Slides for PUBLIC – redacted

NICE National Institute for Health and Care Excellence

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

## Lead team presentation

**Lead team**: James Fotheringham, clinical lead; Nicky Welton, cost lead; Nigel Westwood, lay lead

**ERG**: Kleijnen Systematic Reviews

**Chair**: Amanda Adler

**Technical team**: George Braileanu, Eleanor Donegan, Janet Robertson

**Company**: Astellas Pharma

8th December 2021 – virtual meeting

# Clinical effectiveness

# Issues - clinical effectiveness

| Topic | Question |
|---|---|
| **Roxadustat in pathway** | Appropriate? |
| **Population** | Appropriate? Iron replete in UK? |
| **Comparator** | Appropriate? Class effect?<br>Are there people who cannot take ESAs? |
| **DOLOLMITES trial** | Generalisable to the UK? |
| **DOLOMITES trial results** | Is roxadustat not worse than darbepoetin alfa? |
| **Best use of evidence** | All trials – if so, how combined?<br>DOLOMITE trial only? |
| **Adverse events** | Which to include in model? |

# Anaemia in chronic kidney disease (CKD)

- Haemoglobin (Hb) carries oxygen in blood; anaemia defined by low Hb
- In people with chronic kidney disease (CKD) anaemia is common because unhealthy kidneys make less erythropoietin which helps make red blood cells
- NICE guidelines for anaemia with CKD (NG203) advises aiming for Hb 0–12 g/dL
  - Standard treatment includes iron then, if necessary, erythropoietin stimulating agents
  - MHRA warns when treating anaemia with ESAs to Hb >12g/dL → risk of death + cardiovascular disease
- 5 stages of CKD based on estimated glomerular filtration rate (eGFR) – anaemia increases with worsening renal function
- Anaemia independent predictor for CKD progression and all-cause mortality

| Stage | Description | Anaemia prevalence |
|---|---|---|
| 1 | Normal 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% |

# Patient and carer perspectives - anaemia

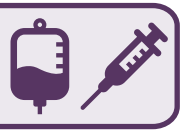
Comments from: Kidney Care UK, patient experts

## Living with anaemia associated with CKD

- Affects everyday life with extreme fatigue and lack energy even for simple tasks
- Negatively affects mental health and impacts on the quality of life of people already living with the challenges of CKD
  - "*Living with CKD for over a decade has been very challenging, but with the added burden of anaemia associated CKD, [it] impacted severely on the quality of my life. I only realised the severity of this during dialysis ... I was always exhausted. I felt extreme fatigue but could not express how I felt to my family because I 'looked fine'. For a few months I couldn't drive, work and some days, not even hold a glass of water or raise my arm. It impacted my mental health ...*"
  - "*..my husband recalls driving me to and from dialysis sessions, staying with me through my treatment, just in case I may not be able to walk back to the car. ...*"
- Anaemia can also affect physical health

# Patient and carer perspectives - treatments

## Experience of current treatments



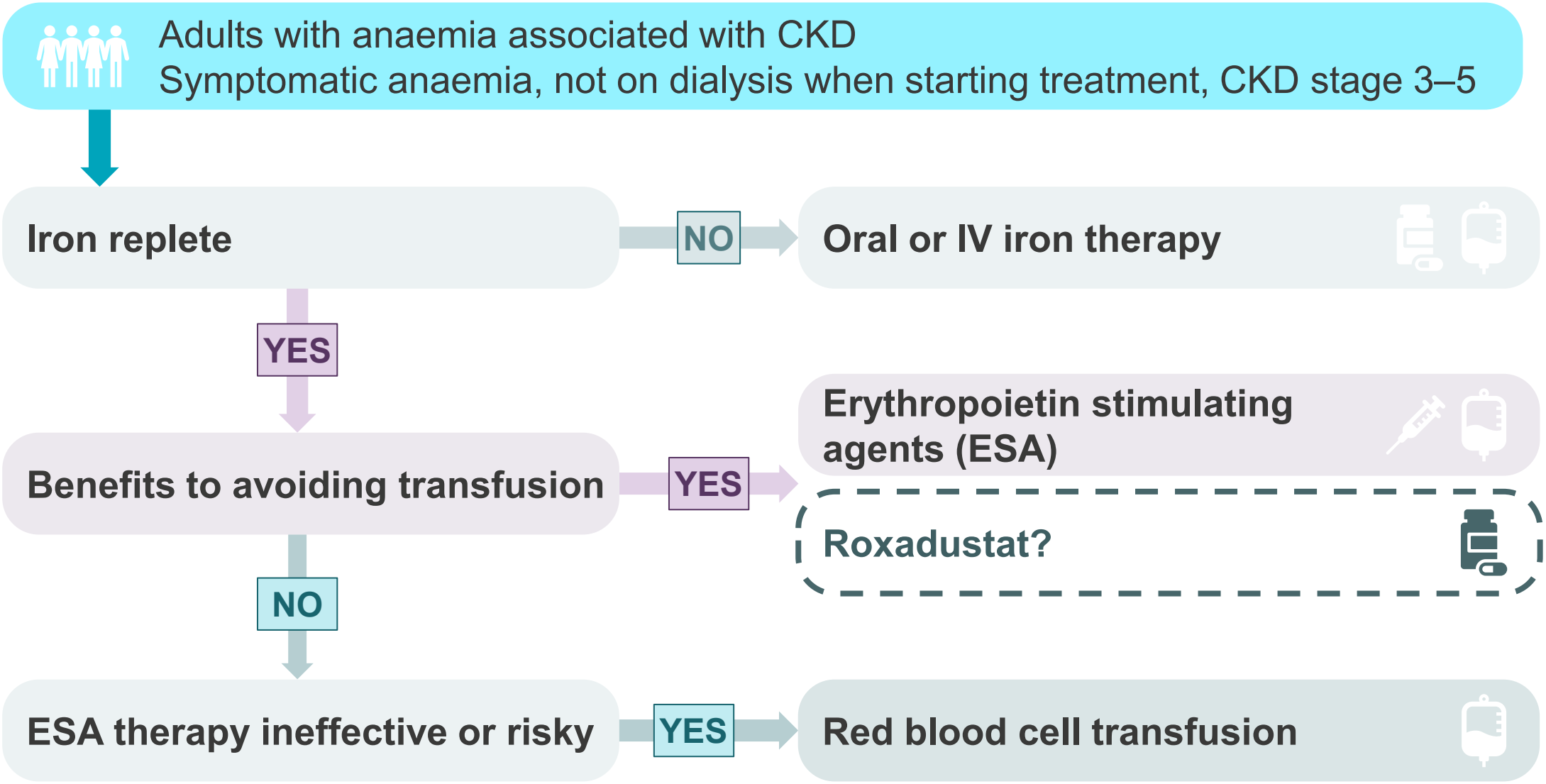
- Many adults find injecting themselves with ESA unpleasant and difficult. Some unable to administer injections themselves and rely on others.
  - "*I struggled to inject myself. The needle was quite long ...*"
  - "*In 2014 I became very ill with CKD and required oral iron and ESA … My teenage daughter was horrified one day ... she seemed to understand taking oral medication but [thought it] barbaric to have an injection and give it to myself.*"
- Side effects of current treatments can be unpleasant and impact on quality of life
  - "*I have had numerous oral iron (sic) which has always caused abdominal discomfort.*"
- Adults with anaemia believe an oral medication would be better:
  - More convenient to administer
  - Avoids training to self-inject and disposing of sharps
  - Requires no refrigeration
  - It would be easier to store when given the requirement for storage and sharps disposal
  - Reduces the need for iron infusions would be advantageous:
  - And transfusions to avoid the risk of producing antibodies that might limit transplant

