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

For publication – redacted

Technology appraisal committee B 11 September 2024

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on anaemia in chronic kidney disease (CKD)

Anaemia significantly contributes to burden of CKD

Causes

- Anaemia: below normal circulating red blood cells (quality and quantity); common in CKD because damaged kidneys produce less erythropoietin, which helps make red blood cells
- In CKD, increases morbidity (including comorbidities) and reduces QoL

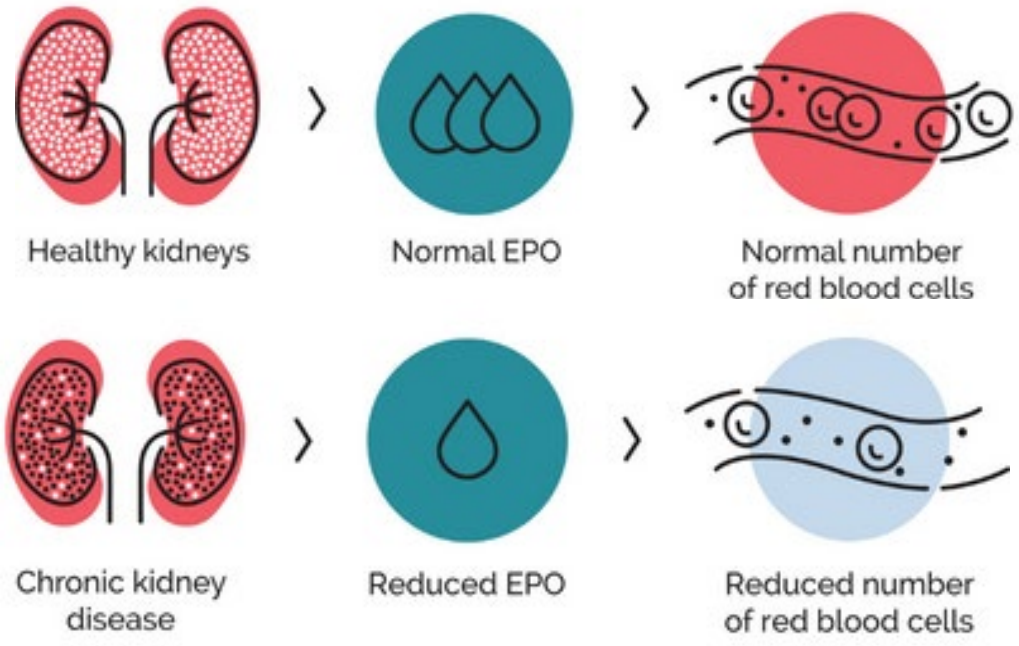
Epidemiology

- 5% of adults (34% aged 75+ years) have stage 3-5; stage 5 is typically dialysis-dependent and up to 90% may have anaemia

Diagnosis

- Investigated if Hb < 110 g/L or symptoms present

CKD and anaemia



* Source: Kidney Health Australia

Symptoms of anaemia and impact on prognosis

- Tiredness, breathlessness, low appetite, lethargy, palpitations, low cognition and concentration (‘brain fog’) reduced libido and immune responsiveness; reversible with treatment; can progress CKD and impact mortality

Abbreviations: CKD, chronic kidney disease; EPO, erythropoietin; Hb, haemoglobin; QoL, quality of life

Clinical perspectives

Oral alternative (vadadustat) useful if ESA not possible or does not increase Hb

Submissions from UK Kidney Association (UK Renal Pharmacy Group), 2 clinical experts

- Treatment aims to prevent and correct anaemia, improve symptoms and quality of life, and reduce morbidity and mortality
- Oral administration may benefit anaemia resistant to ESAs, people unable to take ESAs (i.e. needle phobia or unable to self-inject), and/or having peritoneal dialysis (specialist nurse and refrigeration not needed as typical with ESAs)
- Vadadustat prescribed, initiated and monitored in secondary care; potential change in practices and prescribing, and increased blood tests initially but HIF-PH inhibitors more common with roxadustat used for CKD not on dialysis
- Most important outcomes: Hb levels, MACE* outcomes, iron requirements (and associated risks), cost and time
- Adverse events similar to ESAs apart from diarrhoea which can be difficult in CKD

‘People could receive vadadustat from the hospital, via home care delivery or from their community pharmacy…could provide flexibility and convenience’

* MACE includes all-cause mortality, non-fatal myocardial infarction and non-fatal stroke; Abbreviations: CKD, chronic kidney disease; ESA, erythropoietin stimulating agent; Hb, haemoglobin; HIF-PH; Hypoxia-inducible factor prolyl-hydroxylase; MACE, major adverse cardiovascular events

Patient perspectives

CKD has significant impact on ability to do simple tasks and quality of life

Submissions from Kidney Research UK, 2 patient experts

- Can have significant impact on ability to do simple physical tasks
- 'Mental' strain from symptoms including depression and other symptoms related to the condition, or from stigma and feeling a burden to others
- Provision of information on condition could be improved
- Anaemia in CKD is obstacle to working / employment
- Treatment options limited, particularly if dialysis-dependent, because of the already heavy burden of illness
- No need for cold storage and not requiring injection ideal but burden of injection varies. Side effects like diarrhoea after iron tablets impact quality of life (i.e. preventing travel for work or holiday)
- Treatment that enables more certainty about highs and lows would be valuable

"Really, really extreme fatigue"… "hitting you like a wave"

"People think you're lazy"

"A pill is much easier for patients"

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Abbreviations: CKD, chronic kidney disease; ESA, erythropoietin stimulating agent

Equality considerations

Kidney Research UK:

- Kidney disease disproportionally impacts people from deprived communities and ethnic minority groups who are more likely to develop kidney disease, progress faster to renal failure and require dialysis or a transplant.
    - People from deprived communities are more likely to be diagnosed at a later stage of disease progression and die earlier than other socio-economic groups.
    - People from ethnic minority groups wait on average longer for kidney transplant due to a shortage of kidneys with suitable tissue and blood match.

Company:

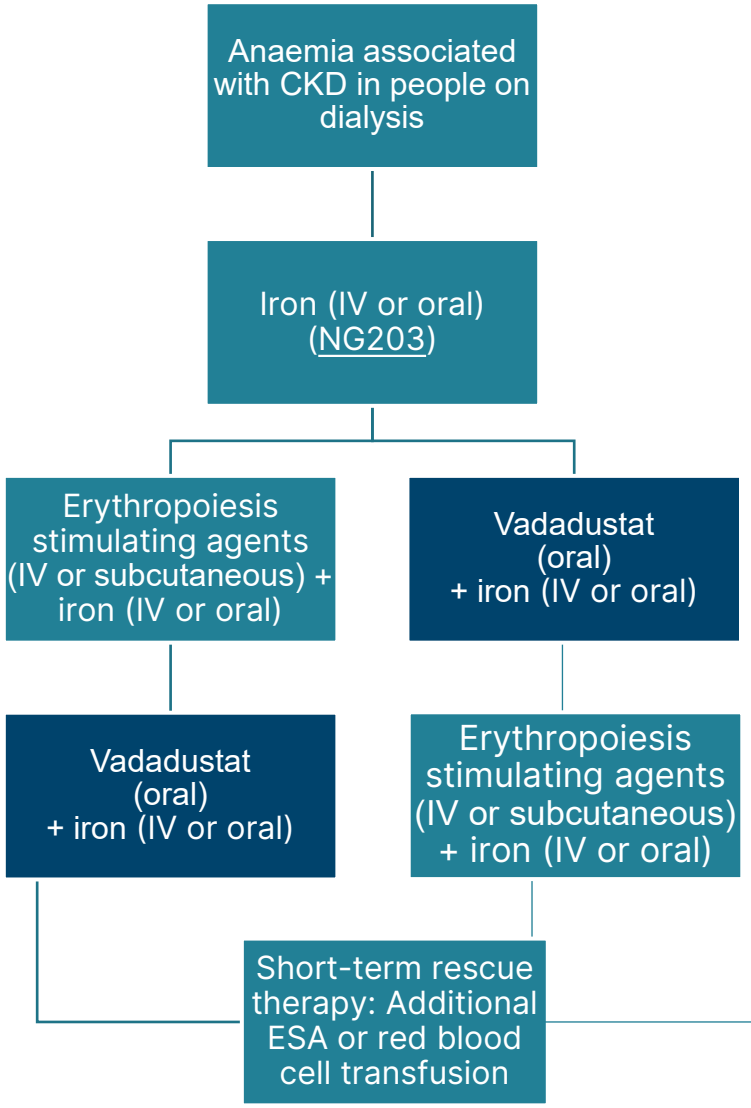
- Could reduce inequality in access given the severity and multi-comorbid nature of disease in people with dialysis-dependent CKD who may have limited ability to access outpatient care for ESAs. Oral option is preferred over existing administration.
- Vadadustat is important option for people whose disease is resistant to ESAs and in whom blood transfusions are more likely to be done and this can reduce suitability for a transplant (if antibodies developed)

Treatment pathway

Pathway of care well-defined with ESAs which can be short-acting up to 3x per week or long-acting weekly or monthly. Choice of ESA based on local contracts.

For people having hemodialysis, ESA usually taken intravenous as part of dialysis.

For people having peritoneal dialysis, ESAs usually subcutaneous self-injected or by a family or healthcare professional.



Dialysis performs function of kidney by filtering and purifying blood:

- Haemodialysis – usually in hospital or dialysis clinic, but can be at home (3x/week for 4 hours)
- Peritoneal dialysis – can be at home (several times a day or overnight)

Red blood cell transfusion:
- rarely needed after ESAs
- should be avoided in transplant-eligible patients, if possible

Is iron used as rescue therapy? Would ESAs be used if vadadustat failed or vice versa?
Is roxadustat continued for people when they start dialysis?

