NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Astellas Pharma
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Kidney Care UK
   b. Renal Pharmacy Group
   c. UK Kidney Association
4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews
5. **Evidence Review Group report – factual accuracy check**
6. **Technical engagement response from company**
7. **Technical engagement responses and statements from experts:**
   a. Prof. Jonathan Barratt, The Mayer Professor of Renal Medicine – clinical expert, nominated by Astellas Pharma
   b. Prof. Sunil Bhandari, Consultant Nephrologist/Physician – clinical expert, nominated by Astellas Pharma and the UK Kidney Association
   c. Mr Guy Hill – patient experts, nominated by Kidney Care UK
8. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews (KSR)

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Roxadustat for treating anaemia in CKD patients

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Contents

Contents 2
Tables and figures 4
Abbreviation list 10
B.1 Decision problem, description of the technology and clinical care pathway 13
B.1.1 Decision problem 13
B.1.2 Description of the technology being appraised 15
B.1.3 Health condition and position of the technology in the treatment pathway 16
B.1.4 Equality considerations 23
B.2 Clinical effectiveness 24
B.2.1 Identification and selection of relevant studies 24
B.2.2 List of relevant clinical effectiveness evidence 24
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence 28
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence 44
B.2.5 Quality assessment of the relevant clinical effectiveness evidence 60
B.2.6 Clinical effectiveness results of the relevant trials 60
B.2.7 Subgroup analysis 73
B.2.8 Meta-analysis 75
B.2.9 Indirect and mixed treatment comparisons 75
B.2.10 Adverse reactions 75
B.2.11 Ongoing studies 78
B.2.12 Innovation 78
B.2.13 Interpretation of clinical effectiveness and safety evidence 79
B.3 Cost effectiveness 81
B.3.1 Published cost-effectiveness studies 81
B.3.2 Economic analysis 82
B.3.3 Clinical parameters and variables 85
B.3.4 Measurement and valuation of health effects 95
B.3.5 Cost and healthcare resource use identification, measurement, and valuation 104
B.3.6 Summary of base-case analysis inputs and assumptions 114
B.3.7 Base-case results 118
B.3.8 Subgroup analysis 129
B.3.9 Validation 129
B.3.10 Interpretation and conclusions of economic evidence 130
B.4 References 133
B.5 Appendices 148
Appendix C. Summary of product characteristics (SmPC) and European public assessment report (EPAR) 149
ANNEX I 149
ANNEX II 180
ANNEX III 183
Appendix D. Identification, selection and synthesis of clinical evidence 216
D.1 Identification and selection of relevant studies 216
D.2 Results 222

D.3 Participant flow 229
Appendix E. Subgroup analysis 235
E.1 ALPS 235
E.2 ANDES 237
E.3 OLYMPUS 238
E.4 DOLOMITES 243
Appendix F. Adverse reactions 248
F.1 ALPS 248
F.2 ANDES 250
F.3 OLYMPUS 252
F.4 DOLOMITES 254
Appendix G. Published cost-effectiveness studies 257
G.1 Identified studies 257
G.2 Description of identified studies 258
G.3 Discussion of included studies 266
Appendix H. Health-related quality of life studies 272
H.1 Identification of studies 272
H.2 Results 294
Appendix I. Cost and healthcare resource identification, measurement and valuation 303
I.1 Identification of studies 303
I.2 Study selection 323
I.3 Results 324
Appendix J. Clinical outcomes and disaggregated results from the model 346
J.1 Clinical outcomes from the model 346
J.2 Disaggregated results of the base-case incremental cost-effectiveness analysis 346
Appendix K. Checklist of confidential information 349
Appendix L. Clinical trials data of dialysis population (HIMALAYAS, PYRENEES, SIERRAS and ROCKIES) 350
L.1 Summary of methodology 350
L.2 Baseline characteristics and demographics 362
L.3 Statistical analysis 366
L.4 Clinical effectiveness results 372

Tables and figures

Table 1. The decision problem 13
Table 2. Technology being appraised 15
Table 3. CKD disease stages by GFR 17
Table 4. Clinical effectiveness evidence (NDD population) 26
Table 5. Summary of trial methodology 33
Table 6. Demographic and baseline characteristics of patients included in trials conducted on NDD population 42
Table 7. Analysis timepoints of clinical trials (NDD population) 45
Table 8. Sequential testing of primary and key secondary efficacy endpoints in the ALPS trial 49
Table 9. Sequential testing of primary and key secondary efficacy endpoints in the ANDES trial 52
Table 10. Sequential testing of primary and key secondary efficacy endpoints in the OLYMPUS trial 54
Table 11. Sequential testing of primary and key secondary efficacy endpoints in the DOLOMITES trial 57
Table 12. Patient randomization in each trial (NDD population) 60
Table 13. Hb response without rescue therapy (FAS population) 61
Table 14. Summary of secondary endpoints 62
Table 15. Time to first use of IV iron during efficacy emergent period (FAS population) 63
Table 16. Hb response without rescue therapy (FAS population) 63
Table 17. Summary of key secondary endpoints 65
Table 18. Time to first use of IV iron ANDES 67
Table 19. Hb response without rescue therapy (FAS population) 68
Table 20. Summary of secondary endpoints 69
Table 21. Time to first use of IV iron during efficacy emergent period (OT+28) 70
Table 22. Hb response during first 24 weeks without use of rescue therapy (PPS population) 70
Table 23. Summary of key secondary endpoints (DOLOMITES) 72
Table 24. Time to first use of IV iron during efficacy emergent period (FAS population) 73
Table 25. CV safety and mortality in placebo controlled NDD pool 76
Table 26. CV safety and mortality in ESA controlled pool 77
Table 27. NDD pooled and DOLOMITES trial key adverse events 78
Table 28. ESA therapies available in the BNF 85
Table 29. Population characteristics 85
Table 30. Health state occupancy at baseline 86
Table 31. Health state occupancy at baseline 86
Table 32. AIC and BIC values 87
Table 33. Coefficients for covariates used in survival analyses 87
Table 34. Median and landmark survival 89
Table 35. Coefficients for Hb level regression analysis 91
Table 36. Coefficients for covariates included in analyses of time to dialysis 94
Table 37. AIC and BIC values for time-to-dialysis 94
Table 38. Population utility norms 95
Table 39. CKD and dialysis utility decrements 96

Table 40. Coefficients for EQ-5D-3L regression analysis 96
Table 41. Health state absolute utilities 97
Table 42. Health state decrements 97
Table 43. Utility values identified from the literature 98
Table 44. Health state decrements from published literature 98
Table 45. Incremental utility associated with alternative methods of drug administration 100
Table 46. Weighted method of administration incremental utility for each treatment arm 100
Table 47. Probability of TRAE in the model 101
Table 48. TRAE event utility decrements 102
Table 49. Summary of utilities used in the model 102
Table 50. Coefficients for roxadustat treatment dose regression analysis 105
Table 51. Coefficients for ESA treatment dose regression analysis 105
Table 52. Average weekly doses applied in the 1st cycle of the economic model .. 105
Table 53. Weekly doses by Hb level applied in the subsequent cycles of the economic model 105
Table 54. Roxadustat costs applied in the model 106
Table 55. Conversion ratios to adjust the clinical trial derived ESA dose 106
Table 56. ESA costs per mcg applied in the model 107
Table 57. Proportion of patients receiving each ESA 108
Table 58. ESA administration costs 109
Table 59. Haemodialysis and peritoneal dialysis costs 110
Table 60. Distribution of patients per type of dialysis 110
Table 61. Regression coefficients for blood transfusion rates 110
Table 62. Probability of receiving a blood transfusion 110
Table 63. Unit costs for blood transfusion 111
Table 64. Regression coefficients for proportion of patients receiving IV iron 112
Table 65. Proportion of patients receiving IV iron 112
Table 66. Dose of IV iron per administration 113
Table 67. IV iron unit costs 113
Table 68. TRAE costs 114
Table 69. Summary of parameters used in the economic analyses 114
Table 70. Main assumptions in the economic model 116
Table 71. Scenarios included in the cost-effectiveness analyses 118
Table 72. Base case cost-effectiveness results 10,000 patients 119
Table 73. Probabilistic sensitivity analysis results 119
Table 74. DSA results 123
Table 75. Scenario analyses results 125
Table 76. Clinical SLR search details (MedlineALL) 217
Table 77. Clinical SLR search strategy (MedlineALL) 217
Table 78. Clinical SLR search details (Embase) 217
Table 79. Clinical SLR search strategy (Embase) 217
Table 80. Clinical SLR search details (DARE) 218
Table 81. Clinical SLR search strategy (DARE) 218
Table 82. Clinical SLR search details (HTA database) 218
Table 83 Clinical SLR search strategy (HTA database) 218
Table 84 Clinical SLR search details (NHS EED) 218
Table 85 Clinical SLR search strategy (NHS EED) 219
Table 86 Clinical SLR search details (CRD Central) 219

Table 87 Clinical SLR search strategy (CRD Central) 219
Table 88 Clinical SLR search details (Econlit) 219
Table 89 Clinical SLR search strategy (Econlit) 219
Table 90 Clinical SLR search details (Pubmed) 220
Table 91 Clinical SLR search strategy (Pubmed) 220
Table 92. Eligibility criteria 221
Table 93. Phase Ib/ II trials 225
Table 94. Phase II/III trials 226
Table 95. Phase III trials 226
Table 96. Additional publications reporting pooled data from phase III trials 228
Table 97: Subgroup Analyses Results from OLYMPUS trial 239
Table 98. Early Treatment Discontinuation (All Randomised Patients) 248
Table 99. Overview of TEAEs and death (SAF population) 249
Table 100. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population) 249
Table 101. Early Treatment Discontinuation 250
Table 102. Adverse events in the ANDES trial (OT+28) 251
Table 103. Summary of most common TEAEs occurring in ≥5% of patients in both treatment arms (OT+28) 251
Table 104. Early Treatment Discontinuation (All randomised patients) 252
Table 105. Adverse events in the OLYMPUS trial (OT+28) 253
Table 106. Summary of most common AEs occurring in ≥5% of patients in both treatment arms (OT+28) 253
Table 107. Early treatment discontinuation (ITT population) 254
Table 108. Overview of TEAEs and death (SAF population) 254
Table 109. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population) 255
Table 110: Cost-effectiveness models relevant for this submission 258
Table 111 Cost-minimization results for Krysanov I. et al. 261
Table 112 Cost-utility results for Maoujoud O. et al. 263
Table 113 Summary of the study characteristics of included studies 269
Table 114 HRQoL SLR search details (Ovid MEDLINE®) 273
Table 115 HRQoL SLR search strategy (Ovid MEDLINE®) 273
Table 116 HRQoL SLR search details (OvidSP) 276
Table 117 HRQoL SLR search strategy (OvidSP) 277
Table 118 HRQoL SLR search details (Health Technology Assessment Database) 280
Table 119 HRQoL SLR search strategy (Health Technology Assessment Database) 280
Table 120 HRQoL SLR search details (NHS EED) 282
Table 121 HRQoL SLR search strategy (NHS EED) 282
Table 122 HRQoL SLR search details (DARE) 284
Table 123 HRQoL SLR search strategy (DARE) 284
Table 124 HRQoL SLR search details (Econlit) 286
Table 125 HRQoL SLR search strategy (Econlit) 286
Table 126 HRQoL SLR search details (PsycINFO) 287
Table 127 HRQoL SLR search strategy (PsycINFO) 287
Table 128 HRQoL SLR search details (PubMed) 288
Table 129 HRQoL SLR search strategy (PubMed) 288
Table 130: Eligibility criteria applied in utility review 292

Table *131*: Summary of included studies 296
Table 132: Overview of utility data for CKD in anaemia 298
Table 133 Cost and resource use SLR search details (Ovid MEDLINE®) 304
Table 134 Cost and resource use SLR search strategy (Ovid MEDLINE®) 304
Table 135 Cost and resource use SLR search details (Embase) 307
Table 136 Cost and resource use SLR search strategy (Embase) 308
Table 137 Cost and resource use SLR search details (HTA) 311
Table 138 Cost and resource use SLR search strategy (HTA) 311
Table 139 Cost and resource use SLR search details (NHS EED) 313
Table 140 Cost and resource use SLR search strategy (NHS EED) 313
Table 141 Cost and resource use SLR search details (DARE) 315
Table 142 Cost and resource use SLR search strategy (DARE) 315
Table 143 Cost and resource use SLR search details (Econlit) 317
Table 144 Cost and resource use SLR search strategy (Econlit) 317
Table 145 Cost and resource use SLR search details (PsycINFO) 318
Table 146 Cost and resource use SLR search strategy (PsycINFO) 318
Table 147 Cost and resource use SLR search details (PubMed) 319
Table 148 Cost and resource use SLR search strategy (PubMed) 320
Table 149: Eligibility criteria applied in utility review 323
Table 150: Summary of included studies 328
Table 151: Base-case clinical outcomes for pre-dialysis anaemic CKD patients treated with roxadustat or ESA 346
Table 152: Summary of QALY per patient by health state 347
Table 153: Summary of costs by health state 347
Table 154: Summary of predicted resource use by category of cost 348
Table 155: Summary of trial methodology (DD population) 355
Table 156: Baseline demographics and disease characteristics of patients included in DD population trials 364
Table 157: Sequential testing of primary and key secondary efficacy endpoints in the HIMALAYAS trial (DD population) 367
Table 158: Sequential testing of primary and key secondary efficacy endpoints in the PYRENEES trial (DD population) 368
Table 159: Sequential testing of primary and key secondary efficacy endpoints in the SIERRAS trial (DD population) 369
Table 160: Sequential testing of primary and key secondary efficacy endpoints in the ROCKIES trial (DD population) 370
Table 161. Hb responder analysis during the first 24 weeks without rescue therapy (PPS population) 372
Table 162. Summary of key secondary endpoints (HIMALAYAS) 373
Table 163. Change from baseline to the average Hb in weeks 28-36 regardless of rescue therapy (PPS population) 374
Table 164. Summary of key secondary endpoints (PYRENEES) 375
Table 165. Hb change from baseline to the average Hb in weeks 28 without having received rescue therapy (PPS population) 376
Table 166. Summary of key secondary endpoints (SIERRAS) 377
Table 167. Change in Hb (g/dL) from baseline to mean during weeks 28 to 36 377
Table 168. Summary of key secondary endpoints (ROCKIES) 378

Figure 1. Anticipated positioning of roxadustat in the clinical pathway of care for anaemia associated with CKD 22

Figure 2. Overview of the roxadustat clinical trials for the NDD and DD CKD populations 25
Figure 3. Study design for ALPS trial 28
Figure 4. Study design for ANDES trial 29
Figure 5. Study design for OLYMPUS trial 30
Figure 6. Study design for DOLOMITES trial 31
Figure 7. Mean (± 95% CI) change from baseline in Hb to week 36 (PPS population) 71
Figure 8. Model schematic 83
Figure 9. Survival curves in the base case analysis 89
Figure 10. Proportion in state over trial period 92
Figure 11. Health state distribution over model time horizon 93
Figure 12. Time to dialysis survival curves 94
Figure 13. Cost-effectiveness (CE) plane 120
Figure 14. Cost-effectiveness acceptability curve (CEAC) 121
Figure 15. Tornado diagram 122
Figure 16. PRISMA diagram (original SLR) 223
Figure 17. PRISMA diagram (updated SLR) 224
Figure 18: Patient Disposition Flowchart in ALPS trial (All Patients) 230
Figure 19: Patient Disposition Flowchart in ANDES trial (All Patients) 232
Figure 20: Patient Disposition Flowchart in OLYMPUS trial (All Patients) 233
Figure 21: Patient Disposition Flowchart in DOLOMITES trial (All Patients) 234
Figure 22: Summary of Subgroup Analyses of the Primary Efficacy Analysis (Full Analysis Set) 235
Figure 23: Subgroup Analysis of Change from Baseline to the Average Hb in Weeks 28 to 36 without Rescue Therapy (Full Analysis Set 236
Figure 24: Subgroup Analysis of Change from Baseline in LDL Cholesterol (Full Analysis Set) 237
Figure 25: Subgroup Analyses of the Primary Efficacy Endpoint (FAS Population) 238
Figure 26: Summary of Subgroup Analyses of the Primary Efficacy Endpoint Without Rescue Therapy (Per Protocol Set) 244
Figure 27: Summary of Subgroup Analyses of the Primary Efficacy Endpoint Regardless of Rescue Therapy (Full Analysis Set) 244
Figure 28: Summary of Subgroup Analyses for Haemoglobin Change from Baseline in Weeks 28 to 36 Without Rescue Therapy (Per Protocol Set) 245
Figure 29: Summary of Subgroup Analyses for Change in LDL Cholesterol from Baseline to Weeks 12 to 28 Regardless of Fasting Status (Full Analysis Set) 245
Figure 30: Summary of Subgroup Analyses for Time to First Intravenous Iron Use (Full Analysis Set) 246
Figure 31: Summary of Subgroup Analyses for SF-36 Physical Functioning Change from Baseline to the Average in Weeks 12 to 28 (Per Protocol Set) 246
Figure 32: Summary of Subgroup Analyses for the SF-36 Vitality Subscore Change From Baseline to the Average in Weeks 12 to 28 by Subgroup (Per Protocol Set) 247
Figure 33: PRISMA diagram to show the number of articles included in the HRQoL evidence (original SLR) 294
Figure 34: PRISMA diagram to show the number of articles included in the HRQoL evidence (SLR update) 295
Figure 35: PRISMA diagram (original SLR) 325
Figure 36: PRISMA diagram (SLR update) 326
Figure 37: Study design for HIMALAYAS trial 351

Figure 38: Study design for PYRENEES trial 352
Figure 39: Study design for SIERRAS trial 353
Figure 40: Study design for ROCKIES trial 354
Figure 41. Mean (±SD) Hb change from baseline to week 52 (FAS population) 372
Figure 42. Mean (± 95% CI) Hb change from baseline to week 36 (PPS population) 374
Figure 43. Mean (±SD) Hb change from baseline to week 52 (FAS population) 376
Figure 44. Mean Hb (g/dL) over time (ITT Analysis Set) 378

Abbreviation list

Abbreviation	Term
ACM	All-cause mortality
AE	Adverse events
AIC	Akaike Information Criteria
ASN	American Society of Nephrology
BIC	Bayesian Information Criterion
BIW	Two times weekly
BL	Baseline
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
CKD	Chronic kidney disease
CRP	C-Reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DARE	Database of Abstracts of Reviews of Effects
DBP	Diastolic blood pressure
DCE	Discrete choice experiments
DD	Dialysis dependent
DRA	European Renal Association
DSA	Deterministic sensitivity analysis
ECDRP	European Commission Decision Reliance Procedure
EDTA	European Dialysis and Transplant Association Congress
EED	Evaluation Database
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study visit
EOT	End of treatment visit
EPO	Erythropoietin
EQ-5D-3L	EuroQol five-dimension three level
EQ-5D-5L	EuroQol five-dimension five level
ESA	Erythropoiesis stimulating agents
ESRD	End-stage renal disease
EU	European union
Exp	Exponential
FAS	Full analysis set
GB	Great Britain
GFR	Glomerular filtration rate
GLM	Generalised linear model
GLMM	Generalised linear mixed model
Hb	Haemoglobin
HCHS	Hospital & Community Health Services
HIF	Hypoxia-inducible factor
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
HST	High Specialised Technology
HTA	Health Technology Assessment

Abbreviation	Term
ICER	Incremental cost-effectiveness ratio
ID	Incident dialysis
IDN	Identification
IPD	Individual patient data
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IU	International units
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
Kg	Kilogram
LDL	Low density lipoprotein
LSM	Least squares mean
MACE	Major adverse cardiovascular events
MAP	Mean arterial pressure
Mcg	Microgram
MDRD	Modification of diet in renal disease
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
Min	Minute
mL	Millilitre
mmol/L	Milli-moles per litre
MoA	Method of administration
NA	Not applicable
NCI CTC	National Cancer Institute- Common terminology criteria for adverse events
NDD	Non dialysis dependent
NHS	National Health Service
NHSCII	NHS cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
ONS	Office for National Statistics
OR	Odds ratio
OT+28	On treatment plus 28 days
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PASLU	Patient Access Schemes Liaison Unit
PEY	Patient exposure years
PF	Physical function
PHI	Prolyl hydroxylases inhibitor
PPS	Per protocol set
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
QW	One time weekly
R	Randomised
RBC	Red blood cells
RRT	Renal replacement therapy
SAF	Safety analysis set
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SF-36	36-Item short form survey
SF-6D	Short-Form Six-Dimension
SG	Standard gamble
SLR	Systematic Literature Review
SmPC	Summary of product characteristics

Abbreviation	Term
SMR	Standardised mortality ratio
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIW	Three times weekly
TRAE	Treatment related adverse events
TSAT	Transferrin saturation
TTO	Time trade-off
Tx	Treatment
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USD	United States Dollar
VAT	Vascular access thrombosis
VT	Vitality
WHO	World Health Organisation
WTP	Willingness to pay

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

B.1.1 Decision problem

Whilst the expected licence for roxadustat covers all adult patients with symptomatic anaemia associated with chronic kidney disease (CKD), in the context of this submission, roxadustat is positioned as an alternative to erythropoiesis stimulating agents (ESA) for the treatment of adult patients with symptomatic anaemia associated with CKD who are non-dialysis dependent (NDD) at the time of treatment initiation. The roxadustat positioning is presented in detail in Section B.1.3.6.

The remaining components of the company submission are consistent with the final National Institute for Health and Care Excellence (NICE) scope and the NICE reference case, as shown in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with anaemia associated with Chronic Kidney Disease (CKD)	Adult patients with symptomatic anaemia associated with CKD who are non-dialysis dependent (NDD) at the time of treatment initiation	See section B.1.3.6
Intervention	Roxadustat	Per scope	NA
Comparator(s)	Erythropoiesis stimulating agents (ESA)	Per scope	NA
Outcomes	• Haemoglobin response • Maintenance of haemoglobin levels • Use of additional therapy (including blood transfusion and intravenous iron) • Hospitalisation • Adverse effects of treatment including major adverse cardiovascular events • Health-related quality of life	Per scope with the exclusion of hospitalisation.	Hospitalisation was not explicitly modelled in the economic model. Hospitalisation rates from the clinical trials were similar for roxadustat, placebo and ESA. Hospitalisation costs were indirectly captured through

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			adverse event management, drug administration and monitoring.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Per scope	NA
Subgroups to be considered	NA	Per scope	NA
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers	Per reference case	NA
Perspective for costs	Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective.	Per reference case	NA
Time horizon	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Per reference case	NA
Synthesis of evidence on health effects	Based on systematic review	Per reference case	NA
Measuring and valuing health effects	Health effects should be expressed in quality adjusted life years (QALY). The EQ-5D is the preferred measure of health-related quality of life in adults.	Per reference case	NA
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Per reference case	NA
Source of preference data for valuation of changes in	Representative sample of the United Kingdom (UK) population	Per reference case	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
health-related quality of life			
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Per reference case	NA
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Per reference case	NA
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Per reference case	NA

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; EPO: erythropoietin; ESA: erythropoiesis-stimulating agents; NA: not applicable; NDD: non-dialysis dependent; NHS: National Health Service; NICE: National Institute for Health and Care Excellence;PSS: Personal Social Services; UK: United Kingdom.

B.1.2 Description of the technology being appraised

Table 2 summarises the details of the technology being appraised in this submission.

The Summary of Product Characteristics (SmPC) is provided in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Roxadustat (Evrenzo™)
Mechanism of action	Roxadustat is a first-in-class oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI). Roxadustat activates the oxygen-sensing HIF pathway to mimic the body's natural response to hypoxia by reversibly inhibiting HIF-PH enzymes that target HIFs for degradation under normal oxygen conditions. Through the inhibition of HIF-PH, it stimulates a coordinated erythropoiesis response that includes the increase of plasma erythropoietin (EPO) levels, regulation of iron transporter proteins and reduction of hepcidin. This results in improved iron bioavailability, increased haemoglobin production and increased red cell mass.
Marketing authorisation/CE mark status	The initial Marketing Authorisation Application was made to the European Medicines Agency (EMA) in April 2020. Application to the Medicines and Healthcare products Regulatory Agency (MHRA) for Great Britain (GB) Marketing Authorisation will be via the European Commission Decision Reliance Procedure. The full dossier as reviewed by the EMA Committee for Medicinal Products for Human Use (CHMP) will be submitted to MHRA, including responses to questions, upon receipt of a positive CHMP opinion. CHMP opinion is expected in June 2021 with the submission to the MHRA in June 2021 also. EMA Marketing Authorisation and MHRA approval of the GB licence are expected in August 2021.
Indications and any restriction(s) as described in the SmPC	Roxadustat is expected to be indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

	Conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason.
Method of administration and dosage	Roxadustat is administered as an oral tablet three times a week and not on consecutive days. For patients initiating anaemia treatment not previously treated with ESA the recommended starting dose of roxadustat is 70 mg three times per week in patients weighing less than 100 kg and 100 mg three times per week in patients weighing 100 kg and over. This dose should be individualised to achieve and maintain target haemoglobin (Hb) levels of 10 to 12 g/dL. The individualised maintenance dose ranges from 20 mg to 400 mg (for DD patients, maximum dose for NDD patients is 300mg) three times per week. For patients converting from an ESA, the recommended starting dose of roxadustat is based on the average prescribed ESA dose in the 4 weeks before conversion (see Summary of Product Characteristics (SmPC) for conversion table).
Additional tests or investigations	Not required
List price and average cost of a course of treatment	Roxadustat will be provided in five different strengths in 12 pill packs (four weeks supply). The proposed UK list prices are as follows: • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] The average yearly cost of roxadustat is £2,696 (assuming three times weekly dose of 70 mg for an average patient weighting less than 100 kg).
Patient access scheme (if applicable)	An application for a confidential simple Patient Access Scheme (PAS) is expected to be submitted and approved by Patient Access Schemes Liaison Unit (PASLU) ahead of the 1st committee meeting. The PAS will be submitted recognising that a discount on roxadustat may be required due to ESA tender prices, ensuring the discount can be quickly amended during the revision process. In line with guidance received by NICE during the decision problem meeting in 12/04/2021, all results are presenting using list prices for roxadustat and ESA

Abbreviations: CHMP: Committee for Medicinal Products for Human Use; CKD: chronic kidney disease; ECDRP: European Commission Decision; EMA: European Medicines Agency; EPO: erythropoietin; Hb: haemoglobin; PAS: Patient Access Scheme; PASLU: PAS Liason Unit; GB: Great Britain;Hb: haemoglobin; HIF-PHI: hypoxia-inducible factor prolyl hydroxylases inhibitor; SmPC: summary of product characteristics; MHRA: Medicines and Healthcare products Regulatory Agency.

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

B.1.3.1 Disease overview

CKD is defined as the presence of kidney structure abnormalities or impaired kidney function for >3 months, with implications on the health status of the affected individual (1). CKD can result from a variety of causes, including diabetes, high blood

pressure and glomerulonephritis (2). CKD is characterised by the progressive loss of kidney function, as measured by the glomerular filtration rate (GFR) – the sum of the filtration rates of all functioning nephrons in the kidney (3). CKD is typically categorised into five stages of decreasing kidney function based on declining GFR (Table 3) (1).

Table 3. CKD disease stages by GFR

Disease stage	Description	GFR (ml/min/1.73m²)
Stage 1	Normal GFR	≥90
Stage 2	Mildly decreased GFR	60 to 89
Stage 3a	Mildly to moderately decreased GFR	45 to 59
Stage 3b	Moderately to severely decreased GFR	30 to 44
Stage 4	Severely decreased GFR	15 to 29
Stage 5	Kidney failure	<15

Note: The CKD stages presented in this table are based on the KDIGO GFR categories. Descriptions are relative to a normal GFR in healthy young adults of approximately 125ml/min/1.73m2. An accepted alternative to measured GFR is to use the CKD Epidemiology Collaboration equations to estimate GFR based on serum creatinine, serum cystatin C, or both. In the latest KDIGO guidance (2012), stage 1 and 2 GFR categories are no longer considered to fulfil the criteria for CKD in the absence of other markers for kidney damage.

Abbreviations: CKD: chronic kidney disease; GFR: glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes.

The prognosis of patients with CKD worsens as the disease progresses and kidney function declines (leading to lower GFR) (4-6). The final stage of the disease (stage 5 CKD) is also referred to as end-stage renal disease [ESRD] (1). Patients with ESRD will require renal replacement therapy (RRT) through dialysis or kidney transplantation in order to maintain sufficient kidney function and avoid premature death (1, 3). While CKD itself is associated with a significant impairment to patient HRQoL, anaemia further exacerbates this burden with symptoms including fatigue, shortness of breath, rapid heartbeat, insomnia, lethargy, headaches, lack of concentration and reduced cognitive function (7-9)

Anaemia is a serious condition that refers to abnormally low levels of haemoglobin (Hb) and/or circulating red blood cells (RBC) in the blood that is insufficient to meet the body's physiological oxygen-carrying needs (1, 3, 10).

Measurement of Hb levels (i.e. the amount of oxygen-carrying protein in the blood) is the typical indicator to define anaemia. Many factors influence Hb levels including gender, age, and altitude (10). The cut-off point to define a 'normal' non-anaemic level varies depending on different guidelines. The World Health Organization (WHO) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines (2012) define anaemia as Hb<12 g/dL in women and Hb<13 g/dL in men (1, 10). NICE recommends investigating and managing anaemia in patients with CKD at Hb<11g/dL or less (11).(11)

B.1.3.2 Aetiology

The aetiology of anaemia associated with CKD is not fully understood, however, in most patients anaemia is thought to be caused by the insufficient production of the hormone erythropoietin (EPO) (8, 12, 13). EPO is regulated by hypoxia-inducible transcription factors (HIF) which are involved in an oxygen-sensing mechanism in the kidney (14). The key function of EPO is to regulate the development of RBCs which contain oxygen-binding Hb molecules that allow these cells to distribute oxygen throughout the body (8, 14, 15). In CKD, there is disruption in the HIF-mediated oxygen-sensing mechanism. This leads to low levels of EPO, which ultimately can contribute to lower the levels of Hb in the blood (8, 12, 13). Disrupted HIF pathways also contribute to excess levels of hepcidin in patients with CKD (via interactions with inflammatory cytokines), which leads to reduced iron absorption and mobilisation (13, 15-17). This disruption of iron levels affects Hb and RBC formation leading to the development of anaemia (13, 15).

Anaemia associated with CKD has been shown to be an independent predictor for CKD progression and all-cause mortality, doubling the risk of cardiovascular disease (CVD) related hospitalisation and mortality (18-20).

B.1.3.3 Epidemiology

Anaemia is common in CKD patients and increases in both prevalence and severity as kidney disease worsens (21-33). In a United Kingdom (UK) observational study with a nationally representative sample (N=1,099,292), 8.6% of patients with CKD stage 3–5 had anaemia. As per NICE guidelines, anaemia was defined as a Hb level lower than 11 g/dL, and anaemia estimates ranged from 5.33% in patients with CKD stage 3a to 42.8% in patients with CKD stage 5 (28).

B.1.3.4 Clinical disease burden of anaemia associated with CKD

Anaemia associated with CKD is associated with a significant clinical burden:

- All-cause mortality: Anaemia doubles the risk of all-cause mortality associated with moderately decreased kidney function, as shown by two US-based studies (18, 34)
- Cardiovascular events: Depleted oxygen levels due to anaemia could increase cardiac output leading to injury (8). In addition, anaemia is

associated with the development of left-ventricular hypertrophy in patients with CKD (1, 8). Two United States (US) studies have shown that anaemia associated with CKD increases the risk of CVD morbidity and mortality (19, 20)

- Potential acceleration of CKD: A US-based study has reported that patients with low levels of Hb/severe anaemia are at a higher risk of progression to ESRD compared with patients with normal/high Hb levels (35)
- Symptoms include fatigue, shortness of breath, rapid heartbeat, insomnia, lethargy, headaches, lack of concentration and reduced cognitive function (7, 8)

B.1.3.5 Clinical treatment pathway

Current treatments for anaemia associated with CKD are efficacious but target one part of the pathophysiology and require careful assessment of the benefit-risk ratio (1, 11, 36).

In England and Wales, the treatment of anaemia associated with CKD are informed by three key guidelines: NICE Guideline NG8, the KDIGO guideline (2012) and the Renal Association clinical practice guideline on Anaemia of Chronic Kidney Disease (1, 11, 36).

These guidelines recommend firstly addressing correctable causes of anaemia associated with CKD such as iron deficiency (11). Iron deficiency is generally treated via either oral or intravenous (IV) iron, with the choice being dependent on the severity of CKD, the patient's dialysis status and previous response to treatments. IV iron may be required by patients who do not tolerate oral iron, as well as by individuals who fail to attain Hb targets within three months of starting oral iron (1).

In instances when a patient's Hb levels do not adequately respond and remain <10g/dL with iron therapy alone, NICE guidelines recommended to offer treatment with an ESA if the patient is likely to benefit in terms of quality of life and physical function (11). Due to ESA's mode of action being reliant on iron repletion, patients treated with ESA are likely to require long-term iron supplementation to maintain therapeutic effect (1, 11).

All ESAs share the same mechanism of action for improving Hb levels (37) and are considered equivalent in terms of efficacy and safety profile (1, 11, 36). NICE Guideline NG8 recommends the choice of ESA should be based on discussion with the patient when initiating treatment and at subsequent reviews, taking into consideration their dialysis status, the route of administration and the local availability of ESA (11). Furthermore, the guideline highlights continuity of drug supply and adequate cold-storage arrangements as a consideration when developing a patient-centred plan for ESA treatment due to the refrigeration requirements associated with ESAs. ESAs require cold-chain storage and transit refrigeration to the patient's home, as well as additional considerations related with disposal (once syringes are used, they become biohazard material and require specific ways of disposal and destruction) (11).

The choice of optimal route of administration for ESA should be informed by various factors including the lifestyle and preferences of the patient, whether they are able to self-administer, subcutaneous versus IV administration, long-acting versus short-acting preparations, frequency of administration and pain of injection (11).

