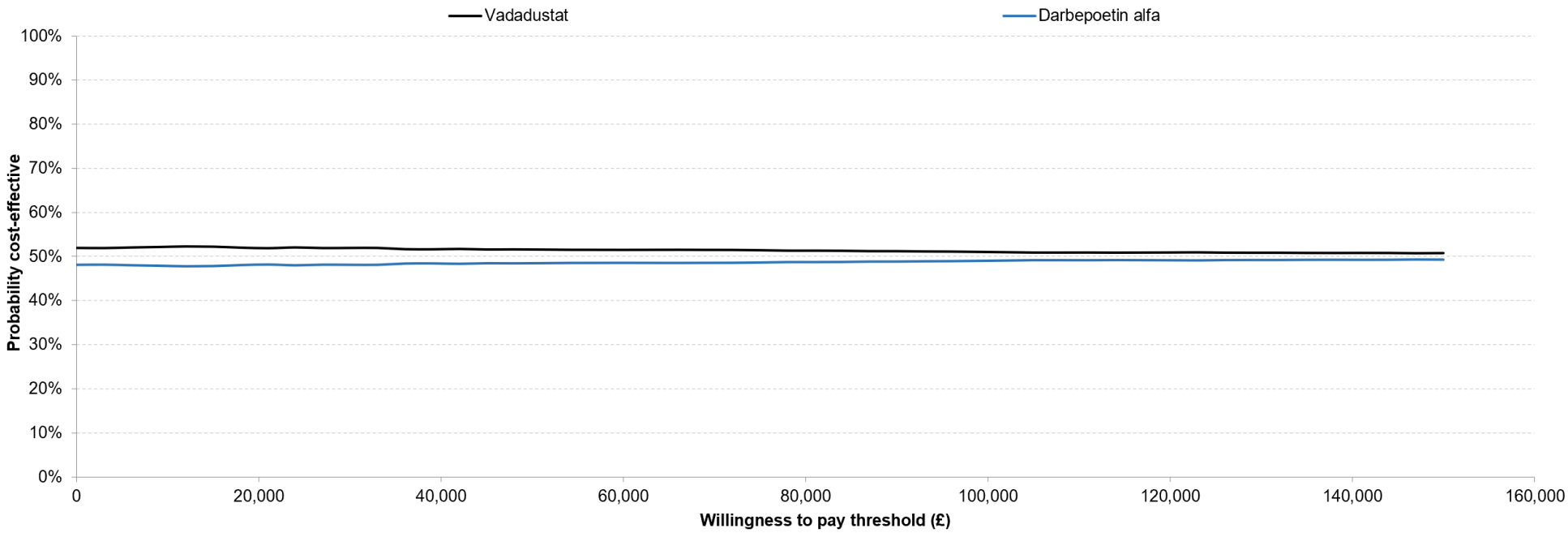
As with the OWSA, several inputs were not included in PSA that the EAG felt should be included (listed above). A list of inputs and changes made in the EAG's sensitivity analysis is presented in Appendix B.

Figure 11: PSA cost-effectiveness plane (analysis ran by EAG on the updated company CEM provided at clarification stage) – at discounted price

[redacted]

Abbreviations: CEM, cost-effectiveness model; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years

Figure 12: PSA cost-effectiveness acceptability curve (CEAC) for vadadustat versus darbepoetin alfa – at discounted price



5.2.3. Scenario analyses

Scenario analyses were provided by the company at submission stage (CS Section B.3.11.4). Key scenarios presented by the company were re-run by the EAG following the corrections to the model post clarification stage. These included:

- Vadadustat treatment waning
  - applied at 1 year
  - Not applied
- Utility increment for mode of administration

Additionally, a number of scenario analyses were requested by the EAG at clarification stage. These were provided by the company as switches in the model. The key scenarios explored were related to:

- Use of the transition probabilities from the INNO$_2$VATE trials directly between MACE health states for vadadustat
- Use of parametric survival models for the extrapolation of mortality
- The source of utility estimates for the dialysis dependent and transplant health states
- Application of parametric models to extrapolate time to discontinuation for both treatment arms
- Using transition probabilities to move patients between Hb categories alongside health states – both in a treatment-specific and a treatment-independent framework
- Application of overall baseline Hb distribution rather than treatment specific

These requested analyses were considered by the EAG to be necessary aspects of the modelling of vadadustat due to both the aim of the treatment and to appropriately align with NICE guidance. The EAG also explored a scenario analysis assuming there is no difference in MACE between vadadustat and darbapoetin alfa.

The deterministic results of each of the scenario analyses listed above are presented in Table 51. In most of the scenario analyses conducted, vadadustat was dominant over darbepoetin

alfa, as per the company base case. In the scenario where the transition probabilities between MACE substates was informed by the INNO$_2$VATE trials, vadadustat was less costly but also less effective than darbepoetin alfa.

Table 51: Key deterministic scenario analysis results – at discounted price

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (£)
Deterministic scenario results applying treatment waning at 1 year					
Vadadustat	[redacted]	4.90	-	-	-
Darbepoetin alfa	[redacted]	4.91	[redacted]	-0.011	[redacted] (SW - Less costly, less effective)
Deterministic scenario results no treatment waning					
Vadadustat	[redacted]	4.98	-	-	-
Darbepoetin alfa	[redacted]	4.91	[redacted]	0.071	[redacted]
Deterministic scenario results applying a utility increment for mode of administration					
Vadadustat	[redacted]	4.96	-	-	-
Darbepoetin alfa	[redacted]	4.92	[redacted]	0.047	Dominant
Deterministic scenario results assuming no MACE difference (i.e., HR =1)					
Vadadustat	[redacted]	4.89	-	-	-
Darbepoetin alfa	313,510	4.91	[redacted]	-0.019	[redacted] (SW - Less costly, less effective)
Deterministic scenario results using INNO$_2$VATE transitions probabilities for MACE sub-states					
Vadadustat	[redacted]	4.87	-	-	-
Darbepoetin alfa	313,510	4.91	[redacted]	-0.039	[redacted] (SW - Less costly, less effective)
Deterministic scenario results using generalised Gamma parametric survival model for mortality extrapolation					
Vadadustat	[redacted]	3.32	-	-	-
Darbepoetin alfa	252,555	3.31	[redacted]	0.010	Dominant
Deterministic scenario results using Cooper et al. (2020[26]) for health state utility values					
Vadadustat	[redacted]	5.55	-	-	-
Darbepoetin alfa	313,510	5.52	[redacted]	0.028	Dominant

	Discounted costs (£)	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained (£)
Deterministic scenario results using parametric extrapolation of TTD (using log-logistic curve for vadadustat arm and Gompertz curve for darbepoetin alfa arm)					
Vadadustat	[redacted]	4.94	-	-	-
Darbepoetin alfa	303,783	4.91	[redacted]	0.023	[redacted]
Deterministic scenario results using transition probabilities to move patients between Hb categories – treatment specific					
Vadadustat	[redacted]	4.93	-	-	-
Darbepoetin alfa	313,510	4.91	[redacted]	0.018	Dominant
Deterministic scenario results using transition probabilities to move patients between Hb categories – treatment independent					
Vadadustat	[redacted]	4.94	-	-	-
Darbepoetin alfa	313,510	4.90	[redacted]	0.042	Dominant
Deterministic scenario results using pooled baseline Hb distribution					
Vadadustat	[redacted]	4.94	-	-	-
Darbepoetin alfa	313,510	4.91	[redacted]	0.023	Dominant

Abbreviations: Hb, haemoglobin; MACE, major adverse cardiovascular event; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

5.3. Model validation and face validity check

An overview of the company's approach taken to validate the submitted cost-effectiveness analysis is provided in Section B.3.14.1 of the CS. A technical internal validity check was done on the model by the model developers based on a quality-control (QC) process. Top-down tests, internal functionality and internal consistency were among the QC checks performed. No formal documentation was provided alongside this description within the company submission.

The model approach and assumptions were validated by clinical and health economic experts. The validation meetings are described in Appendix N. One clinical expert was interviewed on and asked about mortality assumptions, treatment waning, stopping rules, cost inputs, ESA administration, rescue therapy, and utility inputs. One health economic expert was also interviewed via Microsoft Teams and asked similar topics in addition to the appropriateness of the model structure. It was unclear to the EAG, based on what was reported in Appendix N, what information was provided to the experts and how questions were asked.

Although experts provide a useful insight to help support the submission and corresponding assumptions, the EAG considered the approach taken (methods as well as reporting) to be limited, which may hinder the reliability of the feedback obtained. In line with the NICE manual (2022), the EAG would have preferred to see a structured approach to expert elicitation, with multiple experts consulted and clearer reporting of methods taken, and the responses obtained.

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified limitations within the company's base case and explored the impact of parameter values, and assumptions, which the EAG believed were more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis. In Section 6.3, the EAG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2.

6.1. EAG corrections and adjustments to the company's base case model

Due to the size and complexity of the model structure, layout of the model in Excel, and limited description within the CS, the EAG's technical validation QC check was limited. However, the EAG conducted black box face validity checks as well as sheet by sheet checks on key model sheets alongside a cross check of inputs included in the model.

A number of technical errors were identified within the cost-effectiveness model, along with what the EAG has called 'matters of judgement', where the EAG disagreed with the company's modelling approach. A summary of the technical errors and matters of judgement is provided in Table 52, while a full list is provided in Appendix B. The errors identified have a minor impact on results. The biggest change in the company's base case was from correcting the MACE annual costs to be per cycle costs.

Table 52: EAG corrections

Technical errors	Matters of judgement
• Error in where the proportion of patients in 'DD Hx MACE' was taken from in the 'Pat flow' sheets which impacts sensitivity analysis. • Correcting the mortality range in the 'Life Tables' sheet. • Inflating the Hospital consultant cost to 22/23 costs (taken from 20/21 source).	• Not rounding down age to use for the general population utility values. • Not rounding down life-years to apply to a patients age for general population mortality. • Minimum cost per unit used for drug costs instead of the average (does not impact base case).

Technical errors	Matters of judgement
• Corrections made to the calculations to weight the time on treatment per cycle proportions taken from the pooled studies. • Corrected the PD cost to include CAPD National Cost Collection value. • MACE annual costs corrected to be per cycle costs. • Correcting the calculations for Any MACE for the darbepoetin alfa arm and total. • Corrected the time adjustment for AE disutilities. • Inflating stroke costs to 22/23 values (taken from 13/14 source). • Vadadustat drug costs using 98 x 450 mg pack when wastage is considered.	• Applied the drug discount to the pack cost instead of applying to the overall cost per cycle. • Cost inputs and disutilties using normal distribution instead of gamma distribution. • Including missing parameters from OWSA and PSA. • Lower and upper bounds corrected to use the input distribution.

Abbreviations: AE adverse event; DD, dialysis dependent; CAPD, continuous ambulatory peritoneal dialysis; Hx, history; MACE, major adverse cardiovascular event; OWSA, one-way sensitivity analysis; PD, peritoneal dialysis; PSA, probabilistic sensitivity analysis

Table 53: EAG-corrected company base case results – with discount

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG corrected company deterministic base case					
Vadadustat	[redacted]	4.91	-	-	-
Darbepoetin alfa	£288,599	4.89	[redacted]	0.02	Dominant
EAG corrected company probabilistic base case					
Vadadustat	[redacted]	4.91	-	-	-
Darbepoetin alfa	288,917	4.89	[redacted]	0.02	Dominant

Abbreviations: QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG undertook a range of alternative exploratory analyses within the company's model. Whilst some exploratory analyses linked to functionality already within the model provided by the company at submission or post clarification questions, further model edits were also undertaken to try to test structural uncertainty, where possible. Each model scenario is discussed in turn throughout this section.