Abbreviations: CKD, chronic kidney disease; ESA, erythropoietin stimulating agent; IV, intravenous

Vadadustat (Vafseo, MEDICE)

Marketing authorisation	• Treatment of symptomatic anaemia associated with chronic kidney disease in adults on chronic maintenance dialysis • MHRA marketing authorisation in May 2023
Mechanism of action	• Hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) inhibitor: by inhibiting HIF-PH, endogenous erythropoietin (EPO) production is stimulated, increasing iron mobilisation and red blood cell production, resulting in a gradual rise in Hb
Administration	Oral tablets (300 mg/day starting dosage; max dosage 600 mg/day)*
Stopping rule	24 weeks (~6 months) if clinically meaningful increase in Hb levels not achieved
Price	• £297.19 per 28 pack of 300 mg • Annual treatment cost from £3,872.65 (for 300 mg dosage/day) • A patient access scheme is applicable if vadadustat is recommended

* Dose increases of 150 mg are permitted once every four weeks up to a maximum of 600 mg/ day; dose decreases of 150 mg can occur more frequently.

Abbreviations: Hb, haemoglobin; MHRA, medicine & healthcare products regulatory agency

Key issues

Issue	Resolved?	ICER impact
Pooling of data from INNO$_2$VATE trials	For discussion	Unknown
Model structure complexity including use of MACE for substates	For discussion	Large
Treatment costs and discontinuation in model	For discussion	Large
Treatment effect waning	For discussion	Small

= Largest ICER impact

Abbreviations: MACE, major adverse cardiovascular events

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Key clinical trials: INNO$_2$VATE incident and INNO$_2$VATE prevalent*

Both non-inferiority trials with same disease but stage of disease and treatment aim differed

INNO$_2$VATE incident (n = 369)

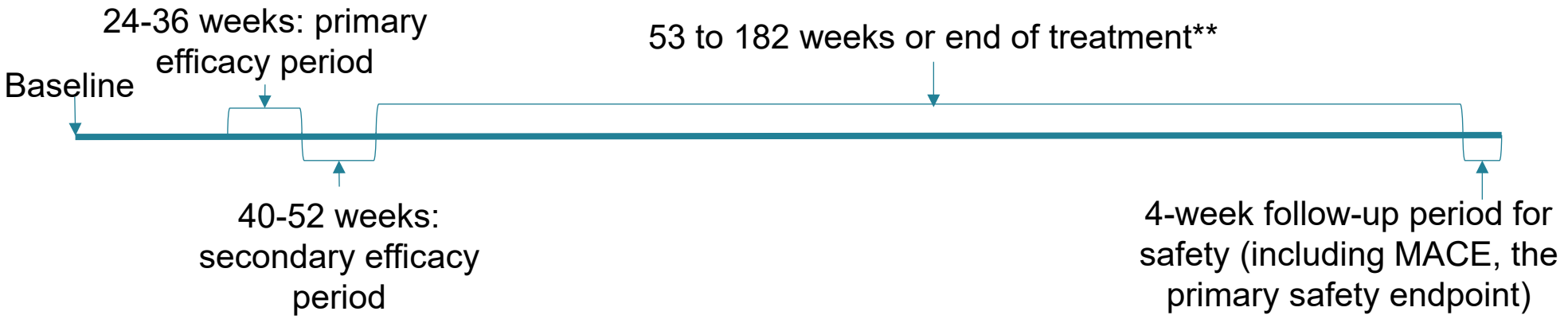
Patients with anaemia who have recently initiated dialysis treatment for DD-CKD

Key primary and secondary outcomes: change in average Hb between baseline and PEP (correction), and then between baseline and SEP (correction and maintenance)

Vadadustat*

Vs

Darbepoetin alfa



INNO$_2$VATE prevalent (n = 3554)

Patients with anaemia who have dialysis treatment for DD-CKD

Key primary and secondary outcomes: change in average Hb between baseline and PEP (maintenance), and then between baseline and SEP (maintenance)

* see appendix ** 300 mg/day with titration to 150-600 mg to achieve Hb 10-12 g/dL, ** of end of study, which occurred once 631 MACE were recorded. Abbreviations: DD-CKD, dialysis-dependent chronic kidney disease; Hb, haemoglobin; MACE, major adverse cardiovascular events; PEP, primary efficacy period; RCT, randomised controlled trial; SEP, secondary efficacy period

Key clinical trial results: proportion in target range (1 of 2)*

Darbepoetin alfa had benefit over vadadustat in proportion with target Hb levels during **primary efficacy period** (24-36 weeks) in both INNO$_2$VATE trials

Primary efficacy period (24-36 weeks) - Patients with average Hb level in target range**

INNO$_2$VATE – incident	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Vadadustat vs darbepoetin alfa
% responders observed (95% CI)	44 (36 to 51)	57 (50 to 64)	-
% responders observed and imputed*** (95% CI)	49 (47 to 51)	61 (59 to 63)	-
% difference (95% CI)	-	-	-0.12 (-0.22 to -0.01)
Odds ratio (95% CI)	-	-	0.6 (0.4 to 0.96)

Primary efficacy period (24-36 weeks) - Patients with average Hb level in target range**

INNO$_2$VATE – prevalent	Vadadustat (N=1777)	Darbepoetin alfa (N=1777)	Vadadustat vs darbepoetin alfa
% responders observed (95% CI)	49 (47 to 52)	53 (51 to 56)	-
% responders observed and imputed*** (95% CI)	54 (53 to 54)	57 (57 to 58)	-
% difference (95% CI)	-	-	-0.03 (-0.07 to 0.00)
Odds ratio (95% CI)	-	-	0.9 (0.76 to 1)

* See appendix. ** geography-specific target range, rounded to nearest whole number. ***calculated as the average n (%) of responders based on 100 imputation datasets Abbreviations: CI, confidence intervals; Hb, haemoglobin

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Key clinical trial results: proportion in target range (2 of 2)*

Darbepoetin alfa had benefit over vadadustat in proportion with target Hb levels during **secondary efficacy period** (40-52 weeks) in INNO$_2$VATE prevalent but was similar in INNO$_2$VATE incident trial

Secondary efficacy period (40-52 weeks) - Patients with average Hb level in target range**

INNO$_2$VATE – incident	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Vadadustat vs darbepoetin alfa
% responders observed (95% CI)	40 (33 to 47)	41 (34 to 48)	-
% responders observed and imputed*** (95% CI)	50 (47 to 54)	50 (47 to 54)	-
% difference (95% CI)	-	-	0 (-0.11 to 0.11)
Odds ratio (95% CI)	-	-	1 (0.64 to 1.59)

Secondary efficacy period (40-52 weeks) - Patients with average Hb level in target range**

INNO$_2$VATE – prevalent	Vadadustat (N=1777)	Darbepoetin alfa (N=1777)	Vadadustat vs darbepoetin alfa
% responders observed (95% CI)	44 (42 to 47)	51 (49 to 53)	-
% responders observed and imputed*** (95% CI)	52 (51 to 53)	58 (57 to 59)	-
% difference (95% CI)	-	-	-0.06 (-0.09 to -0.02)
Odds ratio (95% CI)	-	-	0.8 (0.68 to 0.91)

Does vadadustat have similar efficacy to darbepoetin alfa? (i.e. is it non-inferior) Is this clinically important?

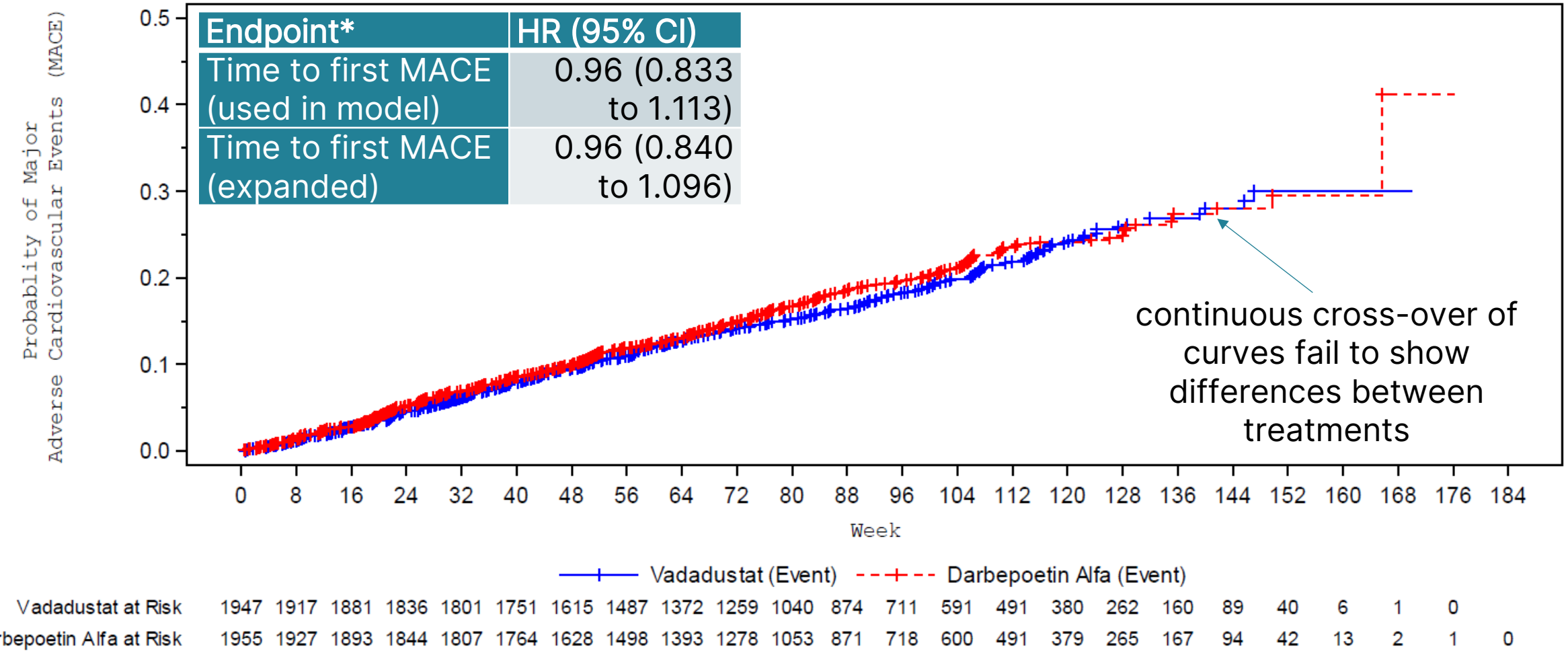
* See appendix. ** geography-specific target range, rounded to nearest whole number. ***calculated as the average n (%) of responders based on 100 imputation datasets Abbreviations: CI, confidence intervals; Hb, haemoglobin

