Slides for PUBLIC only – ACIC information redacted

NICE National Institute for Health and Care Excellence

Roxadustat for treating anaemia in people with chronic kidney disease [ID1483]

2nd Appraisal Committee Meeting

Lead team: James Fotheringham; Nicky Welton; Nigel Westwood

Chair: Charles Crawley

ERG: Kleijnen Systematic Reviews

Technical team: George Braileanu, Rufaro Kausi, Janet Robertson

Company: Astellas Pharma

17th March 2022 – virtual meeting

Appraisal Consultation Document (ACD): Roxadustat not recommended

Why committee made these recommendations

- Company positioned roxadustat as alternative to erythropoiesis-stimulating agents (ESAs)
- DOLOMITES is only relevant trial for decision problem and showed non-inferiority of roxadustat versus darbepoetin alfa (an ESA)
- Company inappropriately estimated roxadustat clinical effectiveness by pooling all roxadustat trials, including placebo-controlled ones
- Cost effectiveness estimates generated from model did not reflect committee's preferred assumptions
- Cost effectiveness estimates for roxadustat against ESAs are uncertain; likely not cost effective

Recap from 1st meeting

Anaemia in chronic kidney disease (CKD)

- Serious condition defined by abnormally low levels of haemoglobin (Hb) or too few red blood cells
- NICE guidelines for anaemia with CKD (NG203): target Hb 10–12 g/dL
  - Standard treatment: iron then, if necessary, erythropoietin stimulating agents
  - MHRA: treating anaemia with ESAs to Hb >12 g/dL → risk of death + cardiovascular disease
- Anaemia increases with worsening renal function and CKD stage
- Anaemia independent predictor for CKD progression and all-cause mortality

Stage	Description	Anaemia prevalence
1	Normal Glomerular filtration rate (GFR)	6%
2	Mildly decreased GFR	3%
3a	Mildly to moderately decreased GFR	5%
3b	Moderately to severely decreased GFR	17%
4	Severely decreased GFR	34%
5	Kidney failure	43%

Roxadustat (Evrenzo, Astellas Pharma)

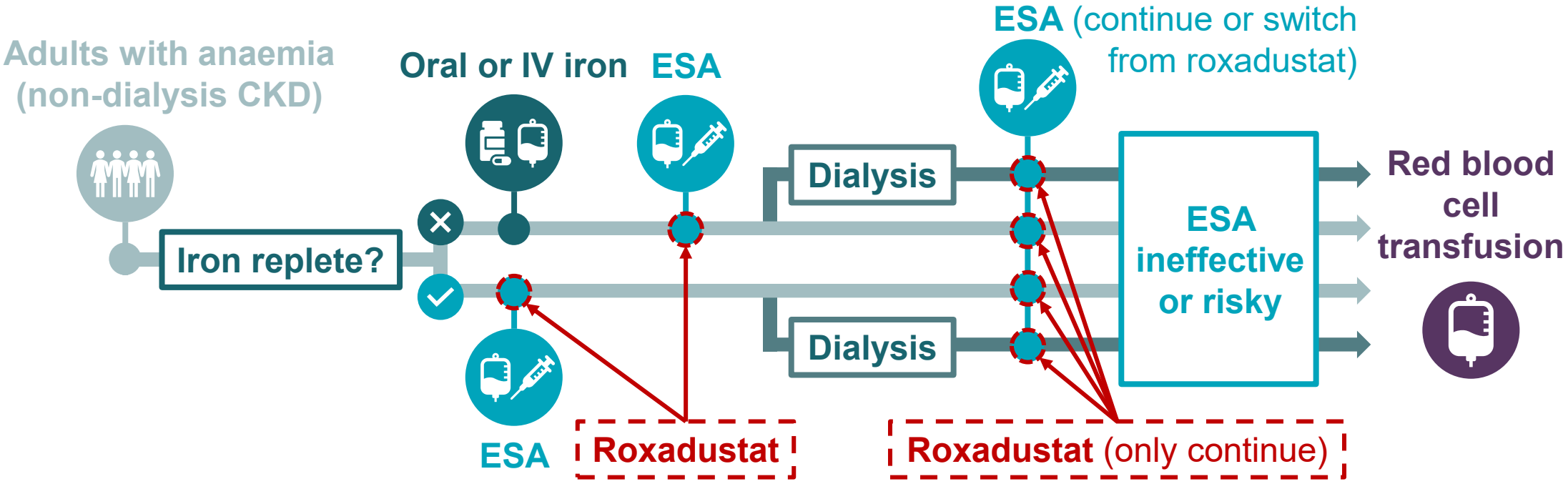
Marketing authorisation	Adults with '**symptomatic** anaemia associated with chronic kidney disease'

Administration and dose	Oral
	Recommended starting dose: based on ESA history and patient weight
	• For anaemia **not** treated with ESA:
	  • 70 mg 3 times per week if patient weighs <100 kg
	  • 100 mg 3 times per week if patient weighs ≥100 kg
	Maintenance dose
	• 20 to 400 mg for dialysis-dependent CKD
	• 20 to 300 mg for non-dialysis-dependent CKD