6.2.1. Scenario 1: Revised model structure

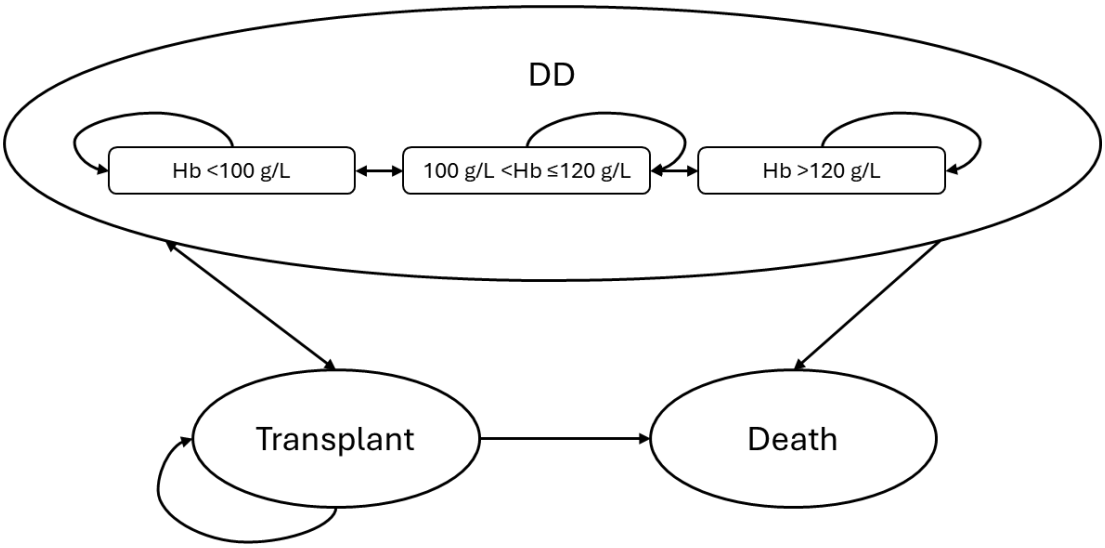
As discussed in Section 4.2.2, the EAG had some concerns with the company's model structure and underlying assumptions. These related to:

- The lack of inclusion of Hb levels within the health states (Section 4.2.2.1).
- The inclusion of MACE sub-states (Section 4.2.2.2).
- Application of the clinical efficacy data in terms of adjustment for median time of dialysis (Section 4.2.2.3).

Based on these concerns, the EAG developed a modified model structure (within the company model provided) which formally incorporated Hb levels within the health states, removed MACE sub-states, and appropriately adjusted data from the UKRR report before incorporating $INNO_2VATE$ data.

The modified model structure is presented in Figure 13. The three main health states are consistent with the company's i.e., 'DD', 'Transplant' and 'Death'. However, there are no subs-states included for differences in MACE events and the 'DD' health state is split by haemoglobin levels '<100 g/L', '100-120 g/L' and '>120 g/L'.

Figure 13: EAG modified model structure



Abbreviations: DD, dialysis dependent; Hb, haemoglobin

The transitions between the three main health states are based on the UKRR annual report data. This is consistent with the company's approach. However, the difference is that the transitions to death are also informed by these data in the EAG's model, instead of using the INNO$_2$VATE trial MACE mortality data. This results in the same health-state occupancy of 'DD', 'Transplant' and 'Death' between the vadadustat and injectable ESA arms. The EAG considered this revised approach to be a more appropriate model structure, based on the evidence on mortality from the INNO$_2$VATE trials and clinical expert opinion received by the EAG that there is expected to be no difference in transplant rates and mortality.

The 'DD' state is further split by patients' Hb levels. These transitions are informed by the INNO$_2$VATE trial data, based on the company's analysis provided post-clarification questions. The pooled distribution of Hb level is the same between both treatment arms at the start of the model, with transitions informed by treatment specific movements between the different Hb categories up to 52 weeks. After 52 weeks, it was assumed that the same transition matrices as used in cycle 4 was used for the duration of the model time horizon.

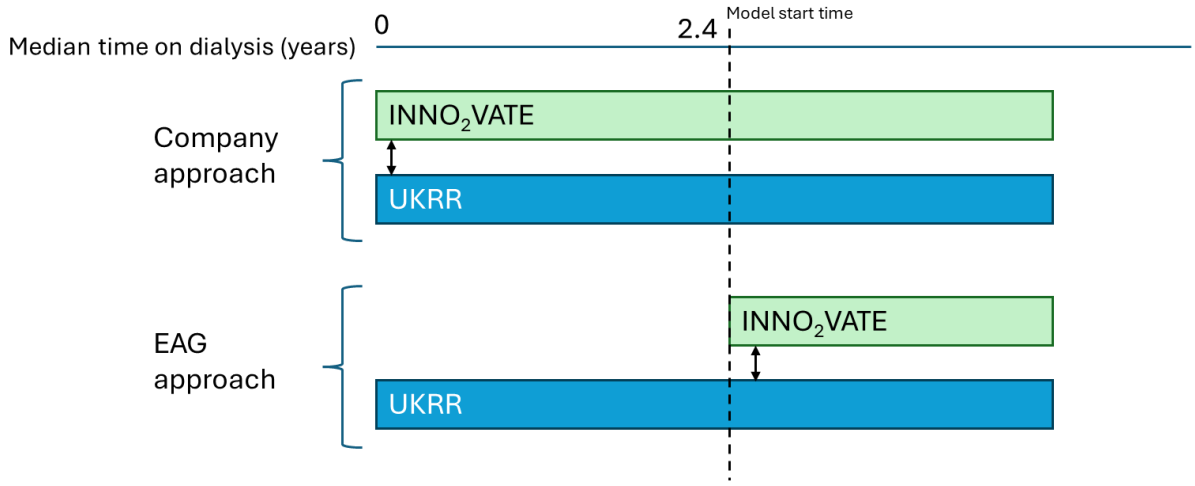
To appropriately account for the difference in median time on dialysis between the UKRR data (which starts from patients receiving dialysis) and the INNO$_2$VATE trials (where patients have been receiving dialysis for an average of 2.4 years), the transition matrix from the UKRR data is taken from cycle 5-10 (i.e., 1 year to 3 year) to inform the first model cycle transitions to best

align with the INNO$_2$VATE trial. The proportion of patients within the 'DD' state from these data are then split between the Hb levels using the transition matrices from the INNO$_2$VATE trials from baseline (with Hb groupings consistent to those indicated by the Company).

This approach and adjustment for time between the datasets (UKKR data and the INNO$_2$VATE trial data), differs from the company's base case, in which both datasets used information from cycle 5-12 – thus ignoring the baseline INNO$_2$VATE trial data and initial data. This created a misalignment in the patient populations between INNO$_2$VATE and the UKRR, which the EAG adjusted for.

A schematic below represents the different adjustment approaches (Figure 14).

Figure 14: Company vs EAG approach to adjust for median time on dialysis



Abbreviations: UKRR; UK Renal Registry

Notes: UKKR data starts from the point of dialysis, whilst the INNO$_2$VATE trial data consisted of patients who had received dialysis for on average, 2.4 years.

6.2.2. Scenario 2: Treatment discontinuation approach

As discussed in Section 4.2.6.6, the EAG preferred approach for treatment discontinuation is the application of parametric distributions to the time to discontinuation data from the INNO$_2$VATE trials using the approach where transplant and death are treated as events. Based on the data provided in the model post clarification questions, Weibull was statistically the best fitting for vadadustat and exponential and gamma were the best fitting for darbepoetin alfa (Table 54). KM data were not available to give an assessment of visual fit, but based on the curves, the log-logistic, log-normal and Gompertz curves look overly optimistic and plateau in

the long-term (Figure 15 and Figure 16). The Weibull and gamma curves sit between the other plausible curves therefore based on statistical fit, in the EAGs base case, the Weibull model was used to extrapolate both arms, with other plausible curve fits presented in scenario analyses.

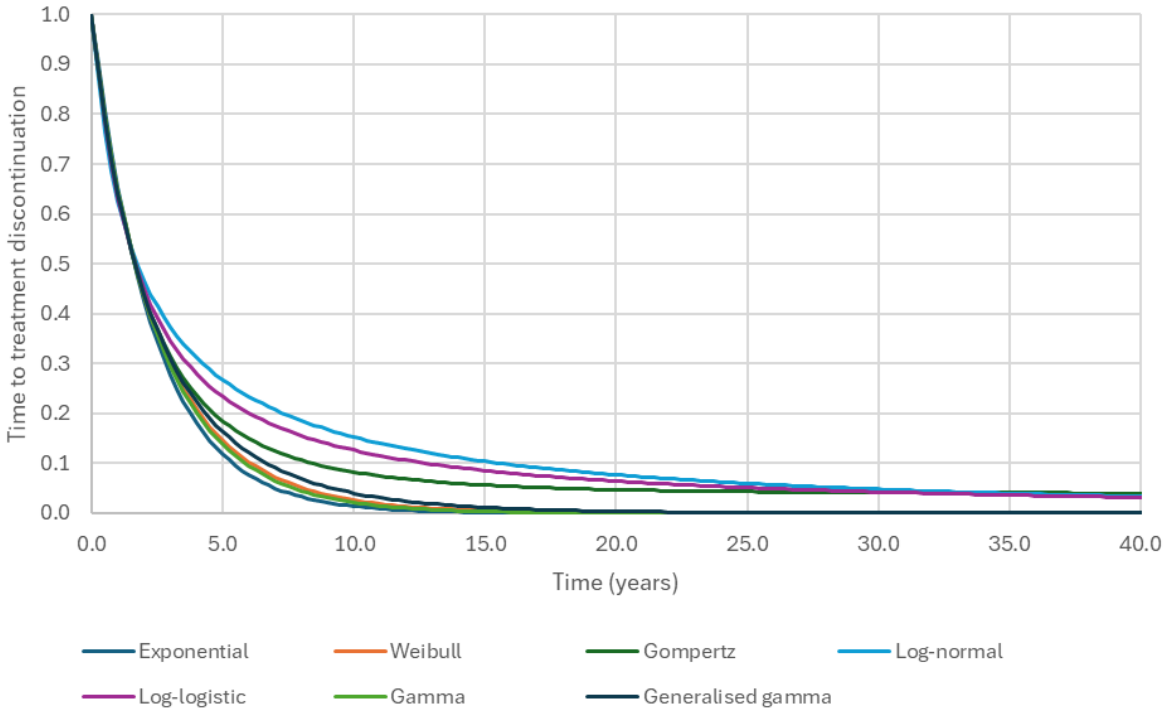
Table 54: Statistical fits for parametric models fit to time to treatment discontinuation data from INNO$_2$VATE trials (event analysis)

Model	Vadadustat				Darbepoetin alfa			
	AIC	Rank	BIC	Rank	AIC	Rank	BIC	Rank
Generalised Gamma	14,691	3	14,708	5	11,420	4	11,437	6
Gamma	14,691	2	14,702	2	11,418	1	11,430	2
Log-logistic	14,699	6	14,710	6	11,423	6	11,434	5
Log-Normal	14,738	7	14,749	7	11,456	7	11,467	7
Gompertz	14,692	4	14,703	4	11,420	3	11,431	4
Weibull	14,690	1	14,701	1	11,419	2	11,430	3
Exponential	14,697	5	14,703	3	11,421	5	11,427	1

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

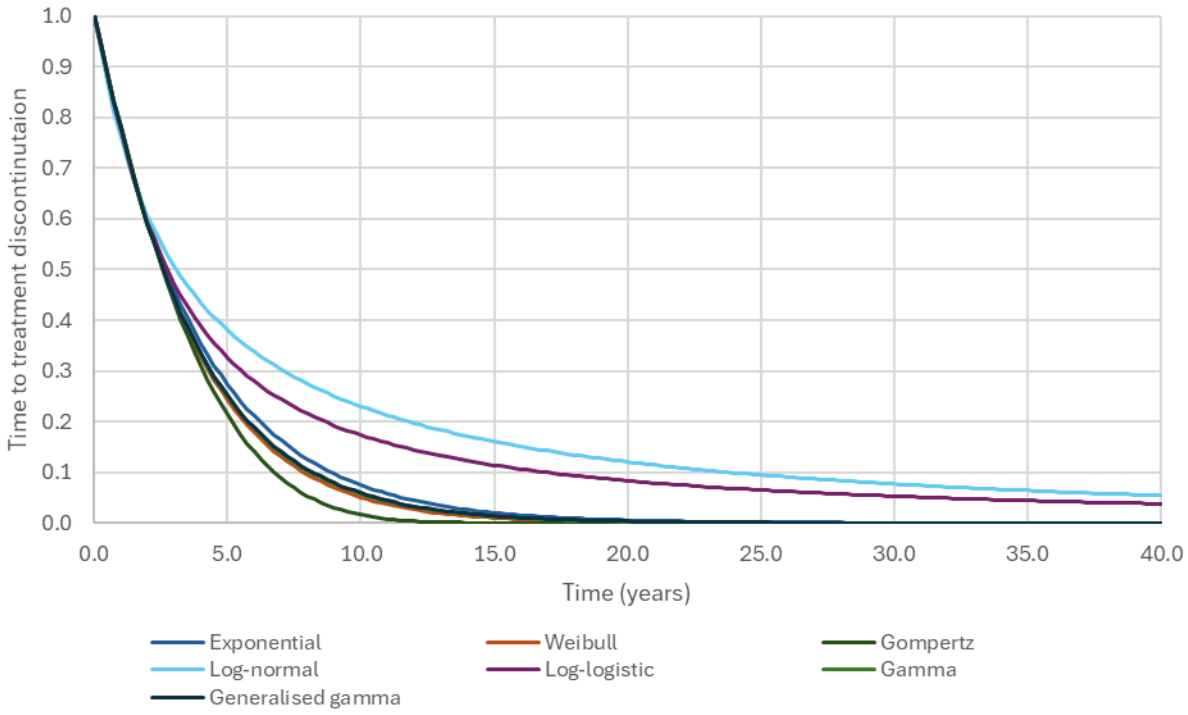
Source: Company response to clarification questions Table 23 & Table 24

Figure 15. Parametric curves fitted to the treatment discontinuation data for each arm of the INNO$_2$VATE trials for vadadustat arm (event analysis)



Source: Replicated from data in the company model

Figure 16. Parametric curves fitted to the treatment discontinuation data for each arm of the INNO$_2$VATE trials for darbepoetin alfa arm (event analysis)



Source: Replicated from data in the company model

The EAG further chose to remove the proportion of patients who had not experienced an adequate response to treatment with vadadustat in cycle 2 of the model, to align with the SmPC (instead of cycle 1 as the company did). This was applied in the EAG modified model structure based on the proportion of patients within the Hb < 100 g/L health state at cycle 2, who are then assumed to discontinue and instead receive injectable ESAs. After this time point, those who discontinued treatment therefore use the injectable ESAs transitions and the injectable ESAs treatment discontinuation curve and drug costs (in line with the company's assumptions). Due to the layout of the company's model structure, the EAG were not able to adapt the model to account for differing discontinuation time points (as Hb levels were not explicit health states). Therefore, the timepoint of patient discontinuing in cycle 2 was only explored within the EAG's modified model structure.