Primary safety endpoint: time to first MACE*

Non-significant hazard ratio at 3 years used in company model

Kaplan-Meier curves of time to first MACE*

Endpoint*	HR (95% CI)
Time to first MACE (used in model)	0.96 (0.833 to 1.113)
Time to first MACE (expanded)	0.96 (0.840 to 1.096)



* MACE includes all-cause mortality, non-fatal myocardial infarction and non-fatal stroke. Expanded MACE also includes hospitalisation for heart failure or thromboembolic events, but excludes vascular access thrombosis.
Abbreviations: HR, hazard ratio; MACE, major adverse cardiovascular events

Key issue: pooling data from INNO$_2$VATE trials

Background

- Company pool INNO$_2$VATE-incident and INNO$_2$VATE-prevalent data using IPD and use in model as if from one trial ('treat-as-one-trial' method)

Company

- Some differences in baseline characteristics between trials (i.e. time on dialysis; see here), but many similar (age, sex, type of dialysis, comorbidity, cause of CKD)
- Trial design, dosing and objectives pre-specified and consistent; pre-specified intention to pool to reflect whole eligible population for both efficacy and safety

EAG comments

- Inappropriate to pool because populations (therefore, treatment aims) and geographical locations differ:
  - INNO$_2$VATE-incident: earlier stage of disease, treatment for correction and maintenance of Hb levels
  - INNO$_2$VATE-prevalent: later stage of disease, treatment for maintenance of Hb levels, not correction
- Pooling method does not consider between-trial variation and lead to narrower confidence interval
- INNO$_2$VATE-prevalent dominated the pooled outcome because it was almost 10 times larger
- Conduct separate economic analyses by trial: limitations because some data only available pooled (including treatment discontinuation parametric models and Hb transition matrices); with EAG's preferred assumptions, vadadustat dominated for prevalent group, but with lower costs and QALYs (southwest quadrant) for incident group; unknown impact with additional data

Does committee consider it appropriate to pool data from both trials or present results separately by trial? If pooled, should it be pooled as one trial, or by meta-analysis?

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Abbreviations: CKD, chronic kidney disease; Hb, haemoglobin; IPD, individual patient data; QALY, quality-adjusted life year

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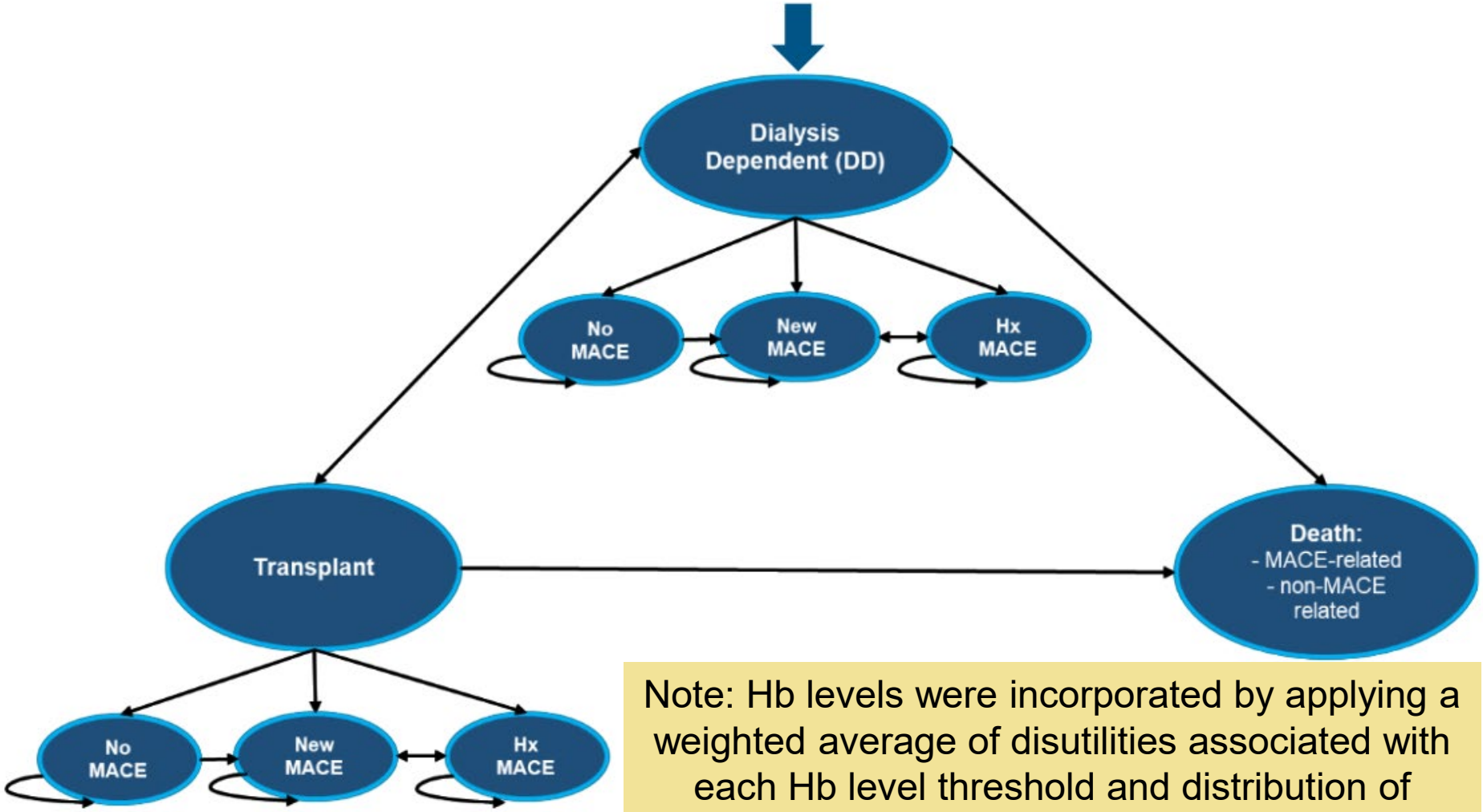
Company's model overview



Note: Hb levels were incorporated by applying a weighted average of disutilities associated with each Hb level threshold and distribution of patients among Hb level thresholds based on $INNO_2VATE$ trials

- Technology affects **costs** by:
  - Higher drug acquisition costs (vadadustat)
  - Lower treatment administration costs
- Technology affects **QALYs** by:
  - Improved MACE including mortality
  - Distribution of Hb levels
- Assumptions with greatest ICER effect:
  - Treatment discontinuation
  - MACE and mortality

Abbreviations: Hx, history of; Hb, haemoglobin; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular events; QALYs, quality-adjusted life years