# Roxadustat (Evrenzo, Astellas Pharma)

| | |
|---|---|
| **Marketing authorisation** | Adults with '**symptomatic** anaemia associated with chronic kidney disease' |
| **Administration and dose** | Oral<br>**Recommended starting dose**: based on ESA history and patient weight<br>• For anaemia **not** treated with ESA:<br>  • 70 mg 3 times per week if patient weighs <100 kg<br>  • 100 mg 3 times per week if patient weighs ≥100 kg<br>**Maintenance dose**<br>• 20 to 400 mg for dialysis-dependent CKD<br>• 20 to 300 mg for non-dialysis-dependent CKD |
| **Other** | A 'physician experienced in the management of anaemia' should start treatment<br>Converting 'dialysis patients otherwise stable on ESA treatment... only... when there is a valid clinical reason' |
| **Mechanism** | Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor |
| **Price** | List prices for 5 different strengths of roxadustat – confidential; prices increase with dosage<br>• **Cost per year:** £2,696 (70mg dose, 3 times per week for weight <100kg)<br>Company has agreed a confidential **patient access scheme - simple discount -** with NHS England |

# 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*




**NICE guidelines recommend avoiding blood transfusions, in people with option for kidney transplant.*

# Company's positioning of roxadustat

*Less likely to be used to treat in CKD 1, 2 or 5 when on dialysis*

## Company

Target population adults with

- **symptomatic anaemia**
- **CKD 3 to 5**
- **not dialysing**

Company chose this based on:

- **Population in clinical trials**
- **Clinical experts:** giving ESA + IV iron not a burden for adults on dialysis
- **Roxadustat license precautions**: Switch patients from ESA to roxadustat only "when there is a valid clinical reason."

## Clinical experts

- Anaemia in CKD 1 or 2 can respond to iron alone
- Difficult to justify roxadustat in dialysis – current therapy IV through dialysis machine
- But patients on peritoneal dialysis may prefer roxadustat
- Some patients cannot take ESAs: chronic inflammation, no response to ESA, averse or struggling with needles.

- *Is the company's positioning of roxadustat in treatment pathway appropriate?*
- *Is the population appropriate? Would UK population be expected to be iron replete?*
- *Is the comparator appropriate? – Class effect?*
- *Are there people who cannot take ESAs?*

# Scope and decision problem

*PICO: Population-intervention-comparison-outcome*

*Population in company submission narrower than scope*

| | NICE scope | Company submission | Justification | ERG |
|---|---|---|---|---|
| **P** | Adults with anaemia associated with CKD | Adults **symptomatic** anaemia CKD 3–5 **not dialysing** at start of treatment | • ESA during dialysis easier on patients<br>• Limited data CKD stage 1 or 2 | • Adults with CKD stage 1 or 2 can have anaemia<br>• NICE comment - regulatory concerns of switching dialysis patients |
| **I** | Roxadustat | | - | - |
| **C** | Erythropoiesis stimulating agents | | - | • Most trials placebo |
| **O** | • Hb response<br>• Hb maintenance<br>• Iron therapy, transfusions<br>• Hospitalisation<br>• Mortality<br>• Adverse events<br>• Health-related quality of life | • All but hospitalisation | • Cost of hospitalisation captured through adverse events, administering drug, monitoring | • Using indirect measures problematic<br>• Not in line with the NICE guidance that indirect (surrogate) outcomes should be used only when direct outcomes are not possible. |

# Roxadustat randomised trials evidence base

*Only 1 trial (DOLOMITES) compared roxadustat with active ESA comparator*

| | ALPS (n=594) | ANDES (n=922) | OLYMPUS (n=2,761) | DOLOMITES (n=616) |
|---|---|---|---|---|
| **Trial design** | Double-blind ✓ | Double-blind ✓ | Double-blind ✓ | Open-label ✗ |
| **Population** | Adults (≥18) ✓<br>Symptomatic anaemia ✗<br>Hb <10.0 g/dL ✓<br>eGFR <60 ✓ | Adults (≥18) ✓<br>Symptomatic anaemia ✗<br>Hb <10.0 g/dL ✓<br>eGFR <60 ✓ | Adults (≥18) ✓<br>Symptomatic anaemia ✗<br>Hb <10.0 g/dL ✓<br>eGFR <60 ✓ | Adults (≥18) ✓<br>Symptomatic anaemia ✓<br>Hb <10.5 g/dL ✓<br>eGFR <60 ✓ |
| **Intervention** | Roxadustat ✓ | Roxadustat ✓ | Roxadustat ✓ | Roxadustat ✓ |
| **Comparator** | Placebo ✗ | Placebo ✗ | Placebo ✗ | Darbepoetin alfa ✓ |
| **1º Outcome** | Hb response ✓ | Hb response ✓ | Hb response ✓ | Hb response ✓ |
| **In model?** | Yes ✓ | Yes ✓ | Yes ✓ | Yes ✓ |

NICE

Age in years. eGFR: estimated glomerular filtration rate in ml/min/1.73 $m^2$; Hb: haemoglobin in g/dL.

# DOLOMITES trial design – non-inferiority

*Phase 3, randomised, open-label trial, 28 countries including UK*
*Excluded patients who could not take ESAs*

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

(N=616)

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

Darbepoetin alfa weight-based dosing (n=293)

**Exclusions:**
- Cancer
- IV iron within 6 weeks
- ESA within 12 weeks
- Transfusion within 8 weeks
- Hereditary + non-CKD anaemia
- Diseases impacting erythropoiesis

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

**1º yes/no**
- Hb response weeks 0–24:

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

**2º**
- Hb Δ from baseline
- LDL cholesterol Δ from baseline
- Time to first IV iron
- Arterial pressure mean Δ from baseline
- Time to 1st hypertension
- Health-related quality of life (SF-36, EQ-5D-5L VAS)

CKD, chronic kidney disease, EQ-5D-5L: EuroQol 5 Dimensions 5 Levels, ESA: erythropoiesis-stimulating agent, IV: intravenous, Hb: haemoglobin, LDL: low density lipoprotein, RBC: red blood cell, SF-36: Short form 36, VAS: visual analogue scale. haemoglobin in g/dL