Mechanism	Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor
Price	List prices (12-tablet packs): • £59.24 (20 mg), £148.11 (50 mg), £207.35 (70 mg), £296.21 (100 mg), £444.32 (150 mg) **Patient access scheme (simple discount)** agreed – company increased discount in response to committee's negative recommendation in 1st meeting

Treatment pathway + positioning of roxadustat

*After iron therapy, as **alternative** to ESA, for anaemia associated with non-dialysis-dependent CKD stage 3–5 at treatment initiation*



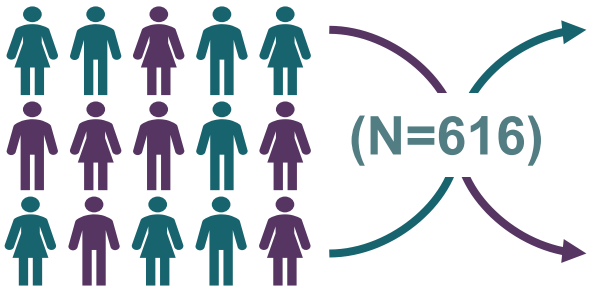
Committee heard at 1st meeting

- Stage 1 and 2 CKD anaemia effectively treated with iron therapy alone
- Roxadustat positioning does not include people on dialysis because of cardiovascular disease safety concerns
- IV iron and ESA administered through haemodialysis machine – roxadustat benefit is for people not on dialysis
- Company did not present evidence for people who cannot take ESAs
- Committee considered company's positioning in the treatment pathway broadly appropriate

DOLOMITES trial – non-inferiority design

Only trial that reflects decision problem

Recruitment → **Randomisation** → **Open-label (104 weeks)** → **Outcomes**



Roxadustat 70/100mg 3/week (n=323)

Darbepoetin alfa weight-based dosing (n=293)

Primary (yes/no)
- Hb response weeks 0–24:

→ if baseline >8g/dL, then Hb ≥11 AND rise of ≥1;
→ if baseline ≤8, then rise of ≥2
→ confirmed, no rescue therapy

- **Roxadustat stopped if Hb ≥13 g/dL**
- Oral iron recommended in roxadustat group to support erythropoiesis

	Description	Comments
Non-inferiority statistical analyses - 1° outcome		
Non-inferiority criteria	If **lower** limit of 2-sided 95% CI **>15%** difference in proportions of responders between groups	No plan for superiority
Analysis population	All randomised patients who received ≥ 1 doses of drug + ≥ 1 post-dose Hb (per protocol set)	Not intention to treat
Non-inferiority statistical analyses - 2° outcomes		
Analysis	Hierarchical testing: 1st non-inferiority then if non-inferior, superiority for some 2º endpoints	Some 2° tested for superiority

DOLOMITES trial results

Roxadustat non-inferior compared to darbepoetin alfa

Type	Outcomes	Roxadustat vs. darbepoetin alfa	Test results
Primary	Hb response (weeks 0–24), % difference	+11.5%	Non inferior
Secondary	**Change from baseline, LSM difference (95% CI)**		
	Hb (g/dL), weeks 28–36	0.01 (-0.13, 0.16)	Non-inferior
	SF-36 PF subscore, weeks 12–28	-1.28 (-2.42, -0.14)	Non-inferior
	SF-36 VT subscore, weeks 12–28	-0.42 (-1.62, 0.78)	Non-inferior
	FACT-An Anaemia Subscale, weeks 12–28	[redacted]	[redacted]
	FACT-An Total Score, weeks 12–28	[redacted]	[redacted]
	EQ-5D-5L VAS, weeks 12–28	[redacted]	[redacted]
	Mean arterial pressure (mmHg), weeks 20–28	-0.36 (-1.57, 0.85)	Non-inferior
		[redacted]	[redacted]
	LDL cholesterol (mmol/L), weeks 12–28	-0.40 (-0.51, -0.29)	Superior
	Time to first occurrence, HR (95% CI)		
	Hypertension, weeks 1–36	0.82 (0.56, 1.22)	Non-inferior
		[redacted]	[redacted]
	IV iron, weeks 1–36	0.46 (0.27, 0.80)	Superior

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EQ-5D-5L: EuroQoL 5 Dimensions 5 Level; FACT-An: Functional Assessment of Cancer Therapy – Anemia, LDL: IV: intravenous, low-density lipoprotein, SF-36: Short-Form 36, VAS: visual analogue scale.