Hb levels and iron status should be assessed when initiating treatment and continually monitored throughout ESA treatment (11). Despite the recommendation to avoid repeated dose escalations in ESA, it is common for ESA doses to be increased over time in clinical practice to maintain effect (11). This is most common in inflamed, ESA-resistant patients who may require large doses of ESA, resulting in limited benefits and significant costs to the NHS (11, 38). In instances where a patient is hyporesponsive to ESA therapy, a blood transfusion may be clinically indicated however, the NICE Guideline advises to avoid blood transfusions where possible in patients for whom a kidney transplant is a treatment option (11). The clinical pathway is summarised in Figure 1.

B.1.3.6 Roxadustat positioning

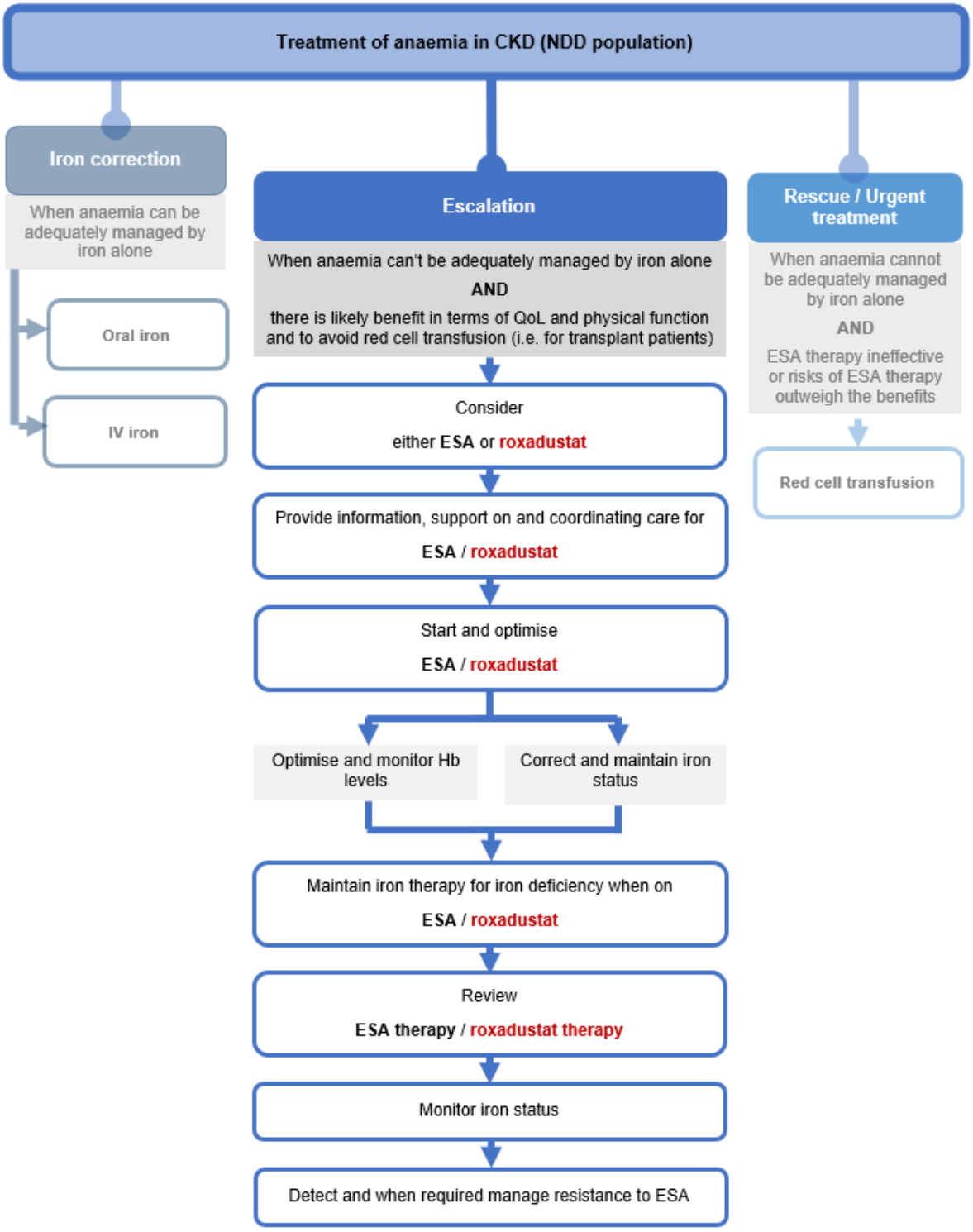
Whilst the expected licence for roxadustat covers all adult patients with symptomatic anaemia associated with CKD, in the context of this submission, roxadustat is positioned as an alternative to ESA for the treatment of adult patients with symptomatic anaemia associated with CKD who are NDD at the time of treatment initiation. This positioning is in line with feedback received from clinical experts who

stated that the oral mode of administration would offer additional benefit to patients who are NDD (as ESA and IV iron represent a much lesser burden for dialysis dependent [DD] patients) (39). In addition, in contrast to ESA, roxadustat does not require cold-chain storage and transit or refrigeration in the patient's home, thus offering additional convenience to patients with anaemia associated with CKD receiving treatment at home. Additional considerations related with sharps disposal from the patient home, also mean roxadustat offers additional benefits for patients receiving treatment at home (once syringes are used, they become biohazard material and require specific ways of disposal and destruction). Furthermore, dialysis patients who are stable on ESA treatment should only be converted to roxadustat if there is a valid clinical reason (40). Data from the UK renal registry suggests that over 90% of patients on dialysis are currently receiving an ESA (41). As the roxadustat SmPC (Appendix C) states that dialysis patients who are stable on ESA treatment should only be converted to roxadustat if there is a valid clinical reason, the company therefore anticipates that roxadustat will not be routinely initiated in dialysis patients.

It should be noted that all four trials on NDD patients (ALPS, ANDES, OLYMPUS, DOLOMITES) allowed patients to continue treatment with roxadustat after initiation of dialysis (42-45). A large proportion of patients enrolled in these trials started dialysis while receiving roxadustat and the clinical and cost-effectiveness results presented in this submission accounts for these patients. In line with this, throughout the submission, the term NDD is used in reference to the patient status at point of treatment initiation. The company anticipates NDD patients appropriately managed with roxadustat will be allowed to continue treatment after initiation of dialysis, with no dose adjustment required (see SmPC in Appendix C).

The positioning of roxadustat in the current clinical pathway is highlighted in Figure 1. The clinical pathway was adapted from the NICE NG8 guideline (11).

Figure 1. Anticipated positioning of roxadustat in the clinical pathway of care for anaemia associated with CKD



Abbreviations: CKD: chronic kidney disease; IV: intravenous; QoL: quality of life; ESA: erytrophoietin stimulating agents; NDD: non-dialysis dependent at treatment initiation; Hb: haemoglobin.

B.1.4 Equality considerations

Astellas are not aware of any issues that this submission would raise regarding inequalities in NICE guidance or protocols for the treatment of patients with symptomatic anaemia associated with CKD.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in July 2019 and updated in March 2021 to identify relevant evidence investigating the effects and safety of roxadustat at any dose, against any other intervention, placebo or best supportive care (BSC), for the treatment of patients with anaemia associated with CKD.

Thirteen trials were identified that assessed roxadustat in patients with anaemia associated with CKD, as follows:

- One phase Ib/II trial
- Four phase II trials
- One phase II/III extension trial
- Eight phase III trials

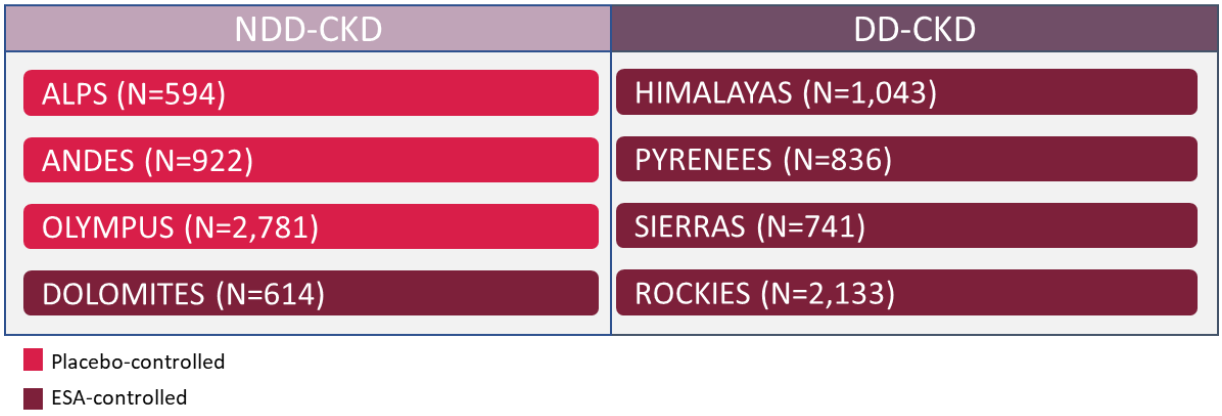
See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to roxadustat in the treatment of anaemia associated with CKD.

The eight phase III trials identified in the SLR constitute the ALPINE phase III clinical development programme for roxadustat for the treatment of anaemia associated with CKD patients, as described in the following sections.

B.2.2 List of relevant clinical effectiveness evidence

The ALPINE phase III clinical development programme for roxadustat for the treatment of anaemia associated with CKD patients consists of eight randomised controlled trials conducted globally. As represented in Figure 2, four trials were conducted in patients commencing roxadustat when not on dialysis (NDD population) (42, 43, 45, 46) and four trials in those commencing roxadustat while on dialysis (DD population) (44, 47-49). Over 9,600 patients were enrolled into the ALPINE programme: 4,911 NDD patients and 4,753 DD patients.

Figure 2. Overview of the roxadustat clinical trials for the NDD and DD CKD populations



Abbreviations: DD-CKD: dialysis-dependent-chronic kidney disease; NDD-CKD: non-dialysis dependent chronic kidney disease

This submission is focussed on patients who are not on dialysis at the point of starting treatment for anaemia associated with CKD. Therefore, the clinical evidence base relevant to this submission compromises of the four trials in the NDD population. Three of which were placebo-controlled (ALPS, ANDES and OLYMPUS) (43, 45, 46) whilst the fourth (DOLOMITES) (42) compared roxadustat to ESA (darbepoetin alfa).

It should be noted that both the clinical evidence and economic case account for CKD disease progression, with [redacted]% patients in the pooled NDD trials dataset progressing to dialysis by the end of the follow up while continuing treatment. (see Section B.3.3.4). The evidence presented is therefore reflective of the continuity of care as expected in clinical practice. Throughout the submission, the term NDD is used to refer to patients with anaemia associated with CKD who are NDD only at the time of treatment initiation, not excluding patients who start dialysis while receiving roxadustat or ESA.

The main design features of the clinical trials for the NDD population are summarised in Table 4, with further details of their design provided in Section B.2.3.1. Evidence for the four trials conducted in DD patients (44, 47-49) are provided as supporting evidence in Appendix L.

Table 4. Clinical effectiveness evidence (NDD population)

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
Study Design	Phase III, multicentre, randomised, double-blind, placebo-controlled trial.	Phase III, multicentre, randomised, double-blind, placebo-controlled trial.	Phase III, multicentre, randomised, double-blind, placebo-controlled trial.	Phase III, multicentre, randomised, open-label, active-controlled trial
Population	Patients with anaemia associated with CKD not on dialysis.	Patients with anaemia associated with CKD not on dialysis.	Patients with anaemia associated with CKD not on dialysis.	Patients with anaemia associated with CKD who have not started dialysis treatment
Intervention	Roxadustat 70/100 mg*‡ (N=391) orally TIW throughout treatment period (minimum 52 weeks up to maximum of 104 weeks or until the last patient randomised to treatment had completed 40 weeks of treatment). From week 4 and every 4 weeks thereafter, dose adjustments were permitted.	Roxadustat 70/100 mg*‡ (N=616) orally TIW (except in patients who had already converted to BIW or QW dosing regimens as a result of being enrolled under previous protocol versions) throughout treatment period (variable for individual patients – minimum treatment duration was 52 weeks with a maximum treatment duration of up to three years after the last patient was randomised). Dose modifications in the protocol v.2 were allowed every 4 weeks to increase and maintain Hb according to a dosing algorithm.	Roxadustat 70 mg‡ (N=1,393) orally TIW throughout treatment period (variable for individual patients - treatment end date was defined based on when the target number of CV events was reached). The maximum treatment period was 4 years. Dose adjustments were permitted from week 4, and at intervals of every 4 weeks until week 52, and then every eight-weeks using a dose adjustment algorithm.	Roxadustat 70/100 mg* (N=323) orally TIW throughout treatment period (104 weeks). From week 4 and every four weeks thereafter, dose adjustments‡ were permitted
Comparator(s)	Placebo (N=203) orally TIW throughout treatment period.	Placebo (N=306) orally TIW throughout treatment period.	Placebo (N=1,388) orally TIW throughout treatment period.	Darbepoetin alfa (N=293) SC or IV, dosed‡ as per the EU SmPC throughout treatment period.
Trial supports application for marketing authorisation?	Yes	Yes	Yes	Yes
Trial used in the economic model?	Yes	Yes	Yes	Yes

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
Rationale for use/non-use in the model	The study provides evidence of efficacy and safety of roxadustat in patients not on dialysis at the time of treatment initiation	The study provides evidence of efficacy and safety of roxadustat in patients not on dialysis at the time of treatment initiation	The study provides evidence of efficacy and safety of roxadustat in patients not on dialysis at the time of treatment initiation	The study provides evidence of efficacy and safety of roxadustat versus ESA in patients not on dialysis at the time of treatment initiation
Reported outcomes specified in the decision problem	• **Hb response and maintenance** • **Rescue medication** • Hospitalisation** • **Quality of life** • **Safety (CV profile)**	• **Hb response and maintenance** • **Rescue medication** • Hospitalisation • **Quality of life** • **Safety (CV profile)**	• **Hb response and maintenance** • **Rescue medication** • Hospitalisation** • **Quality of life** • **Safety (CV profile)**	• **Hb response and maintenance** • **Rescue medication** • Hospitalisation** • **Quality of life** • **Safety (CV profile)**
All other reported outcomes	• LDL cholesterol • Kidney function • Use of IV iron supplementation	• LDL cholesterol • Kidney function • Blood pressure • Use of IV iron supplementation	• LDL cholesterol • Kidney function • Use of IV iron supplementation	• LDL cholesterol • Use of IV iron supplementation

Notes: *The dose of roxadustat was adjusted based on patient's body weight; with patients weighing ≥45.0 kg to ≤70.0 kg receiving 70 mg while those weighing >70.0 kg to ≤160.0 kg receiving 100 mg.
**Hospitalisations were not explicitly modelled in the cost-effectiveness model; ǂAll dose adjustments were made to achieve a Hb target level of 11.0 g/dL and maintain patients' Hb levels between 10.0 g/dL and 12.0 g/dL.

Abbreviations: BIW: twice in week; CKD: chronic kidney disease; ESA: erythropoiesis-stimulating agents; EU: European Union; HRQoL: Health-related quality of life; IV: intravenous; QW: once weekly; SC: subcutaneous; SmPC: summary of product characteristics; TIW: thrice weekly.

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

B.2.3.1 Summary of trials' methodology

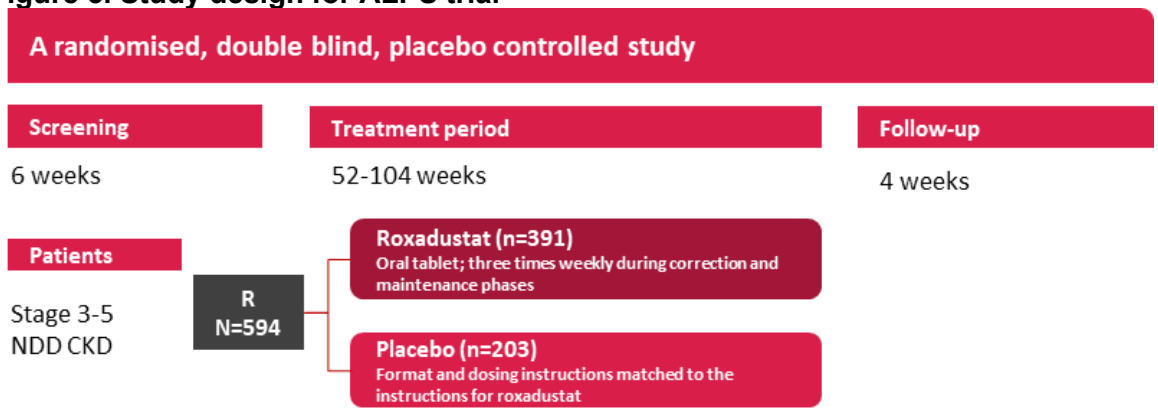
The study design for the clinical trials conducted in NDD population is summarised in Table 5. A summary of each trial's methodology is provided in the sections below.

B.2.3.1.1 ALPS

The ALPS study was a phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with Stage 3, 4 or 5 CKD who were anaemic and not on dialysis at the time of randomisation.

As depicted in Figure 3, the ALPS study consisted of a screening period (up to six weeks), a treatment period (minimum 52 weeks up to a maximum of 104 weeks) and a post-treatment follow-up period (four weeks) (43).

Figure 3. Study design for ALPS trial



Abbreviations: NDD: non-dialysis dependent; CKD: Chronic kidney disease; R: randomised; N: number

Eligible patients were randomised to receive roxadustat or placebo orally three times weekly (TIW) in a 2:1 ratio (50).

The initial roxadustat dose was based on a tiered, weight-based dosing scheme (50):

- Weight ≥45.0 kg to ≤70.0 kg: 70 mg
- Weight >70.0 kg to ≤160.0 kg: 100 mg

The study drug was dosed initially for Hb correction, until patients achieved central Hb values of ≥11.0 g/dL and Hb increased from baseline of ≥1.0 g/dL at two consecutive study visits separated by at least five days (correction period) (50).

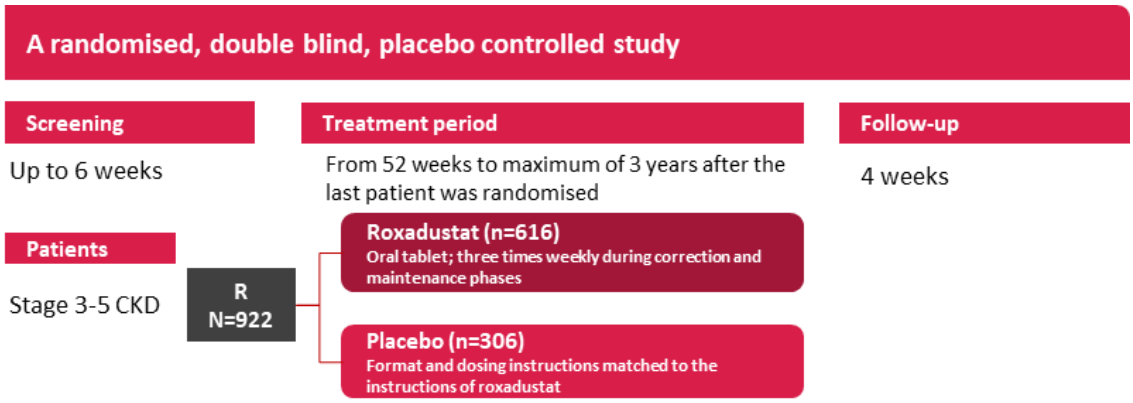
Once Hb correction was reached, patients entered the maintenance period. The aim of the maintenance period was to treat to an Hb level of 11.0 g/dL by maintaining Hb levels between 10-12g/dL (50). From week four and every four weeks thereafter, dose adjustments were permitted. All dose adjustments were made to achieve Hb response and maintain patients' Hb level within the predefined target range.

B.2.3.1.2 ANDES

ANDES was a phase III, multicentre, randomised, double-blind, placebo-controlled trial in anaemic patients with Stage 3, 4 or 5 CKD and not on dialysis at time of randomisation.

As depicted in Figure 4, the ANDES study consisted of a screening period (up to six weeks), a treatment period (variable for individual patients – minimum treatment duration was 52 weeks with a maximum treatment duration of up to three years after the last patient was randomised) and a post-treatment follow-up period (four weeks) (46).

Figure 4. Study design for ANDES trial



Abbreviations: NDD: non dialysis dependent; CKD: chronic kidney disease patients; R: randomised.

Eligible patients were randomised (2:1) to receive roxadustat or placebo orally (46). The initial roxadustat dose was based on a tiered, weight-based dosing scheme (46):

- Weight ≥45.0 kg to <70 kg: 70 mg
- Weight ≥70 kg to ≤160.0 kg: 100 mg

Dosing frequency was TIW throughout the study, except in patients who had already converted to twice weekly (BIW) or once weekly (QW) dosing regimens as a result of being enrolled under previous protocol versions where this was maintained (46).

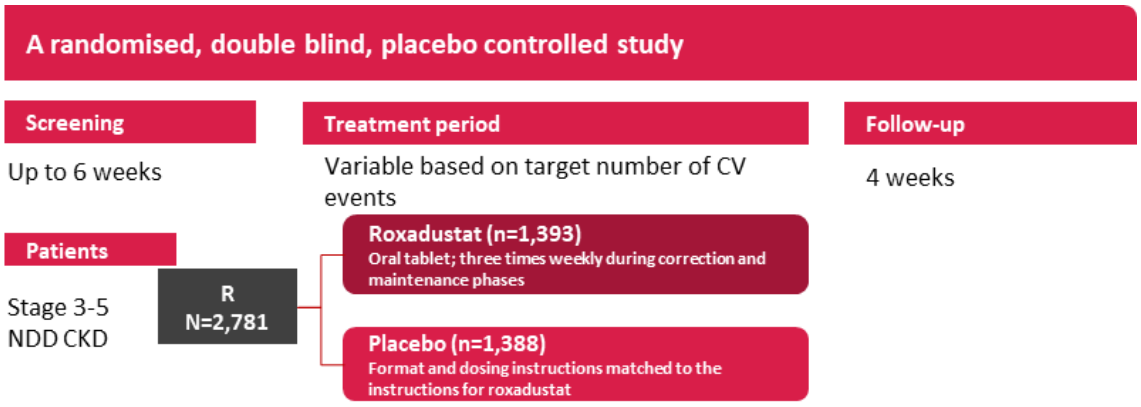
Dose modifications were allowed every four weeks to increase and maintain Hb according to a dosing algorithm (46).

B.2.3.1.3 OLYMPUS

OLYMPUS was a phase III, multicentre, randomised, double-blind, placebo-controlled trial in anaemic patients with Stage 3, 4 or 5 CKD and not on dialysis.

As depicted in Figure 5, the OLYMPUS study consisted of a screening period (up to six weeks), a treatment period (variable for individual patients – treatment end date was defined based on when the target number of cardiovascular (CV) events was reached) and a post-treatment follow-up period (four weeks) (45).

Figure 5. Study design for OLYMPUS trial



Abbreviations: NDD: non dialysis dependent; CKD: chronic kidney disease; R: randomised.

Eligible patients were randomised (1:1) to receive roxadustat or placebo:

- Treatment group 1: patients were initially administered 70mg of roxadustat orally TIW
- Treatment group 2: patients were administered with placebo and dosing instructions matched to the instructions for roxadustat

Treatment was dosed TIW throughout the study unless downward dose adjustment required a change to twice or once weekly dosing (45). Dose adjustments were permitted from week 4, and at intervals of every four weeks until week 52, and every eight weeks thereafter using a dose adjustment algorithm (45).

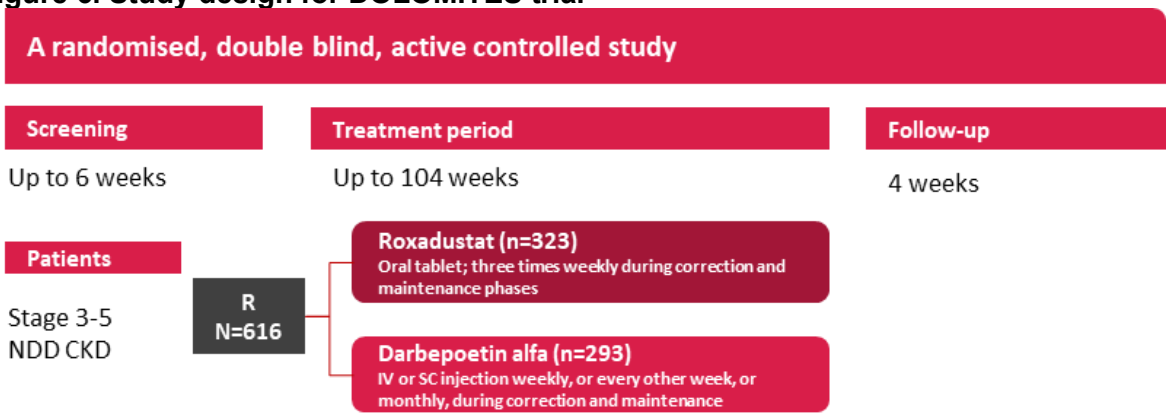
B.2.3.1.4 DOLOMITES

DOLOMITES was a phase III, multicentre, randomised, open-label, active-controlled study designed to provide key efficacy and safety of roxadustat in NDD population of

patients requiring escalation of treatment for anaemia associated with CKD beyond iron supplementation.

As depicted in Figure 6, the DOLOMITES study consisted a screening period (up to six weeks), a treatment period (104 weeks) and a post-treatment follow-up period (four weeks).

Figure 6. Study design for DOLOMITES trial



Abbreviations: NDD: non dialysis dependent; CKD: chronic kidney disease patients; R: randomised; SC: subcutaneous.

Eligible patients were originally randomised 2:1 roxadustat:darbepoetin alfa (protocol v1.0). From protocol v2.0 (dated 18 May 2015) onwards, patients were randomised in a 1:1 ratio to receive either (42):

- Roxadustat TIW, or (42)
- Darbepoetin alfa via subcutaneous (SC) or IV injection, dosed as per the European Union (EU) SmPC (51)

Towards the end of recruitment, the overall number of patients randomised to roxadustat and darbepoetin alfa arms were 323 and 293 respectively.

The initial roxadustat dose was based on a tiered, weight-based dosing scheme: (42)

- Weight ≥45.0 kg to ≤70.0 kg: 70 mg
- Weight >70.0 kg to ≤160.0 kg: 100 mg
- For both roxadustat and darbepoetin alfa, study treatment was dosed initially for Hb correction, until patients achieved Hb levels of ≥11.0 g/dL and Hb increase from baseline of ≥1.0 g/dL as measured at two consecutive study visits separated by at least five days (as assessed by central laboratory) (42)

- Once Hb correction was reached, patients entered the maintenance period. The aim of the maintenance period was to treat to a Hb target level of 11.0 g/dL by maintaining Hb levels between 10.0 g/dL and 12.0 g/dL (42)

From week 4 to week 24, patients were followed-up fortnightly, and, then from week 24 to week 104, they were followed-up every four weeks. After week 4, dose adjustments were permitted. All dose adjustments were made to achieve a Hb response and maintain patients' Hb levels within the predefined target range.

Table 5. Summary of trial methodology

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
Locations where the data was collected	This study was conducted at 153 study centres in 22 countries: Belarus, Belgium, Bulgaria, Colombia, Dominican Republic, Estonia, Georgia, Greece, Guatemala, Hungary, Italy, Panama, Peru, Poland, Romania, Russian Federation, Serbia, South Africa, Spain, Turkey, United Kingdom, and Ukraine.	The study was conducted at 163 sites in the United States, South America, Australia, New Zealand, and Asia.	This study was conducted at 385 study centres in 25 countries: Argentina, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Germany, Hungary, India, Korea, Malaysia, Mexico, Peru, Philippines, Poland, Romania, Russia, Slovakia, Spain, Taiwan, Thailand, Turkey, Ukraine, US, and Vietnam.	This study was conducted at 156 study centres in 28 countries: Austria, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Georgia, Germany, Hungary, Ireland, Israel, Latvia, Macedonia, Montenegro, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain, Ukraine and United Kingdom.
Trial Design	ALPS was a phase III, multicentre, randomised, double-blind, placebo-controlled trial in anaemic patients with stage 3, 4 or 5 CKD who were not on dialysis at the time of randomisation. The study consisted of three study periods: • screening period (up to six weeks) • treatment period (minimum 52 weeks up to maximum of 104 weeks or until the last patient randomised to treatment had completed 40 weeks of treatment)	ANDES was a phase III, multicentre, randomised, double-blind, placebo-controlled trial in anaemic patients with stage 3, 4 or 5 CKD who were not on dialysis at the time of randomisation. The study consisted of three study periods: • screening period (up to six weeks) • treatment period (variable for individual patients – minimum treatment duration was 52 weeks with a maximum treatment duration of up to three years after the last patient was randomised) • post-treatment follow-up period (four weeks)	OLYMPUS was a phase III, multicentre, randomised, double-blind, placebo-controlled trial in anaemic patients with stage 3, 4 or 5 CKD who were not on dialysis at the time of randomisation. The study consisted of three study periods: • Screening period (up to six weeks) • treatment period (variable for individual patients - treatment end date was defined based on when the target number of CV events was reached) • post-treatment follow-up period (four weeks)	DOLOMITES was a phase III, multicentre, randomised, open-label, active-controlled trial in anaemic patients with stage 3, 4 or 5 CKD who were not on dialysis at the time of randomisation. The study consisted of three study periods: • screening period (up to six weeks) • treatment period (104 weeks) post-treatment follow-up period (four weeks)

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	• post-treatment follow-up period (four weeks)			
Key eligibility criteria for participants* **	**Inclusion criteria:** • At least 18 years of age • Diagnosis of CKD, with KDOQI stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's three most recent Hb values during the screening period, obtained at least four days apart, was ≤10.0 g/dL, with a difference of ≤1.0 g/dL between the highest and the lowest values were included in the study • Prior to initiation the patient's ferritin level was ≥30 ng/mL (≥67.4 pmol/L) and transferrin saturation was ≥5%	**Inclusion criteria:** • At least 18 years of age • Diagnosis of CKD, with KDOQI Stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's three most recent Hb values during the screening period, obtained at least four days apart, was <10.0 g/dL, with a difference of ≤1.0 g/dL between the highest and the lowest values • Ferritin levels ≥30 ng/mL at randomisation and transferrin saturation ≥5% **Exclusion criteria:** • ESA treatment within 12 weeks of randomisation • More than one dose of IV iron within 12 weeks before randomisation • RBC transfusion within eight-weeks prior to randomisation	**Inclusion criteria:** • At least 18 years of age • Diagnosis of CKD, with KDOQI Stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's two most recent Hb values during the screening period, obtained at least seven days apart, was <10.0 g/dL • Ferritin levels ≥50 ng/mL at randomisation and transferrin saturation ≥15% • Body weight of 45-160 kg **Exclusion criteria:** • ESA treatment within six weeks of randomisation • Known hereditary haematologic disease such as thalassaemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD • Patient had received an RBC transfusion during the screening period	**Inclusion criteria:** • At least 18 years of age • Diagnosis of CKD, with KDOQI stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's two most recent (prior to randomisation) Hb values during the screening period, obtained at least four days apart, was ≤10.5 g/dL, with a difference of ≤1.0 g/dL **Exclusion criteria:** • ESA treatment within 12 weeks prior to randomisation • Treatment with IV iron within six weeks prior to randomisation • Patient had received an RBC transfusion within eight-weeks prior to randomisation • Known hereditary haematological diseases such as thalassaemia or

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	Exclusion criteria: • ESA treatment within 12 weeks prior to randomisation • Treatment with more than one dose of IV iron within 12 weeks prior to randomisation • Patient had received an RBC transfusion within eight weeks prior to randomisation • Known hereditary haematological diseases such as thalassaemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD	• Known hereditary haematologic disease such as thalassaemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD • Known chronic inflammatory disease that could impact erythropoiesis		sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD • Known chronic inflammatory disease that could impact erythropoiesis
Trial drugs	Group 1: roxadustat 70/100 mg*‡ TIW (N=391) Group 2: placebo TIW (N=203)	Group 1: roxadustat 70/100 mg*‡ TIW (N=616) Group 2: placebo TIW (N=306)	Group 1: roxadustat mg‡ TIW (N=1,393) Group 2: placebo TIW (N=1,388)	Group 1: roxadustat 70/100 mg* TIW (N=323) Group 2: darbepoetin alfa dosed as per the EU SmPC (N=293)

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
Concomitant medications	Permitted concomitant medications: • Statins and Other Substrates for OATP 1B1 • Phosphate Binders and Other Multivalent Cation-containing Drugs and Mineral Supplements • Antihypertensive Medications Disallowed concomitant medications: • Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy) from four weeks prior to randomisation until EOS visit • Androgens from randomisation until EOS visit • Dapsone in any dose amount or chronic use of acetaminophen (paracetamol) >2.0	Permitted concomitant medications: • Statins • Phosphate binders • Therapeutic Phlebotomy Disallowed concomitant medications/therapies/substances: • Contraception	Permitted concomitant medications: • Statins • Phosphate binders • Herbal medicines Disallowed concomitant medications: • Any investigational drug from randomisation until EOS. • Any erythropoietin analogue during the treatment period, except for rescue medication [erythropoietin analogues]). • Iron-chelating agents (e.g., deferoxamine/desferrioxamine, deferiprone or deferaxirox therapy) from four weeks prior to screening until EOS. • Androgens from randomisation onwards until EOS. • Dapsone (at any dose) from randomisation to EOS. • Chronic doses of acetaminophen/paracetamol >2.0 g/day from randomisation until EOS	Permitted concomitant medications: • Statins and Other Substrates for Organic Anion Transporting Polypeptide 1B1 • Phosphate Binders and Other Multivalent Cation-containing Drugs and Mineral Supplements • Antihypertensive Medications Disallowed concomitant medications: • Any ESA within 12 weeks prior to randomisation until EOT. • Intravenous iron within six weeks prior to randomisation. • RBC transfusion within eight-weeks prior to randomisation. • Any investigational drug within 30 days or five half-lives or limit set by national law (whichever is longer), prior to screening until EOS. • Roxadustat or another HIF-PHI at any time prior to randomisation. After randomisation any HIF-PHI other than roxadustat, as allocated by randomisation, until EOS.