Key issue: Complex model structure

Background

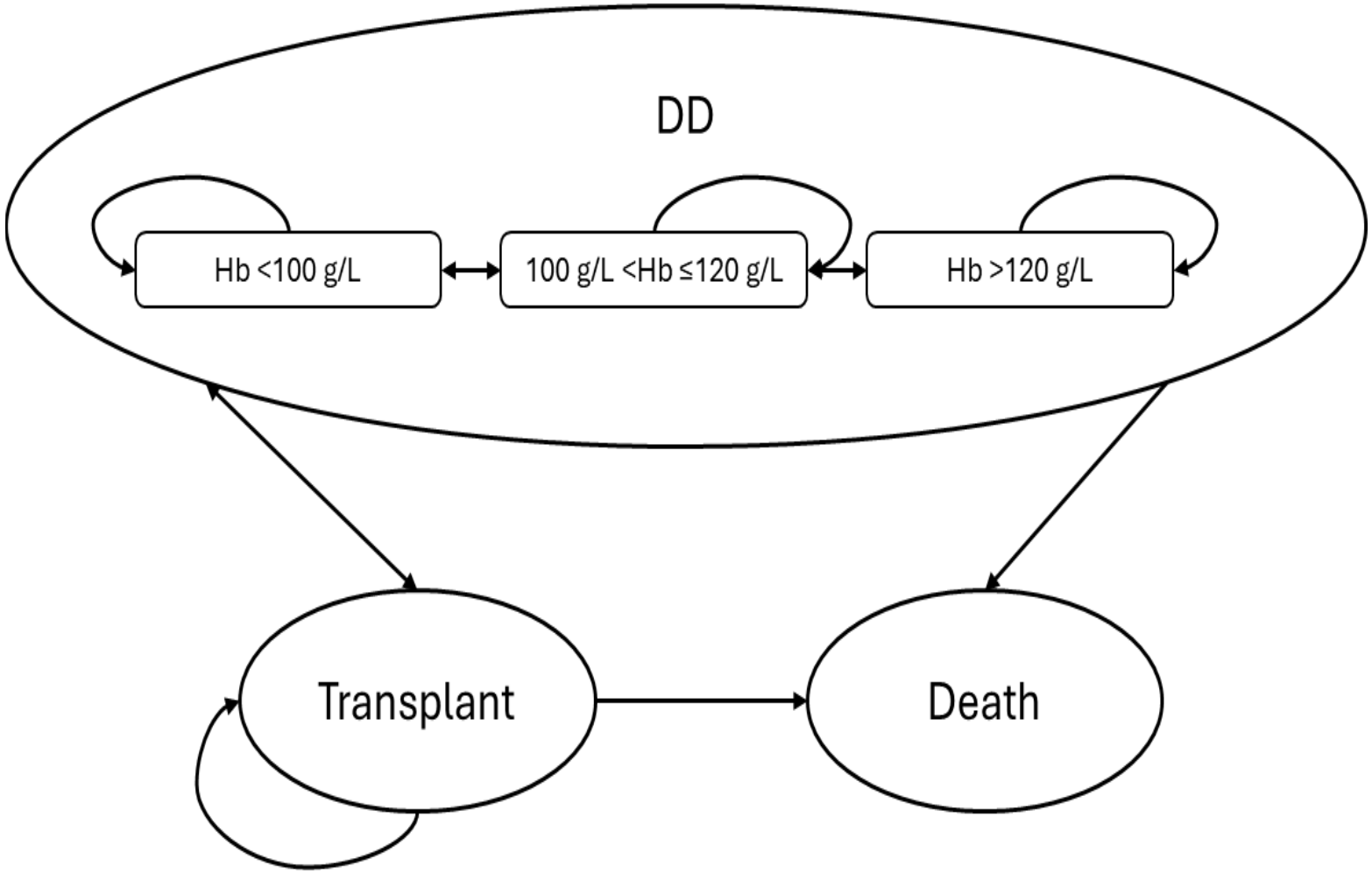
- Company model used 3 main health states and MACE substates; Hb level informed HRQoL only. It noted:
  - this was simpler than roxadustat (TA807) which had 8 states based on different Hb levels
  - use of MACE in transitions best reflects clinical course, reflects impact of MACE on costs and quality of life, and ensures INNO$_2$VATE trials are predominantly used to populate model
    (Note: in model, HR of first MACE event was same for those with and without prior MACE)

EAG comments

- Structure overly complex for decision problem:
  - Disassociates Hb level from structure. Impact on anaemia was key trial aim and outcome. Hb level does not interact with mortality, costs, treatment discontinuation, only used for utility decrements
  - MACE substates: unnecessary since no evidence of difference in MACE (HR confidence interval crosses 1: 0.833 to 1.113)
  - Clinical data: uses UKRR based on patients from start of kidney replacement therapy but company have not adjusted data from registry appropriately (see here)
- Modify model structure (see next slide) removing MACE sub-states, incorporate Hb levels in health states, and adjust UKRR appropriately before incorporating INNO$_2$VATE data

Abbreviations: CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; HRQoL, health-related quality of life; MACE, major adverse cardiovascular events; UKRR, UK renal registry

EAG's amended model structure



Removes MACE sub-states and incorporates Hb levels as substates (rationale)

Transitions between 3 main states use data from UK renal registry annual report (resulting in no differences between arms, in line with clinical input opinion)

Transitions between Hb substates based on INNO$_2$VATE trial data up to week 52; after this, transition matrices from cycle 4 are used for remaining time horizon (42 years)

Does committee consider model with MACE substates appropriate (company approach) or does it prefer the EAG's model which uses substates based on Hb level?

Abbreviations: DD, dialysis-dependent; Hb, haemoglobin; MACE, major adverse cardiovascular events

Key issue: Treatment discontinuation

Background

- Company assume no patients stop treatment after week 52, noting stopping in trial happened in first year which was sufficient to capture stopping from adverse events or suboptimal Hb levels
- Company apply stopping rule if inadequate response to treatment at cycle 1 (week 13); darbepoetin alfa stopping rates applied from cycle 2

EAG comments

- Relevant treatment costs not captured: people likely to stop treatment after 1 year in clinical practice and as seen in trial data at 3 years' follow-up provided at clarification
- Most stopping in trials in first year was because "subject no longer wants to receive study drug"
- EAG base case: parametric survival models extrapolated from trials to inform patients on treatment per cycle
- Stopping rule not applied correctly by company to people with inadequate response (i.e. within Hb < 100 g/L health state): SmPC is at 24 weeks (~6 months), company applied from 13 weeks (cycle 1); EAG applied at 26 weeks (6 months; cycle 2), noting with half cycle correction cycle 1 is week 7 and cycle 2 week 20
- Uncertainty only resolvable with longer term data or clinical expert input to test if models chosen are appropriate beyond 3 years

Abbreviations: Hb, haemoglobin; SmPC, summary of product characteristics

Treatment discontinuation in trials

EAG: participants in trial discontinued treatment after 52 weeks so company approach to assume no stopping after 1 year not appropriate

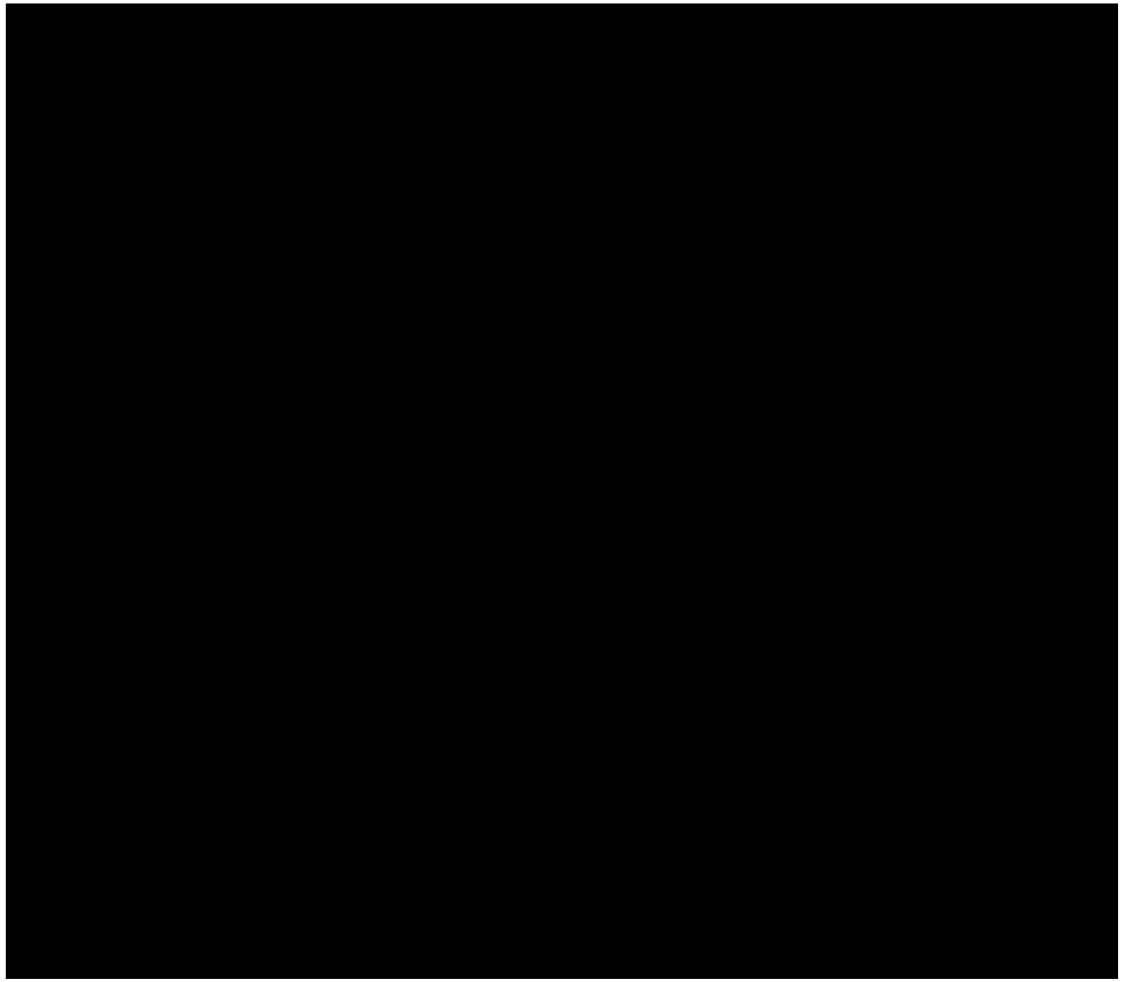
Kaplan-Meier curves from INNO$_2$VATE trials of treatment discontinuation