# DOLOMITES trial – statistical methods

*Non-inferiority trial design*

| | Description | Comments |
|---|---|---|
| Power | >98%, if >80% of patients in each group responded | |
| **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 |
| Choosing margins | High responder rate based on urinary tract infections. 3 placebo-controlled studies show that small differences between roxadustat and an ESA 'would not be relevant.'* | |
| Analysis population* | All randomized patients who received ≥ 1 doses of drug + ≥ 1 post-dose Hb (per protocol set) | Not intention to treat |
| Covariates | • Geographical region<br>• Baseline Hb<br>• CV or cerebrovascular or thromboembolic disease<br>• Baseline eGFR | For 1º and 2º outcomes |
| Analysis | Miettinen and Nurminen approach | |
| **Non-inferiority statistical analyses* - 2° outcomes defined in clinical study report** | | |
| Analysis | Hierarchical testing: 1st non-inferiority then if non-inferior, superiority for some 2º endpoints<br>Mixed model of repeated measures or Cox regression + Kaplan-Meier | Some 2° tested for superiority |

** Supplementary material on selecting non-inferiority margin. Nephrol Dial Transplant (2021) 36: 1616–1628*

# Roxadustat trials – demographics

*Proportion female 51–59%, mean age range 61–67 years*

*Race and region distribution vary substantially across trials*

| Trial Allocation | ALPS | | ANDES | | OLYMPUS | | DOLOMITES | |
|---|---|---|---|---|---|---|---|---|
| | ROX | PBO | ROX | PBO | ROX | PBO | ROX | ESA |
| **Number** | 391 | 203 | 616 | 306 | 1,384 | 1,377 | 323 | 293 |
| **Sex** | | | | | | | | |
| Female | 57% | 51% | 61% | 58% | 59% | 56% | 55% | 56% |
| **Age (years)** | | | | | | | | |
| Mean | 60.6 | 61.7 | 64.9 | 64.8 | 60.9 | 62.4 | 66.8 | 65.7 |
| **Race** | | | | | | | | |
| White | 86% | 90% | 29% | 33% | 45% | 44% | 95% | 96% |
| Black / African American | 3% | 1% | 12% | 9% | 8% | 9% | 2% | 1% |
| Asian | 2% | 0 | 50% | 49% | 39% | 39% | 3% | 3% |
| Other | 9% | 9% | 9% | 9% | 8% | 8% | 0 | 0 |
| **Region** | | | | | | | | |
| Western Europe & Israel | - | - | - | - | - | - | 31% | 29% |
| Central & Eastern Europe | - | - | - | - | - | - | 69% | 71% |
| US | - | - | - | - | 25% | 25% | - | - |
| Ex-US | - | - | - | - | 75% | 75% | - | - |
| Western Europe | 7% | 8% | - | - | - | - | - | - |
| Rest of World | 93% | 92% | - | - | - | - | - | - |

# Roxadustat trials – baseline disease characteristics

*Mean Hb levels 9.1–9.5 g/dL, comorbidities and iron repletion status vary*

| Parameter | ALPS | | ANDES | | OLYMPUS | | DOLOMITES | |
|---|---|---|---|---|---|---|---|---|
| | ROX | PBO | ROX | PBO | ROX | PBO | ROX | ESA |
| | 391 | 203 | 616 | 306 | 1,384 | 1,377 | 323 | 293 |
| **Hb, g/dL mean** | 9.1 | 9.1 | 9.1 | 9.1 | 9.1 | 9.1 | 9.6 | 9.6 |
| ≤8 | 8% | 10% | 8% | 7% | 9% | 10% | 3% | 3% |
| >8 to ≤9 | 92% | 90% | 28% | 32% | 91% | 90% | 97% | 97% |
| >9 | | | 64% | 61% | | | | |
| **Comorbidities** | | | | | | | | |
| Type 2 diabetes, % | 34% | 37% | - | - | 57% | 59% | 44% | 42% |
| CVD history, % | 36% | 44% | 34% | 33% | 30% | 31% | 47% | 48% |
| **Iron repletion (ferritin [F] ng/mL, transferrin saturation [TSAT] %)** | | | | | | | | |
| F <100 & TSAT <20% | - | - | - | - | - | - | 16% | 22% |
| F <100 & TSAT ≥20% | - | - | - | - | - | - | 8% | 8% |
| F ≥100 & TSAT <20% | - | - | - | - | - | - | 20% | 18% |
| F ≥100 & TSAT ≥20% | - | - | - | - | - | - | 56% | 52% |
| F <30 or TSAT <5% | 4% | 3% | - | - | - | - | - | - |
| F 30–100 & TSAT 5–20% | 14% | 14% | - | - | - | - | - | - |
| F 30–100 & TSAT >20% | 12% | 12% | - | - | - | - | - | - |
| F >100 & TSAT 5–20% | 18% | 18% | - | - | - | - | - | - |
| F >100 & TSAT >20% | 52% | 54% | 60% | 56% | 59% | 58% | - | - |

NICE CVD: cardiovascular disease, PBO: placebo.

# DOLOMITES trial design and population

*Not in line with UK practice and guidance; 10% from UK*

- **ERG**: UK and non-UK differ in concomitant medications + other factors
- **Company**: chose not to conduct subgroup analysis of UK population
- **Clinical experts**:
  - DOLOMITES does not reflect Asian/Black/Other
    - UK 13% CKD 4 + 5 (UK Renal Registry 2019) vs DOLOMITES 5%
- DOLOMITES – inclusion criteria not generalisable to UK
  - Prohibiting recent iron inconsistent with UK practice and NICE guidance
    - In UK IV iron offered to patients receiving ESA therapy:
      - [redacted] of UK patients receiving an ESA received IV iron and [redacted] received oral iron (TUNE study; retrospective study of UK population)
  - Different treatment threshold. Hb <11 g/dL should trigger investigation and possible treatment of anaemia:
    - DOLOMITES included lower Hb threshold lower ≤10.5 g/dL