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	g/day from randomisation until EOS visit - Any hypoxia inducible factor HIF-PHI other than roxadustat, as allocated by randomisation, until EOS visit			- Androgens from day of randomisation until EOS. - Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy) from four weeks prior to randomisation until EOS. - Dapsone in any dose amount or chronic use of acetaminophen/paracetamol >2.0 g/day from the day of randomisation until EOS.
Primary outcome	Proportion of patients who achieve an Hb (g/dL) response* defined as: - Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL, or - An increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response	Proportion of patients who achieve an Hb (g/dL) response* defined as: - Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL, or - An increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response	Proportion of patients who achieve an Hb (g/dL) response* defined as: - Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL, or - An increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response	Proportion of patients who achieve an Hb (g/dL) response defined as: - Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL, or - An increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response
Major secondary outcomes	- Hb (g/dL) change from baseline to the average Hb in	- Mean change from baseline in Hb averaged over eight-weeks of treatment at weeks	- Change in Hb from baseline to the average Hb from weeks 28-52 for patients with	- Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period • Change from baseline in LDL (mmol/L) cholesterol to the average LDL cholesterol of weeks 12 to 28 • Use and time to first use of rescue therapy in the first 24 weeks of treatment (incidence rate per 100 patient years at risk) • Change from baseline in SF-36 VT subscore (points) to the average VT subscore of weeks 12 to 28 • Change from baseline in SF-36 PF subscore (points) to the average PF subscore of weeks 12 to 28 • Change from baseline in MAP (mmHg) to the	28 to 36 without rescue therapy • Mean change from baseline in Hb during the evaluation period (defined as week 28 until week 52) in patients with baseline CRP >ULN • Proportion of patients with Hb level ≥10 g/dL between week 28 to 36, without use of rescue therapy • Mean change from baseline in LDL cholesterol averaged over weeks 12 to 28 • Time to and proportion of patients who received rescue therapy (composite of blood/RBC transfusion, ESA use, and IV iron) in the first 52 • Mean change from baseline in SF-36 VT subscore averaged over weeks 12 to 28 • Progression of CKD: rate of change in eGFR over time adjusted by baseline eGFR, censored at dialysis or kidney transplant • Time to and proportion of patients who received RBC transfusion in the first 52 weeks of treatment • Mean change from baseline in SF-36 VT subscore averaged over weeks 12 to 28	baseline hsCRP greater than the ULN • Proportion of total time of interpolated Hb values ≥10 (g/dL) from weeks 28 to 52 • Proportion of total time of interpolated Hb values 10-12 (g/dL) from weeks 28 to 52 • Mean change in LDL cholesterol (mmol/L) from baseline to week 24 • Time to first instance of receiving IV iron, RBC transfusions, or erythropoietin analogue as rescue therapy • Time to and proportion of patients who received first administration of an RBC transfusion as rescue therapy • Change from baseline in SF-36 VT subscore (points) to the average VT subscore of weeks 12 to 28 • Rate of progression of CKD measured by annualised eGFR slope over time • Change from baseline in SF-36 PF subscore (points) to the average PF subscore of weeks 12 to 28	having received rescue therapy within six weeks prior to and during this eight-week evaluation period • Change from baseline in LDL cholesterol (mmol/L) to the average LDL cholesterol of weeks 12 to 28 • Time to first use of IV iron in weeks 1–36 (per 100 patient years at risk) • Change from baseline in SF-36 PF subscore (points) in weeks 12–28 • Change from baseline in SF-36 VT subscore (points) in weeks 12–28 • Change from baseline in MAP (mmHg) to the average MAP value in weeks 20 to 28 • Occurrence and time to first occurrence of hypertension (defined as [SBP ≥170 mmHg and SBP increase from BL ≥20 mmHg] or [DBP ≥110 mmHg and DBP increase from BL ≥15 mmHg]) during weeks 1 to 36

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	average MAP value of weeks 20 to 28 • Occurrence and time to first occurrence of hypertension (defined as either systemic blood pressure >170 mmHg AND an increase from baseline ≥20 mmHg or as diastolic blood pressure >110 mmHg and an increase from baseline of ≥15 mmHg • Rate of progression of CKD measured by annualised eGFR slope over time	• Mean change from baseline in MAP averaged over weeks 20 to 28 • Time to (and proportion of patients with) worsened hypertension		
Pre-planned subgroups	Subgroups were predefined based on the key baseline demographics and disease characteristics including: • Sex: male vs. female • Age: <65, 65-74, ≥75 • Iron repletion status: ferritin ≥100 ng/ml and TSAT ≥20%; ferritin <100 ng/ml or TSAT <20% • CRP: ≤ULN, >ULN • Hb: ≤8, >8	Subgroups were predefined based on the key baseline demographics and disease characteristics including: • Sex: male vs. female • Age: <65, 65-74, ≥75 • CKD stage: Stage 3, 4 or 5 • Iron repletion status: ferritin ≥100 ng/ml and TSAT ≥20%; ferritin <100 ng/ml or TSAT <20% • CRP: ≤ULN, >ULN • Hb: ≤8, >8 - ≤9, >9 • Cardiovascular history: Yes, No	Subgroups were predefined based on the key baseline demographics and disease characteristics including: • Sex: male vs. female • Age: <65, 65-74, ≥75 • Race: White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska native, Other. (Other and Native Hawaiian or Other Pacific Islander were combined in order to assess change in Hb)	Subgroups were predefined based on the key baseline demographics and disease characteristics including: • Sex: male vs. female • Age: <65, 65-74, ≥75 • Geographical region: Western Europe and Israel; and Central and Eastern Europe • History of CVD: Yes, No • eGFR: <30, ≥30, <15, ≥15 • CRP at baseline: ≤ULN, >ULN

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	• Cardiovascular history: Yes, No • eGFR: <15, ≥15, <30, ≥30 • Geographic region: Western Europe and rest of the world.	• eGFR: <10, 10-<15, 15-<30, ≥30 • Geographic region: US, Ex-US*.	• Baseline weight: <70 kg versus ≥70 kg; and <100 kg versus ≥100 kg. • Weight by gender-specific median (four groups) • Body mass index: <30 vs. ≥30 kg/m2 • Geographical region: US vs. Ex-US** • Geographical region: North America, South America, Asia, Europe • CV/ cerebrovascular/ thromboembolic history: Yes, No. • Baseline Hb value: ≤8 g/dL versus >8 g/dL and ≤9 g/dL versus >9 g/dL • Baseline eGFR value: <30 versus ≥30, <15 versus ≥15, and <10 versus ≥10 mL/min/1.73 m2 • Diabetes history: Yes, No. • Baseline C-reactive protein: (≤ULN vs. >ULN • Baseline iron repletion status: ferritin >100 ng/ml and TSAT >20%	TSAT and ferritin: TSAT ≥20% and ferritin ≥100ng/mL, TSAT <20% or ferritin <100 ng/ml

Notes: *Distinct definitions of the primary endpoint (Hb response) for European Union (EU) and United States (US) were defned for the placebo controlled trials (ALPS, ANDES and OLYMPUS), in accordance with the regulators. This submission only presents the definition and results for the EU-based primary endpoint. **Ex-US refers to all the rest of the world except the United States. ***For the complete list of inclusion/exclusion criteria, please refer to the CSR of each study.

Abbreviations: BL: baseline; CKD: chronic kidney disease; CRP: C-reactive protein; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; EOS: end of study; EOT: end of treatment; ESA: erythropoiesis-stimulating agents; EU: European Union; Hb: haemoglobin; HIF-PHI: hypoxia inducible factor-prolyl hydroxylase inhibitor; IV: intravenous; KDOQI: kidney disease outcomes quality initiative; LDL: low density lipoprotein; MAP: mean arterial pressure; MDRD: Modification of diet in renal disease; mmol/L: milli-moles per litre; PF: Physical functioning; RBC: red blood cells; SBP: systolic blood pressure; SF-36: 36-Item short form survey; SmPC: summary of product characteristics; TIW: three times per week; TSAT: transferrin saturation; ULN: upper limit of normal; US: United States; VT: vitality.

B.2.3.2 Baseline characteristics and demographics

An advisory board was conducted with external clinical experts with experience in treating anaemia associated with CKD patients in England. Clinical experts confirmed that the pooled population from the four NDD clinical trials were representative of the patients with anaemia associated with CKD in the UK (39). A comparison of the baseline demographics and characteristics across different treatment arms in trials conducted on the NDD population is given in Table 6. Overall, all the baseline parameters were well-balanced across both arms of each trial. Any notable differences are highlighted below.

B.2.3.2.1 ALPS

Overall, there was no difference in demographics and baseline characteristics between the roxadustat and placebo treatment groups. Both patient populations were predominately <65 years. More than 50% had ferritin >100 ng/mL and transferrin saturation (TSAT) >20%, and mean Hb in both groups was approximately 9.10 g/dL (Table 6) (43).

B.2.3.2.2 ANDES

Overall, there was no notable difference in demographics and baseline characteristics between the roxadustat and placebo treatment groups. Both patient populations were predominantly white, female and aged <65 years with a mean Hb of 9.10 g/dL (Table 6) (46).

B.2.3.2.3 OLYMPUS

Overall, there was no notable difference in demographics and baseline characteristics between the roxadustat and placebo treatment groups. Both patient populations were predominantly white, female and aged <65 years with a mean Hb of approximately 9.10g/dL (Table 6) (45).

B.2.3.2.1 DOLOMITES

In DOLOMITES, the roxadustat and darbepoetin alfa arms were balanced in terms of demographics, baseline disease characteristics and medical history. The majority of patients were white (95.3%) and were recruited in central and eastern Europe (70.1%), with a mean Hb of 9.55 g/dL (Table 6) (42).

Table 6. Demographic and baseline characteristics of patients included in trials conducted on NDD population

		ALPS			ANDES		OLYMPUS			DOLOMITES		
Parameter	**Category/statistic**	**Roxadustat (N=391)**	**ESA (N=203)**	**Total (N=594)**	**Roxadustat (N=616)**	**Placebo (N=306)**	**Roxadustat (N=1384)**	**Placebo (N=1377)**	**Total (N=2761)**	**Roxadustat (N=323)**	**Darbepoetin alfa (N=293)**	**Total (N=616)**
Baseline demographics												
Sex	Male	169 (43.2%)	99 (48.8%)	268 (45.1%)	241 (39.1%)	130 (42.5%)	564 (40.8%)	603 (43.8%)	1167 (42.3%)	145 (44.9%)	129 (44.0%)	274 (44.5%)
	Female	222 (56.8%)	104 (51.2%)	326 (54.9%)	375 (60.9%)	176 (57.5%)	820 (59.2%)	774 (56.2%)	1594 (57.7%)	178 (55.1%)	164 (56.0%)	342 (55.5%)
Age (years)	Mean	60.6	61.7	61.0	64.9	64.8	60.9	62.4	61.7	66.8	65.7	66.3
	SD	13.5	13.8	13.6	12.6	13.2	14.67	14.14	14.43	13.6	14.4	14.0
	Median	62.0	63.0	63.0	66.0	66.0	62.0	63.0	63.0	69.0	69.0	69.0
	(Min, Max)	20, 89	26, 90	20, 90	22, 94	22, 91	19, 100	18, 93	18, 100	19, 91	22, 91	19, 91
Age range (years)	<65	225 (57.5%)	110 (54.2%)	335 (56.4%)	271 (44.0%)	146 (47.7%)	796 (57.5%)	730 (53.0%)	1526 (55.2%)	127 (39.3%)	110 (37.5%)	237 (38.5%)
	65-74	108 (27.6%)	55 (27.1%)	163 (27.4%)	192 (31.2%)	79 (25.8%)	321 (23.2%)	350 (25.4%)	671 (24.3%)	83 (25.7%)	85 (29.0%)	168 (27.3%)
	≥75	58 (14.8%)	38 (18.7%)	96 (16.2%)	153 (24.8%)	81 (26.5%)	267 (19.3%)	297 (21.6%)	564 (20.4%)	113 (35.0%)	98 (33.4%)	211 (34.3%)
Race	White	335 (85.7%)	182 (89.7%)	517 (87.0%)	176 (28.6%)	99 (32.4%)	623 (45.0%)	611 (44.4%)	1234 (44.7%)	306 (94.7%)	281 (95.9%)	587 (95.3%)
	Black or African American	10 (2.6%)	3 (1.5%)	13 (2.2%)	76 (12.3%)	28 (9.2%)	112 (8.1%)	115 (8.4%)	227 (8.2%)	8 (2.5%)	2 (0.7%)	10 (1.6%)
	Asian	9 (2.3%)	0	9 (1.5%)	310 (50.3%)	151 (49.3%)	544 (39.3%)	538 (39.1%)	1082 (39.2%)	9 (2.8%)	10 (3.4%)	19 (3.1%)
	Other	37 (9.5%)	18 (8.9%)	55 (9.3%)	52 (8.8%)	28 (9.1%)	105 (7.6%)	113 (8.2%)	218 (7.9%)	0	0	0
BMI (kg/m²)	N	391	203	594	614	306	1380	1374	2754	322	293	615
	Mean	27.06	27.63	27.26	27.4	27.3	26.68	26.85	26.76	27.95	28.74	28.33
	SD	5.53	5.51	5.52	6.3	6.0	6.009	6.121	6.064	5.76	6.06	5.92
Region	Western Europe and Israel									99 (30.7%)	85 (29.0%)	184 (29.9%)
	Central and Eastern Europe									224 (69.3%)	208 (71.0%)	432 (70.1%)
	US	-	-	-	-	-	343 (24.8%)	340 (24.7%)	683 (24.7%)			
	Ex-US	-	-	-	-	-	1041 (75.2%)	1037 (75.3%)	2078 (75.3%)			
	Western Europe	28 (7.2%)	16 (7.9%)	44 (7.4%)	-	-	-	-	-			
	Rest of the World	363 (92.8%)	187 (92.1%)	550 (92.6%)	-	-	-	-	-			
Baseline disease characteristics												
Hb (g/dL)	Mean	9.08	9.10	9.08	9.10	9.09	9.11	9.10	9.10	9.55	9.55	9.55
	SD	0.76	0.72	0.75	0.75	0.69	0.733	0.742	0.738	0.75	0.69	0.72
	≤8.0	32 (8.2%)	20 (9.9%)	52 (8.8%)	52 (8.4%)	23 (7.5%)	129 (9.3%)	131 (9.5%)	260 (9.4%)	11 (3.4%)	10 (3.4%)	21 (3.4%)
	>8.0	359 (91.8%)	183 (90.1%)	542 (91.2%)	-	-	1255 (90.7%)	1246 (90.5%)	2501 (90.5%)	312 (96.6%)	283 (96.6%)	595 (96.6%)
	>8 - ≤9	-	-	-	173 (28.1%)	97 (31.7%)	-	-	-			

		ALPS			ANDES		OLYMPUS			DOLOMITES		
Parameter	**Category/statistic**	**Roxadustat (N=391)**	**ESA (N=203)**	**Total (N=594)**	**Roxadustat (N=616)**	**Placebo (N=306)**	**Roxadustat (N=1384)**	**Placebo (N=1377)**	**Total (N=2761)**	**Roxadustat (N=323)**	**Darbepoetin alfa (N=293)**	**Total (N=616)**
	>9	-	-	-	391 (63.5%)	186 (60.8%)	-	-	-			
Iron repletion at baseline	Ferritin <100 ng/mL and TSAT <20%									51 (15.8%)	64 (21.8%)	115 (18.7%)
	Ferritin <100 ng/mL and TSAT ≥20%									27 (8.4%)	23 (7.8%)	50 (8.1%)
	Ferritin ≥100 ng/mL and ≤TSAT <20%									63 (19.5%)	54 (18.4%)	117 (19.0%)
	Ferritin ≥100 ng/mL and TSAT ≥20%									182 (56.3%)	152 (51.9%)	334 (54.2%)
	Ferritin <30 ng/mL or TSAT <5%	17 (4.3%)	5 (2.5%)	22 (3.7%)	-	-	-	-	-			
	30 ≤Ferritin <100 ng/mL and 5% ≤TSAT <20%	53 (13.6%)	28 (13.8%)	81 (13.6%)	-	-	-	-	-			
	30 ≤Ferritin <100 ng/mL and TSAT >20%	45 (11.5%)	25 (12.3%)	70 (11.8%)	-	-	-	-	-			
	Ferritin >100 ng/mL and 5% ≤TSAT <20%	72 (18.4%)	36 (17.7%)	108 (18.2%)	-	-	-	-	-			
	Ferritin >100 ng/mL and TSAT >20%	204 (52.2%)	109 (53.7%)	313 (52.7%)	373 (60.6%)	170 (55.6%)	809 (58.5%)	799 (58.0%)	1608 (58.2%)			
eGFR (mL/min/1.73 m^2)	Mean	-	-	-	21.9	22.4	19.69	19.95	19.82			
	SD	-	-	-	11.5	11.4	11.74	11.75	11.74			
CRP	>ULN	245 (63.1%)	135 (66.8%)	380 (64.4%)	-	-	-	-	-	209 (65.3%)	177 (60.4%)	386 (63.0%)
	<ULN	143 (36.9%)	67 (33.2%)	210 (35.6%)	-	-	-	-	-	111 (34.7%)	116 (39.6%)	227 (37.0%)
Type 2 diabetes mellitus	Number (%) of patients	131 (33.5%)	76 (37.4%)	207 (34.8%)	-	-	793 (57.3%)	807 (58.6%)	1600 (58.0%)	141 (43.7%)	124 (42.3%)	265 (43.0%)

Abbreviations: BMI: body mass index; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; kg: kilogram; m2: metre square; min: minute; mL: millilitre; SD: standard deviation; TSAT: transferrin saturation; ULN: upper limit of normal.

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

B.2.4.1 Populations analysed

The following analysis sets were used for the statistical analyses:

- Intention-to-treat (ITT): All randomised patients in each trial
- Full analysis set (FAS): All randomised patients who received at least one dose of study drug and have at least one post-dose Hb assessment
- Per protocol set (PPS): All FAS patients who received at least two weeks of study treatment with valid corresponding Hb measurements.
- Safety analysis set (SAF): All patients that received at least one dose of study drug
- On-treatment plus 28 days set (OT+28): All patients in time period from first administration of the study drug to up to 28 days after last study drug intake.

The primary analysis set was the PPS for the non-inferiority tests and FAS for the superiority, except in OLYMPUS in which mainly ITT was tested (described in more detail in Table 8 to Table 10).

B.2.4.2 Analysis timepoints

The analysis timepoints of each trial are provided in Table 7 (42, 43, 45, 46).

The efficacy analyses conducted in all the trials were sequential and the next analysis was only performed if the previous analysis was statistically significant.

Table 7. Analysis timepoints of clinical trials (NDD population)

Clinical trial	Analysis timepoint*
ALPS	• For primary efficacy endpoint, the first date of the two consecutive visits was used as the date of response • For secondary efficacy endpoints, the following timepoints were analysed: 1. Hb CFB to the average Hb in weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period 2. CFB in LDL cholesterol to the average LDL cholesterol of weeks 12 to 28 3. Use and time to first use of rescue therapy (composite of RBC transfusions, IV iron supplementation and rescue ESA). 4. CFB in SF-36 VT subscore to the average VT subscore of weeks 12 to 28 5. CFB in SF-36 PF subscore to the average PF subscore of weeks 12 to 28 6. CFB in MAP to the average MAP value of weeks 20 to 28 7. Occurrence and time to first occurrence of hypertension (defined as either systemic blood pressure (SBP) >170 mmHg AND an increase from baseline ≥20 mmHg or as diastolic blood pressure (DBP) >110 mmHg and an increase from baseline of ≥15 mmHg 8. Rate of progression of CKD measured by annualised eGFR slope over time • EQ-5D-5L was an additional secondary endpoint • The safety endpoints were analysed during the safety emergent period which was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the analysis last dose date (OT+28)
ANDES	• For primary efficacy endpoint, Hb response during the first 24 weeks of treatment, without rescue therapy (i.e., blood/RBC transfusion, ESA, or IV iron) within six weeks prior to the Hb response was analysed. • For secondary efficacy endpoint, the following timepoints were analysed: 1. Mean CFB in Hb averaged over eight-weeks of treatment at weeks 28 to 36, without rescue therapy within six weeks prior to and during this eight-week evaluation period 2. Mean CFB in Hb during the evaluation period (defined as Week 28 until Week 52) in patients with baseline CRP >ULN 3. Proportion of subjects with Hb level ≥10 g/dL between Week 28 to 36, without use of rescue therapy 4. Effect of maintenance dosing frequencies, pairwise comparisons of roxadustat TIW, BIW and QW vs. pooled placebo were performed in patients treated with roxadustat who achieved Hb response (Hb ≥11 g/dL and Hb increase from baseline ≥1 g/dL at two consecutive visits) within the first 24 weeks of treatment (average Hb level over weeks 28 to 36) 5. Mean CFB in LDL cholesterol averaged over weeks 12 to 28 6. Time to rescue therapy (composite of blood/RBC transfusion, ESA use, and IV iron) in the first 52 weeks of treatment 7. Mean CFB in the SF-36 VT subscore averaged over weeks 12 to 28 8. Rate of change in eGFR over time adjusted by baseline eGFR, censored at dialysis or kidney transplant 9. Times to blood/RBC transfusion in the first 52 weeks of treatment 10. Mean CFB in the SF-36 PF subscore averaged over weeks 12 to 28 11. Mean CFB in MAP averaged over weeks 20 to 28 12. Time to (and proportion of patients with) worsened hypertension (defined as [SBP ≥170 mmHg and SBP increase from BL ≥20 mmHg] or [DBP ≥110 mmHg AND DBP increase from BL ≥15 mmHg]) • EQ-5D-5L was an additional secondary endpoint

Clinical trial	Analysis timepoint*
	- For each safety parameter, unless otherwise specified, the last assessment made prior to the first dose of double-blind study medication was used as the baseline for all analyses.
OLYMPUS	• The primary efficacy endpoint was analysed at two consecutive visits [dates] (with available data) separated by at least five days during the first 24 weeks of treatment without having received rescue therapy (RBC transfusion, ESA therapy, or IV iron) prior to Hb response. The first date of the consecutive visits was used as the date of response. • For secondary efficacy endpoints, the following timepoints were analysed: 1. Mean change in Hb from baseline to the patient's mean value from week 28 to week 52 in patients with baseline hsCRP greater than the ULN 2. The proportion of total time of interpolated (a method used to estimate values for a variable at time points in between visits where actual levels were obtained) Hb values ≥10 g/dL from week 28 until week 52 3. Proportion of total time of interpolated Hb values within the interval 10 to 12 g/dL from week 28 until week 52 4. Mean change from baseline in LDL cholesterol to week 24 5. Time-to-first instance of receiving IV iron, RBC transfusions, or erythropoietin analogue as rescue therapy 6. Time to first administration of an RBC transfusion as rescue therapy 7. Mean change in SF-36 VT subscore from baseline to average VT subscore of weeks 12 to 28 8. Rate of progression of CKD measured by annualised eGFR slope over time 9. Mean change in SF-36 PF subscore from baseline to average PF subscore of weeks 12 to 28 • EQ-5D-5L was an exploratory endpoint • All safety analyses, except for AEs, were performed using the OT+28 analysis set. For each safety variable, the last assessment made on the screening visits or the randomisation visit was used as the baseline for all analyses, unless specified otherwise.
DOLOMITES	• The primary efficacy endpoint was analysed at two consecutive visits (dates) (with available data), separated by at least five days, during the first 24 weeks of treatment without having received rescue therapy prior to Hb response • The final analysis of the primary efficacy endpoint and interim analysis of safety data were performed after all patients had completed at least 36 weeks of study treatment (data cut-off 15 June 2018) • For secondary efficacy endpoints, the following timepoints were analysed: 1. Hb change from BL to the average Hb in weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period 2. Change from BL in LDL cholesterol to the average LDL cholesterol of weeks 12 to 28 3. Time to first intravenous iron use during weeks 1 to 36 4. Change from BL in SF-36 PF subscore to the average PF subscore in weeks 12 to 28 5. Change from BL in SF-36 VT subscore to the average VT subscore in weeks 12 to 28 6. Change from BL in MAP to the average MAP value in weeks 20 to 28 7. Occurrence and time to first occurrence of hypertension (defined as [SBP ≥170 mmHg AND SBP increase from BL ≥20 mmHg] or [DBP ≥110 mmHg AND DBP increase from BL ≥15 mmHg]) during weeks 1 to 36 • EQ-5D-5L was an additional secondary endpoint

Clinical trial	Analysis timepoint*
	• The safety endpoints were analysed at safety emergent period which was defined as the evaluation period from the analysis date of first drug intake up to the minimum between [(analysis date of last dose + 28 days + x), EOS visit date, date of death], with x corresponding to additional days based on the last dosing frequency

Notes: *The efficacy analyses conducted in all the trials were sequential and the next analysis was only performed if the previous analysis was statistically significant.

Abbreviations: AEs: adverse events; BIW: twice per week; BL: baseline; CFB: change from baseline; DBP: diastolic blood pressure; EOS: end of study; ESA: erythropoiesis-stimulating agents; Hb: haemoglobin; hsCRP: high-sensitivity C-reactive protein; IV: intravenous; OT+28: On-treatment plus 28 days; LDL: low density lipoprotein; MAP: mean arterial pressure; PF: physical functioning; QW: once time per week; RBC: red blood cells; SBP: systolic blood pressure; SF-36: 36-Item short form survey; TIW: thrice in week; ULN: upper limit of normal; VT: vitality.

B.2.4.3 Summary of statistical analyses

In the ALPS trial, 300 patients for the roxadustat group and 150 patients for the placebo group were expected to achieve at least 95% power to demonstrate a statistically significant difference with a 5% 2-sided significance level between roxadustat and placebo in the primary endpoint, assuming that the proportion of patients with response in the roxadustat group is at least 65% and in the placebo group is at most 25% (43). More details are provided in the ALPS section below.

In the ANDES trial, based on a two-sided test at the alpha 5% level of significance, 450 patients had >95% power to demonstrate a statistically significant difference between roxadustat and placebo, assuming that the proportion of patients with a Hb response in the roxadustat group was at least 65% and the proportion of patients with a Hb response in the placebo group was at most 25%. More details are provided in the ANDES section below (46).

In the OLYMPUS trial, with a sample size of 450 patients, the study was expected to provide >99% power to detect a 0.75 g/dL difference in mean Hb values between the treatment groups, assuming that the common standard deviation (SD) was 1.2 g/dL, using an analysis of variance test with a 5% two-sided significance level. More details are provided in the OLYMPUS section below (45).

The DOLOMITES trial was designed with 248 and 208 patients for the roxadustat and darbepoetin alfa group respectively to provide at least 98% test power to demonstrate statistical non-inferiority of roxadustat versus darbepoetin alfa in the primary endpoint assuming that the proportion of patients with response in both groups is the same and at least 80% and a non-inferiority margin for the difference of proportions of 15%. The power for the sensitivity analysis of post-amendment 1 data (336 patients) was assumed to be at least 93%. More details are provided in the DOLOMITES section (42).

B.2.4.3.1 ALPS

Statistical comparisons made for each endpoint in the ALPS trial conducted for the pre-dialysis population are defined in Table 8 (43).

Table 8. Sequential testing of primary and key secondary efficacy endpoints in the ALPS trial

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb response	Hb (g/dL) response defined as: • Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL • or an increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response	FAS	The proportion of responders in the primary efficacy variable was analysed using a Cochran-Mantel-Haenszel (CMH) test adjusting for covariates (region, history of cardiovascular, cerebrovascular, or thromboembolic diseases, baseline Hb and baseline eGFR), comparing roxadustat to placebo. The CMH adjusted odds ratio (roxadustat versus placebo) and its 95% confidence interval were provided. Superiority of roxadustat versus placebo was to be declared if the lower bound of the 2-sided 95% confidence interval of the CMH odds ratio is higher than 1. In addition, a 95% confidence interval for the proportion of each roxadustat and Placebo based on the exact method of Clopper-Pearson was presented	**Superiority**
Secondary endpoint(s)				
Hb maintenance	Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period	FAS	Analysis method: MMRM. Categorical Variables: Region, History of CV visits, and visits by treatment. BL Hb and BL eGFR as continuous covariates.	**Superiority**
LDL cholesterol	Change from baseline in LDL (mmol/L) cholesterol to the average LDL cholesterol of weeks 12 to 28	FAS	Analysis method: MMRM.	**Superiority**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
			Categorical Variables: Region, History of CV visits and visits by treatment. BL LDL, BL Hb and BL eGFR as continuous covariates.	
Rescue medication	Use and time to first use of rescue therapy in the first 24 weeks of treatment (incidence rate per 100 patient years at risk)	FAS	Method: Cox regression + Kaplan-Meier. Categorical Variables: Stratified on Region, History of CV and adjusted on BL Hb, BL eGFR as continuous covariates.	**Superiority**
HRQoL	Change from baseline in SF-36 VT subscore (points) to the average VT subscore of weeks 12 to 28	FAS	Analysis method: MMRM. Categorical Variables: Region, History of CV visits and visits by treatment. BL Hb, BL SF-36 VT subscore and BL eGFR as continuous covariates.	**Superiority**
HRQoL	Change from baseline in SF-36 PF subscore (points) to the average PF subscore of weeks 12 to 28	FAS	Analysis method: MMRM. Categorical Variables: Region, History of CV visits and visits by treatment. BL Hb, BL SF-36 PF subscore and BL eGFR as continuous covariates.	**Superiority**
CV profile	Change from baseline in MAP (mmHg) to the average MAP value of weeks 20 to 28*	FAS	Analysis method: MMRM. Categorical Variables: Region, History of CV visits and visits by treatment. BL MAP, BL Hb and BL eGFR as continuous covariates.	**Superiority**
CV profile	Occurrence and time to first occurrence of hypertension (defined as either systemic blood pressure >170 mmHg AND an increase from baseline ≥20 mmHg or as diastolic blood pressure >110 mmHg and an increase from baseline of ≥15 mmHg*	FAS	Analysis method: Cox regression + Kaplan-Meier. Categorical Variables: Stratified on Region and History of CV, and adjusted on BL Hb, BL eGFR as continuous covariates.	**Superiority**
Disease progression	Rate of progression of CKD measured by annualised eGFR slope over time*	FAS	Analysis Method: a random slopes and intercepts model using all available eGFR values (one baseline and all post-treatment values up to end of treatment period or start of dialysis)	**Superiority**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
			Categorical Variables: Baseline Hb, Region, CV history at baseline and the interaction terms (baseline eGFR by timepoint and baseline Hb by timepoint).	

Notes: *These key secondary endpoints were not included in the hierarchical testing procedure.

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; eGFr: estimated glomular filtration rate; FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; LDL: Low Density Lipoprotein; MAP: mean arterial pressure; PF: physical functioning; SF-36: short form 36 health survey questionnaire; US: United States; VT: Vitality.

B.2.4.3.2 ANDES

Statistical comparisons made for each endpoint in the ANDES trial conducted for the NDD population are defined in Table 9 (46).

Table 9. Sequential testing of primary and key secondary efficacy endpoints in the ANDES trial

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb maintenance	Hb (g/dL) response defined as: • Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL • or an increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response	FAS	CMH adjusting for the randomisation stratification factors comparing pooled roxadustat (TIW+BIW+QW) to pooled placebo. The hypothesis was tested at the two-sided alpha = 5% level of significance and was rejected if the p value <0.05 from the test. The 95% CIs based on CMH adjusted odds ratio was reported. In addition, the 95% CIs of the responder rate between treatment groups based on the exact method of Clopper-Pearson were calculated and presented.	**Superiority**
Secondary endpoint(s)				
Hb maintenance	Mean change from baseline in Hb averaged over eight-weeks of treatment at weeks 28 to 36 without rescue therapy	FAS	MMRM model with baseline Hb and eGFR as covariates and treatment group, visit, treatment visit interaction, and the other randomisation stratification factors as fixed effects.	**Superiority**
Hb maintenance	Mean change from baseline in Hb during the evaluation period (defined as week 28 until week 52) in patients with baseline CRP >ULN	FAS	MI ANCOVA model with baseline Hb as a covariate and treatment group, visit, treatment visit interaction, and the above-mentioned stratification factors as fixed effects.	**Superiority**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Hb response	Proportion of patients with Hb level ≥10 g/dL between week 28 to 36, without use of rescue therapy	FAS	CMH adjusting for the randomisation stratification factors.	**Superiority**
Hb maintenance	Hb maintenance by dose frequency: TIW, BIW, QW	FAS	Same method as primary efficacy endpoint	**Superiority**
CV profile	Mean change from baseline in LDL cholesterol averaged over weeks 12 to 28	FAS	MMRM models with baseline LDL cholesterol as a covariate and treatment group, visit, treatment visit interaction, and the above-mentioned stratification factors as fixed effects.	**Superiority**
Rescue medication	Time to rescue therapy (composite of blood/RBC transfusion, ESA use, and IV iron) in the first 52 weeks of treatment	FAS	Cox proportional hazards model	**Superiority**
HRQoL	Mean change from baseline in SF-36 VT subscore averaged over weeks 12 to 28	FAS	MMRM models with baseline LDL cholesterol as a covariate and treatment group, visit, treatment visit interaction, and the above-mentioned stratification factors as fixed effects.	**Superiority**
eGFR	Progression of CKD: rate of change in eGFR over time adjusted by baseline eGFR, censored at dialysis or kidney transplant	FAS	Random slope and intercept model	**Superiority**
Rescue medication	Times to RBC transfusion in the first 52 weeks of treatment	FAS	Cox proportional hazards model	**Superiority**
HRQoL	Mean change from baseline in SF-36 VT sub score averaged over weeks 12 to 28	FAS	MMRM models with baseline LDL cholesterol as a covariate and treatment group, visit, treatment visit interaction, and the above-mentioned stratification factors as fixed effects.	**Superiority**
Blood pressure	Mean change from baseline in MAP averaged over weeks 20 to 28	FAS	MMRM models with baseline LDL cholesterol as a covariate and treatment group, visit, treatment visit interaction, and the above-mentioned stratification factors as fixed effects.	**Superiority**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Blood pressure	Time to (and proportion of patients with) worsened hypertension	FAS	Hazard ratio and its associated 95% CI were computed between the roxadustat group vs. placebo group.	**Superiority**

Abbreviations: BIW: twice weekly; CI: Confidence interval; CKD: Chronic kidney disease; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; hsCRP: high-sensitivity C-Reactive Protein; ITT: intention-to-treat; IV: intravenous; LDL: low Density Lipoprotein; LS: Least square; MAP: mean arterial pressure; N/A not applicable; RBC: red blood cell; QW: once weekly; SF-36: short form 36 health survey questionnaire; TIW: Three times a week; US: United States; ULN: upper limit of normal.