6.2.3. Scenario 3: Definition of rescue therapy

The company applied rescue therapy costs based on the pooled INNO$_2$VATE trials (see Section 4.2.8.3). The rates of patients receiving RBC and rescue injectable ESAs used the narrow

rescue definition. As discussed in Section 3.2.2.5, narrow rescue therapy was therapy attributable to a low Hb (>95 g/L) and/or worsening of symptoms of anaemia. Broad-on treatment rescue therapy was all the rescue therapy received by a trial participant. As such, the EAG preferred broad-on-treatment rescue therapy as it better represented the rescue therapy received by people with DD-CKD in the INNO$_2$VATE trials. Table 55 presents the broad on treatment rescue rates used in this scenario.

Table 55: Rates of receiving RBC and ESA broad-on-treatment rescue therapy

Type of rescue therapy	Vadadustat	ESA
RBC transfusion (rate per 100 PY)	20.17	20.09
ESA (rate per 100 PY)	39.95	14.25
RBC transfusion (probability per cycle)	0.049	0.049
ESA rescue (probability per cycle)	0.095	0.035

Abbreviations: ESA, erythropoietin stimulating agent; PY, patient-year; RBC, red blood cell
Source: INNO$_2$VATE trials

6.2.4. Scenario 4: ESA specific rescue rates for those discontinuing vadadustat treatment

In the company model, a proportion of patients discontinue vadadustat treatment by cycle 2 due to the licensed stopping rule. The rule advises that treatment should stop beyond week 24 if a clinically meaningful increase in Hb levels is not achieved. Patients who discontinue due to the stopping rule are assumed to receive an injectable ESA, and as a result the darbepoetin alfa transition probabilities are used for these patients. However, other treatment specific outcomes are retained, such as rescue therapy rates. This scenario explores the impact of assuming these patients have the same rescue rates as the darbepoetin alfa arm.

6.2.5. Scenario 5: Disutility associated with a 'pill burden'

In the INNO$_2$VATE trials, several patients discontinued treatment due to "subject no longer wishes to receive study drug" (see Section 3.2.2.2). The EAG's clinical experts reasoned that, for both trials, vadadustat discontinuations may be linked to the additional pill burden of a daily oral drug. Prior to the trial more than 90% of participants were on HD and received their ESA through their dialysis, and as such, had no medication burden linked to injectable ESAs. People who were randomised to vadadustat therefore had an additional daily pill on top of the pills they were already taking. As noted in Section 2.3.2, a systematic review found that excessive medication burden led to poorer medication adherence, and reduced quality of life.

The company provided a scenario which applied a utility increment to vadadustat patients on PD to reflect an increase in patients' QoL taking an oral drug compared to injecting themselves (a value of 0.0008, as discussed in Section 4.2.7.3). Advice from the EAG clinicians consulted indicated that the pill burden for patients with CKD is substantial and should not be underestimated and may impact HRQoL. As such, whilst the EAG consider it plausible to have an increment for patients receiving PD who get to avoid IV medicine through vadadustat, it is equally plausible that a decrement may occur to those already requiring IV treatment on HD, who now have an increased pill burden. The EAG has explored applying a utility decrement to vadadustat patients on HD to reflect the reduction in QoL associated with an additional pill burden.

To estimate the size of this utility decrement, the EAG reviewed a paper by Heller et al. (2017),[59] which explored the cost-effectiveness of statins for primary prevention of coronary heart disease and stroke in men aged 45-74 years of age and women aged 55-74 years of age. The analyses explored applying a pill burden decrement of up to 0.00384 QALYs lost per year (equivalent to losing 2 weeks of perfect health over 1 decade derived from patient interviews). This QALY decrement in Heller et al. translated to a decrement of 0.000884 QALYs per cycle for the proportion of patients on HD. This has been applied to the vadadustat arm in addition to the utility increment associated with PD patients. This resulted in a total QALY decrement of -0.00007 per model cycle. The utility increment for injectable ESAs is still applied in this scenario to reflect the improved QoL for patients on PD receiving injectable ESAs every 4 weeks in comparison to every 2 weeks.

6.2.6. Scenario 6: Updated cost sources

The EAG noted that there were a few cost sources that were not the latest source publication available at the time of the submission. In this scenario, the EAG updated these costs to use the latest cost sources.

For the cost of calcium resonium powders (used for hyperkalaemia costs), the company's model based the price on the BNF (calcium polystyrene sulfonate powder), which specified a cost of £82.16 per 300g (12.32 per 45mg). However, the EAG identified a lower cost formulation on BNF, resulting in a price of £11.60 per 45mg (see Section 4.2.8.7). This cost has been implemented in the EAG analyses.

For long-term maintenance cost of stroke, the company used a cost from Xu et al. (2018)[52] who reported a cost per patient in the first year and over 5 years (see Section 4.2.8.6). The EAG identified Patel et al. (2020)[56] as a more recent source of long-term stroke maintenance costs (i.e., after Year 1), which used NHS figures from 2014/2015. The EAG considered Patel et al. a more suitable source, once values were inflated, as this represented a more up to date source. This change resulted in a long-term annual maintenance cost of stroke of £8,876.30.

The differences between company costs and EAG costs are presented in Table 56.

Table 56: Comparison of company and EAG costs

Cost category	Company cost		EAG revised cost	
	Cost	Source	Cost	Source
Hyperkalaemia (Dietitian visit)	£37.00	Could not locate Company's source. PSSRU 2020, used in TA877, is referenced but cost is incorrect (£34.00)	£34.00	PSSRU 2022 - Hospital-based band 4 scientific and professional staff
Hyperkalaemia (calcium resonium)	£12.32	BNF, list price of calcium polystyrene sulfonate powder, both Alliance Healthcare and Roma Pharmaceuticals formulations	£11.64	BNF, NHS indicative price of calcium polystyrene sulfonate powder, Sovereign Medical formulation
Cost of monitoring visit	£126.38	PSSRU 2021 – Hospital-based medical consultant cost per working hour - uplifted to 22/23 costs (after EAG corrections)	£145.00	PSSRU 2022 - Hospital-based medical consultant cost per working hour (including qualifications)
Cost of ESA administration (Home district nurse appointment)	£22.95	PSSRU 2019 – Non-hospital-based band 6 nurse cost per hour of patient contact, adjusted for 15 minutes - uplifted to 22/23 costs (after ERG corrections)	£15.75	PSSRU 2022 - Cost of qualified band 6 nurse cost per working hour (including qualifications), adjusted for 15 minutes
Cost of ESA administration (Hospital administration)	£30.88	PSSRU 2019 – Hospital-based band 6 nurse cost per hour of patient contact, adjusted for 15 minutes - uplifted to 22/23 costs (after ERG corrections)	£14.75	PSSRU 2022 - Cost of hospital-based band 6 nurse cost per working hour (including qualifications) adjusted for 15 minutes

Cost category	Company cost		EAG revised cost	
	Cost	Source	Cost	Source
Long-term stroke maintenance, per year	£5,206.55	Xu et al., 2018 - uplifted to 22/23 costs (after ERG corrections)	£8,876.92	Patel et al., 2020 - uplifted to 22/23 costs

Abbreviations: BNF, British National Formulary; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

6.2.7. Scenario 7: Subgroup analyses

Where INNO2VATE trial data was used to inform the company model, pooled outcomes were used throughout. However, as discussed in Section 3.2.2.2 and 3.2.3.1, the EAG considered that it was inappropriate to pool the heterogeneous efficacy estimates from the trials to inform the economic model. This was emphasised by the patient numbers recruited in each trial as the prevalent trial was nearly 10 times larger than the incident trial, and hence the pooled estimates were heavily imbalanced in favour of $INNO_2VATE$ – prevalent. As such, the pooled estimates informing the model represented people with longer-standing DD-CKD who had been on long-term ESA treatment for their Hb rather than people who had been diagnosed more recently and were new to ESA treatment, or entirely naïve to ESA treatment and had low Hb (Key Issue 1).

The EAG requested the company to provide subgroup analysis based on the individual trials at clarification stage. However, this was not provided. As such, the EAG explored subgroup analysis based on the data available within the company model. Where possible, efficacy parameters related to the incident and prevalent population were separated to create an 'incident' and 'prevalent' subgroup analysis. The main parameters where data were available for individual subgroups were:

- Baseline characteristics.
- Hb levels per treatment arm over time.
- Adverse events.
- Time to treatment discontinuation.
- Average dosing per treatment arm.
- Rescue therapy rates.

A full list of outcomes and data for these subgroup analyses is provided in Appendix A. A limitation of this analysis is that the data were not available individually for all outcomes. The key missing outcomes were MACE (for the company's model), and Hb transitions and treatment discontinuation curves (for the EAG's model). As these data are not available, the pooled data had to be used as a proxy. As such, these scenarios should be interpreted with caution as for these outcomes, values may be more reflective of the prevalent population.

6.2.8. Impact on the ICER of additional clinical and economic analyses

The EAG made the changes described in Sections 6.2.1 to 6.2.7. Each change was made individually to the company's corrected base case. The results of the EAG's exploratory analyses are provided in Table 57.

Table 57: EAG's exploratory analyses

Preferred assumption	Section in EAG report	Incremental		ICER £/QALY	iNMB (WTP = £20,000)		iNMB (WTP = £30,000)	
		Costs (£)	QALYs		iNMB (£)	+/- company base case	iNMB (£)	+/- company base case
EAG corrected company base-case	6.1	[redacted]	0.023	Dominant	[redacted]	-	[redacted]	-
Scenario 1: Revised model structure[a]	6.2.1	[redacted]	-0.003	Dominated	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Treatment discontinuation approach using parametric curves (company model); Weibull (event analysis)	6.2.2	[redacted]	0.023	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Rescue therapy definition as 'broad-on-treatment'	6.2.3	[redacted]	0.023	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Applying treatment specific rescue rates and IV iron costs	6.2.4	[redacted]	0.023	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: Disutility associated with pill burden for vadadustat	6.2.5	[redacted]	0.016	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Updated cost sources	6.2.6	[redacted]	0.023	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7a: Subgroup analyses – Incidence population	6.2.7	[redacted]	0.004	Dominant	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 7b: Subgroup analysis – Prevalent population	6.2.7	[redacted]	0.024	Dominant	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; iNMB, incremental net-monetary benefit; QALY, quality adjusted life year

Notes: **Bold** scenarios indicate these are used within the EAG base case. [a] This scenario includes using treatment discontinuation parametric curves, applying the vadadustat stopping rule at Cycle 2 and using Hb levels informed by transition probabilities

6.3. EAG's preferred assumptions

The EAG has identified several preferred assumptions that are considered to represent a more suitable basis from which to understand the likely impact of vadadustat compared to current injectable ESAs. Results presented here are based on the confidential PAS discount for vadadustat and list prices for comparators.

The EAG preferred base case shows that vadadustat is dominated by injectable ESAs (Table 58). The difference in the cost-effectiveness estimates from the company's base case – which suggested that vadadustat was the dominant treatment – was mainly driven by the assumptions in the EAG's revised model structure regarding treatment discontinuation curves. However, the EAG noted that all results were very close to the origin. This meant that any slight impact on costs or QALYs impacted the conclusions of the cost-effectiveness, with the ICER moving between the different cost-effectiveness plane quadrants. As such, the EAG has also presented the incremental net-monetary benefit (iNMB) in Table 58 to help with interpretation of the impact and cost-effectiveness. The final EAG base case is presented in Table 59.