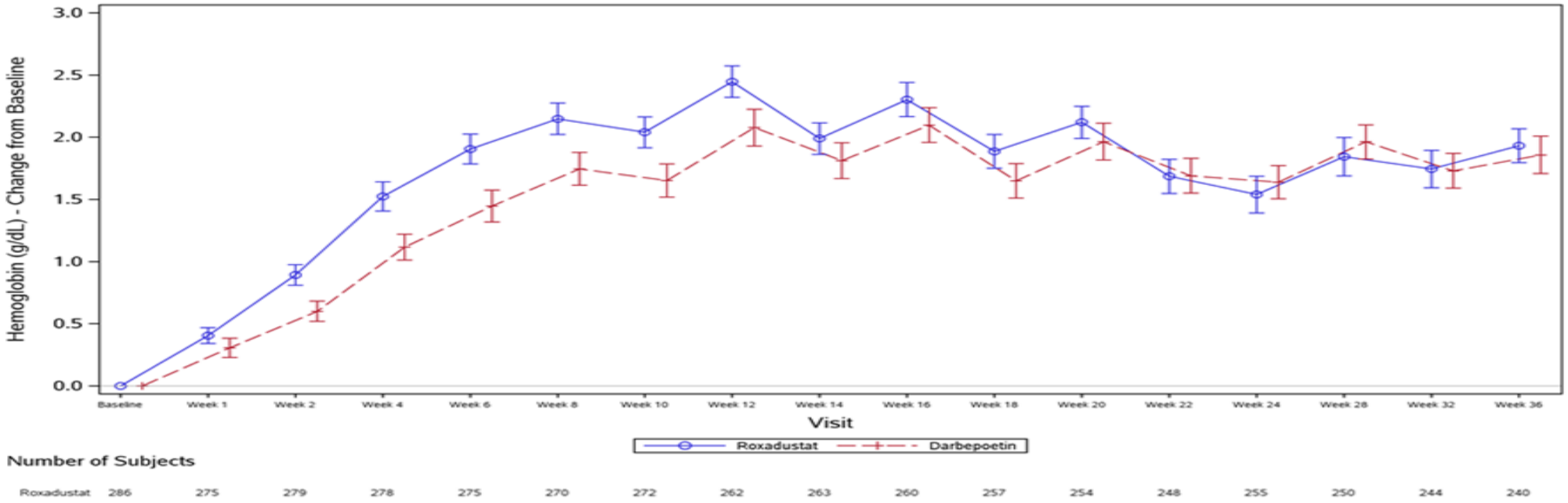
⊙ *Is the DOLOLMITES trial population generalisable to NHS patients who would be offered roxadustat? If not, how is this likely to affect modelling results?*

# DOLOMITES trial results - 1º outcome

*Roxadustat non-inferior compared to darbepoetin alfa in 1º outcome: Hb response and change from baseline in Hb levels*

| 1º outcome | Roxadustat (N=286) | Darbepoetin alfa (N=273) | Difference in proportion | Conclusion |
|---|---|---|---|---|
| **Hb response* (weeks 0–24), n (%)** | 256 (89.5%) | 213 (78.0%) | 11.5% | Roxadustat non-inferior to darbepoetin alpha |

Mean (± 95% CI) change from baseline in Hb level to week 36




- *Does the committee agree that roxadustat is not worse than darbepoetin alpha?*
- *Has the committee seen evidence for people who cannot take ESA?*

# DOLOMITES trial results - 2º outcomes

*Roxadustat non-inferior compared to darbepoetin alfa*

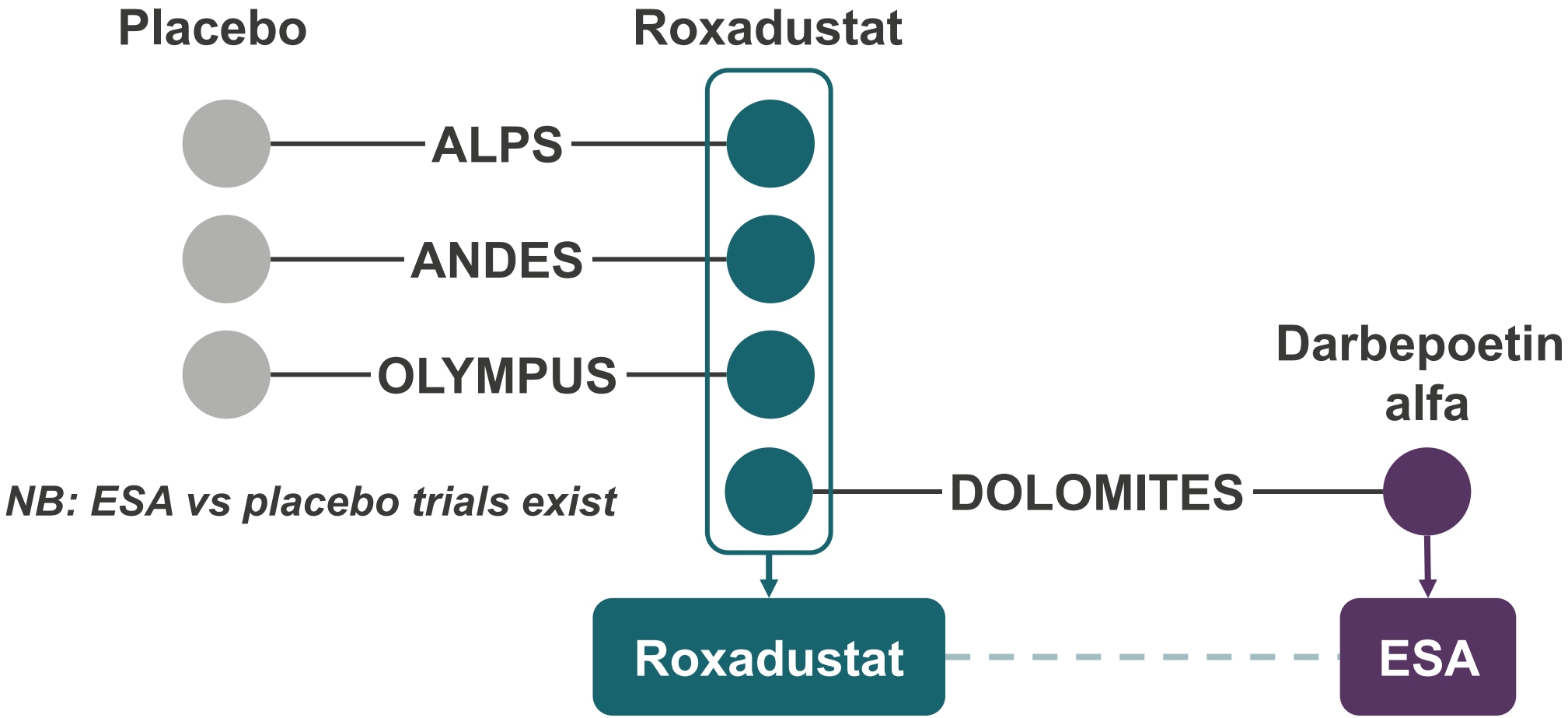
| Secondary outcomes | Roxadustat vs. darbepoetin alfa | Test results |
|---|---|---|
| **Change from baseline, LSM difference (95% CI)** | | |
| Hb (g/dL), weeks 28–36 | 0.01 (-0.13, 0.16) | Non-inferior |
| SF-36 PF subscore, weeks 12–28 | -1.28 (-2.42, -0.14) | Non-inferior |
| SF-36 VT subscore, 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 |

NICE

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.