B.2.4.3.3 OLYMPUS

Statistical comparisons made for each endpoint in the OLYMPUS trial conducted for the NDD population are defined in Table 10 (45).

Table 10. Sequential testing of primary and key secondary efficacy endpoints in the OLYMPUS trial

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb maintenance	Hb (g/dL) response defined as: • Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL • or an increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response	FAS	The proportion of responders in the primary efficacy variable was compared using a CMH test adjusting for geographic region, CV history, baseline Hb (≤8, >8 g/dL), and baseline eGFR (≤30, >30 mL/min/1.73 m^2), for roxadustat compared with placebo.	**Superiority**
Secondary endpoint(s)				
Hb maintenance	Change in Hb from baseline to the average Hb from weeks 28-52 for patients with baseline hsCRP greater than the ULN	ITT	Analogously as the primary efficacy endpoint	**Superiority**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Hb maintenance	Proportion of total time of interpolated Hb values ≥10 (g/dL) from weeks 28 to 52	ITT	ANCOVA with treatment group, geographic region, and CV history as fixed effects and baseline Hb and baseline eGFR as covariates.	**Superiority**
Hb maintenance	Proportion of total time of interpolated Hb values 10-12 (g/dL) from weeks 28 to 52	ITT	ANCOVA with treatment group, geographic region, and CV history as fixed effects and baseline Hb and baseline eGFR as covariates.	**Superiority**
CV profile	Mean change from LDL cholesterol (mmol/L) from baseline to week 24	ITT	ANCOVA with treatment, geographic region and CV history as fixed effects and baseline values for Hb, eGFR and LDL cholesterol as covariates.	**Superiority**
Rescue medication	Time to first instance of receiving IV iron, RBC transfusions, or erythropoietin analogue as rescue therapy	OT+28	Cox proportional hazard model analogously in the OT+28 analysis set. Baseline Hb, baseline eGFR, geographic region, and CV history were included as covariates.	**Superiority**
Rescue medication	Time to first administration of a RBC transfusion as rescue therapy	OT+28	Cox proportional hazard model in the OT+28 analysis set. Baseline Hb, baseline eGFR, geographic region, and CV history were included as covariates.	**Superiority**
HRQoL	Change from baseline in SF-36 VT subscore (points) to the average VT subscore of weeks 12 to 28	ITT	MMRM with treatment, visit, treatment-by-visit interaction, and baseline covariates, including the baseline score, baseline Hb, baseline eGFR, geographic region and CV history, as fixed effects, and patient as a random effect.	**Superiority**
Disease progression	Rate of progression of CKD measured by annualised eGFR slope over time	ITT	MMRM using all post-baseline eGFR values prior to initiation of dialysis/transplant. Baseline eGFR, baseline Hb, geographic region, CV history, treatment group and post-	**Superiority**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
			baseline eGFR measurement time were used as fixed effects, and patient and time as random effects i.e., random intercept and slope	
HRQoL	Change from baseline in SF-36 PF subscore (points) to the average PF subscore of weeks 12 to 28	ITT	MMRM with treatment, visit, treatment-by-visit interaction, and baseline covariates, including the baseline score, baseline Hb, baseline eGFR, geographic region and CV history, as fixed effects, and patient as a random effect	**Superiority**

Abbreviations: CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; hsCRP: high-sensitivity C-Reactive Protein; ITT: intention-to-treat; IV: intravenous; LDL: Low Density Lipoprotein; OT+28: On treatment plus 28 days; ULN: upper limit of normal; US: United states.

B.2.4.3.4 DOLOMITES

Statistical comparisons made for each endpoint in the DOLOMITES trial conducted for the NDD population are defined in Table 11 (42).

Table 11. Sequential testing of primary and key secondary efficacy endpoints in the DOLOMITES trial

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb maintenance	Hb (g/dL) response defined as: • Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL or • An increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response)	PPS	The proportion of responders in the primary efficacy variable was compared using a Miettinen & Nurminen (MN) approach, adjusting for covariates (Region, Baseline Hb values, History of cardiovascular, cerebrovascular or thromboembolic diseases and Baseline eGFR) and comparing roxadustat to darbepoetin alfa. Alternatively, use of standard normal statistic proposed by Gart and Nam was also permitted.	**Non-inferiority was concluded if the margin for the difference between groups is 0.15**
Secondary endpoint(s)				
Hb maintenance	Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period	PPS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL Hb, BL Hb by visit and BL eGFR as continuous covariates.	**Non-inferiority was concluded if the lower bound of the 95% CI of the difference was LSM is >-0.75 g/dL**
LDL cholesterol	Change from baseline in LDL cholesterol (mmol/L) to the average LDL cholesterol of weeks 12 to 28	FAS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by	**Superiority**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
			treatment as categorical variables. BL LDL, BL Hb and BL eGFR as continuous covariates.	
Rescue medication	Time to first use of IV iron in weeks 1–36 (per 100 patient years at risk)	FAS	Method: Cox regression + Kaplan-Meier. Covariates: Stratified on Region, history of cardiovascular, cerebrovascular or thromboembolic disease and adjusted on BL Hb, BL eGFR as continuous covariates.	**Superiority**
HRQoL	Change from baseline in SF-36 PF subscore (points) in weeks 12–28	PPS	Analysis method: MMRM. Covariates: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 PF subscore and BL eGFR as continuous covariates.	**Non-inferiority was concluded if the lower bound of the 95% CI of the difference of LSM was >-3 points**
HRQoL	Change from baseline in SF-36 VT subscore (points) in weeks 12–28	PPS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 VT subscore and BL eGFR as continuous covariates	**Non-inferiority was concluded if the lower bound of the 95% CI of the difference of LSM was >-3 points**
CV profile	Change from baseline in MAP (mmHg) to the average MAP value in weeks 20 to 28	PPS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL MAP, BL Hb and BL eGFR as continuous covariates.	**Non-inferiority was concluded if the upper bound of the 95% CI of the difference of LSM was <1 mmHg**

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
CV profile	Occurrence and time to first occurrence of hypertension (defined as [SBP ≥170 mmHg and SBP increase from BL ≥20 mmHg] or [DBP ≥110 mmHg AND DBP increase from BL ≥15 mmHg]) during weeks 1 to 36	PPS	Analysis Method: Cox regression + Kaplan-Meier. Covariates: Stratified on treatment group, region and history of cardiovascular, cerebrovascular or thromboembolic disease and adjusted on BL Hb, BL eGFR as continuous covariates.	**Non-inferiority was concluded if the lower bound of the 95% CI of the difference was LSM is >-0.75 g/dL**

Abbreviations: BL: baseline; CI: confidence intervals; CV: cardiovascular; DBP: diastolic blood pressure; FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; ITT: intention-to-treat; IV: intravenous; LDL: low density lipoprotein; LSM: least squares mean; MAP: mean arterial pressure; PF: physical functioning; PPS: per protocol set; SBP: systolic blood pressure; SF-36: short form 36 health survey questionnaire; US: United States; VT: vitality.

B.2.4.4 Participant flow

The participant flows for all studies are described in detail in Appendix D, Section D.1.2. The number of patients randomised in each trial are presented in Table 12.

Table 12. Patient randomization in each trial (NDD population)

Trial	Total patients enrolled	Total patients randomised	Randomisation to each study arm	
			Roxadustat	Comparator*
ALPS (43)	1,051	597	394	203
ANDES (46)	1,672	922	616	306
OLYMPUS (45)	5,222	2,781	1,393	1,388
DOLOMITES (42)	930	616	323	293

Notes: *Comparator denotes placebo for ALPS, ANDES and OLYMPUS trials, and darbepoetin alfa for DOLOMITES trial.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Overall, the ALPINE phase III clinical trials for roxadustat met all quality standards and followed good clinical practices. Randomisation in the trials was carried out appropriately such that baseline characteristics were well balanced across treatment arms. Patients and investigators remained blinded throughout the placebo-controlled studies. The quality of study data across all trials presented in this submission was assured through monitoring of investigational centres, provision of appropriate training for study personnel, and use of data management procedures. A good clinical practice audit program was undertaken to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits were conducted by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, which were directed towards all aspects of the clinical study process and its associated documentation.

B.2.6 Clinical effectiveness results of the relevant trials

Unless stated otherwise, all data in this section originate from the ALPS, ANDES, OLYMPUS, and DOLOMITES clinical study reports or key publications (42, 43, 45, 46, 52-55). A summary of the methodology and key results of four phase III trials in DD patients are presented in Appendix L.

The clinical effectiveness results are provided separately for each trial as reported in the CSRs and publications. However, the economic analyses were informed by a

pooled dataset from all four studies in the NDD population. Detailed reports of all analyses conducted on individual patient data (IPD) to inform the economic model are provided in Section B.3 and the IPD Report (56).

B.2.6.1 ALPS

B.2.6.1.1 Primary endpoint

ALPS met its primary endpoint, demonstrating statistical superiority of roxadustat to placebo in terms of response rate to treatment during the first 24 weeks without rescue therapy. The primary analysis was conducted on the FAS population. Overall, 79.2% of patients in the roxadustat treatment group achieved a Hb response compared with 9.9% in the placebo group. The difference in proportions was 69.3% (95% confidence interval [CI]: 63.7%, 75.1%; P<0.001) (Table 13) (43).

Table 13. Hb response without rescue therapy (FAS population)

	Roxadustat (N=389)	Placebo (N=203)	Difference of proportions	Odds ratio
Number of responders, n (%)	308 (79.2%)	20 (9.9%)	69.3%	34.74
95% CI	74.8, 83.1	6.1, 14.8	63.6, 75.1	20.48, 58.93 P<0.001

Abbreviations: CI: confidence intervals; FAS: full analysis set.

B.2.6.1.2 Key secondary endpoints

Key secondary endpoints were analysed in a predefined, sequence. In the sequentially tested key secondary endpoints, superiority of roxadustat versus placebo was demonstrated for Hb change from baseline to the average of weeks 28-36, low density lipoprotein (LDL) cholesterol change from baseline to the average of weeks 12–28, and time to use of rescue medication. The study did not demonstrate statistical superiority of roxadustat versus placebo for changes in the 36-Item Short Form Survey (SF-36) vitality (VT) and physical functioning sub scores (Table 14) (43).

Table 14. Summary of secondary endpoints

Classification	Endpoint	Population assessed	Roxadustat vs. placebo	Test type
Hb maintenance	Change from baseline to the average Hb in weeks 28-36 (g/dL); difference of LSM (95% CI)	FAS	1.599 (1.41, 1.78) P<0.001	Superiority met
LDL Cholesterol	Change from Baseline in LDL cholesterol to the Average LDL Cholesterol (mmol/L) in Weeks 12 to 28	FAS	-0.701 (-0.83, -0.57) P < 0.001	Superiority met
Rescue medication	Use and time to use of rescue therapy during the efficacy emergent period ‡; HR (95% CI)	FAS	0.238 (0.17, 0.33) P<0.001	Superiority met
HRQoL	Change from baseline in SF-36 VT subscore to the average SF-36 VT in weeks 12-28 (points); difference of LSM (95% CI)	FAS	1.127 (-0.19, 2.44) P=0.093	Superiority not met
HRQoL	Change from baseline in SF-36 PF subscore to the average SF-36 PF in weeks 12-28 (points); difference of LSM (95% CI)	FAS	0.713 (-0.56, 1.98) P=0.270	Superiority not met
HRQoL	Change from baseline in the FACT-An AnS to the average of weeks 12 to 28	FAS	[redacted]	[redacted]
HRQoL	Change from baseline in the FACT-An total score to the average of weeks 12 to 28	FAS	[redacted]	[redacted]
CV profile	Change from baseline in MAP to the average MAP value of weeks 20 to 28 (mmHg); difference of LSM (95% CI) *	FAS	[redacted]	[redacted]
CV profile	Occurrence and time to first occurrence of hypertension (defined as either systemic blood pressure >170 mmHg AND an increase from baseline ≥20 mmHg or as diastolic blood pressure >110 mmHg and an increase from baseline of ≥15 mmHg; HR (95% CI)*	FAS	[redacted]	[redacted]
Kidney function	Rate of progression of CKD measured by annualised eGFR slope over time (ml/min per 1.73 m^2); difference of LSM (95% CI) *	FAS	[redacted]	[redacted]

Notes: ‡The efficacy emergent period is defined as the evaluation period from the analysis date of first dose intake up to seven days after the analysis date of last dose or EOT visit, whichever occurs first. *These key secondary endpoints were not included in the hierarchical testing procedure.

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; eGFr: estimated glomular filtration rate; FAS: full analysis set; Hb: haemoglobin; HR: hazard ratio; HRQoL: health-related quality of life; LDL: Low Density Lipoprotein; LSM: least square mean; MAP: mean arterial pressure; PF: physical functioning; SF-36: short form 36 health survey questionnaire; US: United States; VT: Vitality.

B.2.6.1.3 Additional analyses

IV iron supplementation

The incidence rate per 100 patient years at risk for patients receiving IV iron was [redacted] in the roxadustat group ([redacted]) compared with the placebo group ([redacted]), hazard ratio (HR) of [redacted](95% CI: [redacted]; P=[redacted]), showing superiority of roxadustat compared with placebo (Table 15) (43).

Table 15. Time to first use of IV iron during efficacy emergent period (FAS population)

	Roxadustat (n=389)	Placebo (n=203)
Number of patients with IV iron, n (%)	[redacted]	[redacted]
Cumulative time at risk (years)	[redacted]	[redacted]
Incidence rate (per 100 patient years at risk)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value	[redacted]	

Abbreviations: IV: intravenous; HR: hazard ratio; TEAE: treatment-emergent adverse event; NCI CTC: National Cancer Institute - common terminology criteria for adverse events; SAF: safety analysis set.

EuroQol five-dimension five level (EQ-5D-5L)

The mean (SD) change from baseline in the EQ-5D-5L score to the average of weeks 12 to 28 was greater in the roxadustat group [redacted] compared with the placebo group [redacted] Mean change from baseline at week 12 was [redacted] in the roxadustat group compared with [redacted] in the placebo group (43).

B.2.6.2 ANDES

B.2.6.2.1 Primary endpoint

ANDES met its primary endpoint, demonstrating statistical superiority of roxadustat to placebo in terms of response rate to treatment during the first 24 weeks of treatment without patients having received rescue therapy. Overall, 86% of patients in the roxadustat treatment group achieved a Hb response compared with 6.6% in the placebo group. The odds ratio (OR) (OR=77.56 95% CI:44.73, 134.48 p<0.001) was statistically significant and clinically meaningful (Table 16) (46).

Table 16. Hb response without rescue therapy (FAS population)

	Roxadustat (N=608)	Placebo (N=305)	Odds Ratio
Number of responders, n (%)	523 (86.0)	20 (6.6)	77.56
95% CI	83.0, 88.7	4.1, 9.9	44.73, 134.48; P<0.0001

Abbreviations: CI: confidence interval; FAS: full analysis set.

B.2.6.2.2 Key secondary endpoints

In the sequentially tested key secondary endpoints, superiority of roxadustat versus placebo was demonstrated for Hb change from baseline to the average of weeks 28-36, baseline to the average of weeks 28-36 in inflamed patients, LDL cholesterol change from baseline to the average of weeks 12–28, and time to use of rescue medication. The study did not demonstrate statistical superiority of roxadustat versus placebo rate of change in estimated glomerular filtration rate (eGFR) over time (46).

Table 17. Summary of key secondary endpoints

Classification	Outcome	Population assessed	Roxadustat vs. placebo (CI)	Conclusion
Hb maintenance	Mean change from baseline in Hb averaged over eight-weeks of treatment at weeks 28 to 36 without rescue therapy; difference in LSM (95% CI)	FAS	1.88 (1.730, 2.037) P<0.0001	Superiority met
Hb maintenance	Mean change from baseline in Hb during the evaluation period (defined as week 28 until week 52) in patients with baseline CRP >ULN; difference in LSM (95% CI)	FAS	1.90 (1.66, 2.14) P<0.0001	Superiority met
Hb maintenance	Mean change from baseline in Hb averaged over eight-weeks of treatment at weeks 28 to 36 for patients on a QW dose frequency; difference in LSM (95% CI)	FAS	1.64 (1.34, 1.94) P<0.0001	Superiority met
Hb maintenance	Mean change from baseline in Hb averaged over eight-weeks of treatment at weeks 28 to 36 for patients on a BIW dose frequency; difference in LSM (95% CI)	FAS	2.24 (1.96, 2.52) P<0.0001	Superiority met
Hb maintenance	Mean change from baseline in Hb averaged over eight-weeks of treatment at weeks 28 to 36 for patients on a TIW dose frequency; difference in LSM (95% CI)	FAS	1.93 (1.79, 2.08) P<0.0001	Superiority met
Hb response	Proportion of patients with Hb level ≥10 g/dL between week 28 to 36, without use of rescue therapy; odds ratio (95% CI)	FAS	OR: 15.47 (10.79, 22.19) P<0.0001	Superiority met
LDL Cholesterol	Mean change from baseline in LDL cholesterol averaged over weeks 12 to 28; difference in LSM (95% CI)	FAS	-17.26 (-20.65, -13.87) P<0.0001	Superiority met
Rescue medication	Proportion of patients who received rescue therapy in the first 52 weeks of treatment; HR (95% CI)	FAS	0.19 (0.14, 0.28) P<0.0001	Superiority met
HRQoL	Mean change from baseline in SF-36 VT subscore averaged over weeks 12 to 28; difference in LSM (95% CI)	FAS	1.22 (0.15, 2.23) P=0.026	Superiority met
HRQoL	Mean change from baseline in SF-36 PF subscore averaged over weeks 12 to 28; difference in LSM (95% CI)	FAS	0.60 (-0.40, 1.60) P=0.2380	Superiority not met
HRQoL	Changes in FACT-An Anaemia Subscore from baseline to mean value during week 28 to 52	[redacted]	[redacted]	[redacted]
HRQoL	Changes in total FACT-An scores from baseline to mean value during week 28 to 52	[redacted]	[redacted]	[redacted]
HRQoL	Changes in adjusted LS mean EQ-5D-5L index values from baseline to mean value during week 28 to 52	[redacted]	[redacted]	[redacted]
eGFR	Rate of change in eGFR over time adjusted by baseline eGFR, censored at dialysis or kidney transplant; difference in LSM (95% CI)	FAS	2.53 (0.51, 4.55) P=0.0140	Superiority not met

Classification	Outcome	Population assessed	Roxadustat vs. placebo (CI)	Conclusion
Rescue medication	Time to RBC transfusion in the first 52 weeks of treatment; difference in LSM (95% CI)	FAS	0.26 (0.14, 0.45) P<0.0001	Superiority met
Blood pressure	Mean change from baseline in MAP averaged over weeks 20 to 28; OR	FAS	0.36 (0.74, 1.47) P=0.5180	Superiority not met
Blood pressure	Time to (and proportion of patients with) worsened hypertension; OR	FAS	1.16 (0.83, 1.62) P=0.3814	Superiority not met

Abbreviations: BIW: twice weekly; CFB: Change from baseline; CRP: c-reactive protein; eGFR: estimated glomerular filtration rate; FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; hsCRP: high-sensitivity C-Reactive Protein; ITT: intention-to-treat; IV: intravenous; LDL: low density lipoprotein; MAP: mean artierial pressure; OR: odds ratio; QW: Once weekly; TIW: Three time weekly; ULN: upper limit of normal; US: United states.

B.2.6.2.3 Additional analyses

IV iron supplementation

Over the entire treatment period, results for reducing risk of IV iron therapy favoured roxadustat but there was no significant difference between the treatment arms (incidence rate per 100 patient exposure years [PEY], HR: [redacted] (95%: [redacted]; p=[redacted]) (46).

Table 18. Time to first use of IV iron ANDES

Trial	ANDES	
Treatment arms	**Roxadustat (n=608)**	**Placebo (n=305)**
Number of patients with IV iron, n (%)	[redacted]	[redacted]
Cumulative time at risk (years)	[redacted]	[redacted]
Incidence rate (per 100 patient years at risk)	[redacted]	[redacted]
HR	[redacted]	
95% CI	[redacted]	
P value	[redacted]	

Abbreviations: NR: not reported; CI: confidence intervals; HR: hazard ratio; IV: intravenous.

EQ-5D-5L

The mean (SD) change from baseline averaged over Weeks 12-28 in EQ-5D-5L score was [redacted] in the roxadustat arm vs. [redacted]in the placebo arm. The least squared mean difference between the two treatment arms was 2.00 ([redacted]) [95% CI: [redacted]], with p=[redacted](significant improvement in EQ-5D-5L score for roxadustat vs. placebo) (46).

B.2.6.3 OLYMPUS

B.2.6.3.1 Primary endpoint

OLYMPUS met primary endpoint, demonstrating statistical superiority of roxadustat to placebo in terms of response rate to treatment during the first 24 weeks of treatment without patients having received rescue therapy. The primary analysis was conducted on the FAS population. Overall, 77.0% of patients in the roxadustat treatment group achieved a Hb response compared with 8.5% in the placebo group. The relative risk (RR) (RR: 9.12 [95% CI: 7.63, 10.89 p<0.001]) was statistically significant and clinically meaningful (Table 19) (45).

Table 19. Hb response without rescue therapy (FAS population)

	Roxadustat (N=1371)	Placebo (N=1357)	Relative risk
Number of responders n (%)	1055 (77.0%)	115 (8.5%)	9.12
95% CI	N/A	N/A	7.63, 10.89; P<0.001

Abbreviations: CI: confidence intervals; FAS: full analysis set; N/A: not applicable.

B.2.6.3.2 Key secondary endpoints

Key secondary endpoints were analysed in a fixed, predefined sequence (Table 20). In the sequentially tested key secondary endpoints, superiority of roxadustat versus placebo was demonstrated for Hb change from baseline to the average of weeks 28-36, LDL cholesterol change from baseline to the average of weeks 12–28, and time to use of rescue medication. The study did not demonstrate statistical superiority of roxadustat versus placebo for changes in the SF-36 VT and physical functioning subscores (45).

Table 20. Summary of secondary endpoints

Classification	Endpoint	Population assessed	Roxadustat vs. placebo	Test type
Hb maintenance	Change in Hb from baseline to the average Hb from weeks 28-52 for patients with baseline hsCRP greater than the ULN; difference in LSM (95% CI)	ITT	1.13 (0.91, 1.35) P<0.001	Superiority met
Hb maintenance	Proportion of total time of interpolated Hb values ≥10 (g/dL) from weeks 28 to 52 ≥10 (g/dL) from weeks 28 to 52; difference in LSM (95% CI)	FAS	0.50 (0.47, 0.52) P<0.001	Superiority met
Hb maintenance	Proportion of total time of interpolated Hb values 10-12 (g/dL) from weeks 28 to 52; difference in LSM (95% CI)	ITT	0.42 (0.40, 0.45) P<0.001	Superiority met
LDL Cholesterol	Mean change from LDL cholesterol (mmol/L) from baseline to week 24; difference in LSM (95% CI)	ITT	-0.36 (-0.42, -0.29; P<0.001	Superiority met
Rescue medication	Time to first instance of receiving IV iron, RBC transfusions, or erythropoietin analogue as rescue therapy; HR (95% CI)	OT+28	0.26 (0.23, 0.31) P<0.001	Superiority met
Rescue medication	Time to first administration of an RBC transfusion as rescue therapy; HR (95% CI)	OT+28	0.37 (0.30, 0.44) P<0.001	Superiority met
HRQoL	Change from baseline in SF-36 VT subscore (points) to the average VT subscore of weeks 12 to 28; difference in LSM (95% CI)	ITT	0.44 (-0.11, 0.99) P=0.120	Superiority not met
HRQoL	Change from baseline in SF-36 PF subscore (points) to the average PF subscore of weeks 12 to 28; difference in LSM (95% CI)	ITT	0.52 (0.0, 1.05) P=0.051	Superiority not met
HRQoL	Changes in total FACT-An scores from baseline to mean value during week 28 to 52	[redacted]	[redacted]	[redacted]
HRQoL	Changes in adjusted LS mean EQ-5D-5L index values from baseline to mean value during week 28 to 52	[redacted]	[redacted]	[redacted]
HRQoL	Changes in PGIC scores from baseline to mean value during week 28 to 52	[redacted]	[redacted]	[redacted]
Disease progression	Rate of progression of CKD measured by annualised eGFR slope over time; difference in LSM (95% CI)	ITT	-0.51 (nominal P=0.046)	Superiority not met

Abbreviations: BL: baseline; CI: confidence intervals; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; ITT: intention-to-treat; IV: intravenous; OT+28: On-treatment plus 28 days; LSM: least squares mean; LDL: low density lipoprotein; MAP: mean arterial pressure; PF: physical functioning; RBC: red blood cell; SF-36: short form 36 health survey questionnaire; VT: vitality; ULN: upper limit of normal.

B.2.6.3.3 Additional analyses

IV iron supplementation

In the OT+28 set, a [redacted] proportion of patients in the roxadustat group received IV iron compared with the placebo group ([redacted] versus [redacted]%), respectively (HR[redacted] [95% CI: [redacted], p<[redacted]) (45).

Table 21. Time to first use of IV iron during efficacy emergent period (OT+28)

	Roxadustat (n=1384)	Placebo (n=1376)
Number of patients with IV iron, n (%)	[redacted]	[redacted]
Cumulative time at risk (years)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
P value	[redacted]	

Abbreviations: CI: confidence intervals; ESA: erythropoiesis-stimulating agent; IV: intravenous; OT+28: On treatment+28 days.

EQ-5D-5L (Exploratory endpoint)

The mean (SD) change from baseline at Week 12 in EQ-5D-5L in the roxadustat group and the placebo group was [redacted] vs. [redacted] respectively; least squared mean difference: [redacted]; 95% CI: [redacted]. At all other time points (Week 28, Week 52, and from Week 28 to Week 52), change from baseline in adjusted LS mean EQ-5D-5L scores were [redacted] between the two treatment groups (45).

B.2.6.4 DOLOMITES

B.2.6.4.1 Primary endpoint

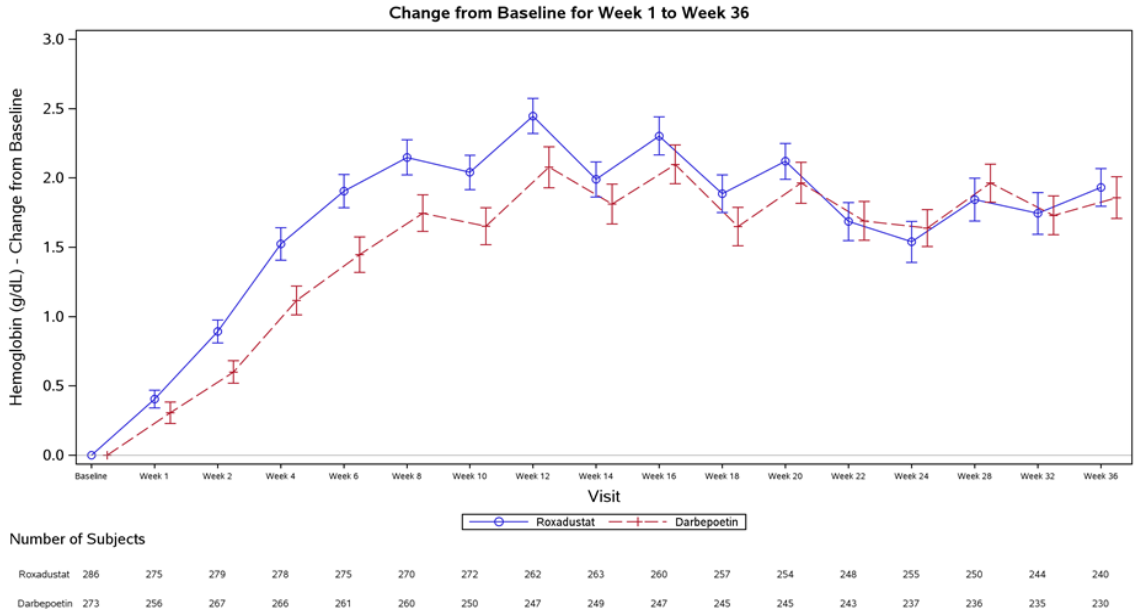
The DOLOMITES trial was the only head-to-head trial of roxadustat vs. ESA in the NDD CKD population. Roxadustat was non-inferior compared to darbepoetin alfa in terms of response to treatment in the first 24 weeks without rescue therapy. The difference in proportion of responders was 11.5% (95% CI: 5.7%, 17.4%); which was substantially larger than the pre-specified margin for non-inferiority (-15%) (Table 22). Change in Hb from baseline to week 36 is shown in Figure 7 (42).

Table 22. Hb response during first 24 weeks without use of rescue therapy (PPS population)

	Roxadustat (N=286)	Darbepoetin alfa (N=273)	Difference in proportion	Odds ratio
Number of responders, n (%)	256 (89.5%)	213 (78.0%)	11.51%	2.48
95% CI	85.4, 92.8	72.6, 82.8	5.66, 17.36	1.53, 4.04

Abbreviations: CI: confidence intervals; Hb: haemoglobin; PPS: per protocol set.

Figure 7. Mean (± 95% CI) change from baseline in Hb to week 36 (PPS population)



Abbreviations: CI: confidence intervals; Hb: haemoglobin; PPS: per protocol set.

B.2.6.4.2 Key secondary endpoints

Most key secondary efficacy endpoints demonstrated non-inferiority of roxadustat to darbepoetin alfa, including Hb change from baseline, health-related quality of life (HRQoL) endpoints, changes in mean arterial pressure (MAP) and occurrence of hypertension. Superiority was demonstrated for change in LDL cholesterol from baseline and time to first IV iron use (Table 23) (42).

Table 23. Summary of key secondary endpoints (DOLOMITES)

Classification	Endpoint	Population assessed	Roxadustat vs. darbepoetin alfa	Conclusion
Hb maintenance	Hb (g/dL) change from baseline to week's 28–36; difference in LSM (95% CI)	PPS	0.015 (-0.132, 0.161) P=0.844	Non-inferiority met
LDL cholesterol	LDL cholesterol (mmol/L) change from baseline to week's 12–28; difference in LSM (95% CI)	FAS	-0.404 (-0.510, -0.297) P<0.001	Superiority met
Rescue medication	Time to first use of IV iron in weeks 1–36; incidence rate (per 100 patient years at risk); HR (95% CI)	FAS	0.46 (0.27, 0.80) P=0.006	Superiority met
HRQoL	Change from baseline in SF-36 PF subscore (points) in weeks 12–28; difference in LSM (95% CI)	PPS	-1.280 (-2.420, -0.141) P=0.028	Non-inferiority met
HRQoL	Change from baseline in SF-36 VT subscore (points) in weeks 12–28; difference in LSM (95% CI)	PPS	-0.420 (-1.622, 0.781) P=0.492	Non-inferiority met
HRQoL	Change from baseline in the FACT-An AnS to the average of weeks 12 to 28	FAS	[redacted]	[redacted]
HRQoL	Change from baseline in the FACT-An total score to the average of weeks 12 to 28	FAS	[redacted]	[redacted]
HRQoL	Change from baseline to weeks 12 to 28 in the EQ-5D-5L VAS	FAS	[redacted]	[redacted]
CV profile	MAP (mmHg) change from baseline to average of weeks 20–28; difference in LSM (95% CI)	PPS	-0.362 (-1.577, 0.852) P=0.558	Non-inferiority met
CV profile	Time to first occurrence of hypertension in weeks 1–36; incidence rate (per 100 patient years at risk) (95% CI)	PPS	HR: 0.827 (0.56, 1.22) P=0.339	Non-inferiority met
CV profile	MAP (mmHg) change from baseline to average of weeks 20–28; difference in LSM (95% CI)	FAS	[redacted]	[redacted]
CV profile	Time to first occurrence of hypertension in weeks 1–36; incidence rate (per 100 patient years at risk) (95% CI)	FAS	[redacted]	[redacted]

Abbreviations: CI: confidence intervals; CV: cardiovascular; BL: baseline; FAS: full analysis set; Hb: haemoglobin; HR: hazard ratio; HRQoL: health-related quality of life; IV: intravenous; LSM: least squares mean; LDL: low density lipoprotein; MAP: mean arterial pressure; PF: physical functioning; PPS: per protocol set; SF-36: short form 36 health survey questionnaire; VT: vitality.

B.2.6.4.3 Additional analyses

Use of IV iron supplementation

A lower proportion of patients in the roxadustat group compared with the darbepoetin alfa group required IV iron during the efficacy emergent period ([redacted]vs [redacted] respectively). The incidence rate per 100 patient years at risk for patients receiving IV iron was lower in the roxadustat group compared with the darbepoetin alfa group ([redacted]vs [redacted]respectively); HR: [redacted](95% CI: [redacted]; p=[redacted]) [redacted] (42).

Table 24. Time to first use of IV iron during efficacy emergent period (FAS population)

	Roxadustat (n=322)	Darbepoetin alfa (n=292)
Number of patients with IV iron, n (%) †	[redacted]	[redacted]
Cumulative time at risk (years)	[redacted]	[redacted]
Incidence rate (per 100 patient years at risk)	[redacted]	[redacted]
HR	[redacted]	
95% CI	[redacted]	
P value	[redacted]	

Notes: † For patients who have received more than one IV iron, only their first event following study treatment is used.

Abbreviations: CI: confidence intervals; FAS: full analysis set; HR: hazard ratio; IV: intravenous.