DOLOMITES trial adverse events

Some adverse events differed between roxadustat and darbepoetin alfa, but company included only major adverse cardiovascular events and vascular access thrombosis

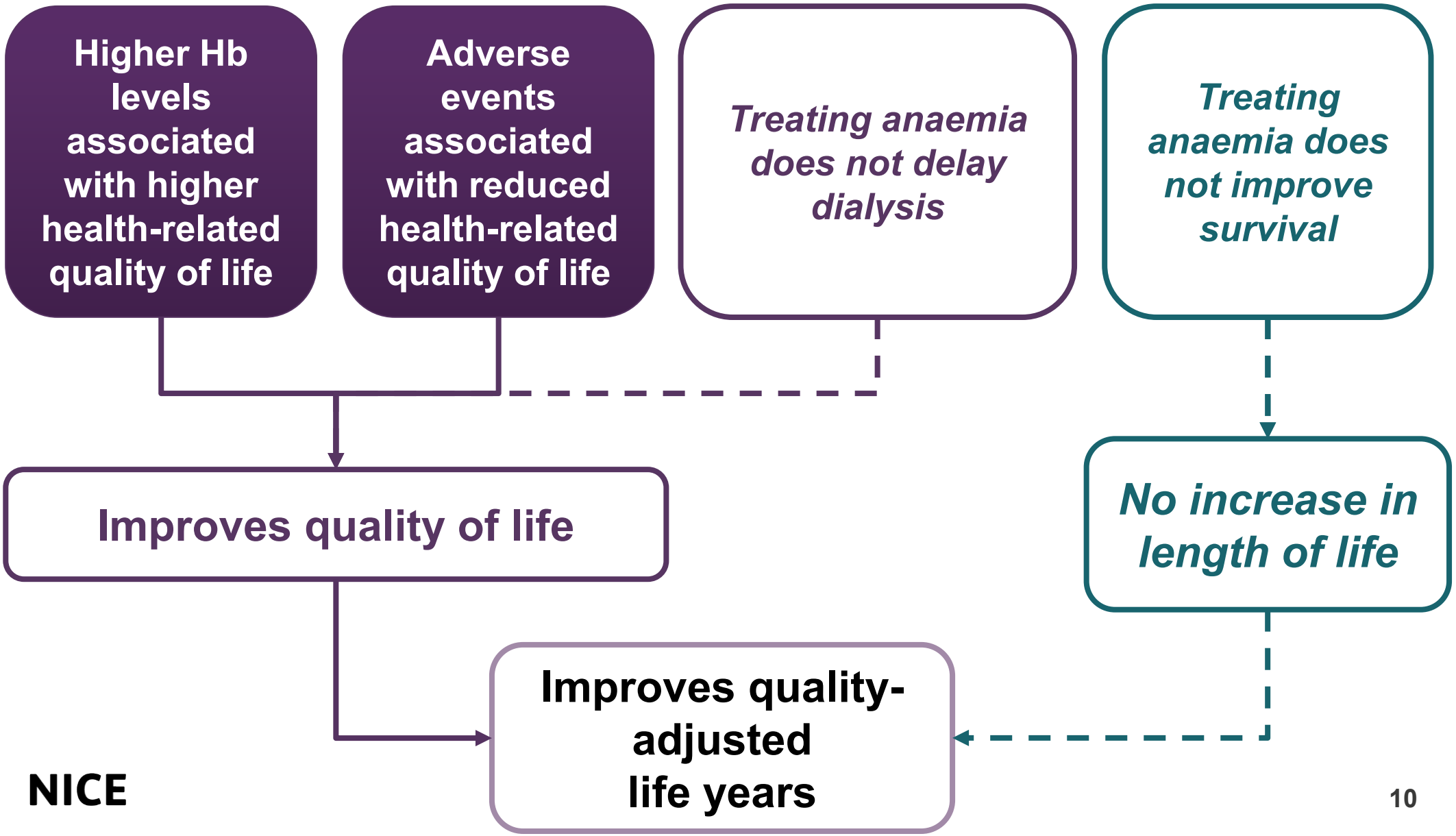
	Pooled trials		DOLOMITES	
	Roxadustat (N=2386)	Placebo (N=1884)	Roxadustat (N=323)	ESA (N=293)
Myocardial infarction	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Vascular access thrombosis	[redacted]	[redacted]	[redacted]	[redacted]

Committee heard at 1st meeting

- Adverse events such as insomnia, headache and nausea are important for patients because they can affect quality of life and roxadustat adherence
- Frequency of adverse events differed up to 2-3% between roxadustat and darbepoetin alfa
- Company explored impact of cardiac failure, pneumonia, and hypertension (grade 3+ in >3% patients) and considered minor impact on cost effectiveness
- Committee concluded that company model should include additional adverse events e.g. those important to patients and impacting quality of life