# Pooling roxadustat trials

*Company pooled all trials and conducted analyses of individual patient data to estimate clinical parameters for roxadustat*



# Pooling trials – company approach

*Pooled population differs from DOLOMITES in CVD and type 2 diabetes*

- Identified differences in baseline patient characteristics prognostic for Hb response
- If not effect modifiers, then 'unjustified to exclude 3 of 4 relevant trials'
- Controlled for trial ID and confounders using hierarchical model structure, which 'cannot be done using fixed/random effect meta-analyses'
- Similar roxadustat dose, dosing schedule and delivery across all trials
- However, large differences in CVD and diabetes

| Baseline characteristic | Pooled | DOLOMITES | | |
|---|---|---|---|---|
| | | Roxadustat | Darbepoetin alfa | Total |
| Number | **4,847** | 323 | 293 | **616** |
| Starting age (years) | 63 | 67 | 66 | 66 |
| Female, % | 58% | 55% | 56% | 55% |
| Cardiovascular disease, % | 38% | 47% | 48% | 48% |
| Type 2 diabetes, % | 56% | 44% | 42% | 43% |
| Median eGFR ml/min/BSA | 17.1 | 17.5 | 18.5 | - |
| % from DOLOMITES | 13% | - | - | 100% |
| % from ALPS | 12% | - | - | - |
| % from ANDES | 19% | - | - | - |
| % from OLYMPUS | 56% | - | - | - |

# Pooling trials – ERG comments

*Pooling all trials for roxadustat may bias comparison with ESA*

- Pooling is an unanchored indirect treatment comparison and likely to be biased.
- To avoid bias, must balance all prognostic factors and effect modifiers across trials
- Pooling removes randomisation → patients not drawn randomly from same population → effect modifiers + prognostic factors not balanced across treatments
- Effect modifiers and prognostic factors may be **unmeasured** for which company cannot control and could bias outcome
- DOLOMITES trial results are less likely to be biased → used in ERG base case

⊙ *What is the best way use trial data to estimate treatment effect?*

1. Pooled? If so, how?
2. Network using placebo-controlled ESA trials
3. DOLOMITES trial data – only –?

⊙ *How should non-inferiority be modelled?*

# 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*

| | Roxadustat (n=323) | Darbepoetin alfa (n=293) |
|---|---|---|
| Oedema peripheral | 49 (15.2) | 36 (12.3) |
| Hyperkalaemia | 38 (11.8) | 42 (14.3) |
| Nausea | 35 (10.8) | 25 (8.5) |
| Hyperphosphataemia | 28 (8.7) | 15 (5.1) |
| Muscle spasms | 25 (7.7) | 15 (5.1) |
| Dyspnoea | 24 (7.4) | 12 (4.1) |
| Headache | 21 (6.5) | 12 (4.1) |
| Insomnia | 19 (5.9) | 8 (2.7) |

| | 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] |

- *What adverse events should company include in model? Note model includes quality of life associated with adverse events*
- *Source of adverse events? Pooled trials or DOLOMITES?*

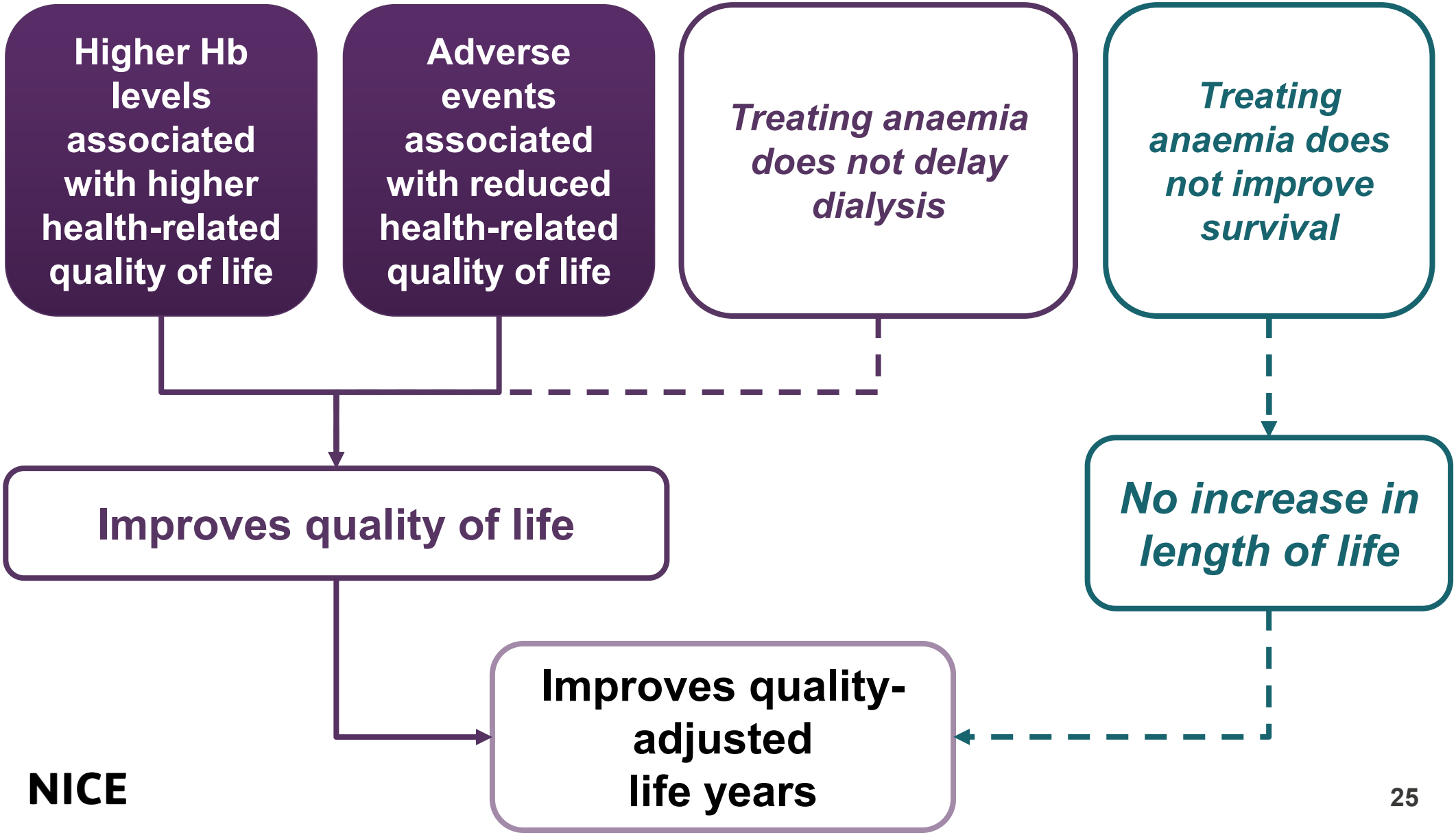
# Cost effectiveness

# Issues - cost effectiveness

| Topic | Question |
|---|---|
| **Model structure** | Appropriate? |
| **Non-inferiority** | Appropriate to model? |
| **8 Hb categories** | Discrete and distinguishable impacts on quality of life? |
| **Utilities by health state** | Is an 'additive' approach appropriate? |
| **Hb level utility decrements** | Committee view on company's regression and transparency? |
| **Distributing patients across Hb states over time** | Committee view on company's regression and transparency? |
| **Extrapolating time to dialysis and to death** | Has the company adequately explained and justified its methods? |
| **Hospitalisations** | How should they be modelled? |
| **Costs of comparator and administering it** | Appropriately modelled? |
| **Other** | Innovative? Equality issues? |