EQ-5D-5L

Mean baseline EQ-5D-5L scores were [redacted] between the treatment groups ([redacted]roxadustat vs [redacted]darbepoetin alfa). There was an increase in EQ-5D-5L scores in both treatment groups' mean change from baseline to the average of weeks 12 to 28 and weeks 36 to 52. This increase was [redacted] in roxadustat group as compared to the darbepoetin alfa group. The mean change from baseline in the EQ-5D-5L scores during weeks 12 to 28 were [redacted]and [redacted], and for weeks 36 to 52 were [redacted]and [redacted]for the roxadustat group and darbepoetin alfa group respectively (42).

B.2.7 Subgroup analysis

Results of the subgroup analyses conducted in all clinical trials are provided in Appendix E.

B.2.7.1 ALPS

The results of all the subgroup analyses were consistent with the results for primary efficacy analysis (proportion of patients who achieve Hb response). The results for

all subgroups assessed (sex, age, region, baseline Hb, baseline CVD history, baseline eGFR, baseline C-reactive protein (CRP) and baseline TSAT and ferritin; P<0.001 for all subgroups) were consistent with the analysis of first key secondary endpoint. For all subgroups assessed (sex, age, region, baseline Hb, baseline CVD history and baseline eGFR; P<0.05 for all subgroups) were consistent with the analysis of the second key secondary endpoints (Hb change from baseline to the average Hb, without rescue therapy and change from baseline in LDL cholesterol to the average LDL cholesterol) (43).

B.2.7.2 ANDES

The subgroup analyses results were consistent with the primary efficacy analysis (proportion of patients who achieve Hb response). It was demonstrated that roxadustat significantly increases Hb compared to placebo irrespective of sex, age, baseline eGFR and CKD stage, as well as baseline Hb, CVD history, iron repletion status, and inflammation status as indicated by baseline CRP level. The treatment effect magnitude in each of these subgroups was consistent with the observed treatment effect for the overall population (46).

B.2.7.3 OLYMPUS

The results of the subgroup analyses of the key secondary endpoint (Change in Hb from baseline to the average Hb) were comparable to the analysis results of the main population. Subgroups include age, gender, race, baseline weight, body mass index (BMI), geographical region, CVD history, baseline Hb value, baseline eGFR value, diabetes history, baseline CRP, and baseline iron repletion status (45).

B.2.7.4 DOLOMITES

The results of all patient subgroup analyses (sex, age, geographical region, Hb at baseline, history of CVD, eGFR, CRP at baseline, TSAT and ferritin) for Hb response rate without rescue therapy (PPS) and regardless of rescue therapy use (FAS) were consistent with the primary efficacy analysis (proportion of patients who achieve Hb response). Results from the subgroup analyses were comparable to the overall population in each of the secondary endpoints (Hb change from baseline to the average Hb, without rescue therapy, change from baseline in LDL cholesterol to the

average LDL cholesterol, time to first use of IV iron and change from baseline in SF-36 PF and VT subscores) (42).

B.2.8 Meta-analysis

Treatment guidelines suggest that all short-acting or long-acting ESA are considered equivalent to each other in terms of efficacy at equivalent doses (1, 11, 36). This has also been validated by several studies concluding equivalent efficacy of ESA (having similar duration of action) at equivalent doses (57-61) and clinical expert feedback (39).

ESA treatment effect was derived from the DOLOMITES study. All other ESA used in the model were assumed to have the same efficacy and safety at equivalent doses (see section B.3.3.3).

B.2.9 Indirect and mixed treatment comparisons

As per the rationale described in section B.2.8, no indirect and mixed treatment comparisons were conducted.

B.2.10 Adverse reactions

This section provides an overview of key safety data from the roxadustat clinical trials conducted in the NDD population (42, 43, 45, 46). The main safety outcome in these trials was major adverse cardiovascular events (MACE) (a composite of all-cause mortality [ACM], myocardial infarction [MI] and stroke), and MACE+ (a composite of ACM, MI, stroke and hospitalisation for either unstable angina or congestive heart failure). The data presented in the following sections for MACE and MACE+ was sourced from the SmPC provided in Appendix C.

Disaggregated results concerning the number of MI, stroke and vascular access thrombosis (VAT) AEs are also detailed in the following sections, as these were the key adverse events included in the economic analyses (see section B.3.4.4)

Additional safety results (early discontinuation and treatment emergent adverse events occurring in ≥5% of patients) are provided separately for each NDD trial in Appendix F.

B.2.10.1 Cardiovascular safety

A meta-analysis of adjudicated MACE and MACE+ events was conducted to synthesize the information from the roxadustat phase 3 program. MACE, MACE+, and ACM outcomes were analysed for two relevant datasets using the pooled hazard ratio (HR) and its 95% confidence interval (CI). The two datasets included:

- A pooled placebo-controlled dataset in NDD patients (includes patients from studies OLYMPUS, ANDES and ALPS)
- A pooled ESA-controlled dataset in NDD and incident dialysis (ID) patients (includes patients from studies DOLOMITES, HIMALAYAS, SIERRAS and ROCKIES)

B.2.10.1.1 MACE

Pooled placebo analysis

In the NDD placebo-controlled trials, the analysis for MACE, MACE+ and ACM included all data from the start of study treatment until the end of post treatment safety follow-up (ITT). HRs were 1.10, 1.07 and 1.08, with upper limits of the 95% CIs of 1.27, 1.21 and 1.26, respectively. The ITT analysis has been included to illustrate an imbalance in risk distribution favouring placebo in the on-treatment analysis. The on-treatment analyses used a Cox model weighted inversely for the probability of censoring (IPCW method) which aims to correct for follow-up time differences between roxadustat and placebo including identified contributors to increased risk and early discontinuation, in particular eGFR determinants and Hb at baseline and over time. Whether any residual confounding is present with this model remains uncertain. The HRs for the on-treatment analyses were 1.26, 1.17 and 1.16 for MACE, MACE+ and ACM, respectively. The results of the analyses are summarized in Table 25.

Table 25. CV safety and mortality in placebo controlled NDD pool

	MACE		MACE+		ACM	
	Roxadustat at n= 2386	Placebo n = 1884	Roxadustat at n= 2386	Placebo n = 1884	Roxadustat at n= 2386	Placebo n = 1884
On treatment						
Number of events (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FAIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	

	MACE		MACE+		ACM	
	Roxadustat at n= 2386	Placebo n = 1884	Roxadustat at n= 2386	Placebo n = 1884	Roxadustat at n= 2386	Placebo n = 1884
ITT						
Number of events (%)						
FAIR						
HR (95% CI)						

Abbreviations: ACM: all-cause mortality; ACM is a component of MACE/MACE+. CI: confidence interval; FAIR: follow-up adjusted incidence rate (number of patients with event/100 patient years); HR: hazard ratio; ITT: intent-to-treat; MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

Pooled ESA analysis

In the Hb correction setting of NDD and ID, patients baseline characteristics and treatment discontinuation rates were comparable between the pooled roxadustat and pooled ESA patients. The analysis for MACE, MACE+ and ACM observed on treatment showed HRs of 0.79, 0.78 and 0.78, with upper limits of the 95% CIs of 1.02, 0.98 and 1.05, respectively. The on-treatment analyses support no evidence of increased cardiovascular safety or mortality risk with roxadustat compared with ESA in CKD patients requiring Hb correction. The results are summarised in Table 26.

The pooled ESA analysis include patients from trials that were not considered relevant to the decision problem covered in this submission, as these patients were receiving dialysis before treatment initiation. However, the DOLOMITES trial (42) was not powered to show a difference in the frequency of MACE between roxadustat and ESA. The pooled ESA analysis was therefore considered the most appropriate to show the comparable risk of CV safety between roxadustat and ESA.

Table 26. CV safety and mortality in ESA controlled pool

	MACE		MACE+		ACM	
	Roxadustat at n= 1083	ESA n =1059	Roxadustat at n= 1083	ESA n = 1059	Roxadustat at n= 1083	ESA n = 1059
On treatment						
Number of events (%)						
FAIR						
HR (95% CI)						

Abbreviations: ACM: all-cause mortality; ACM is a component of MACE/MACE+. CI: confidence interval; FAIR: follow-up adjusted incidence rate (number of patients with event/100 patient years); HR: hazard ratio; ITT: intent-to-treat; MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

B.2.10.1.2 Key adverse events

In a pooled analysis of NDD trials roxadustat showed a higher percentage of patients having MI, stroke, and VAT events compared to placebo (62). Compared to ESA, in the DOLOMITES trial roxadustat showed a smaller percentage of patients having MI and strokes, and a higher percentage of patients having VAT events (Table 27) (62).

Table 27. NDD pooled and DOLOMITES trial key adverse events

	NDD Pooled (OT+28)		DOLOMITES (SAF)	
Number of events(%)	**Roxadustat (N=2386)**	**Placebo (N=1884)**	**Roxadustat (N=323)**	**ESA (N=293)**
MI	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Vascular access thrombosis (VAT)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MI: myocardial infarction, VAT: vascular access thrombosis; SAF: safety analysis set

B.2.11 Ongoing studies

There are currently three ongoing studies investigating roxadustat, however, none are expected to provide additional evidence within the next 12-months. One, being conducted in Japan is not expected to report until 2023, and two in the US which are not relevant for the target population in this submission.

B.2.12 Innovation

Roxadustat is a first-in-class oral HIF-PH offering a new approach to the management of anaemia associated with CKD compared to current standard of care. It leverages the body's natural capacity (oxygen sensing or HIF pathway) to promote a coordinated erythropoiesis, activating several genes that stimulate EPO production and improve iron regulation, overcoming the negative impact of inflammation by downregulating hepcidin (40).

Roxadustat achieves and maintains target Hb response without the need for increased doses over time regardless of patient inflammation status, and reduces the use of IV iron supplementation (42, 43, 45, 46). Due to its oral administration, roxadustat may reduce costs associated with administration of ESA for those patients who cannot self-administer. Roxadustat reduces the need for IV iron infusions, thus reducing the burden associated with IV iron administration (42). In addition, roxadustat does not require cold-chain storage and transit or refrigeration in the patient's home as well as additional considerations related with disposal (once

syringes are used, they become biohazard material and require specific ways of disposal and destruction).

Roxadustat clinical data also supports a comparable benefit/risk profile in terms of cardiovascular and mortality risk compared to ESA (42).

B.2.13 Interpretation of clinical effectiveness and safety evidence

In ALPS, ANDES and OLYMPUS (43, 45, 46) (placebo-controlled trials), roxadustat achieved statistical superiority in the primary endpoint (Hb response rate) and demonstrated an important treatment benefit in achieving and maintaining Hb target doses while reducing the need for IV iron supplementation. In the DOLOMITES trial (42), roxadustat demonstrated non-inferiority against ESA in the primary efficacy endpoint (Hb response and maintenance) and numerically halved the number of non-responders during the first 24 weeks of treatment compared to ESA (10.5% vs. 22.0%). As well, patients receiving roxadustat needed fewer IV iron infusions compared to ESA (42), and placebo (43, 45, 46).

It should be noted that the main endpoint of the DOLOMITES trial (42) (non-inferiority for the primary efficacy endpoint of Hb response using a margin for the difference of proportions of 15% for roxadustat versus darbepoetin alfa, assuming at least 80% of patients in both treatment groups achieved a response) was defined in agreement with the EMA. A non-inferiority trial design is common when assessing the efficacy of a treatment to correct Hb levels versus an active comparator. Hb targets are guideline driven after pivotal trials with ESA demonstrated that increasing Hb levels above these target ranges were linked to adverse outcomes including increased CV risk.

Regarding safety, the key data for the target population were CV events. The analyses of adjudicated MACE (a composite of ACM, MI and stroke), and MACE+ (a composite of ACM, MI, stroke, and hospitalisation for either unstable angina or congestive heart failure) were therefore the main endpoints used to evaluate the safety of roxadustat. Due to lack of statistical power of the individual roxadustat trials to demonstrate significant differences in these composite endpoints, a meta-analysis of MACE and MACE+ was conducted using pooled data from the ALPINE program (42, 43, 45, 46). Given the decision problem presented in this submission, the key results were those analysing the pooled ESA-controlled dataset in NDD and incident

dialysis patients (including patients from DOLOMITES, HIMALAYAS, SIERRAS and ROCKIES clinical trials). In this analysis, roxadustat demonstrated a comparable benefit/risk profile in terms of cardiovascular and mortality risk compared to ESA. It should also be noted that although the DOLOMITES trial was not powered to show differences in MACE and MACE+, the results showed a favourable numerical trend for roxadustat (HRs: 0.81 and 0.90 respectively) (42). This evidence combined with the results of the primary trials shows roxadustat provides a robust benefit on anaemia management while the patient's safety and quality of life is not compromised and, on some levels, remains better as compared to ESA.

Roxadustat is positioned as an alternative to ESA for the treatment of adult patients with symptomatic anaemia associated with CKD who are NDD at the time of treatment initiation. Due to the progressive nature of CKD, it is expected that a proportion of patients whose anaemia is appropriately managed with roxadustat will require dialysis at some point of the CKD treatment pathway. The clinical data presented in this submission includes these patients as in the four NDD clinical trials, patients could continue roxadustat after starting dialysis. In addition, clinical experts confirmed that patients whose anaemia is appropriately managed with roxadustat should be allowed to continue treatment after starting dialysis.

Overall, the efficacy and safety results support a positive benefit/risk assessment of the use of roxadustat in adult patients with symptomatic anaemia associated with CKD who are NDD at the time of treatment initiation.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

In total, 13 publications assessing the cost-effectiveness of treatments for anaemia associated with CKD were identified. Given the characteristics of the identified models in terms of the population of interest, research question, and modelling approach, none of the identified models provided a cost-effectiveness analysis fully aligned with the decision problem covered in this submission. However, one study reported the cost-effectiveness of roxadustat in NDD patients with anaemia associated with CKD. Details of this publication are provided below. Please refer to Appendix G for details of the remaining identified studies.

Hu et al. 2020 (63) explored the efficacy, tolerance, and cost-effectiveness of roxadustat treatment for anaemia in patients with CKD not receiving dialysis. The authors conducted a meta-analysis to evaluate the clinical efficacy and tolerance of roxadustat for the correction of anaemia associated with CKD and developed a Markov model to evaluate the cost-effectiveness of roxadustat against placebo. Anaemia associated with CKD was classified by three disease states: Hb 10–12 g/dL (target), Hb < 10 g/dL (below target), or dead. The patients could remain at the same Hb level, transition to another Hb level, or die. The cycle length of the Markov model was set to three months with a time horizon of five years. Given the focus of this model was patients not receiving dialysis, the time horizon was selected based on the average time NDD patients take to progress to dialysis. Only direct medical costs, including the cost of drugs, routine blood and blood biochemical examinations, management of adverse events, and blood transfusion, were considered in the Markov model. The utility associated with different Hb target levels was based on the literature.

In comparison with placebo, the use of oral roxadustat to treat anaemia associated with CKD in NDD patients was more effective (3.36 quality adjusted life years (QALYs) vs 2.87 QALYs), and costly ($14,282 vs $1,756 United States dollars [USD]) over a five-year interval. The incremental QALY and incremental cost value for roxadustat treatment in comparison with a placebo were 0.49 QALYs and 12,526 USD, respectively, resulting in an incremental cost-effectiveness ratio (ICER) of $25,563 USD per QALY.

B.3.2 Economic analysis

No previous Health Technology Assessment (HTA) submissions for treatments of anaemia associated with CKD were identified, hence there was no precedent in any preferred methods to model this disease area. From the economic analyses identified through literature review no preferred method was identified, as authors employed different modelling methods (empirical models, Markov models and patient level simulations) and assumptions related to long term efficacy survival and QoL. In addition, treatment dose (and costs) for anaemia associated with CKD is highly related to treatment response and varies from patient to patient. Based on our assessment, none of the identified models captured these costs in an accurate manner.

Therefore, a de novo model was developed to estimate the costs and health outcomes of roxadustat for the treatment of symptomatic anaemia associated with CKD from a UK National Health Services (NHS) and Personal Social Services (PSS) perspective.

B.3.2.1 Patient population

In line with the clinical efficacy data presented in section B.2, roxadustat expected indication and the decision problem stated in section B.1, the cost-effectiveness analysis evaluates roxadustat for the treatment of adult patients with symptomatic anaemia associated with CKD who are NDD at the time of treatment initiation (all patients were allowed to continue roxadustat after starting dialysis).

B.3.2.2 Model perspective

The perspective adopted for the analyses is that of the NHS and PSS in England and Wales (in line with current NICE guidance) (64). Unless stated otherwise, all costs are report in pounds sterling (2020/21).

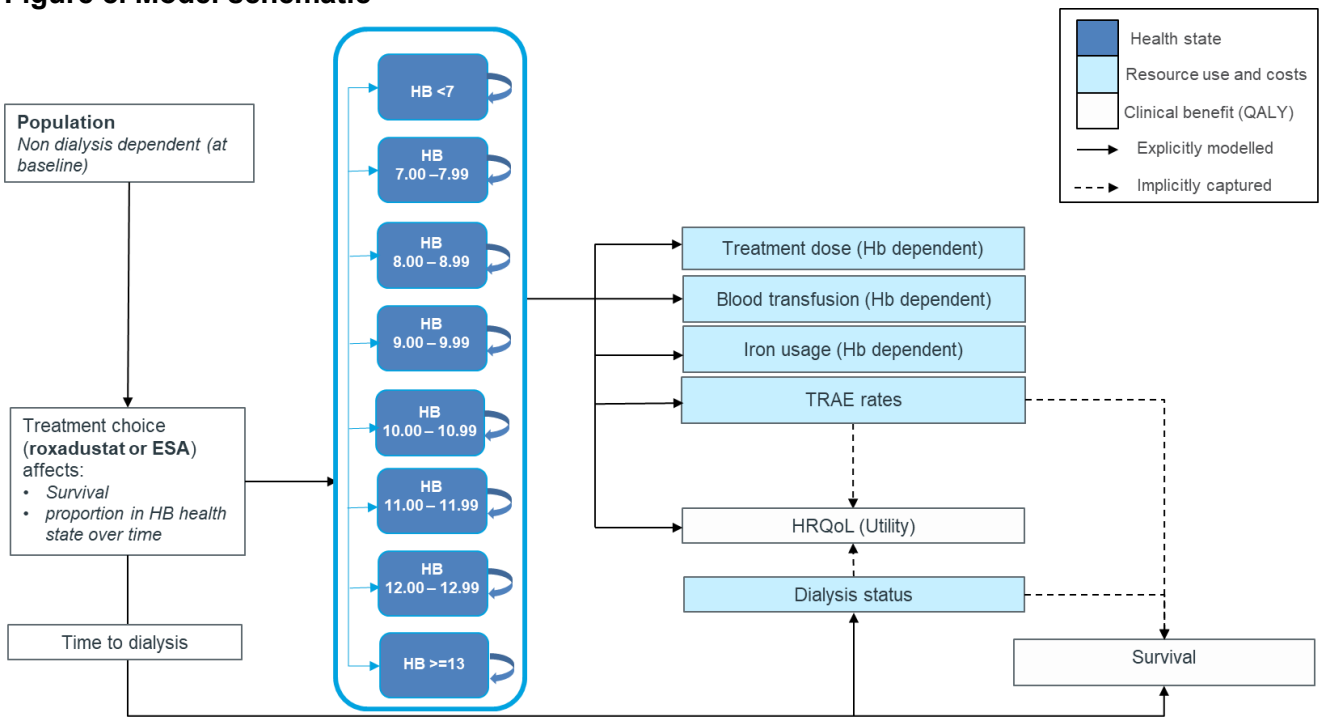
B.3.2.3 Model structure

The model estimated costs and health outcomes for a hypothetical cohort of patients with anaemia associated with CKD over a lifetime horizon (25 years). A three-month cycle was considered appropriate for the decision problem addressed in the model. The key clinical event of Hb level change is expected to occur multiple times a year but not necessarily expected to change rapidly. Considering regular monitoring of Hb

in clinical practice, a three-month cycle was considered appropriate to capture the changes in Hb levels a patient may experience, as well as any resultant changes to therapy.

Eight health states were defined to reflect the anaemia status based on different ranges of Hb levels (Figure 8).

Figure 8. Model schematic



Notes: Hb dependent: These outcomes are dependend on Hb level (i.e., dependent on the regression equation used to estimate Hb level)

Abbreviations: ESA: erythropoiesis-stimulating agents; Hb: haemoglobin; Tx: treatment; IV, intravenous; TRAE: treatment-related adverse events; HRQoL: health-related quality of life; QALY: quality adjusted life year.

A hypothetical patient cohort was modelled on the demographic and baseline characteristics from patients enrolled in the NDD roxadustat clinical trials (42, 43, 45, 46). Patient transitions were allowed between the eight Hb health states and death. The transition probabilities between health states at each cycle were informed by pooled analyses of IPD from the clinical trials as follows:

- The proportion of patients alive at each cycle was estimated using a parametric function fitted to survival data
- Patients alive at the beginning of each cycle were distributed across the eight Hb health states using a multinomial regression equation (time dependent transition probabilities). The treatment (roxadustat or ESA) impacted the transition probabilities over time

- Another parametric function fitted to time to dialysis data was used to estimate the proportion of patients on dialysis

In this process, costs and outcomes assigned for each health state were weighted by the patient distribution in each cycle. Several parameters to estimate costs and QALYs were also informed by IPD:

- Dosage of active therapy received (roxadustat or ESA)
- Supplementary iron usage
- Number of blood transfusions required per cycle
- HRQoL associated with each Hb health state

Outcomes that were captured implicitly within the model structure such as the relationship between dialysis status, survival and HRQoL, and the relationship between treatment related adverse events (TRAE), survival and HRQoL were not analysed directly by any statistical analyses (Figure 8). Instead, the relationship between the model inputs and these outcomes were based on the cohort average from the sample obtained from the non-dialysis trials (42, 43, 45, 46). For example, because survival was an explicitly modelled outcome in the model, the impact of dialysis status on mortality was not modelled directly in the non-dialysis population, but implicitly captured (i.e. it is an average of those who were not receiving dialysis and those that start dialysis treatment). By not directly modelling the relationship between all model inputs and outcomes, we avoid the possibility of double counting the outcome in the cost effectiveness model (CEM) where multiple inputs may have an impact on the outcome.

B.3.2.4 Intervention technology and comparators

The intervention considered for the analysis is roxadustat, a first in class oral HIF-PHI, and the comparator of interest is ESA. As indicated by NG8, ESAs are considered to have equal efficacy at equivalent doses. As such, ESAs have been modelled as a class within the present analysis (11). The primary set of comparators were selected to reflect UK clinical practice by including all available ESA in the British National Formulary (BNF) (65-69), as shown in Table 28.

Table 28. ESA therapies available in the BNF

Treatment	Brand name
Epoetin alfa	Eprex®
Epoetin beta	NeoRecormon®
Epoetin zeta	Retacrit®
Darbepoetin alfa	Aranesp®
Methoxy polyethylene glycol-epoetin beta	Mircera®

ESA are modelled as a class which assumes that the efficacy of treatment will not vary by different types of ESA, as per the UK NICE guidelines (11). As well, the comparators selected are in line with the phase III clinical trials programme of roxadustat described in detail in Section B.2.

Roxadustat is administered orally and ESA are administered either intravenously or subcutaneously.

B.3.3 Clinical parameters and variables

The population baseline characteristics and main clinical inputs informing the model have been obtained via IPD statistical analysis (56) of the non-dialysis trials (42, 43, 45, 46). A set of interrelated statistical equations have been used to generate estimates of the lifetime costs and benefits associated with the interventions of interest. Final model distributions were determined by the lowest Akaike Information Criteria (AIC) score, visual fit to the raw data and clinical plausibility of the long-term extrapolations (validated with clinical experts). Supporting materials around the IPD analysis methodology can be found in the IPD analyses report (56).

B.3.3.1 Patient baseline characteristics

Patient baseline characteristics were informed by the NDD trials (42, 43, 45, 46). Pooling was conducted by merging the different clinical trial datasets into one large dataset, grouping by individual patients. Each clinical trial was assigned a unique study identification to allow for nesting effects to be controlled for in all statistical analyses.

The population characteristics from the pooled dataset of the four NDD trials (42, 43, 45, 46) which included roxadustat, ESA and placebo patients, (42, 43, 45, 46) are presented in Table 29.

Table 29. Population characteristics

Characteristic	Value
Number of individuals	4,847

Starting age of population (years)	63.0
Proportion of patients: male	42.5%
Proportion of patients: female	57.5%
Proportion of patients with CVD history	38.3%
Proportion of patients with diabetes	55.5%
Median baseline eGFR	17.1
Proportion of patients from DOLOMITES	12.7%
Proportion of patients from ALPS	12.2%
Proportion of patients from ANDES	18.8%
Proportion of patients from OLYMPUS	56.3%

Abbreviations: CVD: cardiovascular disease; ESA: erythropoiesis-stimulating agents; eGFR: estimated glomerular filtration rate; NA: not available.

Health state occupancy at baseline is shown in Table 30. The baseline distribution of patients in the clinical trials were used to allocate patients at the start of the first cycle in the model.

Table 30. Health state occupancy at baseline

Health state	Value
Hb <7	[redacted]
Hb 7.00 to 7.99	[redacted]
Hb 8.00 to 8.99	[redacted]
Hb 9.00 to 9.99	[redacted]
Hb 10.00 to 10.99	[redacted]
Hb 11.00 to 11.99	[redacted]
Hb 12.00 to 12.99	[redacted]
Hb >= 13	[redacted]

Abbreviations: Hb: haemoglobin.

At baseline, there are no DD patients, but CKD progression to dialysis is taken into account and modelled as shown in Section B.3.3.4. In the model, the percentage of patients on dialysis after 10 years is [redacted]. Once in this state, the model splits the proportion of patients on haemodialysis and peritoneal dialysis. Data from the DOLOMITES trial was used to inform these parameters, as clinical experts confirmed these were in line with UK clinical practice (Table 31) (39, 42).

Table 31. Health state occupancy at baseline

Dialysis type	Value
Haemodialysis	182 (87.9%)
Peritoneal dialysis	25 (12.1%)

B.3.3.2 Mortality

Annual mortality rates for the general population were sourced from Office for National Statistics (ONS) life tables (70) and converted to three-monthly rates. A standardised mortality ratio (SMR) was then applied to these survival rates to ensure the all-cause mortality rate predicted by the IPD analysis did not happen at a slower rate than the expected mortality rate than that of the CKD population (i.e. this

ensures that using the IPD mortality extrapolations do not cause patients to live longer than expected for individuals with their condition). The SMR applied for NDD patients the model was 3.6, as sourced from a population-based cohort study (71).

The trial population survival was estimated using a range of conventional parametric survival regression models (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised Gamma). The statistical models controlled for treatment, CVD history, diabetic status, trial, baseline GFR and interaction terms between treatment type and baseline eGFR. The AIC, Bayesian information criterion (BIC) values, and graphical checks were used to determine the best fitting function to the data.

Based on statistical information criteria (Table 32), the exponential function was found to be the best in terms of BIC score, as well as long term clinical plausibility and a good visual fit. The extrapolated survival curves derived from the base case assumptions are presented in Figure 9. It should be noted these are shown as used in the model (i.e. constrained by the CKD adjusted general population mortality described in the previous section and assuming no treatment effect. The economic model has the functionality to select all the fitted curves for sensitivity analyses (Section B.3.7.3).

Table 32. AIC and BIC values

Curve	AIC	BIC
Exponential	**6,798**	**6,869**
Weibull	6,796	6,874
Gompertz	6,797	6,875
Log-normal	6,804	6,882
Log-logistic	6,796	6,874
Generalised gamma	6,798	6,882

Notes: *P ≤0.050; [1] Exp(CI).

Abbreviations: AIC: Akaike Information Criterion; Bayesian Information Criterion

The coefficients used to estimate the all-cause mortality curve following the methodology described above are shown in Table 33.

Table 33. Coefficients for covariates used in survival analyses

Parameter	Coefficient
Rate	[redacted]
ESA	[redacted]
Roxadustat[2]	[redacted]
History of CVD – Yes	[redacted]
Diabetic – Yes	[redacted]
Baseline eGFR	[redacted]
ESA: eGFR	[redacted]
Roxadustat: eGFR[2]	[redacted]

Notes: *P ≤0.050; [1] Exp(CI); [2]In the base case analysis this coefficient is not taken into consideration and all patients are assumed to be on ESA for the calculations.

Abbreviations: ESA: erythropoietin stimulating agents; CVD: cardiovascular disease; Exp: exponential; CI: confidence interval; eGFR: glomerular filtration rate

No treatment effect was applied in patient survival in the base case analysis. Data from DOLOMITES reported a favourable non-significant numerical trend benefit in mortality for roxadustat compared to ESA, but clinical experts suggested significant differences in survival would not be expected directly from the anaemia treatment (39, 42). Therefore, in order to reflect these recommendations, the roxadustat related coefficients described in Table 33 were omitted and the mortality estimations for roxadustat were set equal to those for patients treated with ESA.. By doing so, no treatment related effect was considered for the modelled population. A case where roxadustat treatment effect on mortality is incorporated in the mortality estimations is explored as part of the scenario analyses (Section B.3.7.3).

The Kaplan Meier data and extrapolated survival curves derived from the base case assumptions are presented in Figure 9. The extrapolated curves appear to underestimate survival as these were constrained by the CKD adjusted general population mortality (as described above). The economic model has the functionality to select all the fitted curves for sensitivity analyses (Section B.3.7.3).

Figure 9. Survival curves in the base case analysis

Abbreviations: KM: Kaplan Meier

The predicted median, 5-year, 10-year, 20-year, and 25-year survival (based on the exponential distribution, CKD adjusted background mortality and no treatment effect) are presented in Table 34.

Table 34. Median and landmark survival

Survival	Roxadustat	ESA
Median survival (years)		
5-year survival (%)		
10-year survival (%)		
20-year survival (%)		
25-year survival (%)		

Abbreviations: ESA: erythropoiesis stimulation agent.

B.3.3.3 Hb level

In the first cycle of the model, the proportion of patients in each health state at baseline are derived from the respective clinical trials (42, 43, 45, 46) as shown in Table 30.

In order to estimate the proportion of patients in any given Hb health state at any moment of time a multinomial regression model was used, controlling for treatment type, time, CVD history at baseline, diabetic status at baseline and an interaction between time and treatment type. The Hb g/dL were presented as categorical variables. Nesting effects due to the use of multiple studies were controlled for by incorporating study identification as a covariable within the model. The health state 10 ≤ Hb < 10.99 was used as the reference case in all statistical analyses due to it being within the clinical target Hb range (10 ≤ Hb < 12). The model which gave the best fit (in terms of statistical fit, visual fit and clinical plausibility) to the raw data was chosen.

The coefficients used to estimate the proportion in state following the methodology described are shown in Table 35. If a coefficient is greater than 0, the item increases the likelihood a patient will end up in that Hb level compared to the Hb level 10 -11 and if the coefficient is less than 0, the item decreases the likelihood a patient will end up in that Hb level compared to the Hb level 10 -11.

Table 35. Coefficients for Hb level regression analysis

	Intercept	Time[1]	ESA[2]	Roxadustat	Time:ESA[1]	Time: Roxadustat[1]	CVD history at baseline (Yes)	Diabetic at baseline (Yes)	Study OLYMPUS	Study ANDES	Study DOLOMITES
Hb level 0-7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 13-20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001. [1] Time has been log transformed to be log (Time + 1) ;[2] In the model, darbepoetin alfa is being used as a proxy

Abbreviations: ESA: erythropoietin stimulating agents; CVD: cardiovascular disease; Exp: exponential; CI: confidence interval.

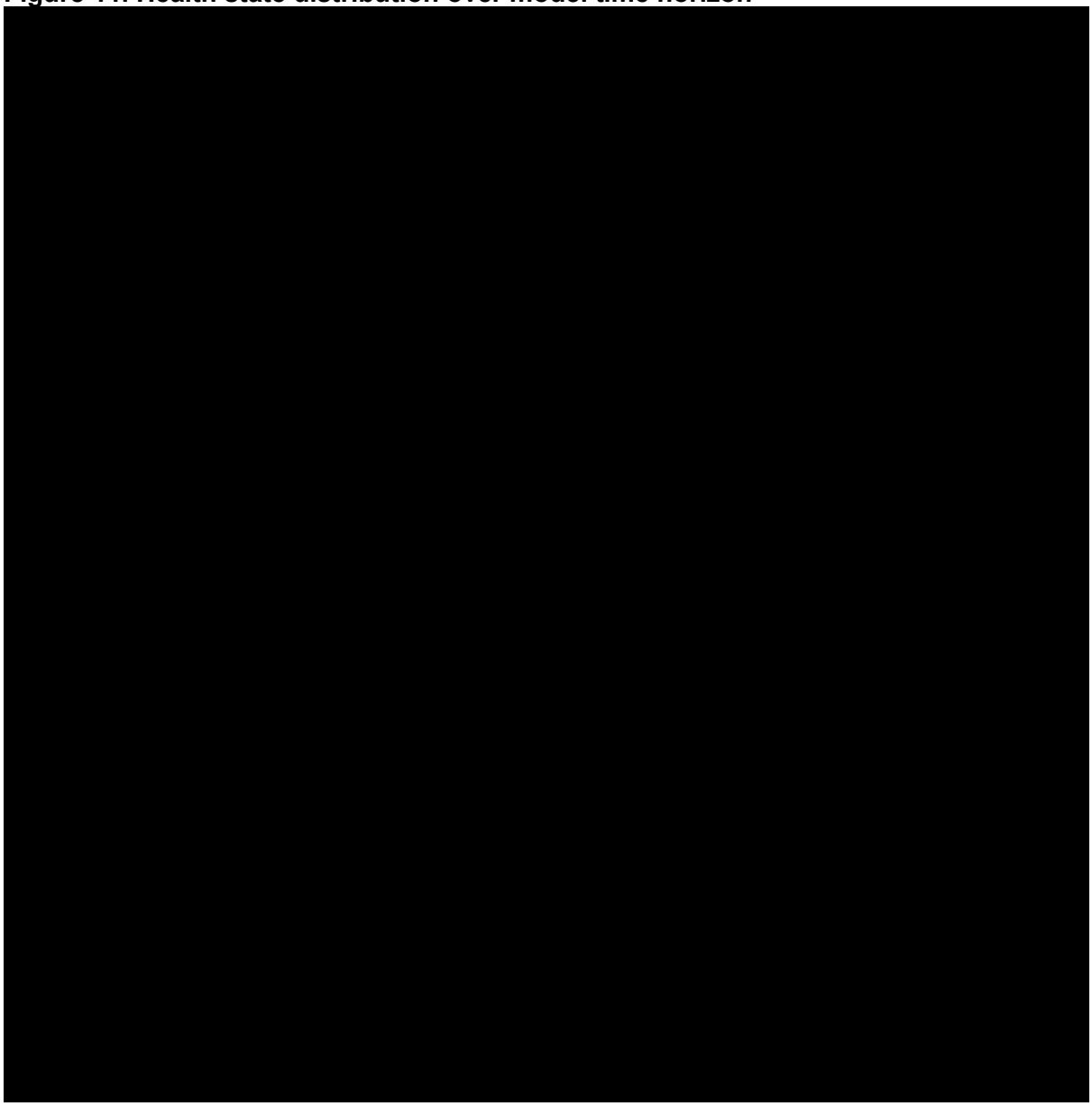
The observed trial data, along with the regressions used to estimate the health state distribution in the model are presented in Figure 10. These data expand the period of the clinical trials and shows that the regressions provide a good fit to the observed data.