How model accrues quality-adjusted life years

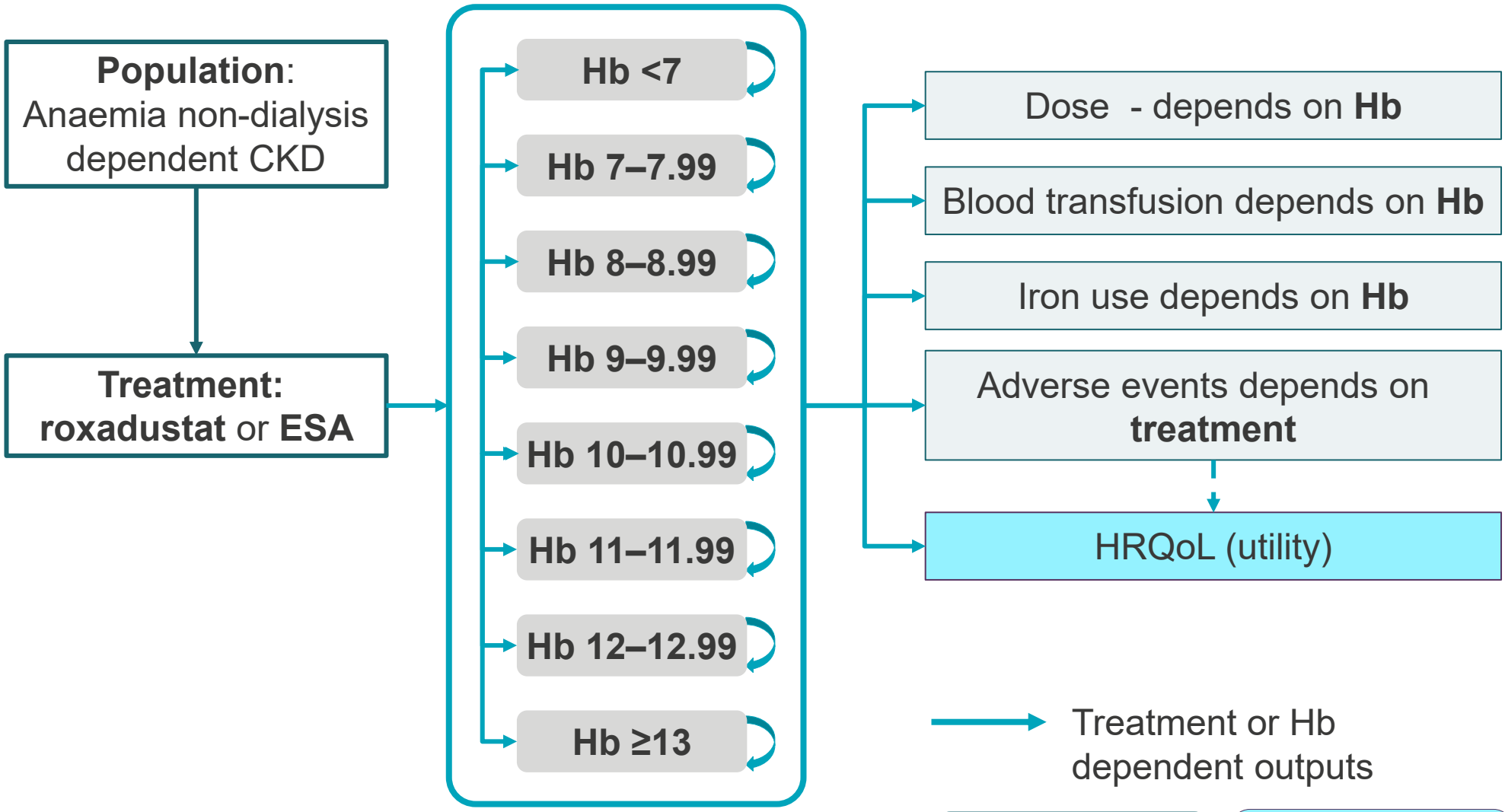
Company assumes roxadustat improves only quality of life



Model structure

Cohort state transition model based on Hb (g/dL)

Treatment effect + transition probabilities from pooled roxadustat trials; 25-year time-horizon



Number of Hb-health states

Company based Hb categories on published literature

- Company chose 8 Hb categories Yarnoff et al. 2016, US cost-effectiveness paper of Hb targets for treating anaemia; Finkelstein et al. 2009 showing that Hb increase of 1 g/dL improves quality of life

Committee heard at 1st meeting

- Unclear how each health state differs in health-related quality of life, costs, and survival
- People with anaemia are not aware of changes in Hb levels - notice improvements in quality of life (e.g. feeling less tired) when Hb >9 g/dL
- Model with health states based on Hb levels below the NICE guideline target range (<10 g/dL), within the target range (10–12 g/dL) and above the target range (>12 g/dL) might reflect clinical practice treatment of anaemia
- Having 8 health states overcomplicates model - not enough data to identify differences for each health state
- Committee considered company's economic model broadly reflects anaemia, but likely includes more health states than necessary

Utilities for each health state

Company used additive approach to calculate health state utilities

- Company calculated utilities for each Hb state from general population age- and sex-adjusted values then subtracting **utility decrements for**:
  - **Hb level** (range from [redacted] to [redacted])
  - **CKD** ([redacted]) and **haemodialysis** (0.352) or **peritoneal dialysis** (0.262)
  - **Adverse events** (stroke, mild [0.350], moderate [0.500], severe [0.730]; myocardial infarction [0.120]; vascular access thrombosis [0.100])