Table 58: EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY	Cumulative iNMB (WTP = £20,000)	Cumulative iNMB (WTP = £30,000)
Company corrected base-case	6.1	Dominant	[redacted]	[redacted]
EAG's revised model structure* *(EAG scenario 1 & 2)*	6.2.1	Dominated	[redacted]	[redacted]
Rescue therapy definition as 'broad-on-treatment' *(EAG scenario 3)*	6.2.3	Dominated	[redacted]	[redacted]
Treatment specific rescue rates and IV iron costs *(EAG scenario 4)*	6.2.4	Dominated	[redacted]	[redacted]
Updated cost sources *(EAG scenario 6)*	6.2.6	Dominated	[redacted]	[redacted]
Utility source for main health states using Cooper et al (2020) *(Post CQ company scenario)*	4.2.7.1	Dominated	[redacted]	[redacted]
Parametric survival curves for long-term mortality; curve = gamma *(Post CQ company scenario)*	4.2.6.4	Dominated	[redacted]	[redacted]

Preferred assumption	Section in EAG report	Cumulative ICER £/QALY	Cumulative iNMB (WTP = £20,000)	Cumulative iNMB (WTP = £30,000)
Subgroup analyses				
EAG preferred assumptions – incidence population *(EAG scenario 7a)*	6.2.7	[redacted]	[redacted]	[redacted]
EAG preferred assumptions – prevalent population *(EAG scenario 7b)*	6.2.7	Dominated	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; iNMB, incremental net-monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay

Notes: *This scenario includes using treatment discontinuation parametric curves, applying the vadadustat stopping rule at Cycle 2 and using Hb levels informed by transition probabilities

Table 59: EAG's base case results – at discounted price

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
EAG deterministic base case					
Vadadustat	[redacted]	3.450			
Darbepoetin alfa	[redacted]	3.453	[redacted]	-0.0033	Dominated
EAG probabilistic base case					
Vadadustat	[redacted]	3.914			
Darbepoetin alfa	[redacted]	3.908	[redacted]	0.0061	[redacted]

Abbreviations: QALYs, quality-adjusted life-years

6.3.1. Confidential appendix

A confidential appendix is provided alongside this EAG report in order to provide model results using confidential prices for comparator treatments.

The confidential appendix provides the following analyses:

- Company base case applying confidential prices for comparator treatments
- EAG base case applying confidential prices for comparator treatments
- EAG scenario analyses applying confidential prices for comparator treatments

Source of confidential prices:

- Commercial medicines unit (CMU) for darbepoetin alfa as supplied by NICE

6.3.2. EAG sensitivity analysis

6.3.2.1. Deterministic sensitivity analysis

As discussed in Section 6.1, there were various changes made by the EAG which affect sensitivity analysis, including changing input distributions, and including inputs which were excluded from the company's sensitivity analysis. The results of the EAG's base case OWSA are presented in Table 60, Figure 17 and Figure 18 which incorporate these additional changes.

Table 60: OWSA: Incremental net-monetary benefit from EAG's base case – discounted price

Parameter	iNMB (WTP = £20,000)		iNMB (WTP £30,000)	
	Lower bound of parameter (£)	Upper bound of parameter (£)	Lower bound of parameter (£)	Upper bound of parameter (£)
Utility, Transplant, No MACE, vadadustat	[redacted]	[redacted]	[redacted]	[redacted]
Utility, Transplant, No MACE, ESA	[redacted]	[redacted]	[redacted]	[redacted]
Utility, DD, No MACE, ESA	[redacted]	[redacted]	[redacted]	[redacted]
Utility, DD, No MACE, vadadustat	[redacted]	[redacted]	[redacted]	[redacted]
IV iron use, ESA, c5+	[redacted]	[redacted]	[redacted]	[redacted]
IV iron use, vadadustat, c5+	[redacted]	[redacted]	[redacted]	[redacted]
Dose per week of vadadustat, year 3	[redacted]	[redacted]	[redacted]	[redacted]
Dose per week of vadadustat, year 1	[redacted]	[redacted]	[redacted]	[redacted]
Dose per week of darbepoetin alfa, year 3	[redacted]	[redacted]	[redacted]	[redacted]
IV iron use, ESA, c1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DD, dialysis-dependent; ESA, erythropoietin stimulating agents; HR, hazard ratio; iNMB, incremental net-monetary benefit; IV, intravenous; MACE, major adverse cardiac events; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year

Figure 17: DSA: Tornado diagram for iNMB results on EAG's base case (WTP = £20,000) – discounted price

[redacted]

Abbreviations: DD, dialysis-dependent; ESA, Erythropoietin stimulating agents; HR, hazard ratio; iNMB, incremental net monetary benefit; MACE, major cardiac adverse event; WTP, willingness-to-pay

Figure 18: DSA: Tornado diagram for iNMB results on EAG's base case (WTP = £30,000) – discounted price

[redacted]

Abbreviations: DD, dialysis-dependent; ESA, Erythropoietin stimulating agents; HR, hazard ratio; iNMB, incremental net monetary benefit; MACE, major cardiac adverse event; WTP, willingness-to-pay

6.3.2.2. Probabilistic sensitivity analysis

The EAG's PSA results using the discounted price of vadadustat are shown in Figure 19 (scatterplot for incremental discounted costs and QALYs) and Figure 20 (CEAC).

As with the OWSA, several inputs were not included in PSA that the EAG felt should be included. A list of inputs and changes made in the EAG's sensitivity analysis is presented in Appendix B.

Figure 19: PSA cost-effectiveness plane (EAG) – at discounted price

Abbreviations: CEM, cost-effectiveness model; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years

Figure 20: PSA cost-effectiveness acceptability curve (CEAC) for vadadustat versus darbepoetin alfa (EAG) – at discounted price

6.3.2.3. Scenario analysis

Key scenarios on the EAG's base case are presented in Table 61.

Table 61: EAG's scenario analyses

Scenario	Incremental costs (£)	Incremental QALYs	ICER £/QALY	iNMB (WTP = £20,000)	iNMB (WTP = £30,000)
EAG base-case	[redacted]	-0.0033	Dominated	[redacted]	[redacted]
Considering utility for mode of administration	[redacted]	-0.0047	Dominated	[redacted]	[redacted]
Long-term mortality curve: Exponential	[redacted]	-0.0033	Dominated	[redacted]	[redacted]
Long-term mortality curve: Generalised gamma	[redacted]	-0.0033	Dominated	[redacted]	[redacted]
Long-term mortality curve: Gompertz	[redacted]	-0.0033	Dominated	[redacted]	[redacted]
TTD curve: Exponential	[redacted]	-0.0033	Dominated	[redacted]	[redacted]
TTD curve: Gamma	[redacted]	-0.0033	Dominated	[redacted]	[redacted]
TTD curve: Generalised gamma	[redacted]	-0.0033	Dominated	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; iNMB, incremental net-monetary benefit; QALY, quality adjusted life year; TTD, time to treatment discontinuation; WTP, willingness-to-pay

6.4. Conclusions of the cost-effectiveness section

The company provided a cost-effectiveness analysis that utilised the pivotal trial data from the INNO2VATE studies and external sources relevant to the patient population. However, the EAG believed the company over complicated their model structure by using health-states based on MACE instead of Hb levels. Sub-states for MACE caused unnecessary complications because there was no evidence to support a difference in MACE or mortality between vadadustat and darbepoetin alfa from the $INNO_2VATE$ trials. This view was further supported by clinical opinion received by the EAG.

The company's model structure allowed patients to discontinue vadadustat based on its stopping rule for insufficient Hb levels. However, the EAG felt that the company discontinued patients one cycle too early. This meant there was a misalignment with the proportion of patients taken off treatment and the proportion of patients estimated to be within the 'Hb' category. Patients who came off treatment were assumed to start injectable ESA treatment.

However, not all the inputs were adjusted, and therefore the model used the vadadustat efficacy inputs through the model time horizon.

The EAG attempted to overcome these issues within their modified model structure. The changes simplified the model such that MACE, and subsequent treatment waning, was removed and Hb levels were formally captured. This revised approach also provided more transparency in the stopping rule associated with patients who had an inadequate response to treatment, who would be expected to discontinue vadadustat.

The biggest differences between the EAG and company models related to costs due to treatment discontinuation. The company potentially overestimated treatment costs by assuming that patients remained on treatment after cycle 4, with no discontinuation thereafter. This assumption was contrary to the INNO$_2$VATE trial data, which reported discontinuation continuing beyond one year. The biggest cost difference between vadadustat and darbepoetin alfa are the drug acquisition and administration costs – other costs have limited impact on overall results.

In both the company's and EAG's base case, vadadustat treatment costs are higher than the darbepoetin alfa treatment costs. However, the company shows a reduction of administration costs for vadadustat, whereas the EAG's base case shows a higher overall administration cost. This was mainly due to how the patients who discontinued vadadustat treatment are modelled. The company's model used darbepoetin alfa's treatment discontinuation from cycle 2, despite patients only just starting darbepoetin alfa treatment. The EAG's model, on the other hand, used the first cycle of darbepoetin alfa's treatment discontinuation curve at the point at which patients come off vadadustat treatment.

Regardless of model structure, the incremental QALYs between vadadustat and darbepoetin alfa remained close to the origin. This meant that the ICER crossed multiple quadrants of the cost-effectiveness plane, switching between dominant, dominated, cost-effective and not cost-effective in scenario analysis. Overall, it is uncertain whether there would be any difference in quality of life between treatment arms and whether this would favour vadadustat or darbepoetin alfa. The EAG's clinical experts did not believe, based on the evidence, that there would be a difference in quality of life, with the exception of patients on PD (having a benefit) and those on HD (having a decrement) due to mode of administration, but no difference in physical functioning.

7. QALY MODIFIER

The company considered that the condition did not meet the criteria associated with a severity modifier and therefore did not present the calculation of the QALY shortfall. This was in line with NICE's new methods and processes.[60]

For completeness, the EAG has assessed the appropriateness of a QALY modifier within this appraisal using the published University of York Schneider tool.[61] This tool uses data from the Office of National Statistics (ONS) for England to generate general population survival with various sources of data to inform utility estimates. Details of the sources used in the Schneider tool are detailed within the tool.

Based on a starting age of 58 years, 44% females, and an estimated QALY gain of 4.89 in the company's corrected base case, a severity weighting is not met in any of the sources included in the Schneider tool (Table 62). This is also the case for the EAG base case, using an estimated QALY gain of 3.45 for injectable ESAs. The EAG agreed with the company that the population does not meet the criteria associated with a severity modifier.

Table 62: Assessment of severity modifier by EAG

Schneider tool scenario	Corrected company base case			EAG base case		
	Absolute shortfall	Proportional shortfall	QALY weight	Absolute shortfall	Proportional shortfall	QALY weight
Reference case: MVH value set + HSE 2014 ALDVMM model (Hernandez Alava et al)	8.48	63.42%	X1	9.92	74.19%	X1
Alternative A: 5L to 3L mapping (Hernandez Alava et al) + HSE 2017 - 2018	8.07	62.28%	X1	9.51	73.39%	X1
Alternative B: 5L to 3L mapping (Van hout et al) + HSE 2017 - 2018	8.16	62.54%	X1	9.60	73.57%	X1
Alternative C: MVH value set + health state profiles	7.99	62.04%	X1	9.43	73.22%	X1
Alternative D: MVH value set + HSE 2012 +14	8.43	63.29%	X1	9.87	74.10%	X1

Abbreviations: ALDVMM, Adjusted Limited Dependent Variable Mixture Model; HSE, Health Survey for England; MVH, Measurement and Valuation of Health; QALY, quality-adjusted life-years

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Appendix A: Subgroup analysis data

Table 63: Subgroup analysis inputs used for the cost-effectiveness model from the INNO$_2$VATE trials

Category	Pooled	INNO$_2$VATE – incident	INNO$_2$VATE – prevalent
Patient characteristics			
Age	57.9	56.0	58.1
Females (%)	43.6%	40.4%	43.9%
History of CKD (%)	49.5%	38.5%	50.6%
Haemodialysis (%)	92.1%	NA	NA
Peritoneal dialysis (%)	7.9%	NA	NA
Time since dialysis (median), years	2.4	0.12	2.64
Hb distribution (%), vadadustat | ESA			
Cycle 0			
<100 g/L	[redacted]	[redacted]	[redacted]
100-120 g/L	[redacted]	[redacted]	[redacted]
>120 g/L	[redacted]	[redacted]	[redacted]
Cycle 1			
<100 g/L	[redacted]	[redacted]	[redacted]
100-120 g/L	[redacted]	[redacted]	[redacted]
>120 g/L	[redacted]	[redacted]	[redacted]
Cycle 2			
<100 g/L	[redacted]	[redacted]	[redacted]
100-120 g/L	[redacted]	[redacted]	[redacted]
>120 g/L	[redacted]	[redacted]	[redacted]
Cycle 3			
<100 g/L	[redacted]	[redacted]	[redacted]
100-120 g/L	[redacted]	[redacted]	[redacted]
>120 g/L	[redacted]	[redacted]	[redacted]
Cycle 4			
<100 g/L	[redacted]	[redacted]	[redacted]
100-120 g/L	[redacted]	[redacted]	[redacted]
>120 g/L	[redacted]	[redacted]	[redacted]
On treatment (%), vadadustat | ESA			
Cycle 1	100% | 100%	100% | 100%	100% | 100%
Cycle 2	93% | 97%	94% | 95%	93% | 97%
Cycle 3	84% | 91%	87% | 91%	83% | 91%
Cycle 4	73% | 83%	70% | 75%	74% | 84%