Figure 10. Proportion in state over trial period

Abbreviations:ESA: erythropoietin stimulating agents; Hb: haemoglobin

To model a lifetime horizon, the health state occupancy was extrapolated using the regressions described above. The resultant health state occupancy (i.e. anaemia level) over the time horizon of the model is represented in Figure 11.

Figure 11. Health state distribution over model time horizon



Abbreviations: Hb: haemoglobin.

B.3.3.4 Time to dialysis

Time to dialysis was estimated using the same parametric survival regression models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised Gamma) used for survival. As before, the parametric models controlled for CVD history, diabetic status, and baseline eGFR. As with patient survival, no treatment effect was included in time to dialysis. This is in line with clinical expert advice and data from the DOLOMITES trial (39, 42).

The coefficients used to estimate the time to dialysis curve are shown in Table 36. If a coefficient is larger than 0 it means an increase in the likelihood of going onto

dialysis, while if it is smaller than 0 it means a decrease in the likelihood of going onto dialysis. Further information as the Variance-Covariance matrix and the Cholesky decomposition are shown in the cost-effectiveness model.

Table 36. Coefficients for covariates included in analyses of time to dialysis

Parameter	Coefficient
Shape	[redacted]
Scale	[redacted]
History of CVD – Yes	[redacted]
Diabetic – Yes	[redacted]
Baseline eGFR	[redacted]

Notes: * P ≤0.050; Exp (CI).

Abbreviations: CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate.

The log-logistic distribution was found to be the best function in terms of long-term clinical plausibility, presenting a long tail capturing a fraction of patients who will never start dialysis (Figure 12), and also gave the best statistical fit (Table 37).

Table 37. AIC and BIC values for time-to-dialysis

Curve	AIC	BIC
Log-logistic	**19,300**	**19,346**
Exponential	19,329	19,368
Weibull	19,330	19,375
Gompertz	19,325	19,370
Log-normal	19,323	19,368
Generalised gamma	19,303	19,355

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Figure 12. Time to dialysis survival curves

Abbreviations: KM: Kaplan Meier

B.3.4 Measurement and valuation of health effects

In accordance with NICE's reference case, health effects in the economic evaluation are expressed in terms of QALYs, which measure both the quality and length of remaining life. A score of zero is equivalent to death and one equivalent to a single year of life at perfect health. This allows for a consistent and standard measurement of patient HRQoL across different interventions and indications.

In the economic model, patient's baseline utilities are estimated based on age gender-adjusted general population norms from Kind *et al* (72) and CKD specific utility decrements. Hb health state utilities were derived from the roxadustat clinical trial data (42, 43, 45, 46) as described in the following sections.

B.3.4.1 Baseline utilities

Firstly, age gender-adjusted general population norms from Kind et al (72) were entered into the economic model. A summary is presented in Table 38.

Table 38. Population utility norms

Age category	Assumed mid-point	Male (SE)	Female (SE)	Source
Under 25	20	0.94 (0.01)	0.94 (0.01)	Kind et al (72)
25 to 34	30	0.93 (0.01)	0.93 (0.01)	
35 to 44	40	0.91 (0.01)	0.91 (0.01)	
45 to 54	50	0.84 (0.02)	0.85 (0.01)	
55 to 64	60	0.78 (0.02)	0.81 (0.02)	
65 to 74	70	0.78 (0.02)	0.78 (0.02)	
Above 75	80	0.75 (0.03)	0.71 (0.02)	

Abbreviations: SE: standard error.

For the starting values to be representative of the population in the CEM, decrements for CKD (using kidney complaints as a proxy) and dialysis were subtracted from the population norms. The absolute utility value for somebody with kidney complaints and a mean age of 44.8 years old was 0.845 (73). In order to use age-adjusted utility values in the model, this was converted into a utility decrement by subtracting the absolute utility value for somebody with kidney complaints from the absolute utility value for the general population at age 45 (0.878 – 0.845). This produced the utility decrement for CKD for each health state (0.033). Further utility decrements were applied specific to whether a person was on haemodialysis or peritoneal dialysis (0.35 and 0.26, respectively) (Table 39). These were sourced from a NICE technology appraisal (NICE TA358, Table B35) (74).

The general population norms, minus the CKD and dialysis decrements, result in the baseline utility value.

Table 39. CKD and dialysis utility decrements

	Utility decrement (SE)	Source
CKD decrement	[redacted]	Derived from Kind et al. (72) and Ara R. and Brazier J.E. (73)
Haemodialysis	0.352 (0.041)	NICE TA358 (74)
Peritoneal dialysis	0.262 (0.049)	

Abbreviations: CKD: chronic kidney disease; SE: standard error; TA: technology appraisal.

B.3.4.2 Health-related quality-of-life data from clinical trials

A generalised linear mixed model (GLMM) with a Gaussian distribution and an identity link was used to predict mean utility score for each Hb level, controlling for CVD history at baseline and diabetic status at baseline (56). This information used for this analysis was derived from the EQ-5D-5L instrument cross-walked to an EuroQol five-dimension three level (EQ-5D-3L) value set. The utility values from the EQ-5D-5L questionnaires were mapped from the clinical trial programmes onto the UK EQ-5D-3L value set using the crosswalk developed by van Hout *et al*. (2012) (75).

The EQ-5D-3L derived utilities were preferred for the base case in accordance with NICE guidelines. Nesting effects from using multiple studies, and repeated measures of subjects were both controlled for, using study identification and unique subject identification as random factors.

The coefficients used to estimate the mean EQ-5D-3L values are shown in Table 40. If a coefficient is smaller than 0 this means the parameter decreases the utility of a patient while if the coefficient is larger than 0 it means the parameter increases the utility of a patient.

Table 40. Coefficients for EQ-5D-3L regression analysis

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]
Diabetic - Yes	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: CVD: cardiovascular disease.

A scenario analysis in was performed in the model using the EQ-5D-5L utility scores directly (without crosswalk).

The health state utilities obtained by the regressions estimated from the clinical trial analysis and model patient characteristics are presented in Table 41.

Table 41. Health state absolute utilities

Health state	Utility (IPD EQ5D-3L)	Utility (IPD EQ5D-5L)
Hb <7	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]
Hb ≥ 13	[redacted]	[redacted]

Abbreviations: Hb, haemoglobin; IPD, Individual patient level data; Hb: haemoglobin; EQ-5D-3L, EuroQol five-dimension three level; EQ-5D-5, EuroQol five-dimension five level.

The utility decrement for each health state was then calculated by subtracting the utility from the reference health state utility (Hb ≥ 13). These utility decrements (Table 42) were subtracted from the baseline utility value to estimate the health state specific utility values.

Table 42. Health state decrements

Health state	Utility (IPD EQ5D-3L)	Utility (IPD EQ5D-5L)
Hb <7	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]
Hb ≥ 13	[redacted]	[redacted]

Abbreviations: Hb, haemoglobin; IPD, Individual patient level data; Hb: haemoglobin; EQ-5D-3L, EuroQol five-dimension three level; EQ-5D-5, EuroQol five-dimension five level.

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

B.3.4.3.1 Literature

A SLR was conducted in February 2019 and updated in March 2021 to identify the relevant HRQoL data available in the published literature. A detailed account of the SLR and update is provided in Appendix H. Although the SLR identified nine studies that provided HRQoL data for anaemic CKD patients, none of the utilities reported in these studies were deemed appropriate for the cost-effectiveness model.

One publication identified during an additional targeted literature review of cost-effectiveness studies in anaemia associated with CKD reported utility values that were deemed appropriate for the cost-effectiveness model. In this study, Yarnoff et al (76) aimed to explore the most cost-effective Hb target for anaemia treatment in

patients with CKD stages 3-4 not on dialysis, based on an already existing microsimulation model of CKD progression.

Table 43. Utility values identified from the literature

Published studies identified in SLR	Utility values (SD) used in the model (scenario analyses)
Yarnoff et al (76)	Utility loss per 1 g/dL decrease in Hb (reference Hb≥13 g/dL): 0.0114 Utility loss from stroke: 0.582 Utility loss from myocardial infarction: 0.12 Utility loss from myocardial infarction: 0.12

Abbreviations: CKD: chronic kidney disease; SD: standard deviation; SLR: systematic literature review.

The relevant extracted utility values are presented in Table 43, and these were added per 1g/dL decrease in Hb level to calculate the utility decrements applied to each health state as shown in Table 44. These values were considered in the model as an alternative way of informing the utility decrements associated to different Hb levels and its impact was explored and further studied in Scenario Analysis 3 (Section B.3.7.3).

Table 44. Health state decrements from published literature

Health state	Utility decrement
Hb <7	0.080
Hb 7.00 to 7.99	0.068
Hb 8.00 to 8.99	0.057
Hb 9.00 to 9.99	0.046
Hb 10.00 to 10.99	0.034
Hb 11.00 to 11.99	0.023
Hb 12.00 to 12.99	0.011
Hb ≥ 13	0.000

Abbreviations: Hb: haemoglobin.

B.3.4.3.2 Patient preference study

Since the EQ-5D instrument is not sensitive to changes in mode of administration, a patient preference study was conducted to estimate the utility gains associated with moving from SC injections at home once every two weeks (reference case) to alternative modes of administration (77). The findings from this study were not included in the base case analysis but have been evaluated in Scenario Analysis 4 (See B.3.7.3).

A discrete choice experiment (DCE) was undertaken to elicit preferences. DCE can be used to estimate outcome equivalents that are valid measures of utility changes consistent with the principles of welfare economics (78). There is an increasing interest in using patient preference data in HTA, and DCE offers a robust approach for generating insights in the relative importance and trade-offs about different

treatment attributes. A similar approach was used in NICE High Specialised Technology (HST) committee's assessment of migalastat for Fabry disease (79).

An online survey was undertaken with 200 patients with anaemia associated with CKD in France, Germany, Spain and the UK (data on file). The survey included a DCE that consisted of a series of treatment choice scenarios. In each scenario participants were asked to choose between two hypothetical treatments for CKD related anaemia. Each treatment was described by five treatment attributes: energy level, mode of administration, need for iron supplements, risk of major cardiovascular event and risk of gastrointestinal side effects. The levels on the 'energy level' attribute were defined as those on the SF-6D vitality scale.

The analysis of participants' choices provided estimates of the marginal value of changes in each attribute. By comparing the marginal values generated by each attribute, it is possible to estimate the change in energy levels that generate the same utility as changing the mode of drug administration ('equivalent change in energy levels' in Table 45). For instance, moving from a SC injection at home once every two weeks to an oral pill at home three times a week would provide patients with 0.58 of the value associated with improving energy levels from "You sometimes have a lot of energy" to "You always have a lot of energy" on the Short-Form Six-Dimension (SF-6D) vitality scale.

Published studies estimate that there is a 0.071 QALY increment associated with moving from one year in the health state "You sometimes have a lot of energy" to one year in the health state "You always have a lot of energy" on the SF-6D vitality scale (80). Given that moving from a subcutaneous injection at home once every two weeks to an oral pill at home three times a week generates [redacted] of the value associated with improving energy levels from "You sometimes have a lot of energy" to "You always have a lot of energy" on the SF-6D vitality scale, after one year this change in method of administration (MoA) generates utility the equivalent of a 0.041 QALY increment [redacted]

Table 45. Incremental utility associated with alternative methods of drug administration

MoA	Equivalent change in energy level*	Equivalent incremental QALY of one year of MoA
Oral pill, once daily, at home	[redacted]	[redacted]
Oral pill, three times weekly, at home	[redacted]	[redacted]
Subcutaneous injection, once every four weeks, at home	[redacted]	[redacted]
Subcutaneous injection, once every two weeks, at home**	Reference level	Reference level

Notes: *Defined as the proportion of the change in utility gained by moving from "You sometimes have a lot of energy" to "You always have a lot of energy" on the SF-6D vitality scale (80). **Reference level

The method adopted to estimate the QALY gains reported in Table 55 varied from those commonly adopt by NICE in two important ways – a DCE was adopted rather than time trade-off (TTO) or standard gamble (SG), and patients' preferences were used rather than general population preferences. Patients' rather than public preferences were elicited as it was thought their experience of subcutaneously MoA's would allow them to provide more insight into the utility gains associated with avoiding such MoAs. A number of authors have made this case for putting more weight on patient preferences (81-83). This is supported by comparisons of patient and public preferences, which conclude that, on average, patients give higher values to their health states than non-patients (84).

DCE was adopted as it is the preference elicitation instrument most frequently used with patients, placing a lower cognitive burden on participants, facilitating online data collection (85). Both TTO and DCE are recommended by the EuroQol Group (86). Direct comparisons of TTO and DCEs when used to estimate value sets of health outcomes provide mixed evidence on the consistency, relative validity and reliability, and ease of completion of the TTO and DCE instruments (87-91).

To calculate the utility increments associated with the modes of administration in each treatment arm, the estimates of utility increments in Table 45 were weighted by the proportion of patients expected to be prescribed each regimen (Table 46).

Table 46. Weighted method of administration incremental utility for each treatment arm

Method of administration	Roxadustat patients (%)	ESA patients (%)
Oral pill, three times weekly, at home	100%	0%
Subcutaneous injection, once every four weeks, at home	0%	35%
Subcutaneous injection, once every two weeks, at home	0%	65%

Method of administration	Roxadustat patients (%)	ESA patients (%)
Weighted utility	[redacted]	[redacted]

Notes: Proportion of patients on each mode of administration is derived from the proportion of patients on each mode of administration within the patient preference study and adjusted to 100% (data on file).

B.3.4.4 Adverse reactions

Patients with CKD and ESRD are at high risk of MACE, and these events are of special relevance as can result in death, worsening of CKD disease, and significantly impact HRQoL. For the patient population considered in the model (i.e. NDD patients who are not adequately managed with IV iron alone and require an ESA), MACE are especially important as increased doses of ESA further expose patients to increased risk of adverse events (92).

The model included three key treatment emergent adverse events (TRAE): two major cardiovascular adverse events (MACE) (stroke and MI) and vascular access thrombosis (VAT). Other adverse events were not explicitly modelled as they were expected to have a substantially lower impact in patients HRQoL and NHS resource use. In addition, rates of TRAEs were similar for roxadustat and ESA (see Appendix F).

These events were modelled separately to apply separate costs and utility decrements to each type of event. Clinical trial data from the NDD trials (42, 43, 45, 46) informed the event rates for the base case analysis. Since there was insufficient data to make a robust regression model linking the risk of MACE and Hb levels, these analyses were not carried out.

B.3.4.4.1 TRAE rates

The three-monthly probability of stroke (haemorrhagic, ischaemic and cerebellar), MI and VAT were derived separately for each treatment arm using the number of events and total patient exposure time (independent of Hb level) derived from pooled NDD dataset (42, 43, 45, 46) . The three-month probability for each adverse event is presented in Table 47.

Table 47. Probability of TRAE in the model

	Number of events	Total exposure in three-monthly cycles	Cycle probability of stroke
Stroke			
ESA (n=293)	[redacted]	[redacted]	[redacted]
Roxadustat (n=2709)	[redacted]	[redacted]	[redacted]

	Number of events	Total exposure in three-monthly cycles	Cycle probability of stroke
MI			
ESA (n=293)	[redacted]	[redacted]	[redacted]
Roxadustat (n=2709)	[redacted]	[redacted]	[redacted]
VAT			
ESA (n=293)	[redacted]	[redacted]	[redacted]
Roxadustat (n=2709)	[redacted]	[redacted]	[redacted]

Abbreviations: ESA: erythropoiesis-stimulating agent; TRAE: treatment related adverse event; MI: myocardial infarction; VAT: vascular access thrombosis

TRAE specific utility decrements applied to the model are presented in Table 48. The stroke decrements were derived from a study by Meenan *et al* (93). This paper presents absolute utilities for minor, moderate and severe stroke. To calculate the utility decrements, the absolute utilities for each event were subtracted from one.

The utility decrement for MI events was sourced from Yarnoff *et al*. 2016 (76).

For VAT events, the utility loss was sourced from Xue *et al* 2010 (94), a study which reported the disutility of VAT with surgical intervention for patients starting on haemodialysis.

Table 48. TRAE event utility decrements

Event	Utility decrement (SE)	Source
Non-disabling stroke	0.350 (0.018)	Meenan et al. 2007 (93)
Moderately disabling stroke	0.500 (0.025)	
Severely disabling stroke	0.730 (0.037)	
Myocardial infarction	0.120 (0.006)	Yarnoff et al. 2016 (76)
Vascular access thrombosis	0.100 (0.005)	Xue et al. 2010 (94)

Abbreviations: SE: standard error.

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

A summary of the utility values included in the model is provided in Table 49.

Table 49. Summary of utilities used in the model

State	Mean utility value (SE)	95% confidence interval	Reference in submission	Justification
Baseline utilities				
Male under 25	0.94 (0.01)	NA	See section B.3.4.1	United Kingdom population norms for EQ-5D
Male 25 to 34	0.93 (0.01)	NA		
Male 35 to 44	0.91 (0.01)	NA		
Male 45 to 54	0.84 (0.02)	NA		
Male 55 to 64	0.78 (0.02)	NA		
Male 65 to 74	0.78 (0.02)	NA		
Male above 75	0.75 (0.03)	NA		
Female under 25	0.94 (0.01)	NA		
Female 25 to 34	0.93 (0.01)	NA		
Female 35 to 44	0.91 (0.01)	NA		
Female 45 to 54	0.85 (0.01)	NA		
Female 55 to 64	0.81 (0.02)	NA		

State	Mean utility value (SE)	95% confidence interval	Reference in submission	Justification
Female 65 to 74	0.78 (0.02)	NA		
Female above 75	0.71 (0.02)	NA		
CKD decrement	0.033 (NA)	NA		Baseline utilities calibration
Haemodialysis decrement	0.352 (0.041)	(0.27164, 0.43236)		
Peritoneal dialysis decrement	0.262 (0.049)	(0.16596, 0.35804)		
Health state utility increments/decrements				
Hb <7	[redacted]	NA	See section B.3.4.2	Based on relevant clinical trial data (42, 43, 45, 46)
Hb 7.00 to 7.99	[redacted]	NA		
Hb 8.00 to 8.99	[redacted]	NA		
Hb 9.00 to 9.99	[redacted]	NA		
Hb 10.00 to 10.99	[redacted]	NA		
Hb 11.00 to 11.99	[redacted]	NA		
Hb 12.00 to 12.99	[redacted]	NA		
Hb ≥ 13	[redacted]	NA		
Adverse events utilities				
Stroke (mild)	0.350 (0.018)	(0.3147, 0.3852)	See section B.3.4.4	Relevant literature due to insufficient data in relevant clinical trials(42, 43, 45, 46)
Stroke (medium)	0.500 (0.025)	(0.4510, 0.5490)		
Stroke (severe)	0.730 (0.037)	(0.6574, 0.8025)		
MI	0.120 (0.006)	(0.1082, 0.1317)		
VAT	0.100 (0.005)	(0.0902, 0.1098)		

Abbreviations: SE: standard error; Hb: haemoglobin; MI: miocardial infarction; VAT: vascular access thrombosis.

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

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Treatment dose

Accurate treatment doses for roxadustat and ESA are challenging to estimate due to the number of dose adjustments made in clinical practice. Starting doses are usually weight dependent but the titrations and optimal maintenance doses are tied to each patient's response to treatment and evolution of Hb levels. Therefore, there is an intrinsic link between the treatment effect and the treatment dose associated with it. To capture this relationship in the model, treatment dosing was estimated from patient level data. The dosing data was split in two datasets:

- Correction phase: up to three months from treatment imitation (i.e. 1st model cycle)
- Maintenance phase: from three months after treatment initiation

The weekly dose in the correction phase (1st model cycle) was estimated as an average from all patients in the roxadustat trials during their first 3 months of treatment. This was deemed long enough to capture the majority of the dose adjustments that patients experienced during the correction phase of the trials. All costs incurred from any dose changes observed in the trials during this phase were accounted for in the average doses used in the model.

For cycles 2 onwards (maintenance phase), a GLMM with a Gamma distribution and a log link was used to predict the mean weekly dose (mg) of roxadustat and ESA for Hb level, controlling for CVD history and diabetic status at baseline. It should be noted that the model is not time dependent and the derived weekly dose from the GLMM is used in all subsequent cycles. The coefficients used to estimate the roxadustat and ESA dose are shown in Table 50 and Table 51 respectively. If a coefficient is smaller than 0 this means the parameter decreases the mean dose assigned to a patient while if the coefficient is larger than 0 it means the parameter increases the mean dose assigned to a patient.

Table 50. Coefficients for roxadustat treatment dose regression analysis

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]
Diabetic - Yes	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: CVD: cardiovascular disease; Hb: haemoglobin.

Table 51. Coefficients for ESA treatment dose regression analysis

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]
Diabetic - Yes	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: CVD: cardiovascular disease; Hb, haemoglobin.

The average weekly roxadustat and ESA doses used in the 1st cycle of the model (correction phase) are presented in Table 52.

Table 52. Average weekly doses applied in the 1st cycle of the economic model

Haemoglobin level	Roxadustat (mg)	ESA (mcg)
Hb level <7	[redacted]	[redacted]
Hb level 7 to 8	[redacted]	[redacted]
Hb level 8 to 9	[redacted]	[redacted]
Hb level 9 to 10	[redacted]	[redacted]
Hb level 10 to 11	[redacted]	[redacted]
Hb level 11 to 12	[redacted]	[redacted]
Hb level 12 to 13	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]

Abbreviations: ESA: erythropoietin stimulating agents; Hb: haemoglobin; mcg: microgram; mg: milligram.

From cycles 2 onwards, the average dose at any given cycle was dependent on the distribution of patients across the Hb health states. Table 53 shows the average dose for a patient with Hb level 10 to 11 and the increments/decrements applied based on the remaining levels.

Table 53. Weekly doses by Hb level applied in the subsequent cycles of the economic model

Haemoglobin level		Roxadustat (mg)	ESA (mcg)
Baseline (Hb level 10 to 11)		[redacted]	[redacted]
	Hb level <7	[redacted]	[redacted]

Haemoglobin level		Roxadustat (mg)	ESA (mcg)
Increment / decrement by Hb level	Hb level 7 to 8	[redacted]	[redacted]
	Hb level 8 to 9	[redacted]	[redacted]
	Hb level 9 to 10	[redacted]	[redacted]
	Hb level 11 to 12	[redacted]	[redacted]
	Hb level 12 to 13	[redacted]	[redacted]
	Hb level >13	[redacted]	[redacted]

Abbreviations: ESA: erythropoietin stimulating agents; Hb: haemoglobin; mcg: microgram; mg: milligram.

B.3.5.1.2 Drug acquisition costs

Roxadustat will be available in several strengths, as presented in Table 54. The model estimates drug costs based on the calculated dose required for each health state (section B.3.5.1.1). Considering the cost per mg/mcg can vary depending on the pack strength, the model uses the cost per mg/mcg of the strength closest to the calculated dose to estimate the drug costs.

Table 54. Roxadustat costs applied in the model

Tablet strength (mg)	Quantity per pack	Cost per pack	Cost per tablet	Cost per mg
20	12	[redacted]	[redacted]	[redacted]
50	12	[redacted]	[redacted]	[redacted]
70	12	[redacted]	[redacted]	[redacted]
100	12	[redacted]	[redacted]	[redacted]
150	12	[redacted]	[redacted]	[redacted]

Abbreviations: mg: milligram.

Different types of ESA are assumed to have equivalent efficacy and safety when given at equivalent doses as per NICE guidelines (11). The CEM includes the drugs that are listed in the BNF under the class of epoetin: epoetin alfa, darbepoetin alfa, epoetin beta, epoetin zeta and methoxy polyethylene glycol-epoetin beta. Conversion of one ESA dose to the equivalent dose of an alternative ESA is not straightforward due to differing half-lives and route of administration of the different drugs (95), with both factors impacting on the dose required to achieve the same effect. Furthermore, half-lives of the drug can differ according to the patient's condition, including dialysis status (95, 96). The model takes a pragmatic approach to estimation of equivalent dose conversion between the available ESA; where the recommended weekly dose (in mcg) derived from the BNF (65-69) was utilised to calculate equivalent dose conversion ratios between the available ESA (Table 55).

Table 55. Conversion ratios to adjust the clinical trial derived ESA dose

ESA	Dose conversion factor
Epoetin alfa	1.40
Darbepoetin alfa	1.00

ESA	Dose conversion factor
Epoetin beta	1.11
Epoetin zeta	1.38
Methoxy polyethylene glycol-epoetin beta	0.62

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: ESA, erythropoietin stimulating agents; Hb, haemoglobin.

The unit cost per injection and per microgram (mcg) of each ESA was derived from the BNF (65-69), converting international units (IU) to mcg where required (97, 98). The cost per injection and microgram for all available formulations of ESA included in the economic model are presented in Table 56.

Table 56. ESA costs per mcg applied in the model

Pack size (mcg)	Injections per pack	Cost per pack	Cost per injection	Cost per mcg
Epoetin Alfa				
8.4	6	£33.18	£5.53	£0.66
16.8	6	£66.37	£11.06	£0.66
25.2	6	£99.55	£16.59	£0.66
33.6	6	£132.74	£22.12	£0.66
42.0	6	£165.92	£27.65	£0.66
50.4	6	£199.11	£33.19	£0.66
67.2	6	£265.48	£44.25	£0.66
84.0	6	£331.85	£55.31	£0.66
168.0	1	£110.62	£110.62	£0.66
252.0	1	£199.11	£199.11	£0.79
336.0	1	£265.48	£265.48	£0.79
Darbepoetin alfa				
10	4	£58.72	£14.68	£1.47
20	4	£117.45	£29.36	£1.47
30	4	£176.17	£44.04	£1.47
40	4	£234.90	£58.73	£1.47
50	4	£293.62	£73.41	£1.47
60	4	£352.35	£88.09	£1.47
80	4	£469.79	£117.45	£1.47
100	4	£587.24	£146.81	£1.47
130	4	£763.24	£190.81	£1.47
150	4	£880.86	£220.22	£1.47
300	1	£440.43	£440.43	£1.47
500	1	£734.05	£734.05	£1.47
Epoetin beta				
4.2	6	£21.05	£3.51	£0.85
16.6	6	£84.17	£14.03	£0.85
24.9	6	£126.25	£21.04	£0.85
33.2	6	£168.34	£28.06	£0.85
41.5	6	£210.42	£35.07	£0.85
49.8	6	£252.50	£42.08	£0.85
83.0	6	£420.85	£70.14	£0.85
166.0	6	£841.71	£140.29	£0.85
Epoetin zeta				
8.3	6	£28.85	£4.81	£0.58
16.6	6	£57.70	£9.62	£0.58
24.9	6	£86.55	£14.43	£0.58
33.2	6	£115.40	£19.23	£0.58
41.5	6	£144.25	£24.04	£0.58

Pack size (mcg)	Injections per pack	Cost per pack	Cost per injection	Cost per mcg
49.8	6	£173.09	£28.85	£0.58
66.4	6	£230.79	£38.47	£0.58
83.0	6	£288.48	£48.08	£0.58
166.0	1	£96.16	£96.16	£0.58
249.0	1	£144.25	£144.25	£0.58
332.0	1	£193.32	£193.32	£0.58
Methoxy polyethylene glycol-epoetin beta				
30.0	1	£44.05	£44.05	£1.47
50.0	1	£73.41	£73.41	£1.47
75.0	1	£110.11	£110.11	£1.47
100.0	1	£146.81	£146.81	£1.47
120.0	1	£176.18	£176.18	£1.47
150.0	1	£220.22	£220.22	£1.47
200.0	1	£293.62	£293.62	£1.47
250.0	1	£367.03	£367.03	£1.47
360.0	1	£528.56	£528.56	£1.47

Abbreviations: mcg: microgram.

The comparator arm in the model was costed based on the proportion of each ESA presented in Table 57. These values were sourced from the TUNE study, a retrospective study aiming to generate real-world evidence documenting treatment patterns, health care resource utilisation, and costs associated with the management of anaemia among patients with non-dialysis-dependent CKD stages 3b to 5 who have initiated ESA therapy in three European countries: Germany, Spain, and the UK (99). Data specific for the UK was used to inform the model base case.

Table 57. Proportion of patients receiving each ESA

ESA	Proportion of patients (%)
Epoetin alfa	[redacted]
Darbepoetin alfa	[redacted]
Epoetin beta	[redacted]
Epoetin zeta	[redacted]
Methoxy polyethylene glycol-epoetin beta	[redacted]

Abbreviations: ESA: erythropoietin stimulating agents.

B.3.5.1.3 Drug administration costs

The TUNE study results suggested that not all ESA patients were able to self-administer (99). In addition, clinical experts contacted by Astellas for model validation suggested that around 20% of patients not on dialysis would require assistance to administer ESA (39). The model assumes that 15% of patients require a home district nurse, with a further 5% requiring hospital administration. Based on hourly costs sourced from the PSSRU (100), and assuming a 15-minute appointment, administration costs per injection were calculated as shown in Table 58. The final weighted cost per patient was applied to every ESA injection and

divided by the dose contained in each of these to allow accounting for this concept when assuming no wastage. ESA administration costs was then applied to those patients not on dialysis along the modelled time horizon.

Table 58. ESA administration costs

Item	Proportion of patients	Cost	Weighted cost per patient
Home district nurse appointment (Band 6, per hour of patient related work [15-minute appointment])	15%	£21.00	£8.16
Hospital administration (Band 6, per hour of patient related nurse work [15-minute appointment])	5%	£28.25	

B.3.5.1.4 Monitoring costs

Based on clinical advice received during the model validation (39), NICE guidance (11) and the roxadustat draft SmPC (Appendix C), both interventions were associated with an average of four monitoring appointments in the first model cycle (the first 12 weeks of treatment) and 1.5 visits for subsequent cycles.

It was assumed that a monitoring visit is conducted by a consultant in a hospital setting. With an hourly cost of £119, and assuming a 15-minute appointment, each monitoring visits costs £29.25 (101).

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Dialysis

The proportion of patients on dialysis in any given model cycle was estimated from the time to dialysis curves presented in section B.3.3.4.

Haemodialysis and peritoneal weekly dialysis costs were calculated from NHS Cost Collection (102) and are presented in Table 59. For haemodialysis the weighted average of healthcare resource group (HRG) codes LD01A and LD02A was used. For peritoneal dialysis the weighted average of HRG codes LD11A and LD12A was used. It was assumed that dialysis occurred three times a week for haemodialysis and seven times a week for peritoneal dialysis (103-105).

The distribution of patients receiving each type of dialysis was derived from roxadustat DOLOMITES data (42) as shown in Table 60. Clinical experts contacted by Astellas confirmed these proportions were representative of UK clinical practice (39).

Table 59. Haemodialysis and peritoneal dialysis costs

Cost item	HRG code	Activity	Unit cost
Haemodialysis			
Haemodialysis catheter	LD01A	430,431	£148.36
Arteriovenous Fistula	LD02A	709,145	£156.64
Peritoneal dialysis			
Continuous Ambulatory	LD11A	309,480	£66.16
Automated	LD12A	570,798	£73.19

Abbreviations: HRG, Healthcare resource group.

Table 60. Distribution of patients per type of dialysis

Cost item	Percentage
Haemodialysis	78.3%
Peritoneal dialysis	21.7%

B.3.5.2.2 Blood transfusion

To estimate the cycle probability of receiving a blood transfusion, a GLMM with a binomial distribution and a logit link was used, controlling for Hb level, treatment type, and CVD history and diabetic status at baseline.

RBC transfusion use estimation

The coefficients used to estimate the proportion requiring an RBC transfusion are shown in Table 61. If a coefficient is larger than 1 it means an increase in the likelihood of RBC transfusion, while if it is smaller than 1 it means a decrease in the likelihood of receiving an RBC transfusion.

Table 61. Regression coefficients for blood transfusion rates

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]
Diabetic - Yes	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: CVD: cardiovascular disease; ESA: erythropoiesis-stimulating agents; Hb: haemoglobin.

The cycle probabilities applied in the model are summarised in Table 62.

Table 62. Probability of receiving a blood transfusion

Health state	Total exposure time (weeks)	Weekly probability of needing a transfusion	Three-month probability of needing a transfusion
Roxadustat			

Health state	Total exposure time (weeks)	Weekly probability of needing a transfusion	Three-month probability of needing a transfusion
Hb <7	[redacted]	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]	[redacted]
Hb ≥ 13	[redacted]	[redacted]	[redacted]
ESA			
Hb <7	[redacted]	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]	[redacted]
Hb ≥ 13	[redacted]	[redacted]	[redacted]

Abbreviations: Hb: haemoglobin; ESA: Erythropoiesis-stimulating agents.

Unit costs

The unit cost for a blood transfusion was sourced from the National Cost Collection 2018/19 (HRG code SA44A) (102). A weighted average cost of a day case and outpatient was calculated.