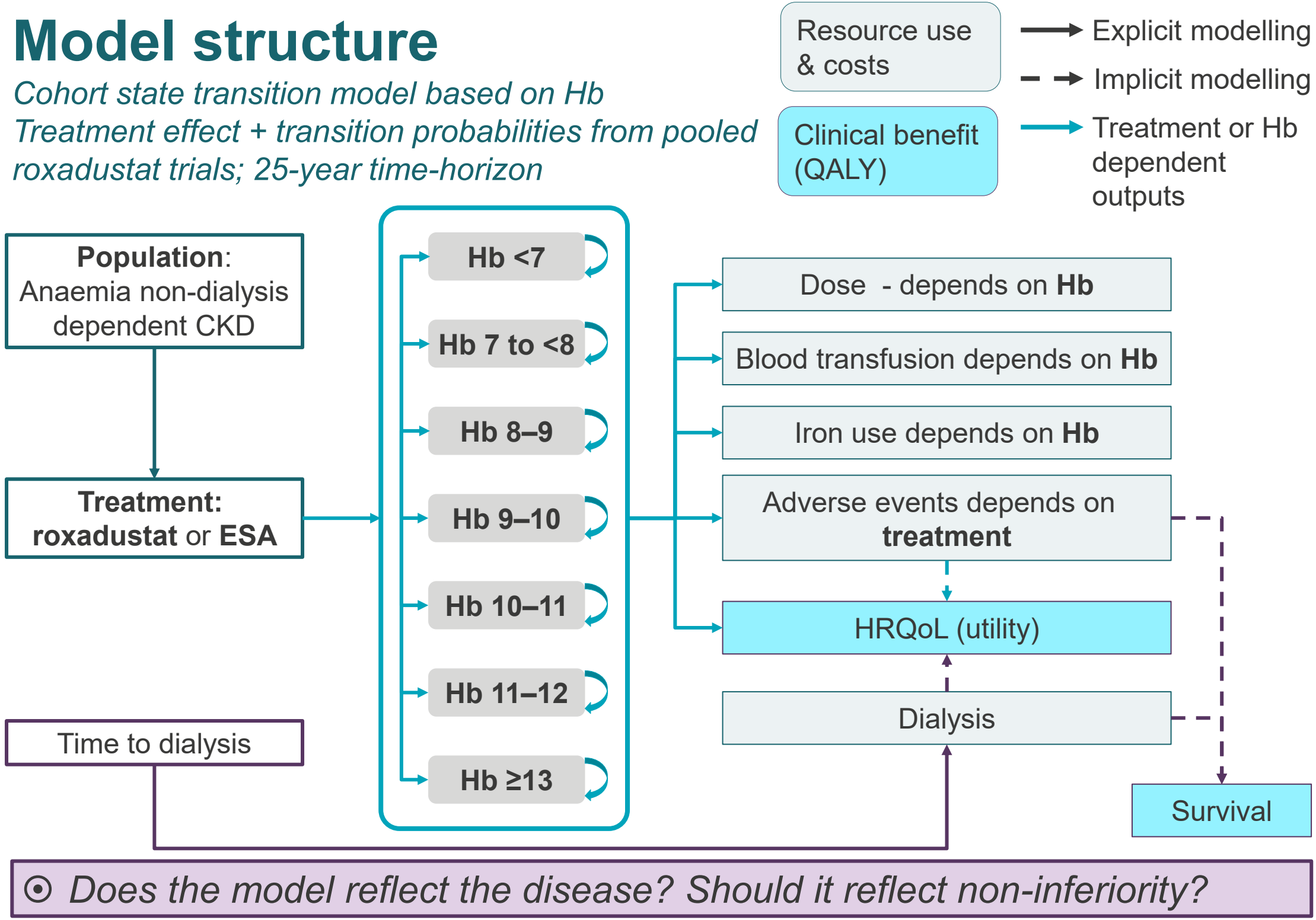
# How model accrues quality-adjusted life years

*Company assumes roxadustat improves only quality of life*



# Model structure

*Cohort state transition model based on Hb*
*Treatment effect + transition probabilities from pooled roxadustat trials; 25-year time-horizon*




⊙ *Does the model reflect the disease? Should it reflect non-inferiority?*

# 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
- **ERG comments:**
  - Yarnoff et al
    - does not describe rationale for Hb categories – and bases categories on another study of transfusion burden with anaemia and CKD in US (Lawler et al. 2010)
    - Uses a microsimulation modelling → does not necessarily imply that 1 g/dL change in Hb level has meaningful impact on quality of life.
  - Finkelstein et al. demonstrated impact of Hb increase only for levels between <11, 11 to <12, 12 to <13, and ≥13 g/dL.
  - Concerns raised during company's model validation
    - Health economist: "*Model might be more robust with less (sic) categories. Do the Hb categories differ in terms of costs or HRQoL?*"
    - Clinician: "*Only 3 Hb ranges are needed: <10, 10–12 (UK target) and ≥12*".

- *Did the company source estimates systematically and appropriately?*
- *Do all 8 Hb categories have discrete and distinguishable impacts on quality of life?*

# 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 (Kind et al. 1999) then subtracting **utility decrements for**:
  - **Hb level** adjusted for CVD + type 1 diabetes from roxadustat trials data
  - **CKD and dialysis status** (from literature and technology appraisals)
  - **Adverse events** (from literature; applied every 3-month cycle)

| | Utility decrement | Source |
|---|---|---|
| CKD | [redacted] | Kind et al. 1999, Ara and Brazier 2011 |
| Haemodialysis | 0.352 | NICE TA358 (tolvaptan for autosomal dominant polycystic kidney disease) |
| Peritoneal dialysis | 0.262 | |
| Mild stroke | 0.350 | Meenan et al. 2007 |
| Moderate stroke | 0.500 | |
| Severe stroke | 0.730 | |
| Myocardial infarction | 0.120 | Yarnoff et al. 2016 |
| Vascular access thrombosis | 0.100 | Xue et al. 2010 |

- **ERG:** company adds utility decrements, but explores no alternatives e.g. multiplicative or min-max values) – multiplicative approach might be preferrable

⊙ *Are health state utilities estimated appropriately? Do values have face-validity? Would committee wish to see scenarios?*

# Hb level utility decrements

*Company estimated Hb level disutilities using regression, but does not supply methods*