Company scenario*: parametric models for treatment discontinuation

Company censor transplant and death and prefer Weibull

Parametric curves for treatment discontinuation for vadadustat arm

Parametric curves for treatment discontinuation for darbepoetin alfa arm

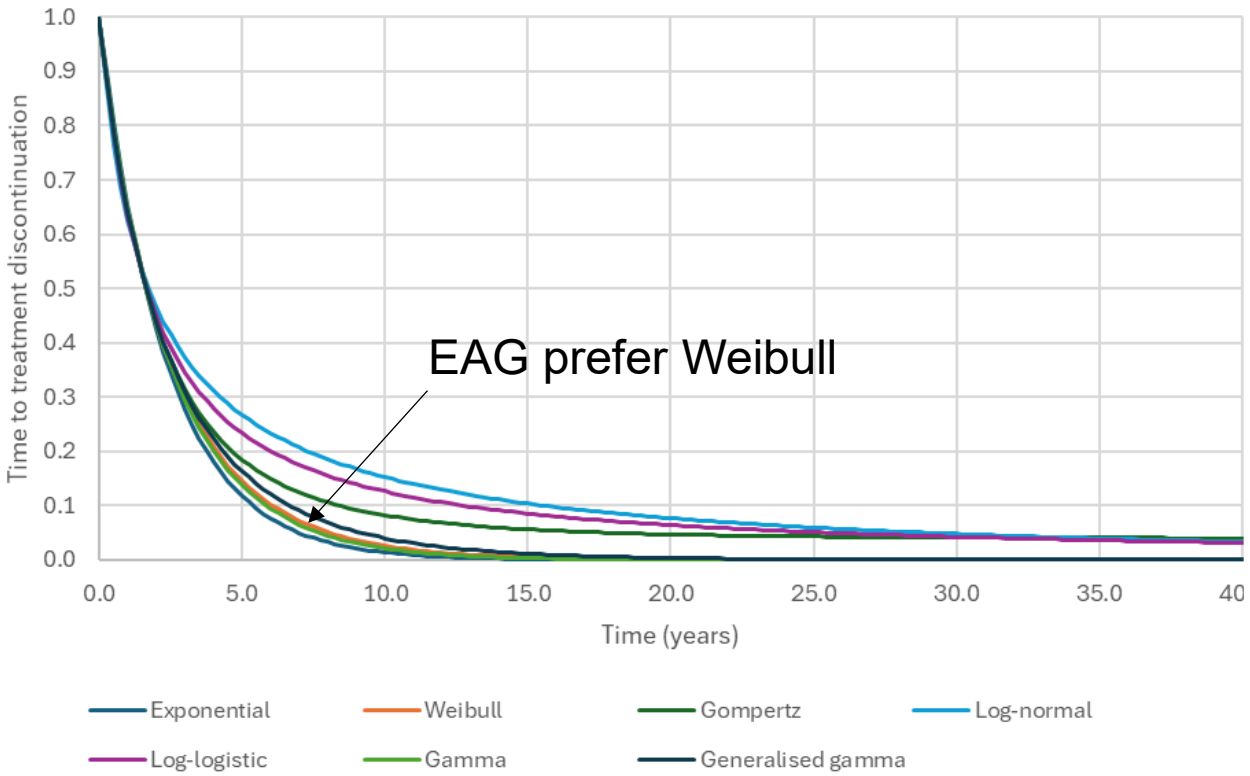


* Company scenario at clarification stage. Abbreviations: KM, Kaplan Meier

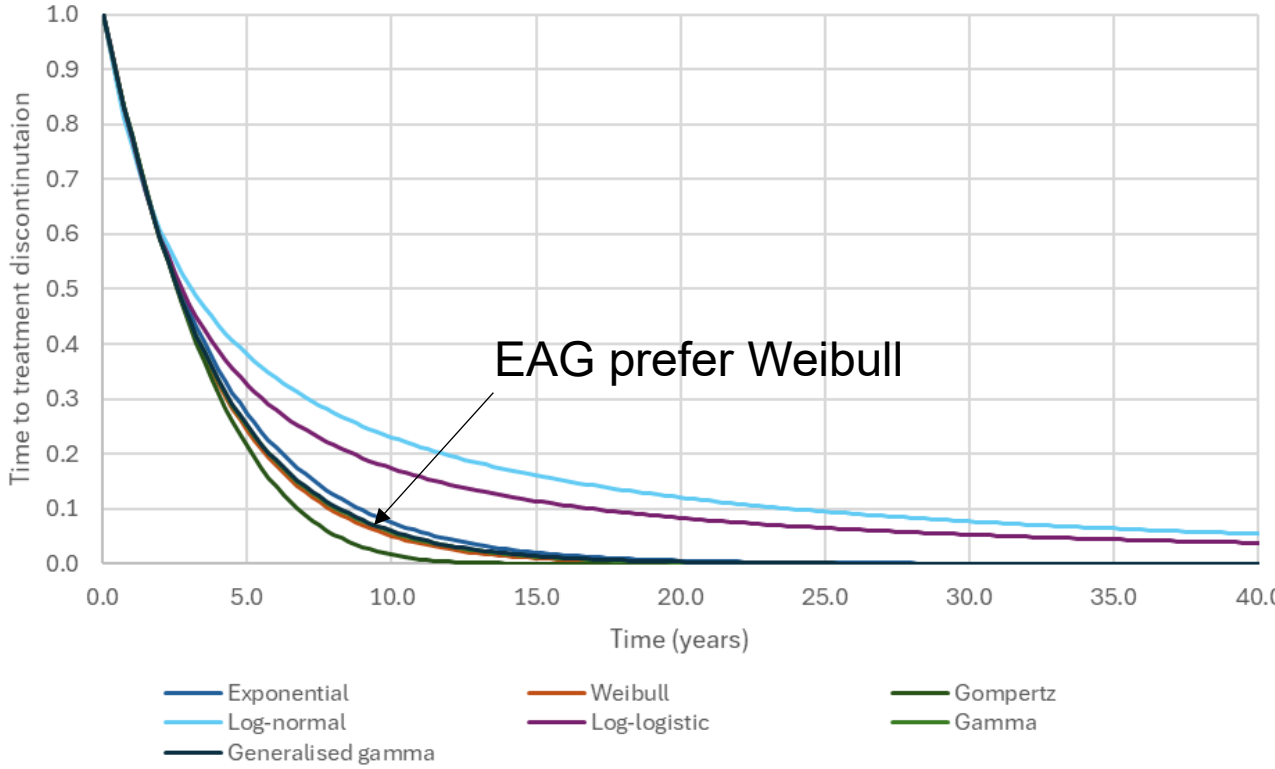
EAG: parametric models for treatment discontinuation

EAG base case consider transplant and death events, remove patients in line with stopping rule at 24 weeks; prefer Weibull curve

Parametric curves for treatment discontinuation for vadadustat arm



Parametric curves for treatment discontinuation for darbepoetin alfa arm



Does committee prefer company assumption of no patients stopping treatment after week 52 or EAG approach to extrapolate treatment discontinuation from trial using parametric models? If extrapolation approach is preferred, what extrapolation is preferred?

Key issue: Treatment waning

Background

- $INNO_2VATE$ trials report data on efficacy up to 3 years show a duration of the treatment effect of MACE (see HR at 3 years used in model)
- Company assume treatment effect of MACE (using HR 0.96 up to 3 years) beyond 3 years up until 5 years. From this point onwards (from cycle 20), equal efficacy between treatments is assumed and transition probabilities for ESAs applied to vadadustat. This treatment effect waning is applied to MACE but not Hb and QoL

Company

- Uncertainty in effects beyond 3 years, waning applied as conservative approach
- Approach validated with clinical expert and waning often used in appraisals to take place at 5 years
- Scenario removing waning decreases ICER

EAG comments

- Unclear rationale for treatment waning applied, particularly when only applied to MACE but not Hb levels
- Waning removed from EAG base case with removal of MACE in model structure

Is it appropriate to include waning of the treatment effect in the model? If so, what period of time is appropriate?

Abbreviations: ESA, erythropoietin stimulating agent; Hb, haemoglobin; ICER, incremental cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular events; QoL, quality of life

Other issue: Utilities used in model

Summary of company approach to utilities and EAG critique

Issue	Company approach	EAG comments
Utility for MACE substates	EQ 5D data from: - Liem et al (2008) for 'no MACE' substates: - meta-analysis of utility values for patients with end-stage renal disease (not specifically anaemia); used in TA807 - Sullivan et al for disutilities applied for each MACE, applied based on type and frequency of events in INNO$_2$VATE	Prefer values from more recent study: - Cooper et al (2020): systematic review of CKD patients' HRQoL scores and detailed utility values for dialysis-dependent and post-transplant patients by CKD stage (not specifically anaemia); company use in scenario at clarification which lowered the ICER Sullivan et al appropriate but thromboembolic events had large decrement so disagree with company assumption not to incorporate this
Utility decrement for Hb categories	Additive approach to applying disutilities: Utility decrement -0.0114 (for 1 g/dL decrease in Hb from a reference of 13 g/dL in Yarnoff et al (2016)) used to calculate utility decrements for each Hb category: 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 mean disutility estimated for each category	Content with company approach. Multiplicative preferred by NICE (and for TA807), but additive approach appropriate, given the source of utilities (Yarnoff et al; different from TA807 which used trial data) provides the disutility between 1 Hb level only – no reference utility to calculate a multiplicative approach provided

Is a more recent source of HRQoL preferred? Should a decrement for thromboembolic events be included in the model? Is the justification for using an additive approach to applying disutilities appropriate?