Committee heard at 1st meeting

- Sources for disutilities date as far back as 1999 → unclear if disutilities reflect current values or generalisable to CKD (from NICE technology appraisal 358 on polycystic kidney disease)
- Company did not explore alternative approaches such as multiplicative, or minimum or maximum values - literature suggests multiplicative approach is preferable
- Using additive approach would lead to implausibly low health-state utility values in some cases because of high disutility values
- Committee preferred health state utilities estimated using multiplicative approach

Regression models for long-term extrapolation

Company used several regression models to estimate:	ERG comments
% of patients across Hb-health states after 1st cycle (multinomial logistic regression model, see appendix slide for details)	• Model based on pooled roxadustat trials data • Unclear if time trends during trials hold over 25-year horizon • Raised by company during validation: "Can we predict Hb state occupancy over a 40-year period from a short-term duration trial?" • Appropriateness and impact of log(time +1) covariate to incorporate time dependency in model unclear, no analyses provided excluding it → ERG did scenario analyses with shorter time horizons to check impact of time • Company did not provide analysis plans or diagnostic plots for assessment
Hb-health state utility values (generalised linear mixed model, see appendix slide for details)	• Company did not provide analysis plans or diagnostic plots for assessment

Committee heard at 1st meeting

- Committee considered it speculative that roxadustat effects seen in clinical trials would last indefinitely over 25 years and wanted to see scenarios altering this assumption.
- Committee concluded that transition probabilities between health states estimated by the company are uncertain because they do not reflect the DOLOMITES trial data.

Hb level utility decrements

Disutilities are uncertain and do not reflect clinical experience

- Company estimated disutilities from roxadustat trials EQ-5D-5L cross-walked to EQ-5D-3L
  - generalised linear mixed model for long-term extrapolation
- **ERG:** company did not provide statistical analysis plan for regression analysis → unable to assess impact

	Health state							
Hb category (g/dL)	<7	7–7.99	8–8.99	9–9.99	10–10.99	11–11.99	12–12.99	>13
Disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Committee heard at 1st meeting

- Company did not reflect regulatory advice to avoid sustained Hb levels greater than 12 g/dL (increased risk of cardiovascular disease) in modelling
- Concerns that company included lower roxadustat doses and costs, reduced iron and blood transfusion use, and no disutility for Hb levels over 12 g/dL → overestimate the cost effectiveness of a treatment which would increase Hb levels over 12 g/dL.

Distributing patients across Hb states over time

Company used multinomial logistic regression model

- Baseline - based on pooled trials data
- Most patients allocated to 9 to < 10 g/dL state; [redacted]
- Multinomial logistic regression model confirmed with clinical experts

Committee heard at 1st meeting

- Distribution of patients based on inappropriately pooled trials data
- Unclear if roxadustat effects seen in clinical trials would last indefinitely over 25-year time horizon
- Extrapolation of benefits from 36-weeks data from DOLOMITES to 25-year period is uncertain
- Company model outputs inconsistent with DOLOMITES result which show non-inferiority of roxadustat compared with darbepoetin alfa
- Stopping rule not included for ESA at Hb >12 g/dL (MHRA advice) and roxadustat at Hb >13 g/dL (DOLOMITES stopping rule)
- Transition probabilities between health states are uncertain because they do not reflect DOLOMITES trial data.

Hospitalisations

Company modelled hospitalisations indirectly based on adverse events

Committee heard at 1st meeting

- Company modelled frequency of hospitalisations indirectly based on adverse events to avoid double counting the costs and quality-of-life effects
- There was too little data to model hospitalisations based on Hb level
- Different hospitalisations rates between roxadustat (58%) and darbepoetin alfa (52%) in DOLOMITES trial
- Company's approach not in line with NICE guidance: indirect (surrogate) outcomes should be used only when direct outcomes are not available
- Committee considered company can model hospitalisations directly and avoid double counting, because it knows which hospitalisations were due to adverse events
- Committee concluded that costs of hospitalisations should be based on hospitalisation rates measured directly from the DOLOMITES trial.

Cost of Roxadustat

- Company estimated roxadustat costs based on doses used during Hb correction phase (up to 3 months after treatment start; estimated from pooled roxadustat arms) and Hb maintenance phases (after 3 months of treatment to lifetime; extrapolated using generalised linear mixed model)

Hb level (g/dL)	Correction phase weekly dose	Maintenance phase weekly dose	Roxadustat cost 1st cycle	Roxadustat cost subsequent cycles
<7	[redacted]	[redacted]	[redacted]	[redacted]
7–7.99	[redacted]	[redacted]	[redacted]	[redacted]
8–8.99	[redacted]	[redacted]	[redacted]	[redacted]
9–9.99	[redacted]	[redacted]	[redacted]	[redacted]
10–10.99	[redacted]	[redacted]	[redacted]	[redacted]
11–11.99	[redacted]	[redacted]	[redacted]	[redacted]
12–12.99	[redacted]	[redacted]	[redacted]	[redacted]
>13	[redacted]	[redacted]	[redacted]	[redacted]

*Reference Hb level to which increments or decrements in dose are applied to.