Category	Pooled	INNO$_2$VATE – incident	INNO$_2$VATE – prevalent
Safety (%), vadadustat | ESA			
Pneumonia	4.4% | 3.9%	3.4% | 2.2%	4.5% | 4.1%
Sepsis	3.2% | 3.3%	0.0% | 0.0%	3.5% | 3.6%
Fluid overload	3.6% | 2.3%	5.0% | 1.6%	3.5% | 2.40%
Hyperkalaemia	0.2% | 0.2%	2.2% | 2.2%	0.0% | 0.0%
IV iron weekly dose, vadadustat | ESA			
Cycle 1	85.6 | 100.6	195.2 | 248.2	71.9 | 83.0
Cycle 2	79.7 | 88.7	154.3 | 219.1	70.1 | 72.9
Cycle 3	82.2 | 81.9	128.5 | 146.6	76.2 | 74.3
Cycle 4	78.4 | 82.3	97.9 | 89.3	76.5 | 81.6
Cycle 5	72.5 | 68.0	60.7 | 87.0	73.4 | 66.5
Frequency of IV use, vadadustat | ESA			
Cycle 1	0.51 | 0.53	0.62 | 0.59	0.50 | 0.52
Cycle 2	0.56 | 0.56	0.69 | 0.64	0.54 | 0.55
Cycle 3	0.57 | 0.57	0.70 | 0.64	0.56 | 0.56
Cycle 4	0.59 | 0.59	0.63 | 0.62	0.58 | 0.59
Cycle 5	0.63 | 0.65	0.63 | 0.76	0.63 | 0.64
RBC rate per 100 PY, vadadustat | ESA	9.4 | 6.8	10.7 | 6.3	9.3 | 6.9
ESA rescue per 100 PY, vadadustat | ESA	30.5 | 8.3	24.3 | 3.5	31.1 | 8.8
Average weekly dose, vadadustat | ESA		NA	NA
Year 1	[redacted] | 32.43		
Year 2	[redacted] | 37.26		
Year 3	[redacted] | 39.78		

Abbreviations; ESA, Erythropoiesis-stimulating agent; IV, intravenous; NA, not available; PY, patient year; RBC, red blood cell

Appendix B: EAG technical model QC

Table 64: EAG findings from technical model QC

Sheet	Technical errors	EAG action	Matters of judgement	EAG action
Settings			There are a few inputs which don't lead anywhere in the model and therefore do not impact results; • 3-month cycle length • PD and HD (lead to parameter sheet but not anywhere else, therefore not captured in sensitivity analysis) • User amendable inputs for comparator distributions	No action taken
Utility_adj			Age rounded down (i.e., age = 57.9 is closer to 58 but rounded down to 57)	Rounded the age to nearest value
PatFlow	Half cycle correction applied incorrectly. Switch is applied in second cycle so the first cycle is not included	Corrected in EAG patient flow sheets. Does not impact base case.	Misalignment between Hb level proportions. DG16 uses cycle 1 cut offs 'Hb_level_vada_cutoff1_c1' but BG16 uses cycle 2 cut offs 'Hb_level_vada_cutoff1_c1'	Corrected in EAG patient flow sheets using the actual proportion of patients in the <100d/L health state
	'DD Hx MACE' takes value from settings instead of parameter sheet	Corrected	Hb cut offs does not account for patients coming off vadadustat treatment.	Corrected in EAG revised model using ESA Hb transitions once stopped vadadustat treatment
Transition probabilities	Inconsistent reporting of vadadustat and ESA transitions from model to Document B	No action		
Life tables	Incorrect ranges in columns R and S	Corrected	Time horizon years are rounded down	Corrected to accrue nearest age according to year

Sheet	Technical errors	EAG action	Matters of judgement	EAG action
	(starts from cycle 0 instead of 1)			
Dosing	Inconsistent reporting of dose with wastage for Epoetin Zeta between model and Document B			
Parameters	Multiple parameters using an assumed SE when these can be used from the trial data	No action	Multiple parameters missing from OWSA or PSA	Included in OWSA and PSA
	Vadadustat with wastage calculation does not have enough tablets for a full 3 months average dose	Corrected to use 98x 450mg tablets if wastage applied	Inappropriate distributions for costs and disutilities (should be using normal distribution)	Corrected
			Drug discounts applied to resulting drug costs instead of drug pack/vial	Corrected
Deterministic results	Incorrectly labelled incremental health outcomes as incremental costs	No action	PD cost should be using both CAPD and APD values from National cost Collection 21/22	Corrected
Input_data	Consultant cost for monitoring is taken from PSSRU 2021, but labelled as PSSRU 2022 and not inflated	Inflated cost		
	Time on treatment calculations incorrect in E174:H175 (referring to wrong cells)	Corrected		
	Frequency of any MACE referring to wrong cells for darbepoetin alfa	Corrected		

Sheet	Technical errors	EAG action	Matters of judgement	EAG action
	Chronic MACE costs are not adjusted per cycle	Adjusted annual costs to per cycle costs		
	AE disutilities do not need to be adjusted by cycle length as they are applied as a one-off.	Adjusted time as 14/365.25		

Abbreviations: AE, adverse events; APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; ESA, Erythropoietin stimulating agents; Hb, haemoglobin; HD, haemodialysis; MACE, major adverse cardiovascular events; OWSA, one-way sensitivity analysis; PD, peritoneal dialysis; PSA, probabilistic sensitivity analysis; SE, standard error

Single Technology Appraisal

Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease [ID3821]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 08 July 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issues concerning the trial/clinical evidence

Issue 1 General misinterpretation of the inferiority design

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 1.4 Key Issue 3 (Page 19), the following is stated: "However, this effect was not statistically significant and there was no evidence from the INNO$_2$VATE trials that suggested there is any difference for vadadustat regarding MACE."	The sentence should be rewritten to make note of the non-inferiority design: "However, given the non-inferiority design, the evidence from the INNO$_2$VATE trials suggests that there is no difference for vadadustat regarding MACE."	The Company believe that there is a fundamental misunderstanding of the INNO$_2$VATE trials. They were designed and powered for non-inferiority, not benefit or advantage/superiority for any endpoint. The source documents do not provide any p value indicating a statistically significant difference and it is unclear to the Company upon which this claim is based.	Amended to: "However, given the non-inferiority design, there was no evidence from the INNO$_2$VATE trials that suggested there is any difference for vadadustat regarding MACE."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3.1 Change in average Hb between baseline and the primary efficacy period (weeks 24 to	The Company request the statement to be removed.	The Company believe that there has been a fundamental misunderstanding in understanding the aim/objective of the	The EAG does not consider this to be a matter of factual inaccuracy. The company is referring to

36) (Page 52), the following is stated: "Given the aim of treatment was to correct Hb, the EAG considered this was a meaningful limitation of vadadustat treatment."		INNO$_2$VATE trial – it was a non-inferiority trial.	the objective of the trial which was to show the non-inferiority of vadadustat to darbepoetin alfa. However, EAG was commenting on the aim of treatment within the trial. The aim of treatment in the trial was either the correction of Hb for people outside the recommended target range, or maintenance of Hb for people within the recommended target range. In this case, the aim of treatment was correction of Hb outside the recommended target range. No changes have been made to the report.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In section 3.2.3.1 Change in average Hb between baseline and the primary	The statement should be rewritten as:	The Company believe that there has been a fundamental misunderstanding in	The EAG does not consider this to be a matter of factual

efficacy period (weeks 24 to 36) (page 52), the following is stated: "The INNO$_2$VATE – prevalent trial found darbepoetin alfa offered a statistically significant (LSM: 1.7 g/L; 95% CI: 1.0, 2.3) increase in Hb over vadadustat at the PEP (24 to 36 weeks; Table 9)."	"The INNO$_2$VATE – prevalent trial found darbepoetin alfa offered a numerical increase (LSM: -1.7 g/L; 95% CI: -0.23, -0.10) increase in Hb over vadadustat at the PEP (24 to 36 weeks; Table 9). Non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the lower bound of the 95% CI was above the prespecified non-inferiority margin of -0.75 g/dL."	understanding the aim/objective of the INNO$_2$VATE trial – it was a non-inferiority trial, and results should be interpreted in light of this design. The source documents do not provide any p value indicating a statistically significant difference. Moreover, the confidence intervals are within the prespecified margin. As described in Head et al 2012, statistically, a non-inferiority trial differs from an equivalence trial because the delta is only one-sided towards negative delta (it is not at zero). Non-inferiority is claimed if the lower bound of the CI of the treatment effect show non-inferior efficacy (and safety). Essentially the non-inferiority margin defines the cut off beyond which the point estimate does not demonstrate non-inferiority. Thus, it is unclear to the Company upon which the	inaccuracy. The figures reported by the EAG were correct. There is no minus sign because the text reports the change for darbepoetin vs vadadustat, while in Table 9 on the following page there is a minus sign because it reports results in the other direction – i.e. the change for vadadustat vs darbepoetin. For clarity, the EAG have stated that the treatment met the prespecified non-inferiority margin in the text and expanded on the non-inferiority margin in Section 3.2.2.5 of the report.

		claim of a statistically significant increase is based. The text should be amended to include the non-inferiority test as per page 53 of Document B. In addition, there were errors in the data points reported in the text.	

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In section 3.2.3.1 Haemoglobin response / maintenance of haemoglobin levels (Page 52), the following is stated: "The aim of treatment in the primary efficacy period (PEP) of the $INNO_2VATE$ – incident trial was correction of low Hb levels (haemoglobin response), but the aim in the secondary efficacy period (SEP) was maintenance of Hb levels"	The Company request it to be changed to – "the aim of the treatment was to show non-inferiority of vadadustat to ESA for all outcomes"	The Company believe that there has been a fundamental misunderstanding in understanding the aim/objective of the $INNO_2VATE$ trial – it was a non-inferiority trial.	The EAG does not consider this to be a matter of factual inaccuracy. The company is referring to the objective of the trial which was to show the non-inferiority of vadadustat to darbepoetin alfa. However, EAG was commenting on the aim of treatment within the trial. The aim of treatment in the trial was

			either the correction of Hb for people outside the recommended target range, or maintenance of Hb for people within the recommended target range. No changes have been made to the report.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In section 3.2.3.1 Change in average Hb between baseline and the primary efficacy period (weeks 40 to 52) (page 54), the following is stated: "In line with the PEP results, darbepoetin alfa offered a statistically significant increase in Hb over vadadustat at 40 to 52 weeks."	The Company request the statement to be changed to "In line with the PEP results, darbepoetin alfa offered a numerical increase in Hb over vadadustat at 40 to 52 weeks. In this analysis the lower bound of the 95% CI was above -0.75 g/dL, therefore, the non-inferiority of vadadustat to darbepoetin alfa was demonstrated since the prespecified non-inferiority margin was -0.75 g/dL."	The Company believe that there has been a fundamental misunderstanding in understanding the aim/objective of the INNO$_2$VATE trial – it was a non-inferiority trial, and results should be interpreted in light of this design. The source documents do not provide any p value indicating a statistically significant difference and the confidence intervals are well within the predefined margin. Thus, it is unclear to the Company upon which this claim is based. As per page 55	The EAG does not consider this to be a matter of factual inaccuracy. The figures reported by the EAG were correct. However, for clarity, the EAG have stated that the treatment met the prespecified non-inferiority margin and expanded on the non-inferiority margin in Section 3.2.2.5 of the report.

		of Document B a statement reflecting this non-inferiority should be added to reflect the trial design.	