Abbreviations: CKD, chronic kidney disease; Hb, haemoglobin; MACE, MACE, major adverse cardiovascular events; ICER, incremental cost-effectiveness ratio

Other issue: Rescue therapy definition

Background

- Rescue therapy during the trial included ESAs or red blood cell transfusion.
- Company categorised rescue used into narrow and broad-on-treatment:
  - Narrow: ESA therapy given for low Hb (<95 g/L) and/or worsening anaemia symptoms; red blood cell transfusion therapy given for low Hb or moderate to severe anaemia symptoms (used in company model)
  - Broad-on-treatment: use of any ESA, outside of trial comparator dose; for red blood cell transfusion, same as narrow definition but also included instances of any acute or severe loss of blood

Company

- Company used narrow definition in the model as this better captures the indication and scope (i.e. renal anaemia); broad-on-treatment includes instances unrelated to anaemia such as use of ESA due to accidents and operations

EAG comments

- Different definitions of rescue therapy not clear
- Prefer broad-on-treatment definition in model because it better reflects the trials

Is the difference between narrow or broad-on-treatment definitions of rescue therapy clear? Which should be used in the model?

Abbreviations: ESA, erythropoietin stimulating agent; Hb, haemoglobin; ICER, incremental cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular events; QoL, quality of life

Summary of company and EAG base case assumptions*

Assumptions in company and EAG base case

	Assumption	Company base case	EAG base case
Key issues	**Model structure**	Sub-states including MACE (MACE hazard ratio informs treatment effectiveness)	Sub-states including Hb levels (MACE hazard ratio not used; used Hb levels from trial)
	Vadadustat stopping rule applied	From cycle 1 (3 months)	From cycle 2 (6 months), aligned with SmPC
	Treatment discontinuation	Landmark estimates (from trial) and assume no discontinuations after 52 weeks	Parametric survival curves applied to time to discontinuation from trials
	Treatment waning	Applied at 5 years to MACE	Removed
Small/unknown impact	**Utility scores****	Liem et al (2008)	Cooper et al (2020)
	Cost sources (details)	PSSRU 2019, 2020, 2021	PSSRU 2022
	Mortality	Logarithmic regression	Parametric curves
	Rescue rates	Vadadustat rescue rates used throughout time horizon	ESA rescue rates applied to those who discontinued vadadustat because of stopping rule
	Rescue therapy definition**	Narrow	Broad-on-treatment

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* See appendix for additional EAG amendments to company base case, **more details on previous slides. Abbreviations: ESA, erythropoietin stimulating agent; Hb, haemoglobin; MACE, major adverse cardiovascular events; PSSRU, Personal Social Services Research Unit; SmPC, summary of product characteristics

Cost-effectiveness results

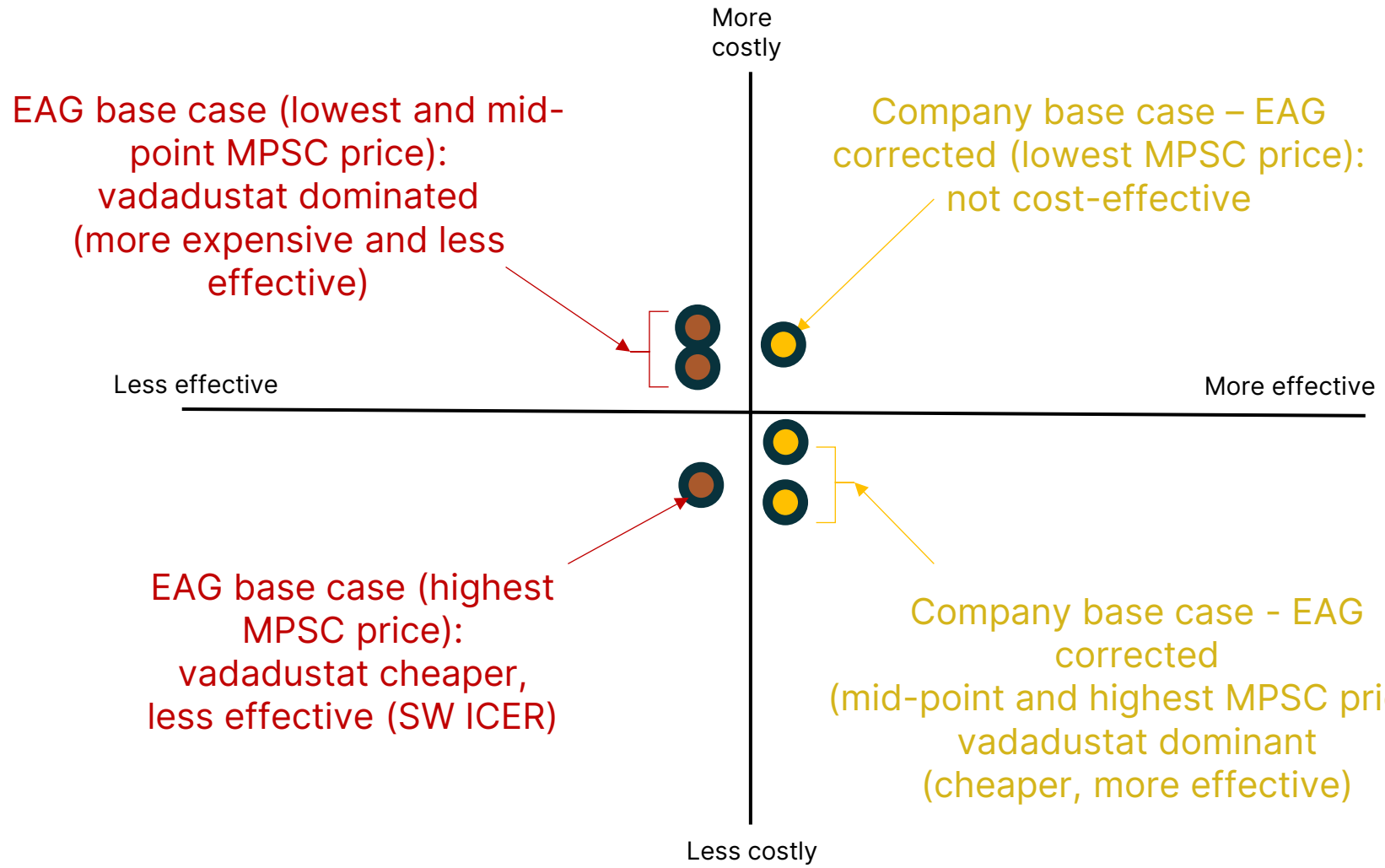
All ICERs are reported in PART 2 slides

because they include confidential discounts*

*Medicines Procurement and Supply Chain (MPSC) (previously known as the Commercial Medicines Unit (CMU) prices used for erythropoiesis stimulating agents (ESAs) and intravenous iron applied. Because of the varying dosage schedules and frequencies of ESA prices the EAG have calculated the cost per cycle for all ESAs to determine the low and high MPSC prices (midpoint = [low + high]/2).

Cost effectiveness outcomes vary

Cost-effectiveness depends on price of ESA; small incremental QALYs means results easily ‘move quadrants’



Clinical expert: ‘Cost effectiveness of vadadustat relative to ESA will depend on price paid for ESAs…across the UK’

Abbreviations: ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; MPSC, medicines procurement and supply chain (previously known as the Commercial Medicines Unit (CMU); QALY, quality adjusted life year; SW, southwest

EAG exploratory analyses (midpoint MPSC* prices)

Vadadustat dominated in all but revised model structure with parametric curve for treatment discontinuation gave opposite results

No.	Scenario (applied to company base case)	Incremental costs (£) versus ESAs	Incremental QALYs versus ESAs	ICER (£/QALY) versus ESAs
	Company base case (EAG-adjusted)	See part 2	0.023	Dominant
1	Revised model structure + parametric curve for treatment discontinuation**	↑ Increase	-0.003	Dominated
2	Parametric (Weibull) treatment discontinuation curve**	↓ Decrease	0.017	Dominant
3	Rescue therapy 'broad-on-treatment'**	↑ Increase	0.023	Dominant
4	Treatment-specific rescue rates and IV costs**	↓ Decrease	0.023	Dominant
5	Disutility for pill burden	↔ Equal	0.016	Dominant
6	Updated cost sources**	↓ Decrease	0.023	Dominant
7a	INNO$_2$VATE incident population	↑ Increase	0.004	Dominant
7b	INNO$_2$VATE prevalent population	↓ Decrease	0.024	Dominant

* Formerly, Commercial Medicines Unit (CMU) prices. ** Included in EAG base case. Abbreviations: ESA, erythropoietin stimulating agent; ICER, incremental cost-effectiveness ratio; IV, intravenous; MPSC, medicines procurement and supply chain; OS, overall survival; QALY, quality-adjusted life year

EAG deterministic scenario analysis (midpoint MPSC* prices)

Vadadustat dominated in all analyses

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus ESAs	Incremental QALYs versus ESAs	ICER (£/QALY) versus ESAs
	EAG base case	See part 2	-0.0033	Dominated
1	Apply utility decrement for pill burden for haemodialysis	↔ Equal	-0.0047	Dominated
2	Exponential mortality curve**	↑ Increase	-0.0033	Dominated
3	Generalised gamma mortality curve**	↓ Decrease	-0.0033	Dominated
4	Gompertz mortality curve**	↓ Decrease	-0.0033	Dominated
5	Exponential TTD curve***	↔ Equal	-0.0033	Dominated
6	Gamma TTD curve***	↔ Equal	-0.0033	Dominated
7	Generalised gamma TTD curve***	↔ Equal	-0.0033	Dominated

* Formerly, Commercial Medicines Unit (CMU) prices, ** Gamma in EAG base case, *** Weibull in EAG base case. Abbreviations: ESA, erythropoietin stimulating agent; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Potential benefits not captured in the QALY

Company: societal benefits and environmental impact of vadadustat not captured

Company:

- Cost savings behind NHS: spill-over effects of progressively debilitating disease on patients, their caregivers and society could result in cost savings beyond NHS to individuals and other sectors of society
- Environmental impact: shift to oral treatment may reduce people attending kidney care centres which could help NHS achieve sustainable nephrology care and reduce environmental impact by reducing single-use plastics, saving energy/fuel, reducing carbon footprint (because of avoidance of transportation).
- (EAG clinical expert: no impact to attendance at kidney care centres because main reason for attendance is confidence with dialysis equipment)

Clinical experts:

- Environmental impact compared with ESAs: reduced need for special disposal requirements of needles and cold chain storage
- Reduced training requirements for patient administration and healthcare professionals like district nurse
- Benefits of alternative treatment regimen would not be captured in the QALY

Lead team:

- Potential benefits for people with ESA resistance not captured as not explicitly captured in evidence base

Abbreviations: ESA, erythropoiesis stimulating agent, QALY, quality-adjusted life year

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Key issue	ICER impact	Slide
Pooling of data from INNO$_2$VATE trials	Unknown 	15
Model structure complexity including use of MACE for substates	Large 	18
Treatment costs and discontinuation in model	Large 	20
Treatment effect waning	Small 	24

Abbreviations: MACE, major adverse cardiovascular events

Thank you.