Committee heard at 1st meeting

- Company did not include treatment stops in model, despite DOLOMITES stopping rule for roxadustat
- Clinical experts would change dosage in clinical practice to keep Hb levels within target range (i.e. between 10 and 12 g/dL)

Costs of erythropoiesis stimulating agents (ESAs)

ESAs modelled as class; company unaware of discount to NHS

- Considers all 5 ESAs in British National Formulary (BNF) and assumes equal efficacy at equivalent doses
- Used darbepoetin alfa as reference; then used a 'dose conversion' based on weekly dose (in micrograms) for other ESAs from BNF
- % receiving each ESA from TUNE – unpublished observational retrospective study of medical records UK population

ESA	Dose conversion ratio	% used in model
1. Darbepoetin alfa - reference	[redacted]	[redacted]
2. Epoetin alfa	[redacted]	[redacted]
3. Epoetin beta	[redacted]	[redacted]
4. Epoetin beta (methoxy polyethylene glycol)	[redacted]	[redacted]
5. Epoetin zeta	[redacted]	[redacted]

Committee heard at 1st meeting

- No clear or reliable sources of national ESA distributions
- Some hospitals or trusts purchase only 1 type of ESA rather than a basket of ESAs
- Committee would like to see scenarios with different distributions of ESAs

Appraisal consultation document (ACD) – conclusions and uncertainties (1/2)

Section	Committee conclusion	To discuss	ACD
The condition	Position of roxadustat is appropriate	✗	3.3
Clinical effectiveness	DOLOMITES is the only clinical trial relevant for decision problem	✗	3.4
	Roxadustat is non-inferior compared with darbepoetin alfa (and ESA by proxy)	✗	3.5
	Company did not combine data from all roxadustat trials appropriately	✗	3.6
Cost effectiveness	Economic model includes more health states than necessary	✓	3.7
	Health states transition probabilities are uncertain and do not reflect DOLOMITES trial	✓	3.8
	It is speculative that the roxadustat effects seen in clinical trials would last indefinitely over 25 years.	✓	3.8
	It is inappropriate to extrapolate benefits for roxadustat over 25 based only on 12 weeks of data.	✓	3.8

Appraisal consultation document (ACD) – conclusions and uncertainties (2/2)

Section	Committee conclusion	To discuss	ACD
Cost effectiveness	Company did not model stopping rule for ESAs or roxadustat when Hb levels exceed 12 and 13 g/dL.	✓	3.8
Utility values	Committee prefers health-state utilities estimated using multiplicative approach	✗	3.9
	Disutility for dialysis and Hb level are uncertain and do not reflect patient and clinical experience	✓	3.10
	Modelling does not reflect harms and costs of Hb levels >12 g/dL	✓	3.10
Costs in the economic model	Hospitalisations costs should be based on hospitalisation rates directly from DOLOMITES	✓	3.11
	Model should include additional adverse events	✓	3.12
	Roxadustat costs are appropriate, but should be based on data from DOLOMITES	✓	3.13
	ESA costs are uncertain	✓	3.14

Summary of responses to appraisal consultation document

ACD consultation responses

Received consultation responses from:

- Company: Astellas Pharma

No responses received from other consultees

Committee preferred assumptions and company's revised base case

ACD #	Preferred assumptions	Company revised base case	ERG critique
3.6	Use DOLOMITES only or network meta-analysis of ESA versus placebo	Yes DOLOMITES only	No issues
3.7	Use fewer model health states or fully justify using 8 health states	No; no additional justification provided	Same issue as previously
3.8	Transition probabilities are based on data from the entire 36 weeks of DOLOMITES	Provided clarification (factual inaccuracy)	No issues
3.8	Provide justification for the regression model used to extrapolate beyond the trial period	Not provided	N/A
3.9	Use multiplicative approach to estimate health-state utilities	Yes	No issues
3.10	Harms and costs of Hb levels >12 g/dL are reflected in the modelling	Yes Hb >13 g/dL only	Unclear what was done
3.11	Estimate hospitalisation costs based on hospitalisation rates directly from DOLOMITES	No	Same issue as previously

Committee preferred assumptions and company's revised base case

ACD #	Preferred assumptions:	Company revised base case	ERG critique
-	Include ESA administration costs for people who start having peritoneal dialysis	Yes	No issues
3.12	Include additional adverse events	No	Same issue as previously
3.13	Estimate roxadustat costs that reflect the DOLOMITES trial	Yes	No issues
3.13	Include stopping rule in DOLOMITES and other regulatory recommendations for safety	Yes	Some issues

Scenario analysis	Company included	ERG critique
Benefits of roxadustat do not last indefinitely over the 25-year time horizon	Yes	No issues
Use different distributions of ESA	Yes	No issues

Key issues

Economic model includes more health states than necessary	• Is the company's justification sufficient for using a model with 8 health states based on 1 g/dL Hb increments?
Provide justification for the regression model used to extrapolate beyond the trial period	• Is the uncertainty of the regression model underpinning the economic model acceptable?
Modelling does not reflect harms and costs of Hb levels >12 g/dL	• Has the company sufficiently captured the costs and harms of Hb >12 g/dL?
Hospitalisations costs should be based on hospitalisation rates directly from DOLOMITES	• Does the committee accept that there is no significant difference in the rate of hospitalisations?
Model should include additional adverse events	• Is the consideration of only grade 3+ AEs acceptable?