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In section 3.2.3.1 Proportion of patients with average Hb value within geography-specific target range (PEP / SEP) (page 55), the following is stated: "The $INNO_2VATE$ – incident trial found darbepoetin alfa to have a statistically significant benefit (OR: 0.6; 95% CI: 0.40, 0.96) over vadadustat in the proportion of people with average Hb value within geography-specific target range in the PEP"	The statement should be rewritten as: "The $INNO_2VATE$ – incident trial found darbepoetin alfa to have a numerical benefit (OR: 0.6; 95% CI: 0.40, 0.96) over vadadustat"	The Company believe that there has been a fundamental misunderstanding in understanding the aim/objective of the $INNO_2VATE$ trial – it was a non-inferiority trial, and results should be interpreted in light of this design. The source documents do not provide any p value indicating a statistically significant difference and the confidence intervals are well within the predefined margin. Thus, it is unclear to the Company upon which this claim is based.	The EAG does not consider this to be a matter of factual inaccuracy. The figures reported by the EAG were correct. The EAG did not consider it appropriate to use the proportion difference of 15% as a non-inferiority margin because it was not prespecified in the trial protocol. However, in this case, the non-inferiority margins quoted by the company (-15%, 15%) were not met by this outcome. The EAG have stated concerns related to the non-inferiority margin in

			Section 3.2.2.5 of the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

In section 3.2.3.1 Proportion of patients with average Hb value within geography-specific target range (PEP / SEP) (page 55), the following is stated: "The INNO$_2$VATE – prevalent trial found darbepoetin alfa to have a statistically significant benefit over vadadustat in the proportion of people with average Hb value within geography-specific target range at both the PEP (OR: 0.9; 95% CI: 0.76, 1.00) and the SEP (OR: 0.8; 95% CI: 0.68, 0.91)"	The statement should be rewritten as: "The INNO$_2$VATE – prevalent trial found the proportion of randomised patients within the target Hb range (10.0 to 11.0 g/dL for US and 10.0 to 12.0 g/dL for Europe and ROW) during the PEP (weeks 24 to 36) was not statistically lower in the vadadustat treatment group than the darbepoetin alfa treatment group but numerically lower for vadadustat versus darbepoetin alfa the SEP (weeks 40 to 52). However, the non-inferiority of vadadustat to darbepoetin alfa was demonstrated given the non-inferiority criterion of proportion difference of -15%, i.e., -0.15, was met at both time points."	The Company believe that there has been a fundamental misunderstanding in understanding the aim/objective of the INNO$_2$VATE trial – it was a non-inferiority trial, and results should be interpreted in light of this design. The source documents do not provide any p value indicating a statistically significant difference and the confidence intervals are well within the predefined margin. Thus, it is unclear to the Company upon which this claim is based. The text at this point in the EAG report should be amended as per pages 27 and 28 in Appendix M (as sourced from the trial CSRs) to reflect accurate interpretation of the trial results.	The EAG does not consider this to be a matter of factual inaccuracy. The figures reported by the EAG were correct. The EAG did not consider it appropriate to use the proportion difference of 15% as a non-inferiority margin because it was not prespecified in the trial protocol and it was not clear how it was formulated. The EAG have stated concerns related to the non-inferiority margin in Section 3.2.2.5 of the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3.1 Number of red blood cell transfusion episodes received (page 59), the following is stated: "The INNO$_2$VATE – prevalent trial found a statistically significant benefit for darbepoetin alfa over vadadustat (rate ratio: 1.4; 95% CI: 1.05, 1.74)."	The statement should be rewritten as: "The INNO$_2$VATE – prevalent trial found a benefit for darbepoetin alfa over vadadustat"	The Company believe that there has been a fundamental misunderstanding in understanding the aim/objective of the INNO$_2$VATE trial – it was a non-inferiority trial, and results should be interpreted in light of this design. The source documents do not provide any p value indicating a statistically significant difference and the confidence intervals are well within the predefined margin. Thus, it is unclear to the Company upon which this claim is based.	The EAG does not consider this to be a matter of factual inaccuracy. The figures reported by the EAG were correct and difference between treatments was statistically significant. No non-inferiority margin was prespecified for transfusion episodes. No changes have been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3.2 subgroup analyses (Page 65), the following is stated: "There were no significant differences between the effectiveness estimates of vadadustat versus darbepoetin alfa in the any of the subgroups analysed in the INNO$_2$VATE – incident trial. The EAG noted that there was an increased numerical benefit for darbepoetin alfa over vadadustat in people with an Hb less than 95 g/L compared to people with 95 g/L or more for the change from baseline in haemoglobin outcomes (PEP and SEP). The EAG interpreted this to be the result of darbepoetin alfa's statistically significant benefit over vadadustat at correcting people's Hb in the PEP of treatment. People	The statement should be rewritten as: "As expected from the non-inferiority trial design, no notable differences in efficacy were demonstrated between vadadustat and darbepoetin alfa, in any subgroups, supporting the conclusion that vadadustat was non-inferior to darbepoetin alfa".	The INNO$_2$VATE trials were non-inferiority trials (they were not designed to show superior/additional benefit). As such, there will be no statistical significance associated in any clinical outcomes. Furthermore, the source documents do not provide any p value indicating a statistically significant difference and the confidence intervals are well within the predefined margin. Thus, it is unclear to the Company upon which this claim is based.	The EAG does not consider this to be a matter of factual inaccuracy. The EAG interpreted the subgroup results from the INNO$_2$VATE – incident trial with reference to the overall study results. No changes have been made to the report.

with an Hb of 95 g/L or more did not require substantial correction of their Hb and the advantage of darbepoetin alfa over vadadustat was reduced.”			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3.2 subgroup analyses (Page 66), the following is stated: The EAG did not consider any of the small differences in efficacy within the subgroups to be notable.	The statement should be rewritten as: "As expected from the non-inferiority trial design, no notable differences in efficacy were demonstrated between vadadustat and darbepoetin alfa, in any subgroups, supporting the conclusion that vadadustat was non-inferior to darbepoetin alfa".	The INNO$_2$VATE trials were non-inferiority trials (they were not designed to show superior/additional benefit). As such, there will be no statistical significance associated in any clinical outcomes.	The EAG does not consider this to be a matter of factual inaccuracy. No changes have been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3.3 adverse events (Page 67), the following is stated: "The EAG's clinical experts were not aware of any plausible mechanism driving a difference in MACE outcomes between treatment arms. The trial	The statement should be rewritten as: "The trial was powered to test non-inferiority, and no difference in terms of MACE outcomes was observed between the treatment arms, supporting the demonstration that vadadustat was non-inferior to darbepoetin alfa."	Faster or rapid increase in Hb can lead to increased MACE outcomes. Given vadadustat does not cause a rapid increase in Hb levels, there is no higher risk of MACE outcomes.	Thank you for the feedback. The EAG has altered the report in line with amendment proposed by the company.

was not powered to detect a difference in MACE, but given their expert's advice, the EAG considered it reasonable to assume no difference in MACE between the treatment arms."			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In section 3.4 Conclusions of the clinical effectiveness (Page 69), the following is stated: "The results of the two clinical trials showed that darbepoetin alfa had a statistically significant benefit over vadadustat at correcting a person's Hb levels and at maintaining a person's Hb within the recommended target range."	The statement should be rewritten as: "the two clinicals trials demonstrated non-inferiority of vadadustat to darbepoetin alfa for correcting or maintaining Hb levels within the recommended target range."	Both INNO$_2$VATE trials showed non-inferiority for vadadustat for primary and secondary efficacy endpoints. The study was not powered to show benefit, simply non-inferiority. This has been an important misinterpretation throughout the EAG report. The source documents do not provide any p value indicating a statistically significant difference and it is unclear to the Company upon which this claim is based.	The EAG have edited the report to reflect that the statistically significant benefit of darbepoetin alfa over vadadustat for changing average Hb between baseline and both the primary and secondary efficacy period was within the pre-specified non-inferiority margin. However, the EAG maintain that no non-inferiority margin was pre-specified for the maintenance of Hb within geography-specific target. Therefore, the EAG continued to state that there

			was a statistically significant benefit of darbepoetin alfa over vadadustat for maintenance.

Issue 2 Classification of vadadustat

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
A number of statements in the report appear to classify vadadustat as an ESA: In section 2.3.2 (Page 26), the following is stated: "Figure 1 shows the proposed positioning of vadadustat, an oral ESA" In section 2.3.2 (page 26), the following is stated: "In the positioning proposed by the Company, vadadustat could be offered to people as their first ESA treatment" In section 2.3.2 Administration: oral versus	The statements should be rewritten as: "Figure 1 shows the proposed positioning of vadadustat, a HIF-PHI" "In the positioning proposed by the Company, vadadustat could be offered to people as their first HIF-PHI treatment" "Therefore, the EAG do not consider that there would be any significant saving of qualified nurse time (from not having to undertake ESA injections) if an increased use of HIF-PHIs led to a reduction in use of injectable ESAs." "However, they also agreed that a HIF-PHI, which could be easily stored, may be preferred to an injectable ESA by people on PD who cannot receive the	The Company request their product not be misclassified as an 'oral ESA'. Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) with a different mode of action to ESAs; they are different classes.	Thank you for the correction. The EAG has edited the report to label vadadustat as a hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) enzyme inhibitor (HIF-PHI) rather than an oral ESA.

injection (Page 27), the following is stated: "Therefore, the EAG do not consider that there would be any significant saving of qualified nurse time (from not having to undertake ESA injections) if an increased use of oral ESAs led to a reduction in use of injectable ESAs." In section 2.4 Critique of Company's definition of decision problem (Page 30), the following is stated: "However, they also agreed that an oral ESA, which could be easily stored, may be preferred to an injectable ESA by people on PD who cannot receive the injectable ESA administered IV into the dialysis lines." In section 3.4 Conclusions of the clinical effectiveness (Page 69), the following is stated:	injectable ESA administered IV into the dialysis lines." "Given the benefit in efficacy of darbepoetin alfa over vadadustat, and the similar safety profiles, the Company emphasised the benefits of a HIF-PHI (vadadustat) over injectable ESAs in administration, and also in support of home therapies."		

“Given the benefit in efficacy of darbepoetin alfa over vadadustat, and the similar safety profiles, the Company emphasised the benefits of an oral ESA (vadadustat) over injectable ESAs in administration, and also in support of home therapies.”			

Issue 3 Target population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.3.2 Vadadustat may also be an important treatment option for people resistant to injectable ESAs (Page 27), the following is stated: “The Company do not formally suggest vadadustat may be useful for this population”	The Company request removing this statement as it is factually inaccurate.	Sub-group analyses shared in the submission documents demonstrate suitability for the DD-CKD population as a whole. MEDICE make no mention of this subpopulation being excluded from the target population.	Thank you for the correction. This line has been removed from the report.

Issue 4 Exclusion criteria of INNO$_2$VATE trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.3.2 Vadadustat may also be an important treatment option for people resistant to injectable ESAs (Page 28), the following is stated: "However, the INNO$_2$VATE – incident trial excluded people who met the criteria of injectable ESA resistance within eight weeks prior to or during screening"	The statement that the INNO$_2$VATE – incident trial excluded patients who could be considered ESA-resistant is factually inaccurate. The Company request removal of this statement.	Patients with ESA resistance according to criteria given in section 2.3.1 were not excluded from the INNO$_2$VATE trials. Only patients with red blood cell transfusion within 4 weeks prior to or during the Screening period were excluded. Moreover, a subgroup analysis of patients according to baseline ESA dosage revealed that 6% of patients had baseline ESA doses >300 IU/kg/week, which is reflective of ESA resistance (Chertow et al. ERA 2024 Abstract #2063). The Company suggest a fundamental misunderstanding by the EAG of the non-inferiority INNO$_2$VATE trial design.	The EAG maintain that the INNO$_2$VATE – incident trial excluded people who met the criteria of injectable ESA resistance. Table 4 in Document B detailed the following exclusion criterion: Patients that met criteria of ESA resistance within eight weeks prior to or during screening defined as follows: - epoetin >7,700 units/dose three times per week or >23,000 units per week; - darbepoetin alfa >100 µg/week; - methoxy polyethylene glycol-epoetin beta

			>100 µg every other week or >200 µg every month. However, for clarity, the EAG have updated the description of ESA resistance in Section 2.3.1 to align with the company's criteria in the $INNO_2VATE$ – incident trial.

Issue 5 Comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.4 Critique of Company's definition of decision problem (Page 29), the following is stated: "The comparators in the final scope were injectable ESAs. Erythropoietin, epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta"	The statement should be rewritten as: "The comparators in the final scope were ESAs. Epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta"	Erythropoietin is a class of treatment, not a specific comparator treatment option. The statement for final scope should be amended to align with that issued in the NICE final scope, as presented in Table 1 on page 10, Document B.	Thank you for the correction. Erythropoietin has been removed from the list of injectable ESAs.

Issue 6 Discontinuation data from the CSR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.2.2 Dropouts (Page 44), the following is stated: "In the vadadustat arm, [redacted] people discontinued for this reason compared to [redacted] in the darbepoetin alfa arm".	The sentence should be rewritten as: "In the vadadustat arm, [redacted] people discontinued for this reason compared to [redacted] in the darbepoetin alfa arm".	The INNO$_2$VATE – prevalent CSR (page 55 of 219) mentions [redacted] patients in vadadustat arm no longer wants to receive the study drug.	Thank you for this correction. The report has been altered in line with the proposed amendment.