Table 63. Unit costs for blood transfusion

HRG Code	Patient type	Activity	Unit cost
SA44A	Day case	117,906	£530
SA44A	Outpatient	8,113	£308
Average			£516

Abbreviations: HRG: healthcare resource group.

B.3.5.2.3 IV Iron supplementation

IV iron use in the model is based in both the proportion of patients requiring the intervention, and the dose required. A generalised linear model (GLM) with a binomial distribution and a log link was used to estimate the proportion of patient needing IV iron, controlling for Hb level, treatment type, study ID, CVD history at baseline, diabetic status at baseline, as well as an interaction between Hb level and treatment type. To estimate mean weekly IV iron dose, a GLMM with a Gaussian distribution and an identity link was used, controlling for treatment type, CVD history at baseline and diabetic status at baseline. Repeated measures of subjects were controlled for, using a unique subject identification for each participant as a random factor. Analysis showed that Hb had no significant effect on the average weekly dose

of IV iron, and this evidence was confirmed by clinical experts during the model validation. Therefore, the same IV iron dose was applied for all health states.

IV iron use estimation

The coefficients used to estimate the proportion of patients needing IV iron treatment are shown in Table 64. If a coefficient is larger than 1 it means an increase in the likelihood of needing IV iron treatment, while if it is smaller than 1 it means a decrease in the likelihood of needing IV iron treatment.

Table 64. Regression coefficients for proportion of patients receiving IV iron

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]
Diabetic - Yes	[redacted]	[redacted]	[redacted]
STUDY: OLYMPUS	[redacted]	[redacted]	[redacted]
STUDY: ANDES	[redacted]	[redacted]	[redacted]
STUDY: DOLOMITES	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: CVD: cardiovascular disease; ESA: erythropoiesis-stimulating agents; Hb: haemoglobin.

The weekly and three-month cycle probabilities of requiring IV iron are summarised in Table 65.

Table 65. Proportion of patients receiving IV iron

Health state	Total exposure time (weeks)	Weekly probability of needing IV iron	Cycle probability of needing IV iron 1
Roxadustat			
Hb <7	[redacted]	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]	[redacted]
ESA			
Hb <7	[redacted]	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]	[redacted]

Notes: [1] Cycle probability is calculated as follows: 1) Calculate the number of weeks in 3 months, the cycle length [52/12*3 = 13] 2) Use this to convert the weekly probability into a cycle probability [1-exp(-(5/998)*13) = 6.47% (excluding rounding errors that do not occur in the CEM)]. ** If the capped values are selected, the weekly probability will be capped at 0.02% and 1.11% for the weekly and cycle probability of requiring IV iron, respectively.

Abbreviations: CVD: cardiovascular disease; ESA: erythropoiesis-stimulating agents; Hb: haemoglobin; IV: intravenous.

To estimate the dose of IV iron, a single predictive GLMM model was used for all Hb levels. The derived weekly mean doses of IV iron for patients on roxadustat and ESA are detailed in Table 66. The model assumes that patients requiring IV iron take a dose every cycle.

Table 66. Dose of IV iron per administration

Intervention	Per cycle dose of IV iron (mg)
Roxadustat	[redacted]
ESA	[redacted]

Abbreviations: ESA: erythropoiesis-stimulating agents; IV: intravenous; mg: milligram.

Unit costs

The cost per mg of IV iron was calculated by a weighted average of the types of IV iron preparations shown in Table 67. The costs per unit were derived from the BNF (106-108) and the quantity prescribed (to calculate the weighted average) were sourced from the TUNE study (99) UK specific data. The same quantities were assumed for both treatment arms in the economic model.

Table 67. IV iron unit costs

Name	Cost per vial	Cost per mg	Use
Iron Isomaltoside (Pharmacosmos)	£16.95	£0.17	[redacted]
Iron Sucrose (Venofer)	£8.70	£0.09	[redacted]
Ferric Carboxymaltose (Ferinject)	£19.10	£0.19	[redacted]
Average cost per mg			£0.17

Abbreviations: mg: milligram.

The IV iron administration cost was derived from the National Cost Collection 2018/2019 (102). A weighted average of the cost of HRG codes SA04G to SA04L was calculated, leading to a cost of £274.73 per administration. This cost was applied once a week to the proportion of patients who received IV iron.

B.3.5.3 Adverse reaction unit costs and resource use

The stroke, MI and VAT acute costs were sourced from the NHS Cost Collection (102). The weighted average cost of a non-disabling (CC score 0-6), moderately disabling (CC score 8-12) and severely disabling (CC score 13+) stroke was calculated from non-elective long stay patients, (HRG codes AA35A - AA35F). These costs were multiplied by the proportion of patients with each severity of stroke (109) (48.5%, 42.6% and 8.8% for non-disabling, moderately disabling and severely disabling stroke, respectively).

The cost of an MI event was calculated from non- elective long stay patients, including excess bed days (HRG codes EB10A – EB10E).

VAT acute costs were calculated based on HRG codes YR48Z and YQ42Z.

The long term stroke and MI costs were sourced from literature (110, 111) and inflated to 2020/21 prices using Hospital and Community Health Services (HCHS) and NHS Cost Inflation Index (CII) pay and prices inflation indices from the PSSRU (101). It was assumed that no lifetime cost is associated with VAT, in alignment with the feedback received by clinical experts during the model validation. The acute and lifetime costs (assumed four-year for stroke and one year for MI) were summed and applied to the expected number of TRAEs in each cycle of the model. These costs are presented in Table 68.

Table 68. TRAE costs

TRAE	Unit cost	Source
Non-disabling stroke (acute)	£2,960	NHS Cost Collection (102)
Moderately disabling stroke (acute)	£3,999	
Severely disabling stroke (acute)	£6,912	
Long term stroke	£4,767	Xu et al. inflated with PSSRU index (101, 110)
Stroke total	£8,519*	
MI (acute)	£2,367	NHS Cost Collection (102)
Long term MI	£680	TA317, inflated with PSSRU index (101, 111)
MI total	£3,047	
VAT (acute)	£3,601	NHS Cost Collection (102)
Long term VAT	£0	Assumed
VAT total	£3,601	

Notes: *Applies proportions of 48.5%, 42.6% and 8.8% to non-disabling, moderately disabling and severely disabling stroke, respectively.

Abbreviations: MI: myocardial infarction; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; TA: technology appraisal; TRAE: Treatment-Related Adverse Event; VAT: Vascular Access Thrombosis.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of the main model parameters is provided in Table 69

Table 69. Summary of parameters used in the economic analyses

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Model settings			
Cycle length in months	3	None	Section B.3.2
Time horizon in years	25	None	
Discount rate effects and costs	3.5%	None	
Population	1,000	None	
Population characteristics			
Average starting age of population	62.8 years	None	Section B.3.3.1
Proportion of patients - male	43%	None	

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Proportion of patients - female	58%	None	
Proportion of patients with CVD history	38%	None	
Proportion of patients with diabetes	56%	None	
Median baseline eGFR	17.1	None	
Haemodialysis	78.3%	None	Section B.3.5.2.1
Peritoneal dialysis	21.7%	None	
Health state occupancy at baseline			
Hb <7	[redacted]	None	Section B.3.3.1
Hb 7.00 - 7.99	[redacted]	None	
Hb 8.00 - 8.99	[redacted]	None	
Hb 9.00 - 9.99	[redacted]	None	
Hb 10.00-10.99	[redacted]	None	
Hb 11.00-11.99	[redacted]	None	
Hb 12.00-12.99	[redacted]	None	
Hb >= 13	[redacted]	None	
Mortality			
CKD hazard ratio	3.60	SE:0.05, Beta	
Mortality regression parameters	-	Multivariate normal	Section B.3.3.2
Proportion in state			
Proportion in state parameters	-	Multivariate normal	Section B.3.3.3
Time to dialysis			
Time to dialysis regression parameters	-	Multivariate normal	Section B.3.3.4
Health-related quality-of-life			
Health-related quality-of-life data used in the cost-effectiveness analysis	-	Multivariate normal	Section B.3.4
Blood transfusion			
Blood transfusion regression parameters	-	Multivariate normal	Section B.3.5.2.2
Iron supplementation			
IV iron supplementation regression parameters	-	Multivariate normal	Section B.3.5.2.3 and Table 64
Treatment dose			
Roxadustat dose	-	Multivariate normal	Section B.3.5.1.1
ESA dose	-	Multivariate normal	
Drug costs			
Roxadustat cost	-	None	Section B.3.5.1.2
ESA cost	-	None	Section B.3.5.1.2
Home district nurse appointment cost	£21.00	None	Section B.3.5.1.3
Outpatient administration resource use	15%	None	
Hospital administration	£28.25	None	
Inpatient administration resource use	5%	None	
ESA proportions			
Epoetin alfa	[redacted]	None	Section B.3.5.1.2
Darbepoetin alfa	[redacted]	None	
Epoetin beta	[redacted]	None	
Epoetin zeta	[redacted]	None	
Methoxy polyethylene glycol-epoetin beta	[redacted]	None	
Monitoring costs			

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Initial correction phase resource use (first 12 weeks of treatment)	4	None	Section B.3.5.1.4
Maintenance phase resource use (post 12 weeks of treatment)	1.5	None	
Inpatient monitoring visit	£29.25	None	
Severity distribution of stroke			
Non-disabling stroke	48.5%	Beta	Section B.3.4.4
Moderately disabling stroke	42.6%	Beta	
Severely disabling stroke	8.8%	Beta	
Health state costs			
Blood transfusion cost	£516	Gamma	Section B.3.5.2 & B.3.5.3
Monitoring costs	£30	Gamma	
Haemodialysis	£461	Gamma	
Peritoneal Dialysis	£495	Gamma	
IV iron cost	£0.17	Gamma	
IV iron administration	£275	Gamma	
Total cost of stroke	£8,518.66	Gamma	
Total cost of MI	£3,047	Gamma	
Total cost of VAT	£3,601	Gamma	
Proportion of patients requiring home district nurse	17%	None	
Unit cost of ESA administration by a district nurse	£21.00	None	
TRAEs inputs			
Stroke – Roxadustat	[redacted]	SE: 0.0003, Beta	B.3.4.4 Adverse reactions
Stroke – ESA	[redacted]	SE: 0.0003, Beta	
MI – Roxadustat	[redacted]	SE: 0.0005, Beta	
MI – ESA	[redacted]	SE: 0.0006, Beta	
VAT – Roxadustat	[redacted]	SE: 0.0004, Beta	
VAT – ESA	[redacted]	SE: 0.0001, Beta	

Abbreviations: CVD, Cardiovascular disease; CKD, Chronic kidney disease; CI, confidence interval; Hb, haemoglobin, SE; Standard error; MI, Myocardial infraction; ESA; Erythropoiesis stimulating agent; TRAEs, Treatment related adverse events; HRQoL, Health related quality of life; IV, intravenous.

B.3.6.2 Assumptions

Table 70. Main assumptions in the economic model

Assumption	Justification
The model is informed by a pooled analysis of all four trials conducted in the NDD population	The key parameters driving the model engine were informed by IPD analyses from the roxadustat NDD clinical trials. The baseline characteristics of the patients across the four NDD roxadustat trials were balanced and the pooled population baseline demographics and clinical characteristics were considered representative of the UK population by clinical experts. Pooling the NDD trials was considered the most appropriated approach to generate robust estimations from the regression equations. This is aligned with the general principle of the NICE methods guide of basing the analysis on data from all relevant studies of the best available quality. The statistical analyses controlled for treatment and make use of a much larger dataset to estimate the effect of roxadustat and ESA. The approach was validated with HTA experts.

Assumption	Justification
It is assumed that roxadustat and ESA are administered for the patient's lifetime	Treatment discontinuation rates were not modelled directly in the statistical analyses due to a lack of long term follow up data to model its impact accurately in both treatment arms. Instead, treatment discontinuation was treated as a censoring event in all statistical analyses (in line with the EMA submission). Additionally, it was assumed that a patient not responding to a specific ESA class would be managed with a different ESA (ESA are considered equivalent in terms of efficacy and safety profile by different guidelines (1, 11, 36)). A patient receiving roxadustat can only currently switch to ESA (as the only available alternative treatment). As the cost effectiveness model assumes both treatments have the same survival profile, similar list prices and similar impacts on proportion in state, it is unlikely that switching from roxadustat to ESA would have a substantial impact on the cost effectiveness analysis.
No treatment effect is applied on survival	The regression analysis performed based on IPD suggests a small incremental benefit for roxadustat on patient survival ([redacted]). No treatment effect was applied to patient survival in the model. This was in line with expert clinical opinion to not expect significant differences in survival directly from anaemia treatment. The implementation of a treatment related mortality effect has been tested in scenario analyses.
No treatment effect is applied on time to dialysis	As with patient survival, no treatment effect was included in time to dialysis. This is in line with clinical expert advice and data from the DOLOMITES trial (i.e. no significant differences between roxadustat and ESA were identified).
Treatment doses, IV iron usage, blood transfusion and quality of life are dependent on the Hb level	The treatment effect of roxadustat is modelled through the effect on the Hb level. In turn, the patient's Hb level in the model affects the resource use (treatment dose, IV iron, etc) and HRQoL (health state utilities) accrued in each cycle. These dynamics are captured in the regressions fitted to patient level data from the relevant NDD roxadustat trials (42, 43, 45, 46) This was deemed the most accurate manner to estimate the treatment effect on roxadustat in the model, as the relationship between Hb levels and resource use and utility are not well established in the literature.
Dialysis status is not linked to survival and transition probabilities between Hb level health states	Dialysis status does not explicitly impact survival or Hb level in the model. Patients on dialysis receive a utility decrement and accrue the dialysis associated costs. However, it should be noted that the analysis did not censor patients when dialysis started. Therefore, any impact of dialysis on Hb level, treatment doses and HRQoL has been indirectly captured in the trial outcomes used to model the patient cohort.

Abbreviations: ESA; Erythropoiesis stimulating agent; EMA, European Medicines Agency; IV: intravenous; Hb: haemoglobin; QoL: quality of lifen NDD: non-dialysis dependent; HRQoL: health-related quality of lfie.

B.3.6.3 Scenario analyses

Several scenario analyses were performed to explore the uncertainties and the robustness of the model. Table 71 provides an overview of the scenarios analysed.

Table 71. Scenarios included in the cost-effectiveness analyses

#	Scenario description	Justification
1	Using alternative distribution for all-cause mortality	Exponential distribution was selected as the base case curve to estimate mortality. These scenarios explore the impact of the alternative parametric distributions in the model outcomes
2	Using alternative distribution for time to dialysis	Log-logistic distribution was selected as the base case curve to estimate time to dialysis. These scenarios explore the impact of the alternative parametric distributions in the model outcomes
3	Using alternative values to inform QoL (by Hb level)	QoL 3.1 Investigate model sensitivity associated with the utility based on EQ-5D-5L 3.2 Investigate the sensitivity of results to alternative source of data (76)
4	Applying utilities associated with method of administration	A patient preference study (see section B.3.4.3.2) was conducted to estimate the utility gains associated with moving from subcutaneous injections at home once every two weeks to oral administration.(77) This scenario evaluates the cost-effectiveness of roxadustat when these utility gains are modelled.
5	Using shorter time horizons (5 and 10 years)	To access when how benefits of roxadustat are accrued over the patient's lifetime 5.1 Time horizon of 5 years 5.2 Time horizon of 10 years 5.3 Time horizon of 35 years
6	ESA cost increase (5%, 10%)	ESA are provided in syringes or pens that require cold storage and, in some cases, specialised disposal. These can present an additional cost burden as they require additional and separate space, respectively. Once a syringe is used it becomes biohazard material and always requires specialist disposal and destruction which also presents cost burden. Furthermore, not all staff can handle biohazard material due to safety reasons. Due to the challenges in quantifying these costs, they were considered in the base case. This scenario aims to capture the costs associated with cold chain storage and disposal. Two variations were performed: 6.1 5% increase on ESA drug acquisition costs 6.2 10% increase on ESA drug acquisition costs
7	Comparator arm (ESA proportion) based on clinical trials	Investigate model sensitivity associated with ESA classes and conversion factors used to estimate equivalent ESA doses. 7.1 100% Epoetin alfa use 7.2 100% Darbepoetin alfa use 7.3 100% Epoetin beta use 7.4 100% Epoetin zeta use 7.5 100% Methoxy polyethylene glycol-epoetin beta use

Abbreviations: ESA; Erythropoiesis stimulating agent; IV: intravenous; Hb: haemoglobin; QoL: quality of life; OS: overall survival; IPD: individual patient data.

B.3.7 Base-case results

On average, a patient treated with roxadustat gains [redacted] additional QALYs (discounted) compared to a patient treated with ESA over a lifetime horizon. The additional QALYs with roxadustat are achieved with total costs per patient increasing by [redacted]. Roxadustat treatment for anaemic CKD patients is more effective and costly

than ESA, resulting in an ICER of [redacted] (Table 72). Additional clinical outcomes and disaggregated costs are provided in Appendix J.

Table 72. Base case cost-effectiveness results 10,000 patients

	Roxadustat	ESA
Total costs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental QALYs	[redacted]	
ICER	[redacted]	
NMB (£20,000 per QALY)	[redacted]	

Abbreviations: ESA, erythropoiesis-stimulating agents, QALY: quality adjusted life year, LY: life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit.

B.3.7.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to account for multivariate and stochastic uncertainty in the model. The uncertainties in the individual parameters for treatment effect, costs, and utilities were characterised using probability distributions and analysed with a Monte Carlo simulation of 10,000 iterations.

An overview of the probabilistic sensitivity analysis results for the cost effectiveness are shown in **Error! Not a valid bookmark self-reference.**. Overall, the probabilistic sensitivity analysis results produced slightly lower mean values than the base case analysis with a dominant ICER ([redacted]) and net monetary benefit (NMB) of £[redacted]. The probabilistic sensitivity analysis (PSA) mean produced slightly lower incremental costs for roxadustat ([redacted]- [redacted] in the base case) for a similar QALY gain ([redacted]) and roxadustat was the dominant strategy.

Table 73. Probabilistic sensitivity analysis results

	Roxadustat	ESA
Total costs (95% CI)	[redacted]	[redacted]
Total QALYs (95% CI)	[redacted]	[redacted]
Incremental costs (95% CI)	[redacted]	
Incremental QALYs (95% CI)	[redacted]	
ICER (95% CI)	[redacted]	
NMB £20,000 per QALY (95% CI)	[redacted]	

Abbreviations: CI: confidence interval, ESA: erythropoiesis-stimulating agents, QALY: quality adjusted life year, ICER: incremental cost effectiveness ratio, NMB: net monetary benefit.

The individual results of the probabilistic sensitivity analysis were plotted in cost effectiveness planes to visualise the distribution of possible ICERs relative to the

ESA (Figure 13). Each dot represents one Monte Carlo simulation where the effectiveness input parameters are sampled from their distributions. A total of 10,000 of such simulations were performed. The black line represents a willingness to pay (WTP) threshold of £20,000 per QALY gained and the red circle represents the mean output from the PSA.

Figure 13. Cost-effectiveness (CE) plane

Abbreviations: QALY: quality adjusted life year.

At list prices, the probability of roxadustat being cost effective versus ESA was [redacted] considering a threshold of £20,000/QALY (Figure 14). In addition, in [redacted] of the simulations, roxadustat was the dominant treatment option.

Figure 14. Cost-effectiveness acceptability curve (CEAC)

Abbreviations: QALY: quality adjusted life year, CEAC: cost-effectiveness acceptability curve.

B.3.7.2 Deterministic sensitivity analysis (DSA)

DSA was conducted by varying key input parameters within their 95% confidence interval or their most plausible ranges. It should be noted that parameters related to the regression models used to estimate key parameters were not included in the DSA.

Variables for which no confidence interval and/or SD or error was available have been varied by an arbitrary range of ±25%. The results were plotted in a tornado diagram (Figure 15) and summarised in Table 74.

Figure 15. Tornado diagram

Abbreviations: ICER: incremental cost-effectiveness ratio; IV: intravenous; MI: miocardial infarction; QALY: quality adjusted life year; VAT: vascular access thrombosis.

Overall, the DSA results suggest that the results of the cost effectiveness of roxadustat compared to ESA are relatively stable when key parameters are varied across their standard error or reported upper and lower ranges. Broadly, ICERs remained within the cost-effectiveness range usually accepted by NICE for all parameters tested.

Based on these results, the biggest driver of the model is [redacted] This is a consequence of the weight of this baseline characteristic in the regressions used to estimate Hb level occupancy, mortality, time to dialysis, roxadustat and ESA treatment doses, IV iron supplementation and blood transfusion. Varying this parameter from [redacted] ICER results oscillated between [redacted] and roxadustat dominance (£[redacted]).

Other significant drivers are the costs adverse events (VAT and MI) and blood transfusions. Although the differences in the rates of these events between roxadustat and ESA are not significant, the total incremental QALYs between were very low ([redacted]) hence, changes in these costs (very small in comparison to the total costs) had non-negligible impact on the ICER and NMB.

The remaining parameters included in the DSA had a very limited impact on the model outcomes.

Table 74. DSA results

Parameter	Inputs			ICER		NMB	
	Base case	Low	High	Low	High	Low	High
Discount rate - costs	3.5%	1.5%	6.0%				
Discount rate - QALYs	3.5%	1.5%	6.0%				
Proportion of patients with CVD history*	38.3%	28.7%	47.9%				
Proportion of patients with diabetes*	55.5%	41.6%	69.4%				
Proportion on haemodialysis*	78.3%	58.7%	97.9%				
Blood transfusion cost	£516	£387	£645				
Oral iron cost	£0.001	£0.001	£0.001				
IV iron cost	£0.17	£0.13	£0.21				
IV iron administration cost	£275	£206	£343				
Weighted cost of stroke	£8,625	£6,468	£10,781				
Weighted cost of MI	£3,057	£2,293	£3,821				
Weighted cost of VAT	£3,601	£2,701	£4,502				
Non-disabling stroke utility decrement	0.350	0.263	0.438				
Moderately disabling stroke utility decrement	0.500	0.375	0.625				
Severely disabling stroke utility decrement	0.730	0.548	0.913				
Myocardial Infarction utility decrement	0.120	0.090	0.150				
VAT adverse event utility decrement	0.100	0.075	0.125				

Notes: *These variables are population dependent

Abbreviations: DSA: deterministic sensitivity analysis: ESA: erythropoiesis-stimulating agents, QALY: quality adjusted life year, CVD: cardiovascular disease, IV: intravenous, MI: miocardial infarction, VAT: vascular access thrombosis, Hb: haemoglobin. g: gram, dl: deciliter.

B.3.7.3 Scenario analyses

To further investigate the uncertainties in the model, several scenario analyses were performed. These were designed to evaluate the uncertainties around the key input parameters and assumptions implemented in the model, as described in section B.3.6.3. Table 75 shows an overview of the scenario analysis results.

Table 75. Scenario analyses results

N	Description	Roxadustat		ESA		ICER	NMB
		Costs	QALYs	Costs	QALYs		
1.1	Alternative all-cause mortality distribution (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.2	Alternative all-cause mortality distribution (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.3	Alternative all-cause mortality distribution (Log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.4	Alternative all-cause mortality distribution (Log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1.5	Alternative all-cause mortality distribution (Generalised Gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.1	Alternative time to dialysis distribution (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.2	Alternative time to dialysis distribution (Gompertz)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3	Alternative time to dialysis distribution (Log-normal)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.4	Alternative time to dialysis distribution (Exponential)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.5	Alternative time to dialysis distribution (Gem Gamma)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.1	Alternative values to inform QoL (EQ5D- 5L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3.2	Alternative values to inform QoL (Published sources)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Applying utilities associated with method of administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.1	Shorter time horizon (5 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.2	Shorter time horizon (10 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5.3	Longer time horizon (35 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.1	ESA cost increase due to cold chain wastage and disposal (5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2	ESA cost increase due to cold chain wastage and disposal (10%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.1	100% Epoetin alfa use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N	Description	Roxadustat		ESA		ICER	NMB
		Costs	QALYs	Costs	QALYs		
7.2	100% Darbepoetin alfa use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.3	100% Epoetin beta use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.4	100% Epoetin zeta use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7.5	100% Methoxy polyethylene glycol-epoetin beta use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ESA: erythropoiesis-stimulating agents, QALY: quality adjusted life year, IPD: individual patient data, ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit

.

The resulting ICERs ranged from roxadustat dominancy to £[redacted] and the NMBs from £[redacted] to -£[redacted] for the comparison of roxadustat with ESA. Most of the tested scenarios resulted in ICERs and NMBs that were only marginally different from the base case results, further illustrating the robustness of the base case results for cost-effectiveness.

Scenarios 1.1 to 1.5 explore the uncertainty related to the different parametric functions used to extrapolate patient survival. As explained in section B.3.3.2, for this case the exponential function was selected as the most adequate one based on BIC and AIC goodness of fit measures. All the different functions applied in these scenarios; Weibull, Gompertz, log-normal, and generalised gamma, resulted in small variations from the base case results with ICER and NMB oscillating from £[redacted] to £[redacted] and £[redacted] to £[redacted] respectively. These scenarios showed that the model is not sensitive to the method used to extrapolate survival.

Scenarios 2.1 to 2.5 explore the uncertainty related to the different parametric functions used to estimate time to dialysis. As explained in section B.3.3.4, the log-logistic distribution was found to be the most suitable function in terms of long-term clinical plausibility, presenting a long tail capturing a fraction of patients who will never start dialysis and had the best statistical fit based on the AIC and BIC scores. Overall, all the scenarios resulted in similar ICERs and NMBs with a very small variation from the base case results, indicating that the distribution chosen for the time to dialysis is not a driver of the model outcomes.

Scenarios 3.1 and 3.2 explore the uncertainty around HRQoL data used to estimate utilities in the model. The base case analysis used EQ-5D-5L data cross walked to EQ-5D-3L to inform the Hb utility decrements. In scenario 3.1, the effect of the cross walk was evaluated by using the EQ-5D-5L as collected in the clinical trials to estimate the utilities associated with each Hb level. This scenario yielded results very similar to the base case. In scenario 3.2, utilities associated with each Hb level were derived from published data. The utility decrements for lower Hb levels were higher when estimated from these data, which results in roxadustat as the dominant strategy. These results were expected as roxadustat increases the Hb level over the patient's lifetime, compared to ESA.

The impact of the roxadustat administration route in patients' QoL was explored in Scenario 4.

A patient preference study was conducted to estimate the utility gains associated with moving from SC injections to oral formulations, as described in section B.3.4.3.2. The additional benefit associated with roxadustat resulted in [redacted] additional QALYs gained versus ESA, and a lower ICER (£[redacted]/QALY), in comparison with the base case. It should be noted that although he EQ-5D instrument is not sensitive to changes in mode of administration, the QoL data used in the base case (EQ-5D-3L), was treatment specific and collected from the clinical trial population. Therefore, some of the benefits associated with roxadustat mode of administration may have been overestimated in this scenario.

As discussed in section B.3.2.3, a 25-year time horizon was selected for the model as it is sufficiently long to capture the all life-time costs and benefits for patients with anaemia associated with CKD. Scenarios 5.1 to 5.3 evaluate the model sensitivity to the time horizon chosen for the analyses. The 5- and 10-years scenario results show that the incremental benefit of roxadustat over ESA is present after 5 years and is maintained over the patient's lifetime (as shown by the consistent ICERs obtained for 5, 10 and 25 year time horizons). In turn, the 35-year scenario shows that the base case analysis captures all the incremental differences between roxadustat and ESA, as the outcomes of these scenarios are very similar.

ESA require cold-chain storage and transit refrigeration to the patient's home, as well as additional considerations related with disposal (once syringes are used, they become biohazard material and require specific ways of disposal and destruction). Scenarios 6.1 and 6.2 explore the impact of applying a mark-up of 5% and 10%, respectively to ESA drug acquisition costs. In both scenarios, roxadustat was the dominant strategy, providing more QALYs for a lower cost. We acknowledge that accurate estimation of costs associated with cold-chain storage and disposal would require a more detailed approach than the simplified depiction in this scenario. Nevertheless, the scenarios showed that even considering a small increase in the accounted costs associated with ESA have a significant impact on the cost-effectiveness of roxadustat.

All ESAs in the model were considered equivalent to each other in terms of efficacy at equivalent doses. As noted in section B.3.5.1.2, equivalent doses were estimate using conversion factors. However, there is considerable uncertainty in the estimated conversion factors as individualised doses could not be considered in these calculations. In scenarios 7.1 to 7.5, all parameters were the same as the base case analysis, except the type of ESA used in the comparator arm. For the scenario with 100% darbepoetin alfa, no conversion factors were required, as the ESA doses in the model were estimated from the DOLOMITES trial (100% darbepoetin alfa). Costs per patient in the ESA arm varied from £[redacted] (ICER: £[redacted]/QALY) with 100% epoetin zeta, to £[redacted] (roxadustat dominant) with 100% darbepoetin alfa. It should be noted that all assumptions related to ESA conversion factors increased the ICER for roxadustat, as the scenario where no conversion factors were used was the most favourable for roxadustat.

B.3.8 Subgroup analysis

No subgroup analysis has been conducted.

B.3.9 Validation

B.3.9.1 Technical quality control of the cost effectiveness model

A check of internal validity was performed by the model developers using a quality control process. This involved checks on the selection and results of different modelling options, calculation spot checks, cross checks against source data and extreme value scenarios to check if the model behaved logically.

The quality check explored the following general aspects of the model:

- Top down tests. This involved systematic variation of the model input parameters to establish whether changes in inputs results in predictable changes in the model outputs. These tests were designed to identify failures in model logic or material computation errors
- Model internal functionality (e.g. testing of all key model parameters, extreme value testing). The following aspects of the spreadsheet were identified as key

areas for detailed checking: Markov traces; translation of drug prices, complications and resource use into state costs

- Internal consistency. Accuracy of input data. This was checked by comparing the model inputs in Excel against the data sources referenced.

Overall, the validation identified no issues with the computational accuracy of the model.

B.3.9.2 External validation of cost-effectiveness analysis

The model approach and assumption has been validated by clinical and health economic experts during a series of meetings carried out during the first quarter of 2021 (39). During these meetings, no structural or major modelling aspects were highlighted, and all other insights were incorporated into the clinical positioning and modelling approach.

B.3.10 Interpretation and conclusions of economic evidence

This submission demonstrates the cost effectiveness of roxadustat vs. ESA for the treatment of anaemia associated with CKD in patients who are NDD at the time of treatment initiation. Our base case analysis lead to a favourable deterministic ICER of £[redacted] per QALY when comparing roxadustat to ESA.

The probabilistic sensitivity analysis resulted in slightly lower incremental costs for roxadustat (-£[redacted] in the base case) for a similar QALY gain ([redacted]), and roxadustat was the dominant strategy. Roxadustat remained cost effective in [redacted] of the probabilistic sensitivity analysis iterations, with a further [redacted] of iterations showing roxadustat as a dominant strategy. Scenario analyses highlighted that the cost-effectiveness results were most sensitive to [redacted]

Nevertheless, all assumptions related to these parameters increased the ICER for roxadustat in the base case, in comparison with the alternative scenarios tested in section B.3.7.3.

The presented cost effectiveness analysis is generalizable to UK practice. The baseline characteristics (Table 29) of the pooled population from the roxadustat NDD clinical trials (42, 43, 45, 46) included in the model was validated by UK clinical

expert (39). It was noted that the modelled baseline characteristics were aligned with the UK patient population and that the pooled dataset (including the four NDD trials) (42, 43, 45, 46) reflected the heterogeneity expected in UK daily practice (39).

Regarding the treatment pathway, the model was designed to reflect the UK clinical practice as per NICE guidelines for the management of anaemia associated with CKD (28). These guidelines recommend ESA treatment initiation when a patient's Hb level does not adequately respond to iron therapy alone and remains lower than 10g/dL (28). Iron supplementation in combination with ESA and blood transfusions, although not routinely recommended, is a treatment option for some patients. Both the modelled treatment pathway and clinical data underpinning the results are aligned with these treatment recommendations, as rescue therapies such as IV iron supplementation and blood transfusions were allowed in the trials and explicitly modelled based on these data.

The main strengths of the economic assessment are:

- The model structure captures the complex relationship between treatment effect (i.e., Hb level), drug doses, need for rescue therapy and HRQoL
- Efficacy and safety data are based on a pooled dataset of four large clinical trials (42, 43, 45, 46) with patient demographics and baseline characteristics aligned with UK clinical practice (39)
- Several alternative scenarios are presented allowing for the assessment of uncertainty, including alternative modelling approaches and sources to inform efficacy and safety inputs

The main limitations of the economic assessment are:

- Lifetime extrapolations (i.e., 25 years) of the main clinical endpoints modelled (Hb level, drug doses, IV iron use, blood transfusions and HRQoL) were based on data from roxadustat NDD clinical trials (42, 43, 45, 46), with limited follow up time
- The link between risk of adverse events and Hb level was not explicitly modelled, as the number of events was not sufficient to derive a robust regression model

In summary, roxadustat is a new oral therapy that will provide an innovative treatment option for patients and a cost-effective use of UK NHS resources. The economic evidence presented highlights the added value of roxadustat over ESA in the management of patients with anaemia associated with CKD who are NDD at the time of treatment initiation.

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B.5 Appendices

Appendix C. Summary of product characteristics (SmPC) and European public assessment report (EPAR)

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 20 mg film-coated tablets
Evrenzo 50 mg film-coated tablets
Evrenzo 70 mg film-coated tablets
Evrenzo 100 mg film-coated tablets
Evrenzo 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Evrenzo 20 mg film-coated tablets
Each tablet contains 20 mg of roxadustat.

Evrenzo 50 mg film-coated tablets
Each tablet contains 50 mg of roxadustat.

Evrenzo 70 mg film-coated tablets
Each tablet contains 70 mg of roxadustat.

Evrenzo 100 mg film-coated tablets
Each tablet contains 100 mg of roxadustat.

Evrenzo 150 mg film-coated tablets
Each tablet contains 150 mg of roxadustat.