Economic model includes more health states than necessary (1/2)

- Company retains 8 health state model structure using 1 g/dL Hb increments based on published cost-effectiveness analyses (e.g. Glenngård et. al. 2008) and the positive correlation between Hb levels and utility seen in roxadustat clinical trials (see Figure).
- However, figure may be misleading because Y axis does not start from 0 → differences between Hb categories not as profound (redrawn figure available in Appendix slides)

Figure showing utility values by increasing Hb level (observed data in red and predicted values in blue)

Economic model includes more health states than necessary (2/2)

- Company also argues that there is a relationship between Hb level increments and treatment dose (roxadustat and ESA) which justifies 1 g/dL Hb increments.
- Modelling fewer health states may miss differences between treatment arms e.g. moving from 7 to 10 g/dL is not the same change in quality of life and costs as moving from 9 to 10 g/dL.

[redacted]

[redacted]

⊙ *Is the company's justification sufficient for using a model with 8 health states based on 1 g/dL Hb increments?*

Provide justification for the regression model used to extrapolate beyond the trial period

- Company has not provided any justification or statistical analysis plans for regression models despite repeated requests
- **ERG:** multinomial logistic regression model for Hb-health state distribution extrapolation and generalised linear mixed model for Hb level disutilities underpin economic model → potentially large impact on cost effectiveness estimates
  - ERG unable to assess regression models → uncertain
  - Company revised base case uses regression models based on DOLOMITES only data, but no details provided for assessment → uncertain

⊙ *Is the uncertainty of the regression model underpinning the economic model acceptable?*

Modelling does not reflect harms and costs of Hb levels >12 g/dL

- Company included option to add stroke, myocardial infarction (MI) and vascular access thrombosis (VAT) for Hb levels >13 g/dL
  - Hb-specific risks of MI and VAT not available in published literature → company applies risk of stroke to MI and VAT
- Company applied harms and costs to all Hb health states → considers impact on cost effectiveness negligible because % time spent in health state Hb >13 g/dL is [redacted] (roxadustat) and [redacted] (ESA) of patient lifetime
- However, % time spent in >12 g/dL Hb health states is [redacted] for roxadustat and [redacted] for ESA → impact likely to be greater than Hb >13 g/dL
  - Difference in % inconsistent with roxadustat (13 g/dL) and ESA (12 g/dL) stopping rules → roxadustat expected to have longer time in Hb-health states >12 g/dL
- **ERG:** difference of time in health state >13 g/dL nearly [redacted] between roxadustat and ESA
  - harms and costs should be applied to health states >12 g/dL

	Roxadustat		ESA	
Hb level (g/dL)	Time in health state (years)	% of patient lifetime	Time in health state (years)	% of patient lifetime
12–12.99	[redacted]	[redacted]	[redacted]	[redacted]
≥13	[redacted]	[redacted]	[redacted]	[redacted]
Patient lifetime	[redacted]	-	[redacted]	-

⊙ *Has the company sufficiently captured the costs and harms of Hb >12 g/dL?*

It is inappropriate to extrapolate benefits for roxadustat over 25 years based only on 12 weeks of data

- Company states “health state transition probabilities and extrapolation of benefit are based on the entire length of trial data, not 12 weeks”.
  - First 12 weeks of DOLOMITES data used to determine distribution at baseline
  - Confirmed all statistical analysis and baseline characteristics in revised base case based on DOLOMITES only
- Company used all data available for extrapolations, including from patients with data up to 104 weeks of treatment
- **ERG:** details of extrapolation based on DOLOMITES trial data and additional data from patients with up to 104 weeks of treatment not provided → unable to assess impact → uncertain

Company did not model stopping rule for ESAs or roxadustat when Hb levels exceed 12 and 13 g/dL

- Company included stopping rule for roxadustat for Hb level >13 g/dL
  - Hb >13 has [redacted] disutility in company model → stopping rule removes accrual of roxadustat treatment costs
  - Dialysis and adverse events disutilities are still applied
- **ERG:** adjustment implicitly assumes that stopping rule only affects costs and not estimated effectiveness of roxadustat.
  - Stopping rule not accounted for in regression model extrapolations and transition probabilities
- Company did not include stopping rule for ESA
  - Considered that model already reflects stopping rule for ESA because darbepoetin alfa dosing in DOLOMITES trial was in line with the Summary of Product Characteristics

⊙ *Has the company met committee preference?*
⊙ *Is ESA dosing in DOLOMITES reflective of UK clinical practice?*

Hospitalisations costs should be based on hospitalisation rates directly from DOLOMITES

- Company calculated a hospitalisations incident rate ratio by combining the valid "other" hospitalisations category with the exposure time used in the economic model for adverse events, and found no significant difference in the rate of hospitalisations between roxadustat and ESA.