Issue 7 Discontinuation reason

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.2.2 Dropouts (Page 44), the following is stated: "The EAG's clinical experts reasoned that for both trials, vadadustat discontinuations may be linked to the additional pill burden of a daily oral drug."	The Company request amending it to – "No exact reasons for discontinuations were known. As noted in the EPAR, trial investigators considered the difference in discontinuations between vadadustat and darbepoetin alfa may be due to the open-label trial design and subjects may have preferred to switch to a product which effect and dosing were well known (standard of care)".	The Company believe that this is speculation, and no evidence is available to support these claims. Even though there are no exact reasons known for these discontinuations, the EMA EPAR notes (page 171) that the difference in early discontinuations between vadadustat and darbepoetin	The EAG do not consider this to be a matter of factual inaccuracy. The EAG's clinical experts offered their assessment of the reasons why a substantially higher proportion of people in the vadadustat arms no longer wished to receive the study drug. No

		alfa may be due to the open-label trial design. The opinion of the experts involved in the clinical trial should be reflected in the EAG report text. Furthermore, it is stated in the EMA EPAR (page 137) that treatment compliance was apparently high throughout the pivotal studies. As detailed in the clarification response, the most frequent reasons for discontinuations suggest that subjects may have preferred to switch to a product which effect and dosing were well known (standard of care). Even though discontinuations were more frequent in the vadadustat treatment group, the frequency of subjects completing the trial was similar for vadadustat and darbepoetin alfa, showing that subjects in both groups were followed-up for MACE and TEAEs even though they discontinued.	changes have been made to the report.

Issue 8 Proportion of patients using PD

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.2.4 Comparator (Page 45), the following is stated: "143 (8.0%) of people in the darbepoetin alfa arm of the INNO$_2$VATE – prevalent trial, were using PD during the trial."	The sentence should be rewritten as: "143 (8.1%) of people in the darbepoetin alfa arm of the INNO$_2$VATE – prevalent trial, were using PD during the trial."	The INNO$_2$VATE – prevalent CSR (Page 142 of 219) mentions 143 (8.1%) patients were on PD in the darbepoetin alfa treatment group.	The EAG do not consider this to be factually inaccurate. There were 1777 people in the darbepoetin alfa treatment arm and 143 (8.047%) were on PD. No changes have been made to the report.

Issue 9 Incorrectly defined Hb levels

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.2.5 Use of additional therapy; ESA rescue therapy (Page 47), the following is stated: "ESA narrow rescue therapy was given due to low Hb (>95 g/L) and/or worsening of symptoms of anaemia"	The statements should be rewritten as: "ESA narrow rescue therapy was given due to low Hb (<95 g/L) and/or worsening of symptoms of anaemia"	The ">" sign denotes greater than while "<" sign denotes less than. ESA rescue therapy was given if Hb was less than 95g/L (as stated in the response to NICE clarification question A8 and in vadadustat EPAR page 83/190).	Thank you for this correction. The report has been altered in line with the proposed amendment.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.2.5 3.2.3.1 Use of additional therapy (Page 58) where the following is stated: "As discussed in Section 3.2.2.5, narrow rescue therapy was therapy attributable to a low Hb (>95 g/L)".	The statements should be rewritten as: "As discussed in Section 3.2.2.5, narrow rescue therapy was therapy attributable to a low Hb (<95 g/L)".	The ">" sign denotes greater than while "<" sign denotes lesser than. ESA rescue therapy was given if Hb was lesser than 95g/L (as stated in the response to NICE clarification question A8 and in vadadustat EPAR page 83/190).	Thank you for this correction. The report has been altered in line with the proposed amendment.

Issue 10 Misnumbering of a cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.2.5 Outcomes; Adverse effects of treatment including major adverse cardiovascular events (Page 47), the following is stated: "Summaries of TEAEs in each trial were presented in Section B.1.10 of the CS"	The statement should be rewritten as: "Summaries of TEAEs in each trial were presented in Section B.2.10 of the CS"	The summary of TEAEs was presented in section B.2.10 of the CS.	Thank you for this correction. The report has been altered in line with the proposed amendment.

Issue 11 Meta-analysis methodology

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3., page 52, the EAG states: "At the clarification stage (Question A3), the company provided a fixed effect meta-analysis for this outcome, alongside the pooled individual patient data (IPD) results. However, given the heterogeneity of results from the two trials, the EAG considered a random effects meta-analysis to be a more appropriate model for this analysis."	The statement that a random effects meta-analysis is more appropriate is factually inaccurate. The Company suggests removing the mention that one is more appropriate than the other as there is justification in the literature that the Company's approach is also appropriate. The sentence should read: "At the clarification stage (Question A3), the company provided a fixed effect meta-analysis for this outcome, alongside the pooled individual patient data (IPD) results. However, given the heterogeneity of results from the two trials, the EAG considered a random effects meta-analysis for this analysis."	Based on Gelman 2006, the acquired wisdom in the field of meta-analysis is that applying a random effect on less than 5 data points/studies (as a thumb rule) results in a likely poorly identified posterior distribution for the between-study heterogeneity. This means that the estimate of the between-study heterogeneity will likely include values that, on reflection, are implausibly high or low. As a result, when only two studies are pooled, fixed effects are preferred on pragmatic grounds.	The EAG do not consider this to be a matter of factual inaccuracy. The Cochrane Handbook stated that fixed-effect meta-analyses ignore heterogeneity. However, a random-effects meta-analysis may be used to incorporate heterogeneity among studies. Thus, the EAG consider the statement to be in-line with current best-practice. No changes have been made to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

In section 3.2.3., page 52-53, the EAG states: "The fixed effect meta-analysis found a statistically significant benefit for darbepoetin alfa over vadadustat in increasing a person's Hb. Although it was clear from the point estimate that INNO2VATE – prevalent, the larger trial, dominated the meta-analysis."	The sentence should be rewritten as follows to remove mention of statistical significance: "The fixed effect meta-analysis found that vadadustat was non-inferior to darbepoetin alfa in increasing Hb levels of patients. Although it was clear from the point estimate that $INNO_2VATE$ – prevalent, the larger trial, dominated the meta-analysis."	In light of the non-inferiority design, it is inappropriate to interpret the results of a meta-analysis of non-inferiority trials in terms of statistically significance; interpretation should rather be applied in terms of the non-inferiority margin. The threshold is the margin and this should be considered in the interpretation of results for the meta-analysis in a similar way the trial results should be interpreted as highlighted in Issue 1.	The EAG does not consider this to be a matter of factual inaccuracy. The figures reported by the EAG were correct. However, for clarity, the EAG have clarified that the results did not meet the pre-specified non-inferiority margin in the text.

Issue 12 Confidence intervals for pooled data

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
In section 3.2.3.1 Change in average Hb between baseline and the primary efficacy period (weeks 24 to	The statements should be rewritten as: "However, the pooled IPD (treat-as-one-trial method) disregarded study-to-study variation."	This statement is unsubstantiated. The pooled IPD may theoretically lead to narrower confidence intervals, but the EAG has not	The EAG does not consider this to be a matter of factual inaccuracy. In each case (see Tables 9 and 10 in the EAG's report), the

36) (page 53), the following is stated: "However, the pooled IPD (treat-as-one-trial method) disregarded study-to-study variation, which led to narrower confidence intervals." In section 3.2.3.1 Change in average Hb between baseline and the primary efficacy period (weeks 40 to 52) (page 54), the following is stated: "However, the pooled IPD (treat-as-one-trial method) disregarded study-to-study variation and led to narrower confidence intervals."		presented any evidence to show that it did in fact do so.	pooled IPD results demonstrate narrower confidence intervals than the fixed effects meta-analysis. No changes have been made to the report.

Issue 13 Data on change in average Hb between baseline and the primary efficacy period (weeks 24 to 36)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3.1 Table 9 (Page 53), the following is mentioned: "$INNO_2VATE$ – incident Mean SD 9.9 (12.26)"	The text should be rewritten as: "$INNO_2VATE$ – incident Mean SD 9.9 (12.76)"	The $INNO_2VATE$ – prevalent CSR (Page 142 of 219) mentions 12.76.	Thank you for this correction. The report has been altered in line with the proposed amendment.

Issue 14 Data on change in average Hb between baseline and the secondary efficacy period (weeks 40 to 52)

Description of problem

In section 3.2.3.1 Table 10 (Page 54-55), the following is mentioned:

$INNO_2VATE$ – prevalent	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)	Treatment comparison vadadustat versus darbepoetin alfa
Change from baseline			
Mean (SD)	11.0 (110.8)	30.0 (110.3)	-
Least squared mean (SEM)	19.0 (3.2)	36.0 (3.2)	-17.0 (3.3)
95% CI	12.0, 25.0	29.0, 42.0	-23.0, -10.0

Description of proposed amendment

The Company request replacing all the values in these columns with the following:

$INNO_2VATE$ – prevalent	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)	Treatment comparison vadadustat versus darbepoetin alfa
Change from baseline			
Mean (SD)	1.5 (11.78)	3.5 (11.31)	-
Least squared mean (SEM)	2.3 (3.5)	4.1 (3.3)	-1.8 (0.35)

Justification for amendment

The proposed values correspond correctly with the data presented in $INNO_2VATE$ – prevalent CSR Table 23 (Page 82-83 of 219).

EAG response

Thank you for this correction. The report has been altered in line with the proposed amendment.

	95% CI	1.6, 2.9	3.4, 4.8	-2.5, -1.2		

Issue 15 Data on number of red blood cell transfusion episodes received

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3 Table 13 (Page 59), the following is mentioned: INNO$_2$VATE – incident: Vadadustat (N=181); Darbepoetin alfa (N=188); Treatment comparison vadadustat – darbepoetin alfa Number of RBC transfusion episodes: 13; 8; -	The Company request replacing all the values in these columns with the following: INNO$_2$VATE – incident: Vadadustat (N=181); Darbepoetin alfa (N=188); Treatment comparison vadadustat – darbepoetin alfa Number of RBC transfusion episodes: 23; 15; -	The proposed values correspond correctly with the data presented in Appendix M Table 5 and INNO$_2$VATE – incident CSR Table 27 (Page 97 of 6587).	Thank you for this correction. The report has been altered in line with the proposed amendment.

Issue 16 Data on number of ESA rescue therapy episodes received

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.2.3 Table 15 (Page 62), the following is mentioned: **INNO$_2$VATE – prevalent**: **Vadadustat (N=1,777)**; **Darbepoetin alfa (N=1,777)**; **Treatment comparison vadadustat versus darbepoetin alfa** Number of RBC transfusion episodes: 620; 249; -	The Company request replacing all the values in these columns with the following: **INNO$_2$VATE – prevalent**: **Vadadustat (N=1,777)**; **Darbepoetin alfa (N=1,777)**; **Treatment comparison vadadustat versus darbepoetin alfa** Number of RBC transfusion episodes: 620; 249; -	The proposed values correspond correctly with the data presented in Appendix M Table 21 and INNO$_2$VATE – prevalent CSR section 11.1.1.3.9.4 (Page 101 of 219).	Thank you for highlighting this error. The table has been corrected in line with Table 21 in Appendix M.

Rate ratio (95% CI)	-	-	3.5 (3.08, 4.04)	Rate ratio (95% CI)	-	-	3.5 (3.08, 4.04)		
p-value[a]	-	-	<0.0001	p-value[a]	-	-	<0.0001		
Number (%) of patients without any episodes	68.9 (84.73)	52.0 (60.94)	-	Number (%) of patients without any episodes	1,148 (64.9)	1,520 (85.9)	-		

Issue 17 Pooling of efficacy outcome data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.4 Conclusions of the clinical effectiveness (Page 69), the following is stated: "However, the Company pooled the inconsistent efficacy outcome data for use in the economic model. In pooling the efficacy data, the estimates were weighted heavily in favour of the substantially larger $INNO_2VATE$ – prevalent trial."	The statement should be rewritten as: "The Company pooled the efficacy outcome data for use in the economic model."	This is an unbalanced statement that implies that this is not an appropriate approach, but this reflects the EAG's opinion, which differs from the perspective of the designers of the trial and the analysis. The Company believe that the weighting towards the $INNO_2VATE$ – prevalent trial is appropriate, as this reflects the actual population to be treated.	The EAG does not consider this to be a matter of factual inaccuracy. As stated in the report, the EAG were concerned that it was inappropriate to pool the $INNO_2VATE$ trials data. This was because the aim of treatment did not always align between the trials and the populations recruited to each trial were at different points on the treatment pathway. No changes have been made to the report.

Issue 18 Rate of ESA rescue therapy episodes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.4 Conclusions of the clinical effectiveness (Page 69), the following is stated: "However, people on vadadustat arms had substantially higher rates of ESA rescue therapy episodes."	The statement should be rewritten as: "However, people on vadadustat arms had comparable rates of ESA rescue therapy episodes."	ESA rescue therapy analysis were impaired by differential definitions in treatment groups. For vadadustat it was any ESA therapy, for darbepoetin it was any ESA different from darbepoetin. But as non-SPC conform increases of darbepoetin dose (e.g., dose increases >50% or >100% to the prior dose may be seen as "ESA-rescue", post hoc analysis revealed comparable amounts of ESA-rescue therapy with changing definitions.	The EAG does not consider this to be a matter of factual inaccuracy. People in the vadadustat arms had higher rates of ESA rescue therapy episodes than those in the darbepoetin alfa arms. In Section 3.2.3.1 of the report, the EAG explained the company's concerns that ESA rescue therapy was not adequately collected in the INNO$_2$VATE trials. However, despite this uncertainty, the EAG considered the ESA rescue therapy as recorded by the trial investigators to be the most robust estimate. No

			changes have been made to the report.