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

Supplementary appendix

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Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with symptomatic anaemia associated with chronic kidney disease on chronic maintenance dialysis	Same	None
Intervention	Vadadustat	Same	None
Comparators	ESAs	Same (class effect assumed)	None
Outcomes	Haemoglobin response, maintenance of haemoglobin levels, use of additional therapy (i.e. blood transfusion and IV iron), hospitalisation, mortality, adverse effects of treatment including MACE, HRQoL	HRQoL not measured in trials	Often not reported clearly or consistently (including by trial); IV iron measured but not reported in clinical results
Subgroups	Previous exposure to ESAs, if evidence allows	Clinical evidence from $INNO_2VATE$ - incident but no economic analyses – no clinically meaningful differences	Unable to conduct cost effectiveness analyses in model

Abbreviations: ESA, erythropoiesis stimulating agent; HRQoL, health-related quality of life; IV, intravenous

Key clinical trials*

Clinical trial designs and outcomes

	INNO$_2$VATE incident (n = 369)	INNO$_2$VATE prevalent (n = 3554)
Design	Phase 3 open-label RCT (non-inferiority)	Phase 3 open-label RCT (non-inferiority)
Population	Patients with anaemia who have recently initiated dialysis treatment for DD-CKD	Patients with anaemia who have dialysis treatment for DD-CKD
Type of dialysis	89% HD, 10% PD, 1% both or unknown	92% HD, 8% PD, 1% both or unknown
Intervention	Vadadustat**	Vadadustat**
Comparator(s)	Darbepoetin alfa	Darbepoetin alfa
Duration	52 weeks (correction weeks 0-23, maintenance 24-52); long-term to end of treatment or 182 weeks and for safety + 4 weeks post-treatment	52 weeks (conversion and maintenance weeks 0-23, maintenance 24-52); long-term to end of treatment or 182 weeks and for safety + 4 weeks post-treatment
Primary and key secondary outcomes**	Correction of low Hb levels, then maintenance from 24-36 weeks (PEP) and 40-52 weeks (SEP)	Maintenance of Hb levels from 24-36 weeks (PEP) and 40-52 weeks (SEP)
Locations	North America, South America, Europe, Asia	North America, South America, Europe, Asia, Australasia, and UK (5 centres)
Used in model?	Yes	Yes

* see main deck, ** 300 mg/day with titration to 150-600 mg to achieve Hb 10-12 g/dL. Abbreviations: DD-CKD, dialysis-dependent chronic kidney disease; Hb, haemoglobin; HD, haemodialysis; PEP, primary efficacy period; PD, peritoneal dialysis; RCT, randomised controlled trial; SES, secondary efficacy period

$INNO_2VATE$ trials: baseline characteristics*

Baseline characteristics in $INNO_2VATE$ trials

	$INNO_2VATE$ incident (n = 369)	$INNO_2VATE$ prevalent (n = 3554)
Age (years; mean, SD)	56 (14.7)	58.1 (13.9)
Sex (% female)	40.4%	43.9%
Years since CKD diagnosis (mean, SD)	4.5 (6.9)	6.8 (6.5)
Type of dialysis (% in centre haemodialysis)	88.6%	92.4%
Years since dialysis started (mean, SD)	0.14 (0.9) vadadustat 0.15 (0.28) darbepoetin alfa	4.0 (4.0) vadadustat 3.9 (4.0) darbepoetin alfa
Baseline Hb (g/dL; mean, SD)	9.190 (1.138)	10.239 (0.837)
Prior IV iron use (%)	70.2%	76%
Transfusion within 4-weeks of randomisation (%)	4.1%	1.7%
Prior ESA usage (%)	50.8% vadadustat 45.2% darbepoetin alfa	100%
History of diabetes (%)	54.5%	55.4%
History of cardiovascular disease (%)	38.5%	50.6%

* see main deck. Abbreviations: CKD, chronic kidney disease; DD-CKD, dialysis-dependent; ESA, erythropoiesis stimulating agent; g/DL, grams per deciliter; Hb, haemoglobin; SD, standard deviation

Key clinical trial results: primary efficacy outcome*

Vadadustat is not inferior to darbepoetin alfa at increasing Hb levels

Baseline to **primary efficacy period** (24-36 weeks) change in Hb**

INNO$_2$VATE – incident	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Vadadustat versus darbepoetin alfa
Mean change from baseline (SD) (g/L)	9.9 (12.76)	14.2 (14.14)	-
Least squares mean (SEM, 95% CI)	12.6 (1.09, 10.5 to 14.8)	15.8 (1.08, 13.7 to 17.9)	-3.1 (1.10, -5.3 to -1.0)

Baseline to **primary efficacy period** (24-36 weeks) change in Hb **

INNO$_2$VATE – prevalent	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)	Vadadustat versus darbepoetin alfa
Mean change from baseline (SD) (g/L)	1.1 (11.08)	3.0 (11.03)	-
Least squares mean (SEM, 95% CI)	1.9 (0.32, 1.2 to 2.5)	3.6 (0.32, 2.9 to 4.2)	-1.7 (0.33, -2.3 to -1.0)

Clinical expert: clinically meaningful change in Hb is 10 g/L

Darbepoetin alfa appears to have a benefit over vadadustat but this is within company's pre-specified non-inferiority margin for mean Hb change from baseline (-7.5 to 7.5 g/L) so the evidence shows it is not inferior to darbepoetin alfa

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* see main deck.** Only pooled outcome was used in EAG model because other key inputs were not available by trial. Abbreviations: CI, confidence intervals; Hb, haemoglobin; SD, standard deviation; SEM, standard error of mean

Key clinical trial results: secondary efficacy outcome*

Vadadustat is not inferior to darbepoetin alfa at increasing Hb levels

Baseline to **secondary efficacy period** (40-52 weeks) change in Hb

INNO$_2$VATE – incident	Vadadustat (N=181)	Darbepoetin alfa (N=188)	Vadadustat versus darbepoetin alfa
Mean change from baseline (SD) (g/L)	11.5 (13.45)	13.6 (15.68)	-
Least squares mean (SEM, 95% CI)	14.2 (1.32, 11.7 to 16.8)	15.0 (1.36, 12.3 to 17.6)	-0.7 (1.34, -3.4 to 1.9)

Vadadustat not inferior to darbepoetin alfa

Baseline to **secondary efficacy period** (40-52 weeks) change in Hb

INNO$_2$VATE – prevalent	Vadadustat (N=1,777)	Darbepoetin alfa (N=1,777)	Vadadustat versus darbepoetin alfa
Mean change from baseline (SD) (g/L)	1.5 (11.78)	3.5 (11.31)	-
Least squares mean (SEM, 95% CI)	2.3 (3.5, 1.6 to 2.9)	4.1 (3.3, 3.4 to 4.8)	-1.8 (0.35, -2.5 to -1.2)

Darbepoetin alfa appears to have a benefit over vadadustat but this is within the company's pre-specified non-inferiority margin for mean Hb change from baseline (-7.5 to 7.5 g/L) so the evidence shows it is not inferior to darbepoetin alfa

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* see main deck. **Only pooled outcome was used in EAG model because other key inputs were not available by trial; Abbreviations: CI, confidence intervals; SD, standard deviation; SEM, standard error of mean

Key clinical trial results – trial data combined*

Vadadustat is not inferior to darbepoetin alfa at improving Hb levels

Vadadustat (N=1,958) vs darbepoetin alfa (N=1,965)
from INNO$_2$VATE – incident and INNO$_2$VATE – prevalent trials

Method of combining data	Change in average Hb level from baseline and primary efficacy period (24-36 weeks)
Fixed effects meta-analysis: mean difference (95% CI; g/L)	-1.8 (-2.7 to -1.0) p-value < 0.0001
Pooled results: Least squares mean difference (95% CI; g/L)	-1.8 (-2.4 to -1.2)

Method of combining data	Change in average Hb level from baseline and secondary efficacy period (40-52 weeks)
Fixed effects meta-analysis: mean difference (95% CI; g/L)	-1.7 (-2.7 to -0.8) p = 0.0002
Pooled results: Least squares mean difference (95% CI; g/L)	-1.7 (-2.4 to -1.1)