- Company estimates decrements from roxadustat trials EQ-5D-5L cross-walked to EQ-5D-3L
  - generalised linear mixed model, controlled for cardiovascular disease + type 1 diabetes
  - study and subject ID included as random factors to control for nesting
  - missing data assumed 'missing at random'
- **ERG:** company did not provide:
  - statistical analysis plan for regression analysis → unable to assess impact
  - amount or pattern of missing data → ERG questions 'missing at random assumption' → missing data could be because patients unwell and unable to complete EQ-5D questionnaire → higher utilities favour roxadustat

| Health state | Utility decrement | Health state utility |
|---|---|---|
| Hb <7 | [redacted] | [redacted] |
| Hb 7 to <8 | [redacted] | [redacted] |
| Hb 8 to <9 | [redacted] | [redacted] |
| Hb 9 to <10 | [redacted] | [redacted] |
| Hb 10 to <11 | [redacted] | [redacted] |
| Hb 11 to <12 | [redacted] | [redacted] |
| Hb 12 to <13 | [redacted] | [redacted] |
| Hb ≥13 | [redacted] | [redacted] |

⊙ *What is committee's view on company's regression and transparency?*

# Distributing patients across Hb states over time

*Company used multinomial logistic regression model*

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

**Distribution baseline**


**Multinomial logistic regression**

- Model covariates:
  - log(time +1)
  - baseline CVD
  - baseline diabetes
  - treatment placebo, ESA or roxadustat
  - Which trial (ALPS, ANDES, OLYMPUS, DOLOMITES)
  - interaction between treatment type and log(time +1)

**After 1st cycle**


⊙ *What is committee's view on company's regression and transparency?*

# Extrapolating % of people in each state beyond trials

| Company approach | ERG comments |
|---|---|
| No treatment waning | - |
| Controlling for study in regression | • Pooling breaks randomisation → should interpret results as though data are observational |
| Covariates included:<br>log(time+1)<br>log(time+1) * treatment<br><br>Used time dependency when extrapolating | • Unclear whether time trends during trials hold over 25-year horizon, especially interaction treatment * time<br>• Raised by company during validation: "Can we predict Hb state occupancy over a 40-year period from a short-term duration trial?"<br>• Company did not provide analyses excluding time as covariate or interaction term, so impact unclear → ERG did scenario analyses with shorter horizons to check impact of time |
| Model included covariates not "statistically significant" | • Company did not provide statistical analysis plan → ERG unable to assess impact unclear decision criteria to select and exclude candidate covariates and interaction terms |
| Multinomial logistic regression model | • Not clear if this is the best model |
| Multinomial logistic regression model assessed visually by comparing predictions to observed data | • Unclear how company interpretated visual inspection and suitability of multinomial logistic regression model |

⊙ *Has the company adequately explained and justified its methods?*

# Extrapolating time to dialysis and to death

*Company assumed no difference between roxadustat and ESA; unclear why company chose log-logistic and exponential functions*

- Used parametric survival models based on pooled roxadustat trials
- Time-to-dialysis
  - log-logistic 'best function in terms of long-term clinical plausibility'
- Time-to-death
  - exponential 'best BIC score, as well as long term clinical plausibility and a good visual fit'
- ERG: goodness of fit statistics (AIC/BIC) were very similar for the other regression models
  - Company did not provide statistical analysis plan for estimating regression models → ERG unable to assess impact

| Function | Dialysis | | Mortality | |
|---|---|---|---|---|
| | AIC | BIC | AIC | BIC |
| **Log-logistic** | **19,300** | **19,346** | 6,796 | 6,874 |
| **Exponential** | 19,329 | 19,368 | **6,798** | **6,869** |
| Weibull | 19,330 | 19,375 | 6,796 | 6,874 |
| Gompertz | 19,325 | 19,370 | 6,797 | 6,875 |
| Log-normal | 19,323 | 19,368 | 6,804 | 6,882 |
| Generalised gamma | 19,303 | 19,355 | 6,798 | 6,882 |

⊙ *Has the company adequately explained and justified its methods?*
⊙ *Are log-logistic and exponential functions appropriate?*

# Are times to dialysis and death plausible?

- Company estimated % of people alive and dialysing after 10 years at [redacted]
  - Haemodialysis (88%) and peritoneal dialysis (12%) based on DOLOMITES
  - Stated 'clinical experts… deemed the long-term extrapolation values to be reasonable for a cohort with an average starting age of ~65 years'.
- **ERG:** DOLOMITES trial better than pooled trials for % of people alive at 5 and 10 years – closer to UK renal registry data (table below).

| Time point | UK renal registry | Pooled trials | DOLOMITES trial |
|---|---|---|---|
| **5 years** | 73% | [redacted] | [redacted] |
| **10 years** | 56% | [redacted] | [redacted] |

⊙ *Are the proportion of people on dialysis and alive plausible?*

# Hospitalisations

*Company modelled hospitalisations indirectly based on adverse events*

| Company | ERG |
| --- | --- |
| • Do not expect roxadustat to affect hospitalisations<br>• Most hospitalisations in trials because of 'adverse events' → modelling both would double count costs and quality of life<br>• Similar rates of hospitalisation for roxadustat and ESA in DOLOMITES, justifies modelling hospitalisations through adverse events | • Hospitalisation rates should measured + modelled directly<br>• Important to explore both expected AND **unexpected** adverse events.<br>• [redacted] to [redacted] of hospitalisations **not** due to adverse events<br>• Company suggests reasons for hospitalisation are always known<br>• NICE guidance advised using indirect (surrogate) outcomes only when direct outcomes are not possible. |

NICE

⊙ *How should hospitalisations be modelled?*

# Cost of Roxadustat

- Company estimated roxadustat costs based on doses used during Hb correction phase (up to 3 months after treatment start) and Hb maintenance phases (after 3 months of treatment to lifetime)
  - Correction phase: weekly dose estimated from pooled roxadustat arms
  - Maintenance phase: weekly dose extrapolated using generalised linear mixed model (controlling for cardiovascular disease and type 1 diabetes)
- Company used roxadustat cost per mg ([redacted]) to calculate roxadustat cost per cycle

| Hb level | Correction phase weekly dose | Maintenance phase weekly dose | Roxadustat cost 1st cycle | Roxadustat cost subsequent cycles |
|---|---|---|---|---|
| <7 | [redacted] | [redacted] | [redacted] | [redacted] |
| 7 to <8 | [redacted] | [redacted] | [redacted] | [redacted] |
| 8 to <9 | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 to <10 | [redacted] | [redacted] | [redacted] | [redacted] |
| 10 to <11 | [redacted] | [redacted] | [redacted] | [redacted] |
| 11 to <12 | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 to <13 | [redacted] | [redacted] | [redacted] | [redacted] |
| >13 | [redacted] | [redacted] | [redacted] | [redacted] |

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

NICE ⊙ *Would Roxadustat stop at Hb of 12 g/dL as with ESAs?*

# How company calculates costs of comparator

*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 - observational retrospective study of medical records UK population. ERG: Uncertain → did scenarios analysis

| 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] |

⊙ *Is the distribution of ESAs from TUNE study generalisable to clinical practice?*

# Costs of administering ESAs

*Company included ESA administration costs for 20% of patients*

Company assumed:

- 15% require home district nurse
- 5% require in-hospital administration

ERG:

- Company's figures based on clinical expert opinion → ERG did scenario analysis

⊙ *Should administration costs be added to proportion of patients not on dialysis? Should a portion of people on roxadustat also incur charges?*

# ERG base case and scenario analyses

| Analysis | Description / assumptions |
|---|---|
| **Base case** | DOLOMITES data only instead of pooled trials |
| **Scenario analyses** | |
| **Extrapolation of time trends from trials** | • Shorten time horizon to 5 years<br>• Shorten time horizon to 10 years |
| **Proportion of patients receiving each ESA agent** | **All patients receive**<br>• darbepoetin alfa *or*<br>• epoetin alfa *or*<br>• epoetin beta *or*<br>• epoetin beta (methoxy polyethylene glycol) *or*<br>• epoetin zeta |
| **ESA administration costs** | Excluded |

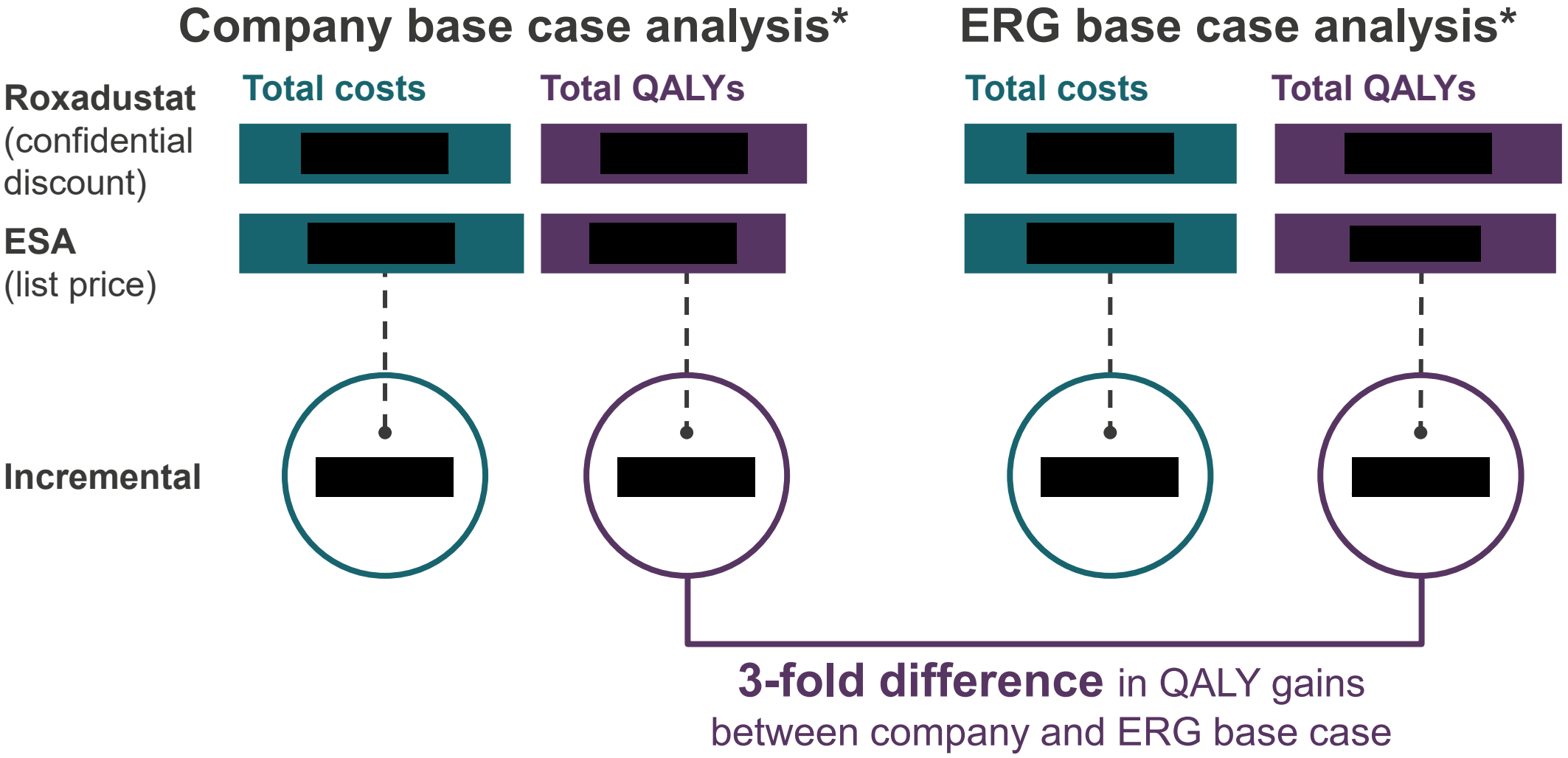
# Innovation, equality issues and end of life criteria

| | |
|---|---|
| **Innovation** | • First-in-class hypoxia-inducible factor prolyl hydroxylase inhibitor<br>• Provides additional treatment option for anaemia with CKD<br>• May simplify management through mechanism of action that stimulates erythropoietin production and improves iron metabolism → may reduce need for iron transfusions<br>• Oral administration versus IV or subcutaneous ESA → may reduce administration costs associated with ESA<br>• Reduced requirements for cold-chain storage and special sharps disposals |
| **Equalities** | • Home administration of ESA more challenging for people on low incomes, dexterity problems and English 2nd language |
| **End-of-life** | • Company does not model a survival benefit |

⊙ *Is roxadustat innovative? Associated with inequalities? Meets end-of-life?*

# Quality-adjusted life years (QALYs)

*Incremental QALYs very small; ESAs have substantial discounts to NHS*




*Includes roxadustat confidential PAS discount and ESA list prices → analyses only shown to illustrate QALY differences for transparency, not used to inform committee decision-making.

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

# Appendix / back-up slides

# Adverse events included in model

*Including more adverse events may not change cost effectiveness*

- Company explored impact of grade 3+ adverse events occurring in >3% of DOLOMITES trial population i.e. [redacted]

| Adverse event | [redacted] | [redacted] | [redacted] | Total | Incremental |
|---|---|---|---|---|---|
| **% patients** | | | | | |
| Roxadustat | [redacted] | [redacted] | [redacted] | | |
| ESA | [redacted] | [redacted] | [redacted] | | |
| **Cost / disutility per event (from TA622 [sotagliflozin for type 1 diabetes] and TA712 [enzalutamide for prostate cancer])** | | | | | |
| Cost | £2,964 | £2,526 | £364 | | |
| Disutility | -0.00290 | -0.00575 | -0.00440 | | |
| **Weighted cost** | | | | | |
| Roxadustat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ESA | [redacted] | [redacted] | [redacted] | [redacted] | |
| **Weighted disutility** | | | | | |
| Roxadustat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ESA | [redacted] | [redacted] | [redacted] | [redacted] | |

NICE

⊙ *Should company model all adverse events?*