Issue 19 Burden of self-injection

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.4 Conclusions of the clinical effectiveness (Page 69), the following is stated: "Therefore, the EAG did not accept that injectable ESAs provided a challenge for self-administration, and understood that the principal barrier to home therapies was undertaking dialysis unsupervised not administration of ESAs."	The Company request to delete the statement.	The statement is unsubstantiated. There is a lot of literature evidencing the associated challenges of self-administration of injection. For example, Pagel and Hylander 2013 concluded that a range of barriers may influence patients' ability to self-inject ESAs, including injection fear, uncertainty of procedure, impaired vision, impaired hand function, difficulty handling injection technique, and convenience. Given the existence of literature supporting a view contrary to the view taken by the EAG, the Company request to delete this statement to	The EAG does not consider this to be a matter of factual inaccuracy. The EAG reported advice of their clinical experts on the barriers to home therapies for people with DD-CKD. No changes have been made to the report.

		provide a balanced representation.	
In section 3.4 Conclusions of the clinical effectiveness (Page 69), the following is stated: "Prior to the trial, over 90% of people received their injectable ESA through administered IV into the dialysis lines, and the EAG understood this did not present a medication burden."	The statement should be rewritten as: "Prior to the trial, over 90% of people received their injectable ESA through administered IV into the dialysis lines."	The statement is not supported by peer-reviewed evidence. The Company believe this is merely the EAG's opinion.	The EAG does not consider this to be a matter of factual inaccuracy. The EAG reported advice from their clinical experts on the medication burden faced by people with DD-CKD. No changes have been made to the report.

Issue 20 Treatment efficacy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.4 Conclusions of the clinical effectiveness (Page 70), the following is stated: "On the basis of the above conclusions, the EAG considered that, despite its reduced efficacy,	The statement should be rewritten as: "On the basis of the above conclusions, the EAG considered that vadadustat may be a preferred treatment option for people on PD who value the flexibility afforded them by an	The part of the sentence that states that vadadustat has reduced efficacy is incorrect as the clinical trials robustly demonstrated non-inferiority. This was reflected in the EMA EPAR which states on p184: non-inferiority of vadadustat	The EAG understood that darbepoetin alfa offered a statistically significant benefit over vadadustat in maintaining an average Hb value within geography-specific target

vadadustat may be a preferred treatment option for people on PD who value the flexibility afforded them by an oral treatment that does not require cold-chain storage.”	oral treatment that does not require cold-chain storage.”	to darbepoetin alfa for the primary efficacy endpoint was demonstrated in the Randomized, FAS and the PP population analyses. In the randomized population, vadadustat was shown to be non-inferior to darbepoetin alfa at the PEP (Weeks 24 to 36) in treating anaemia associated with CKD in subjects on chronic dialysis since the lower bound of the 95% CI (-0.53, -0.23) for the LS mean difference in the change from baseline was above the prespecified non-inferiority margin of -0.75 g/dL in each study.	range (Table 11, EAG report). However, the benefit of darbepoetin alfa in changing a person’s Hb lay within the pre-specified non-inferiority margin. The EAG have edited the report to reflect this.

Issue 21 Burden of pill medication

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 3.4 Conclusions of the clinical effectiveness	The Company request to delete the statement.	The Company believe that this is speculation, and there is no evidence available to support the claim that it was pill	The EAG do not consider this to be a matter of factual inaccuracy. The EAG’s

(Page 70), the following is stated: "The EAG considered the substantially higher attrition in the vadadustat arms in the INNO$_2$VATE trials to be related to the increased pill burden imposed by the use of an additional daily oral medication" In section 6.2.5 Scenario 1: Revised model structure (Page 133), the following is stated: "The EAG's clinical experts reasoned that, for both trials, vadadustat discontinuations may be linked to the additional pill burden of a daily oral drug. Prior to the trial more than 90% of participants were on HD and received their ESA through their dialysis, and as such, had no medication burden linked to injectable ESAs. People who were randomised to vadadustat		burden which drove the higher discontinuation rate with vadadustat versus darbepoetin alfa. In fact, there are no exact reasons known for these discontinuations. In fact, the EMA EPAR notes (page 171) that the difference in early discontinuations between vadadustat and darbepoetin alfa may be due to the open-label trial design; no mention of pill burden was made in the EMA EPAR. Moreover, it is stated in the EMA EPAR (page 137) that treatment compliance was apparently high throughout the pivotal studies. If a reason is to be postulated then the reasoning from the EMA EPAR should at least be included to provide a balanced representation. Furthermore, while the study mentioned gives a good estimate of pill burden in PD and HD patients, an important question is whether one	clinical experts offered their assessment of the reasons why a substantially higher proportion of people in the vadadustat arms no longer wishes to receive study drug. No changes have been made to the report.

therefore had an additional daily pill on top of the pills they were already taking. As noted in Section **Error! Reference source not found.**, a systematic review found that excessive medication burden led to poorer medication adherence, and reduced quality of life.”		additional tablet would essentially modulate medication burden. Moreover, it must be considered that UK-guidelines see an important place for HIF-PHI treatment in PD patients, where the burden of SC self-injection will be reduced and thus the overall burden of medication intake will be reduced and not raised. Finally, it should be noted the argument for poor medication adherence and reduced quality of life also holds true for injectables. As such the Company request removal of this statement at this point.	

Issues concerning the economic assessment

Issue 22 Model analysis inputs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 1.3 Key Issue 1 (Page 17-18), the following is stated: "However, this was subject to some limitations, for separated data were not available for some model inputs. Therefore, some key inputs still relied on pooled estimates."	The sentence should be rewritten as: "However, this was subject to some limitations as separate analyses are possible for Hb but not for MACE outcomes. Therefore, some key inputs still relied on pooled estimates."	The only model inputs used from the pooled data were MACE outcomes, for which the trial design specified a priori should be a pooled analysis to ensure sufficient power to assess the trial hypothesis of non-inferiority.	Amended to: "However, this was subject to some limitations, for separated data were not made available to the EAG for some model inputs. Therefore, some key inputs still relied on pooled estimates." This refers to the Hb level transition probabilities and treatment discontinuations Kaplan-Meier data requested at clarification stage.

Issue 23 Mistaken timing of secondary efficacy period in INNO$_2$VATE trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.2.1 Hb levels (Page 78), the following is stated: "The EAG noted that the primary efficacy endpoint and the key secondary efficacy endpoint of the INNO$_2$VATE trial (change in Hb from baseline to weeks 24 to 36 and weeks 40 to 36) are not used as part of the model structure presented (and instead used to inform HRQoL only)."	The statement should be rewritten as: "The EAG noted that the primary efficacy endpoint and the key secondary efficacy endpoint of the INNO$_2$VATE trial (change in Hb from baseline to weeks 24 to 36 and weeks 40 to 52) are not used as part of the model structure presented (and instead used to inform HRQoL only)."	The Company believe the primary efficacy endpoint timing was not correctly stated. In line with the INNO$_2$VATE trials CSRs, the secondary efficacy period took place from weeks 40 to 52.	Amended to 52.

Issue 24 Main ESA used in the UK

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.4 Interventions and	The Company request the statement be removed as it is factually incorrect	This is not supported by the NHS data from the renal registry (see Birnie et al	Removed the reference to not being the main

comparators (Page 82), the following is stated: "Therefore, darbepoetin alfa may not be the main injectable ESA used throughout the UK"	based on prescribing data available from the NHS renal registry.	2017, NICE TA807 2022, budget impact assessment; UK Renal Registry 23rd Annual Report).	injectable ESA and amended to: "Therefore, darbepoetin alfa may not be used throughout the UK."

Issue 25 Interpretation of cost-effectiveness model scenario analysis using MACE IPD data directly for the vadadustat arm

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.6.3 MACE events (Page 86), the following is stated: "This supported the EAG's conclusion that, overall, there is no evidence of a difference in MACE between vadadustat and injectable ESAs (given the HR approach gives a slight incremental LY and QALY benefit vs using the IPD approach)."	The Company request removal of the statement.	The Company believe this statement is incorrect. The originally submitted model was designed in a manner that did not allow for the direct use of IPD MACE data for the vadadustat arm. Therefore, direct application of IPD MACE data in the vadadustat arm led to overall life-year and QALY loss for vadadustat in the respective scenario analysis. The result of this scenario analysis itself does not support the claim of no difference in MACE events	Amended to: "The EAG considered this to support the conclusion that, overall, there is no evidence of a difference in MACE between vadadustat and injectable ESAs (given the HR approach gives a slight incremental LY and QALY benefit vs using the IPD approach)." To reflect that this is the EAG's opinion on what

		between the vadadustat and darbepoetin alfa arms.	the scenario demonstrates.

Issue 26 Mistake in Hb level category measurement

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.6.5 Haemoglobin level (Page 91), Table 29, row 3 for original distributions, vadadustat, contains the following input: "≥120 g/dL" category.	The input should be rewritten as: "≥120 g/L"	The Company believe this is a typographical error that needs to be corrected.	Corrected

Issue 27 Modelled treatment discontinuation cycle

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 4.2.6.6 Treatment discontinuation (Page 92), the following is stated: "Patients are discontinued treatment from model cycle 1 (week 11)"	The statement should be rewritten as: "Patients are discontinued treatment from model cycle 1 (week 13)"	Model cycle 1 is week 13.	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 6.2.1 Scenario 1: Revised model structure (Page 103), Figure 13 contains several Hb level categories under “DD” health state. One of these categories is marked as “Hb < 120 g/L”.	The category in the figure should be rewritten as: “Hb > 120 g/L”.	The Company believe this is a typographical error that needs to be corrected. In the paragraph above Figure 13 in the EAG report (page 128), Hb level categories are defined “ ‘<100 g/L’, ‘100-120 g/L’ and ‘>120 g/L’ “ which does not align with Figure 13.	Figure 13 has been corrected.

Issue 28 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Throughout the EAG report darbepoetin alfa is referred to as “darbopoetin alfa” or “darbopoetin”	The Company request to refer to the drug mentioned as “darbepoetin alfa”, to be applied throughout the EAG report.	The Company believe this is a typographical error that needs to be corrected.	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 6.2.2 Scenario 2: Treatment discontinuation approach (Page 132), the following is stated: "After this time point, those who discounted treatment therefore use the injectable ESAs transitions and the injectable ESAs treatment discontinuation curve and drug costs (in line with the Company's assumptions)."	The statement should be rewritten as: "After this time point, those who discontinued treatment therefore use the injectable ESAs transitions and the injectable ESAs treatment discontinuation curve and drug costs (in line with the Company's assumptions)."	The Company believe this is a typographical error that needs to be corrected.	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 6.2.3 Scenario 3: Definition of rescue therapy (Page 132), the following is stated: "The rates of patients receiving RBS and rescue injectable ESAs used the narrow rescue definition."	The statement should be rewritten as: "The rates of patients receiving RBC and rescue injectable ESAs used the narrow rescue definition."	The Company believe this is a typographical error that needs to be corrected.	Corrected

Issue 29 Error in WTP level for iNMB calculation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 6.2.8 Impact on the ICER of additional clinical and economic analyses (Page 138), Table 57, the following is stated in the last column heading: "iNMB (WTP = £20,000)".	The statement should be rewritten as: "iNMB (WTP = £30,000)".	The Company believe this is a typographical error that needs to be corrected. Similar tables below (for example, Table 58) contained WTP values of £20,000 and £30,000 for the iNMB calculation, while in Table 57 the WTP value of £20,000 is repeated twice.	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.2.1 Deterministic sensitivity analyses (Page 116), Table 50, column headings are incorrectly merged; under column under iNMB (WTP = £20,000) and	The table should be redrawn as below with two columns each under iNMB (WTP = £20,000) and iNMB (WTP = £30,000):	The Company believe this is a typographical error that needs to be corrected.	Corrected

three columns under iNMB (WTP = £30,000) in the following manner:

iNMB (WTP = £20,000)	iNMB (WTP £30,000)		
Lower bound of parameter (£)	**Upper bound of parameter (£)**	**Lower bound of parameter (£)**	**Upper bound of parameter (£)**

iNMB (WTP = £20,000)		iNMB (WTP £30,000)	
Lower bound of parameter (£)	**Upper bound of parameter (£)**	**Lower bound of parameter (£)**	**Upper bound of parameter (£)**