Treatment	Number of patients with events	Total exposure in 3-monthly cycles	Cycle probability of Hospitalisation
Adverse event related hospitalisations (Incident rate ratio: [redacted])			
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]
Other' related hospitalisations (Incident rate ratio: [redacted])			
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]

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⊙ *Does the committee accept that there is no significant difference in the rate of hospitalisations?*

Model should include additional adverse events

- Company considers only grade 3+ adverse events likely to affect costs and utilities → chose not to include additional adverse events in model because frequency of grade 3+ events was comparable between roxadustat and ESA → unlikely to impact cost effectiveness estimates.
- However, some grade 2 adverse events can also affect costs and utilities

Adverse event	Total (grade 2+)		Total (grade 3+)	
	Roxadustat	Darbepoetin alfa	Roxadustat	Darbepoetin alfa
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyperphosphatemia	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]

⊙ *Is the consideration of only grade 3+ adverse events appropriate?*
⊙ *Should grade 2+ adverse events be considered?*

It is speculative that the roxadustat effects seen in clinical trials would last indefinitely over 25 years

- Company included option to change roxadustat effects over model time horizon i.e. roxadustat benefit equals to that of ESA
- Company provides 3 scenarios
  - Roxadustat efficacy **matches ESA efficacy** immediately after DOLOMITES trial (month 25 in the model)
  - Roxadustat efficacy **gradually declines from end of DOLOMITES**, matching ESA by **year 3** in the model
  - Roxadustat efficacy **gradually declines from end of DOLOMITES**, matching ESA by **year 5** in the model
- **Tech team + committee ACD conclusion**: roxadustat is non-inferior compared with ESA
- **ERG:** Company's scenarios and ERG scenarios limiting time horizon appropriate for exploring long-term roxadustat effects uncertainty

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⊙ *Has the company met committee preference?*

Non-inferiority trial design impact on results

- Company considers non-inferiority trial design can still demonstrate roxadustat improvement over darbepoetin alfa
  - e.g. DOLOMITES primary efficacy analysis powered to allow demonstration of statistical non-inferiority if outcome difference between roxadustat and darbepoetin alfa arm no more than pre-specified and justified amount (non-inferiority margin of -15%)
  - Powering of study has no impact on resulting point estimates of efficacy → roxadustat superiority to darbepoetin alfa could be observed while allowing claim of statistical non-inferiority
  - "There is nothing in the design of a non-inferiority study that prevents the estimates of test treatment outcome being favourable compared with those of the comparator."
- **ERG:** company comment does not address points raised by ERG about non-inferiority margin being inadequately justified

⊙ *Has the company provided any evidence for the superiority of roxadustat over ESA?*

Because of confidential discounts for ESAs, all cost-effectiveness analyses are presented in private Part 2

Appendix slides

Multinomial logistic regression model for Hb-health state distribution extrapolation

- Baseline - based on pooled trials
- Hb-health state 10.00-10.99 g/dL as reference
- Covariates included
  - treatment type (placebo, ESA or roxadustat)
  - time (log transformed to be log(time +1); see notes for more detail)
  - CVD history at baseline
  - diabetic status at baseline
  - study ID (ALPS, ANDES, OLYMPUS, DOLOMITES); used to account for nesting effects
  - interaction between treatment type and log (time +1)
- Most patients allocated to 9 to <10 g/dL state; [redacted]
- Multinomial logistic regression model confirmed with clinical experts

Generalised linear mixed model for Hb level utility decrements

- Utility decrements based on pooled trials data
- Included covariates: cardiovascular disease history and diabetic status at baseline
- Study ID and subject included as random factors to account for nesting effects

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7 g/dL	[redacted]	[redacted]	[redacted]
Hb level 7-7.99 g/dL	[redacted]	[redacted]	[redacted]
Hb level 8-8.99 g/dL	[redacted]	[redacted]	[redacted]
Hb level 9-.99 g/dL	[redacted]	[redacted]	[redacted]
Hb level 11-11.99 g/dL	[redacted]	[redacted]	[redacted]
Hb level 12-12.99 g/dL	[redacted]	[redacted]	[redacted]
Hb level >13 g/dL	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]
Diabetic - Yes	[redacted]	[redacted]	[redacted]

* P ≤0.050, ** P ≤0.010, *** P ≤0.001

Economic model includes more health states than necessary – redrawn figure

Figure showing utility values by increasing Hb level (observed data in red and predicted values in blue)