Darbepoetin alfa appears to have a benefit over vadadustat for change in average Hb level from baseline to the PEP or SEP, but this is within company's pre-specified non-inferiority margin (-7.5 to 7.5 g/L) so the evidence shows it is not inferior to darbepoetin alfa

Note: only data up to 52 weeks was available for this outcome and used in EAG model. The MACE HR (which were only provided for pooled trial populations) used in company model had follow-up up to 3 years

Abbreviations: CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; MACE, MACE, major adverse cardiovascular events; PEP, primary efficacy period; RCT, randomised controlled trial; SEP, secondary efficacy period

* see main deck

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	INNO$_2$VATE trials (mean 57.9 years, 92% HD, 49.5% prior MACE)
Intervention efficacy	HR of MACE from INNO$_2$VATE trials
Comparator efficacy	IPD from pooled INNO$_2$VATE trials (darbepoetin alfa as proxy for ESAs)*
Utilities	Published literature (see here)
Costs	BNF, INNO$_2$VATE (dosing: year 1-2 dose as per trial, then year 3 dosage onwards)**, National Cost Collection 2021/2022, NHS trust and NHS foundation trusts 2023, PSSRU***, TA807 (monitoring costs), Kerr 2012 (long-term transplant); long-term maintenance with MACE: TA317, TA679, Xu et al. 2017
Resource use	Administration assumptions: TA807, Michalopoulos et al. 2022; rescue therapy: INNO$_2$VATE; number of donars: Organ Donation and Transplant: Activity Report 2022/23; type of dialysis: UK Kidney Association 25th annual report

* Efficacy assumed equivalent for all ESAs (other ESAs explored in scenario analyses). ** Company: ESA dosages from SmPCs for ESAs other than darbepoetin alfa and conversion factors were applied to calculate weekly dosages. EAG: dosages used not fully in line with SmPCs and method for dose conversion was not consistent with TA807, which it preferred. *** EAG: exact source not always clear but was not PSSRU 2022, which it preferred

Abbreviations: BNF, British National Formulary; ESA, erythropoietin stimulating agent; HD, haemodialysis; HR, hazard ratio; IPD, individual patient data; MACE, major adverse cardiovascular events; PSSRU, Personal Social Services Research Unit

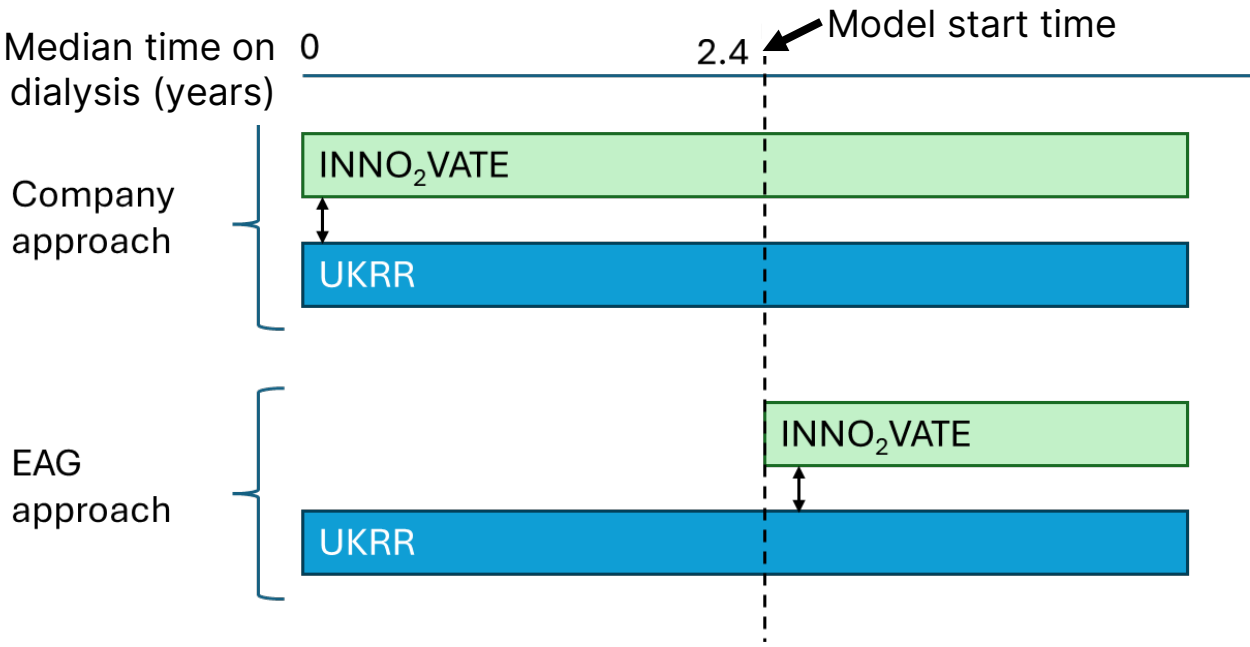
Use of UK renal registry in model*

Background

- Company use UK renal registry and INNO$_2$VATE trial to inform median time on dialysis
- UKRR include patients from when they start on dialysis, but INNO$_2$VATE trials include patients who have had dialysis for median 2.4 years
- To account for differences, company adjust starting transition matrix

EAG comments

- Company did not time-adjust UKRR data before applying INNO$_2$VATE data; transition matrices from cycles 5-12 (1-3 years) incorporating data from both UKRR and INNO$_2$VATE used from model start. Initial INNO$_2$VATE trial data before Q4 not used
- EAG use transition matrix from UKRR from cycle 5-10 (1-3 years) to inform first model cycle transition to align better to INNO$_2$VATE data; INNO$_2$VATE baseline transition matrices then applied to proportion of patients at different Hb levels in dialysis-dependent state



Does committee prefer the company or EAG's approach to adjusting for time in dialysis?

Abbreviations: Hb, haemoglobin; Q4, quarter 4; UKRR, UK renal registry

* see main deck

Increased pill burden

Background

- More patients stopped treatment with vadadustat compared with darbepoetin alfa (50.6% vs 36.7%), partly because they preferred a product with known effect and dosing (i.e. ESA; 12.0% versus 5.8%).

EAG comments

- EAG's clinical expert: may be because of increased pill burden with vadadustat, particularly for those on haemodialysis (89 - 92% of trial populations) who otherwise have ESAs as part of haemodialysis
- Systematic review found average pill burden for dialysis-dependent CKD is 15 per day; pill burden results in poorer adherence and lower QoL
- Pill burden not captured in company model apart from discontinuations. Scenario including utility decrement for vadadustat taken with haemodialysis had small impact on ICER

Company (in factual accuracy check)

- Conclusion that difference in early discontinuations is due to pill burden is speculation; may be because of open-label trial design. Treatment compliance was high throughout trial

Clinical expert comments

- An additional tablet may not be as attractive to people taking ESAs as part of haemodialysis, but may be preferred by some having home haemodialysis

Would pill burden with vadadustat be a significant barrier to people already taking an average 15 pills per day? Should a utility decrement be used in the model for people having haemodialysis taking vadadustat?

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Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; QoL, quality of life

Evidence on people with ESA resistance

Background

- Clinical experts note that one group in whom vadadustat may be particularly helpful is those who have resistance to ESAs or hyporesponsiveness, when the blood does not contain target Hb levels despite usual doses of ESA or require increasingly higher doses to maintain Hb concentration

EAG comments

- People who met the criteria of injectable ESA resistance were not included in the trials:
  - $INNO_2VATE$ – incident excluded people who met the criteria of injectable ESA resistance within eight weeks prior to or during screening
  - $INNO_2VATE$ – prevalent only included people currently maintained on ESA therapy and excluded people with hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients

Company

- Patients with ESA resistance not excluded. 6% of patients had baseline ESA doses > 300 IU/kg/week (Chertow et al)

Clinical expert comments

- Would not expect difference in effect of vadadustat in people with prior ESA resistance due to difference in mechanism of action. People with ESA resistance excluded from $INNO_2VATE$ trials but criteria for exclusion differs from guideline definition of ESA resistance

Would vadadustat be used after ESA including people with ESA resistance?

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Abbreviations: ESA, erythropoietin stimulating agent; IU, international unit

Additional EAG amendments to company base case*

Technical errors and matters of judgement applied to company base case

Technical errors	Matters of judgement
Correct error where proportion of patients in 'DD Hx MACE' is taken from in 'Pat flow' sheets (impacting sensitivity analysis)	Not rounding down age to use for general population utility values
Correct mortality range in 'Life Tables' sheet	Not rounding down life-years to apply to patients' age for general population mortality
Inflating hospital consultant and stroke costs to 22/23 (taken from 20/21 source and 13/14 source)	Minimum cost per unit used for drug costs (company use average; no impact on base case)
Corrections to calculations to weight time on treatment per cycle proportions from pooled studies	Applied drug discount to the pack cost instead of overall cost per cycle
Correct PD cost to include CAPD National Cost Collection value	Cost inputs and disutilities using normal distribution (company use gamma)
Correct MACE annual costs to per cycle costs	Including missing parameters from OWSA and PSA
Correct 'Any MACE' calculations for darbepoetin alfa arm and total	Lower and upper bounds corrected to use input distribution
Correct time adjustment for AE disutilities	-
Vadadustat drug costs using 98 x 450 mg pack when wastage considered	-

* see main deck. Abbreviations: AE, adverse events; CAPD, continuous ambulatory peritoneal dialysis; DD, dialysis-dependent; Hx, history; MACE, major adverse cardiovascular events; OWSA, one-way sensitivity analysis; PD, peritoneal dialysis; PSA, probabilistic sensitivity analysis