Excipient(s) with known effect
Each 20 mg film-coated tablet contains 40.5 mg of lactose, 0.9 mg of Allura Red AC aluminium lake and 0.21 mg soya lecithin.
Each 50 mg film-coated tablet contains 101.2 mg of lactose, 1.7 mg of Allura Red AC aluminium lake and 0.39 mg soya lecithin.
Each 70 mg film-coated tablet contains 141.6 mg of lactose, 2.1 mg of Allura Red AC aluminium lake and 0.47 mg soya lecithin.
Each 100 mg film-coated tablet contains 202.4 mg of lactose, 2.8 mg of Allura Red AC aluminium lake and 0.63 mg soya lecithin.
Each 150 mg film-coated tablet contains 303.5 mg of lactose, 3.7 mg of Allura Red AC aluminium lake and 0.84 mg soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablets).

Evrenzo 20 mg tablets
Red, oval tablets (approximately 8 mm × 4 mm) with '20' debossed on one side.

Evrenzo 50 mg tablets
Red, oval tablets (approximately 11 mm × 6 mm) with '50' debossed on one side.

Evrenzo 70 mg tablets
Red, round tablets (approximately 9 mm) with '70' debossed on one side.

Evrenzo 100 mg tablets
Red, oval tablets (approximately 14 mm × 7 mm) with '100' debossed on one side.

Evrenzo 150 mg tablets
Red, almond-shaped tablets (approximately 14 mm × 9 mm) with '150' debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Evrenzo is indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

4.2 Posology and method of administration

Treatment with roxadustat should be initiated by a physician experienced in the management of anaemia. All other causes of anaemia should be evaluated prior to initiating therapy with Evrenzo, and when deciding to increase the dose.

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. In addition to the presence of symptoms of anaemia, criteria such as rate of fall of haemoglobin (Hb) concentration, prior response to iron therapy, and the risk of need of red blood cell (RBC) transfusion could be of relevance in the evaluation of the individual patient's clinical course and condition.

Posology
The appropriate dose of roxadustat must be taken orally three times per week and not on consecutive days.

The dose should be individualised to achieve and maintain target Hb levels of 10 to 12 g/dL as described below.

Roxadustat treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting Evrenzo.

Starting dose at treatment initiation
Adequate iron stores should be ensured prior to initiating treatment.

Patients not currently treated with an erythropoiesis-stimulating agent (ESA)
For patients initiating anaemia treatment not previously treated with ESA the recommended starting dose of roxadustat is 70 mg three times per week in patients weighing less than 100 kg and 100 mg three times per week in patients weighing 100 kg and over.

Patients converting from an ESA
Patients currently treated with an ESA can be converted to roxadustat, however, conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason (see sections 4.4 and 5.1).

Conversion of non-dialysis patients otherwise stable on ESA treatment has not been investigated. A decision to treat these patients with roxadustat should be based on a benefit-risk consideration for the individual patient.

The recommended starting dose of roxadustat is based on the average prescribed ESA dose in the 4 weeks before conversion (see Table 1). The first roxadustat dose should replace the next scheduled dose of the current ESA.

Table 1. Starting doses of roxadustat to be taken three times per week in patients converting from an ESA

Darbepoetin alfa intravenous or subcutaneous dose (micrograms/week)	**Epoetin intravenous or subcutaneous dose (IU/week)**	**Methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous dose (micrograms/monthly)**	**Roxadustat dose (milligrams three times per week)**
Less than 25	Less than 5,000	Less than 80	70
25 to less than 40	5,000 up to 8,000	80 up to and including 120	100
40 up to and including 80	More than 8,000 up to and including 16,000	More than 120 up to and including 200	150
More than 80	More than 16,000	More than 200	200

ESA: erythropoiesis-stimulating agent

Dose adjustment and Hb monitoring
The individualised maintenance dose ranges from 20 mg to 400 mg three times per week (see section *maximum recommended dose*). Hb levels should be monitored every two weeks until

the desired Hb level of 10 to 12 g/dL is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated.

The dose of roxadustat can be adjusted stepwise up or down from the starting dose 4 weeks after treatment start, and every 4 weeks thereafter except if the Hb increases by more than 2 g/dL, in which case the dose should be reduced by one step immediately. When adjusting the dose of roxadustat, consider the current Hb level and the recent rate of change in Hb level over the past 4 weeks, and follow the dose adjustment steps according to the dose adjustment algorithm described in Table 2.

The stepwise dose adjustments up or down should follow the sequence of the available doses: 20 mg-40 mg-50 mg-70 mg-100 mg-150 mg-200 mg-250 mg-300 mg-400 mg (only for CKD patients on dialysis).

Table 2. Dose adjustment rules

Change in Hb over the previous 4 weeks[1]	**Current Hb level (g/dL):**			
	Lower than 10.5	**10.5 to 11.9**	**12.0 to 12.9**	**13.0 or higher**
Change in value of more than +1.0 g/dL	No change	Reduce dose by one step	Reduce dose by one step	Withhold dosing, monitor Hb level and resume dosing when Hb is less than 12.0 g/dL, at a dose that is reduced by two steps
Change in value between -1.0 and +1.0 g/dL	Increase dose by one step	No change	Reduce dose by one step	
Change in value of less than -1.0 g/dL	Increase dose by one step	Increase dose by one step	No change	

The dose of roxadustat should not be adjusted more frequently than once every 4 weeks, except if Hb increases by more than 2 g/dL at any time within a 4-week period, in which case the dose should be reduced by one step immediately.

[1]Change in haemoglobin (Hb) over the previous 4 weeks = (present Hb value) – (previous Hb value drawn 4 weeks ago).

If additional dose reduction is required for a patient already on the lowest dose (20 mg three times per week), do not reduce the 20 mg dose by breaking the tablet, but reduce the dose frequency to twice per week. If further dose reduction is needed, the dose frequency may be further reduced to once weekly.

Maintenance dose

After stabilisation to target Hb levels between 10 to 12 g/dL, the Hb levels should continue to be monitored regularly and the dose adjustment rules followed (see Table 2).

Patients starting dialysis while on roxadustat treatment
No specific dose adjustment is required for CKD patients who start dialysis while on treatment with roxadustat. Normal dose adjustment rules (see Table 2) should be followed.

Concomitant roxadustat treatment with inducers or inhibitors
When initiating or discontinuing concomitant treatment with strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8, or inhibitors (e.g. probenecid) of UGT1A9: the Hb levels should be monitored routinely and the dose adjustment rules followed (see Table 2; see also sections 4.5 and 5.2).

Maximum recommended dose
Patients not on dialysis do not exceed a roxadustat dose of 3 mg/kg body weight or 300 mg three times per week, whichever is lower.

Patients on dialysis do not exceed a roxadustat dose of 3 mg/kg body weight or 400 mg three times per week, whichever is lower.

Missed dose
If a dose is missed, and there is more than 1 day until the next scheduled dose, the missed dose must be taken as soon as possible. If one day or less remains before the next scheduled dose, the missed dose must be skipped, and the next dose must be taken on the next scheduled day. In each case, the regular dosing schedule should be resumed thereafter.

Special populations
Elderly
No adjustment of the starting dose is required in elderly patients (see section 5.2).

Patients with hepatic impairment
No adjustment of the starting dose level is required in patients with mild hepatic impairment (Child-Pugh class A) (see sections 4.4 and 5.2).

Caution is recommended when prescribing roxadustat to patients with moderate hepatic impairment. The starting dose is to be reduced by half or to the dose level that is closest to half the starting dose when initiating treatment in patients with moderate hepatic impairment (Child-Pugh class B). Evrenzo is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C) as the safety and efficacy has not been evaluated in this population (see sections 4.4 and 5.2).

Paediatric population
Safety and efficacy of roxadustat in paediatric patients under 18 years of age have not been established. No data are available.

Method of administration
Evrenzo film-coated tablets are to be taken orally with or without food. Tablets are to be swallowed whole and not chewed, broken or crushed due to the absence of clinical data under these conditions, and to protect the light-sensitive tablet core from photodegradation.

The tablets should be taken at least 1 hour after administration of phosphate binders (except lanthanum) or other medicinal products containing multivalent cations such as calcium, iron, magnesium or aluminium (see sections 4.5 and 5.2).

4.3 Contraindications

Evrenzo is contraindicated in the following conditions:
- Hypersensitivity to the active substance, peanut, soya or to any of the excipients listed in section 6.1.
- Third trimester of pregnancy (see sections 4.4 and 4.6).
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Cardiovascular and mortality risk
Overall, the cardiovascular and mortality risk for treatment with roxadustat has been estimated to be comparable to the cardiovascular and mortality risk for ESA therapy based on data from direct comparison of both therapies (see section 5.1). Since, for patients with anaemia associated with CKD and not on dialysis, this risk could not be estimated with sufficient confidence versus placebo, a decision to treat these patients with roxadustat should be based on similar considerations that would be applied before treating with an ESA . Further, several contributing factors have been identified that may impose this risk, including treatment non-responsiveness, and converting stable ESA treated dialysis patients (see sections 4.2 and 5.1). In the case of non-responsiveness, treatment with roxadustat should not be continued beyond 24 weeks after the start of treatment (see section 4.2). Conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason (see section 4.2). For stable ESA treated patients with anaemia associated with CKD and not on dialysis, this risk could not be estimated as these patients have not been studied. A decision to treat these patients with roxadustat should be based on a benefit risk consideration for the individual patient.

Thrombotic vascular events
The reported risk of thrombotic vascular events (TVEs) should be carefully weighed against the benefits to be derived from treatment with roxadustat particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep vein thrombosis [DVT] and pulmonary embolism [PE]). Deep vein thrombosis was reported as common and pulmonary embolism as uncommon amongst the patients in clinical studies. The majority of DVT and PE events were serious.

Vascular access thrombosis (VAT) was reported as very common amongst the CKD patients on dialysis in clinical studies (see section 4.8).

In CKD patients on dialysis, rates of VAT in roxadustat-treated patients were highest in the first 12 weeks following initiation of treatment, at Hb values more than 12 g/dL and in the setting of Hb rise of more than 2 g/dL over 4 weeks. It is recommended to monitor Hb levels and adjust the dose using the dose adjustment rules (see Table 2) to avoid Hb levels of more than 12 g/dL and Hb rise of more than 2 g/dL over 4 weeks.

Patients with signs and symptoms of TVEs should be promptly evaluated and treated according to standard of care. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration for the individual patient.

Seizures
Seizures were reported as common amongst the patients in clinical studies receiving roxadustat (see section 4.8). Roxadustat should be used with caution in patients with a history of seizures (convulsions or fits), epilepsy or medical conditions associated with a predisposition to seizure activity such as central nervous system (CNS) infections. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration of the individual patient.

Serious infections
The most commonly reported serious infections were pneumonia and urinary tract infections. Patients with signs and symptoms of an infection should be promptly evaluated and treated according to standard of care.

Sepsis
Sepsis was one of the most commonly reported serious infections and included fatal events. Patients with signs and symptoms of sepsis (e.g., an infection that spreads throughout the body with low blood pressure and the potential for organ failure) should be promptly evaluated and treated according to standard of care.

Inadequate response to therapy
Inadequate response to therapy with roxadustat should prompt a search for causative factors. Nutrient deficiencies should be corrected. Intercurrent infections, occult blood loss, haemolysis, severe aluminium toxicity, underlying haematologic diseases or bone marrow fibrosis may also compromise the erythropoietic response. A reticulocyte count should be considered as part of the evaluation. If typical causes of non-response are excluded, and the patient has reticulocytopenia, an examination of the bone marrow should be considered. In the absence of an addressable cause for an inadequate response to therapy, Evrenzo should not be continued beyond 24 weeks of therapy.

Hepatic impairment
Caution is warranted when roxadustat is administered to patients with moderate hepatic impairment (Child-Pugh class B). Evrenzo is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C) (see section 5.2).

Pregnancy and contraception
Roxadustat should not be initiated in women planning on becoming pregnant, during pregnancy or when anaemia associated with CKD is diagnosed during pregnancy. In such cases, alternative therapy should be started, if appropriate. If pregnancy occurs while

roxadustat is being administered, treatment should be discontinued and alternative treatment started, if appropriate. Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of Evrenzo (see sections 4.3 and 4.6).

Misuse
Misuse may lead to an excessive increase in packed cell volume. This may be associated with life-threatening complications of the cardiovascular system.

Excipients
Evrenzo contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Evrenzo contains Allura Red AC aluminium lake (see section 6.1) which may cause allergic reactions.
Evrenzo contains traces of soya lecithin. Patients who are allergic to peanut or soya, should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on roxadustat
Phosphate binders and other products containing multivalent cations
Co-administration of roxadustat with phosphate binders sevelamer carbonate or calcium acetate in healthy subjects decreased roxadustat AUC by 67% and 46% and C_{max} by 66% and 52%, respectively. Roxadustat may form a chelate with multivalent cations such as in phosphate binders or other products containing calcium, iron, magnesium or aluminium. Staggered administration of phosphate binders (at least 1 hour apart) had no clinically significant effect on roxadustat exposure in patients with CKD. Roxadustat should be taken at least 1 hour after administration of phosphate binders or other medicinal products or supplements containing multivalent cations (see section 4.2). This restriction does not apply to lanthanum carbonate, as the co-administration of roxadustat with lanthanum carbonate did not result in a clinically meaningful change in the plasma exposure of roxadustat.

Modifiers of CYP2C8 or UGT1A9 activity
Roxadustat is a substrate of CYP2C8 and UGT1A9. Co-administration of roxadustat with gemfibrozil (CYP2C8 and OATP1B1inhibitor) or probenecid (UGT and OAT1/OAT3 inhibitor) in healthy subjects increased roxadustat AUC by 2.3-fold and C_{max} by 1.4-fold. Monitor Hb levels when initiating or discontinuing concomitant treatment with gemfibrozil, probenecid, other strong inhibitors or inducers of CYP2C8 or other strong inhibitors of UGT1A9. Adjust the dose of roxadustat following dose adjustment rules (see Table 2) based on Hb monitoring.

Effects of roxadustat on other medicinal products

OATP1B1 or BCRP Substrates

Roxadustat is an inhibitor of BCRP and OATP1B1. These transporters play an important role in the intestinal and hepatic uptake and efflux of statins. Co-administration of 200 mg of roxadustat with simvastatin in healthy subjects increased the AUC and C_{max} of simvastatin 1.8- and 1.9-fold, respectively, and the AUC and C_{max} of simvastatin acid (the active metabolite of simvastatin) 1.9- and 2.8-fold, respectively. The concentrations of simvastatin and simvastatin acid also increased when simvastatin was administered 2 hours before or 4 or 10 hours after roxadustat. Co-administration of 200 mg of roxadustat with rosuvastatin increased the AUC and C_{max} of rosuvastatin 2.9- and 4.5-fold, respectively. Co-administration of 200 mg of roxadustat with atorvastatin increased the AUC and C_{max} of atorvastatin 2.0- and 1.3-fold, respectively.

Interactions are also expected with other statins. When co-administered with roxadustat, consider this interaction, monitor for adverse reactions associated with statins and for the need of statin dose reduction. Refer to statin prescribing information when deciding on the appropriate statin dose for individual patients.

Roxadustat may increase the plasma exposure of other medicinal products that are substrates of BCRP or OATP1B1. Monitor for possible adverse reactions of co-administered medicinal products and adjust dose accordingly.

Roxadustat and ESAs

It is not recommended to combine administration of roxadustat and ESAs as the combination has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy, women of childbearing potential and contraception

There are no data on the use of roxadustat in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Roxadustat is contraindicated during the third trimester of pregnancy (see sections 4.3 and 4.4).

Roxadustat is not recommended during the first and second trimester of pregnancy (see section 4.4).

If pregnancy occurs while Evrenzo is being administered, treatment should be discontinued and switched to alternative treatments, if appropriate (see section 4.3).

Breast-feeding

It is unknown whether roxadustat/metabolites are excreted in human milk. Available animal data have shown excretion of roxadustat in milk (for details see section 5.3). Evrenzo is contraindicated during breast-feeding (see sections 4.3 and 5.3).

Fertility

In animal studies, there were no effects of roxadustat on male and female fertility. However, changes in rat male reproductive organs were observed. The potential effects of roxadustat on

male fertility in humans is currently unknown. At a maternally toxic dose, increased embryonic loss was observed (see section 5.3). Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of Evrenzo.

4.7 Effects on ability to drive and use machines

Roxadustat has minor influence on the ability to drive and use machines. Seizures have been reported during treatment with Evrenzo (see section 4.4). Therefore, caution should be exercised when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Evrenzo was evaluated in 3542 non-dialysis dependent (NDD) and 3353 dialysis dependent (DD) patients with anaemia and CKD who have received at least one dose of roxadustat.

The most frequent (≥10%) adverse reactions associated with roxadustat are hypertension (13.9%), vascular access thrombosis (12.8%), diarrhoea (11.8%), peripheral oedema (11.7%), hyperkalaemia (10.9%) and nausea (10.2%).

The most frequent (≥1%) serious adverse reactions associated with roxadustat were sepsis (3.4%), hyperkalaemia (2.5%), hypertension (1.4%) and deep vein thrombosis (1.2%).

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies are listed in this section by frequency category.

Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3. Adverse reactions

MedDRA System organ class (SOC)	**Frequency category**	**Adverse reaction**
Infections and infestations	Common	Sepsis
Metabolism and nutrition disorders	Very common	Hyperkalaemia
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Common	Seizures, headache
Vascular disorders	Very common	Hypertension, vascular access thrombosis (VAT)[1]
	Common	Deep vein thrombosis (DVT)

Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Constipation, vomiting
Hepatobiliary disorders	Uncommon	Hyperbilirubinaemia
Respiratory, thoracic, mediastinal disorders	Uncommon	Pulmonary embolism
General disorders and administration site conditions	Very common	Peripheral oedema

[1]This adverse reaction is associated with CKD patients who were on dialysis while receiving roxadustat.

Description of selected adverse reactions

Thrombotic vascular events

In CKD patients not on dialysis, DVT events were uncommon, occurring in 1.0% (0.6 patients with events per 100 patient years of exposure) in the roxadustat group, and 0.2% (0.2 patients with events per 100 patient years of exposure) in the placebo group. In CKD patients on dialysis, DVT events occurred in 1.3% (0.8 patients with events per 100 patient years of exposure) in the roxadustat group and 0.3% (0.1 patients with events per 100 patient years of exposure) in the ESA group (see section 4.4).

In CKD patients not on dialysis, pulmonary embolism was observed in 0.4% (0.2 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 0.2% (0.1 patients with events per 100 patient years of exposure) in the placebo group. In CKD patients on dialysis, pulmonary embolism was observed in 0.6% (0.3 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 0.5% (0.3 patients with events per 100 patient years of exposure) in the ESA group (see section 4.4).

In CKD patients on dialysis, vascular access thrombosis was observed in 12.8% (7.6 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 10.2% (5.4 patients with events per 100 patient years of exposure) in the ESA group (see section 4.4).

Seizures

In CKD patients not on dialysis, seizures occurred in 1.1% (0.6 patients with events per 100 patient years of exposure) in the roxadustat group, and 0.2% (0.2 patients with events per 100 patient years of exposure) in the placebo group (see section 4.4).

In CKD patients on dialysis, seizures occurred in 2.0% (1.2 patients with events per 100 patient years of exposure) in the roxadustat group, and 1.6% (0.8 patients with events per 100 patient years of exposure) in the ESA group (see section 4.4).

Sepsis

In CKD patients not on dialysis, sepsis was observed in 2.1% (1.3 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 0.4% (0.3 patients with events per 100 patient years of exposure) in the placebo group. In patients on dialysis, sepsis was observed in 3.4% (2.0 patients with events per 100 patient years of exposure) in the

roxadustat group, compared to 3.4% (1.8 patients with events per 100 patient years of exposure) in the ESA group (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single supratherapeutic doses of roxadustat 5 mg/kg (up to 510 mg) in healthy subjects were associated with a transient increase in heart rate, an increased frequency of mild to moderate musculoskeletal pain, headaches, sinus tachycardia, and less commonly, low blood pressure, all these findings were non-serious. Roxadustat overdose can elevate Hb levels above the desired level (10 - 12 g/dL), which should be managed with discontinuation or reduction of roxadustat dosage (see section 4.2) and careful monitoring and treatment as clinically indicated. Roxadustat and its metabolites are not significantly removed by haemodialysis (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-anaemic preparations, other anti-anaemic preparations, ATC code: B03XA05.

Mechanism of action
Roxadustat is a hypoxia-inducible factor, prolyl hydroxylase inhibitor (HIF-PHI). The activity of HIF-PH enzymes controls intracellular levels of HIF, a transcription factor that regulates the expression of genes involved in erythropoiesis. Activation of the HIF pathway is important in the adaptative response to hypoxia to increase red blood cell production. Through the reversible inhibition of HIF-PH, roxadustat stimulates a coordinated erythropoietic response that includes the increase of plasma endogenous erythropoietin (EPO) levels, regulation of iron transporter proteins and reduction of hepcidin (an iron regulator protein that is increased during inflammation in CKD). This results in improved iron bioavailability, increased Hb production and increased red cell mass.

Pharmacodynamic effects

Effects on QTc and heart rate
A thorough QT (TQT) study in healthy subjects with roxadustat at a single therapeutic dose of
2.75 mg/kg and a single supratherapeutic dose of 5 mg/kg (up to 510 mg) did not show a prolongation of the QTc interval. The same thorough QT study demonstrated a

placebo-corrected heart rate increase of up to 9 to 10 bpm at 8 to 12 h post-dose for the 2.75 mg/kg dose and 15 to 18 bpm at 6 to 12 h post-dose for the dose of 5 mg/kg.

Clinical efficacy and safety

Development program in anaemia with CKD

Efficacy and safety of roxadustat were evaluated for at least 52 weeks in a globally conducted phase 3 program comprising of 8 multicentre and randomized studies in non-dialysis dependent (NDD) and dialysis-dependent (DD) CKD patients with anaemia (see Table 4).

Three studies in stage 3-5 CKD NDD patients were double-blind and placebo-controlled studies (ALPS, 1517-CL-0608; ANDES, FGCL-4592-060; OLYMPUS, D5740C00001) and one study was open-label ESA-controlled (DOLOMITES, 1517-CL-0610) using darbepoetin alfa as comparator. All NDD studies assessed efficacy and safety in ESA-untreated patients by correcting and thereafter maintaining Hb in the target range of 10 to 12 g/dL (Hb correction setting).

Four open-label ESA-controlled DD studies (control: epoetin alfa and/or darbepoetin alfa) in patients on haemodialysis or peritoneal dialysis assessed the efficacy and safety in different settings:

- in a Hb correction setting (HIMALAYAS, FGCL-4592-063).
- in an ESA conversion setting converting patients from treatment with an ESA to maintain Hb in the target range (PYRENEES, 1517-CL-0613; SIERRAS, FGCL-4592-064).
- or combining the Hb correction and ESA conversion approaches (ROCKIES, D5740C00002).

Patients in the NDD studies had CKD stage 3 to 5 and were not receiving dialysis. All patients had an average Hb ≤10.0 g/dL except patients in the DOLOMITES study (1517-CL-0610), which allowed an average Hb ≤10.5 g/dL. Ferritin levels were required to be ≥30 ng/mL (ALPS, 1517-CL-0608; ANDES, FGCL-4592-060), ≥50 ng/mL (OLYMPUS, D5740C00001) or ≥100 ng/mL (DOLOMITES, 1517-CL-0610). Except for those in the (OLYMPUS, D5740C00001) study, which allowed ESA treatment until 6 weeks prior to randomization, patients could not have received any ESA treatment within 12 weeks of randomization.

Patients in the DD studies had to be on dialysis: stable DD for patients in the PYRENEES study (1517-CL-0613), which was defined as dialysis for longer than 4 months; or incident (ID), DD for patients in the HIMALAYAS study (FGCL-4592-063), which was defined as dialysis ≥2 weeks but ≤4 months. Patients in the SIERRAS (FGCL-4592-064) and ROCKIES studies (D5740C00002) included both stable (approximately 80% to 90%) and ID (approximately 10% to 20%) DD patients. Ferritin was required to be ≥100 ng/mL in all patients. All patients required intravenous or subcutaneous ESA for at least 8 weeks prior to randomization, except those patients in the HIMALAYAS study (FGCL-4592-063) which excluded patients who had received any ESA treatment within 12 weeks prior to randomization.

Treatment with roxadustat followed the principles of dosing instructions as described in section 4.2.

Demographics and all baseline characteristics across individual studies were comparable between the roxadustat and control groups. The median age at randomization was 55 to 69 years, with between 16.6% and 31.1% in the 65-74 age range, and between 6.8% and 35% who were ≥75 years of age. The percentage of female patients ranged from 40.5% to 60.7%. The most commonly represented races across the studies were White, Black or African American and Asian. The most common CKD aetiologies were diabetic and hypertensive nephropathy. Median Hb levels ranged from 8.60 to 10.78 g/dL. Approximately 50-60% of NDD patients and 80-90% of DD patients were iron replete at baseline.

Data from seven phase 3 studies were pooled in two separate populations (three NDD and four DD) (see Table 4).

Three placebo-controlled NDD Studies (2,386 patients on roxadustat; 1,884 patients on placebo) were included in the NDD pool. Data from the phase 3 ESA-controlled NDD DOLOMITES study (1517-CL-0610; 323 patients on roxadustat and 293 patients on darbepoetin alfa) are not included in the NDD pooled analyses as this study is the only open-label, active-controlled study in the NDD population.

Four ESA-controlled DD Studies (2,354 patients on roxadustat; 2,360 patients on ESA [epoetin alfa and/or darbepoetin alfa]) were included in the DD pool. Within the DD pool, two sub pools were established to reflect the two different treatment settings:

- Patients in the DD population who were on dialysis for greater than 2 weeks and less than 4 months were termed incident (ID) DD patients (ID DD pool) reflective of the Hb correction setting.
- The DD patients who were on dialysis after this threshold of four months were termed stable DD patients (Stable DD pool) reflective of the ESA conversion setting.

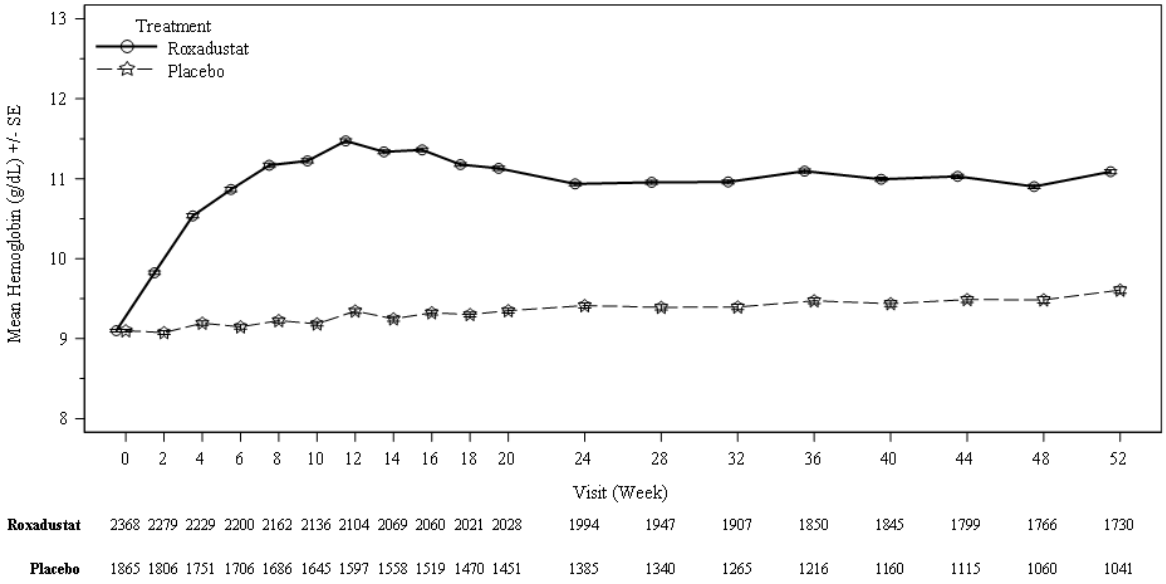
Table 4. Overview on Roxadustat phase 3 development program in anaemia with CKD

Studies in NDD patients				
	Placebo-controlled studies (NDD pool)			**ESA-control (Darbepoetin alfa)**
Setting	Hb correction			
Study	ALPS (1517-CL-0608)	ANDES (FGCL-4592-060)	OLYMPUS (D5740C00001)	DOLOMITES (1517-CL-0610)
Randomized (roxadustat/comparator)	594 (391/203)	916 (611/305)	2760 (1384/1376)	616 (323/293)
Studies in DD patients				
	ESA-controlled studies (DD pool) (Epoetin alfa or Darbepoetin alfa)			
Setting	ESA conversion		Hb correction	ESA conversion and Hb correction
Study	PYRENEES (1517-CL-0613)	SIERRAS (FGCL-4592-064)	HIMALAYAS (FGCL-4592-063)	ROCKIES (D5740C00002)
Randomized (roxadustat/comparator)	834 (414/420)	740 (370/370)	1039 (522/517)	2101 (1048/1053)

DD: dialysis dependent; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; NDD: non-dialysis dependent.

NDD CKD patients
Efficacy results
Course of Hb during treatment
In clinical studies, roxadustat was effective in achieving and maintaining target Hb levels (10-12 g/dL) in patients with CKD anaemia not on dialysis (see Figure 1).

Figure 1. Mean (SE) Hb (g/dL) over time up to week 52 (FAS); NDD pool (Hb correction)



FAS: full analysis set; Hb: haemoglobin; NDD: non-dialysis dependent; SE: standard error.

Key Hb efficacy endpoints in NDD CKD patients

In NDD patients in need of anaemia treatment for Hb correction, the proportion of patients who achieved Hb response during the first 24 weeks was higher in the roxadustat group (80.2%) compared with placebo (8.7%). There was a statistically significant increase in Hb from baseline to weeks 28 to 36 in the roxadustat group (1.91 g/dL) compared with placebo (0.14 g/dL) and the lower limit of the 95% confidence interval is above 1. In the NDD studies, an increase in Hb of at least 1 g/dL was achieved with a median time of 4.1 weeks (see Table 5).

In the open-label ESA-controlled NDD DOLOMITES (1517-CL-0610) study, the proportion of patients who achieved Hb response during the first 24 weeks was non-inferior in the roxadustat group (89.5%) compared with darbepoetin alfa (78%) (see Table 5).

Table 5. Key Hb efficacy endpoints (NDD)

Population	**NDD CKD patients**			
Setting	**Hb correction**		**Hb correction**	
	NDD pool (FAS)		**DOLOMITES (PPS)** 1517-CL-0610	
Endpoint/Parameter	**Roxadustat n= 2368**	**Placebo n= 1865**	**Roxadustat n= 286**	**Darbepoetin alfa n= 273**

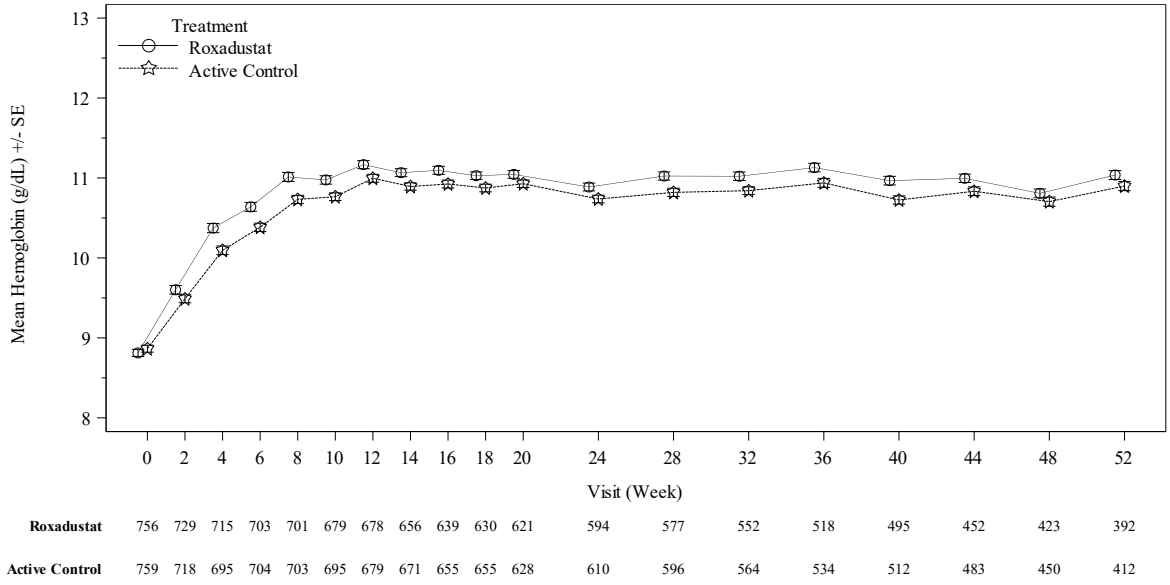
Proportion of patients who achieved Hb response[1]				
Responders, n (%) [95% CI]	1,899 (80.2) [78.5, 81.8]	163 (8.7) [7.5, 10.1]	256 (89.5) [85.4, 92.8]	213 (78.0) [72.6, 82.8]
Difference of proportions [95%	71.5 [69.40, 73.51]		11.51 [5.66, 17.36]	
Odds ratio [95% CI]	40.49 [33.01, 49.67]		2.48 [1.53, 4.04]	
P value	< 0.0001		ND	
Change from baseline in Hb (g/dL)[2]				
Mean (SD) baseline	9.10 (0.74)	9.10 (0.73)	9.55 (0.76)	9.54 (0.69)
Mean (SD) CFB	1.85 (1.07)	0.17 (1.08)	1.85 (1.08)	1.84 (0.97)
LS mean	1.91	0.14	1.85	1.84
LS mean difference [95% CI]	1.77 [1.69, 1.84]		0.02 [-0.13, 0.16]	
P value	< 0.0001		0.844	

CFB: change from baseline; CI: confidence interval; CKD: chronic kidney disease; FAS: full analysis set; Hb: haemoglobin; LS: Least squares; ND: not done; NDD: non-dialysis dependent; PPS: per protocol set; SD: standard deviation.
[1]Hb response within the first 24 weeks
[2]Change from baseline in Hb to Weeks 28 to 36

a
a

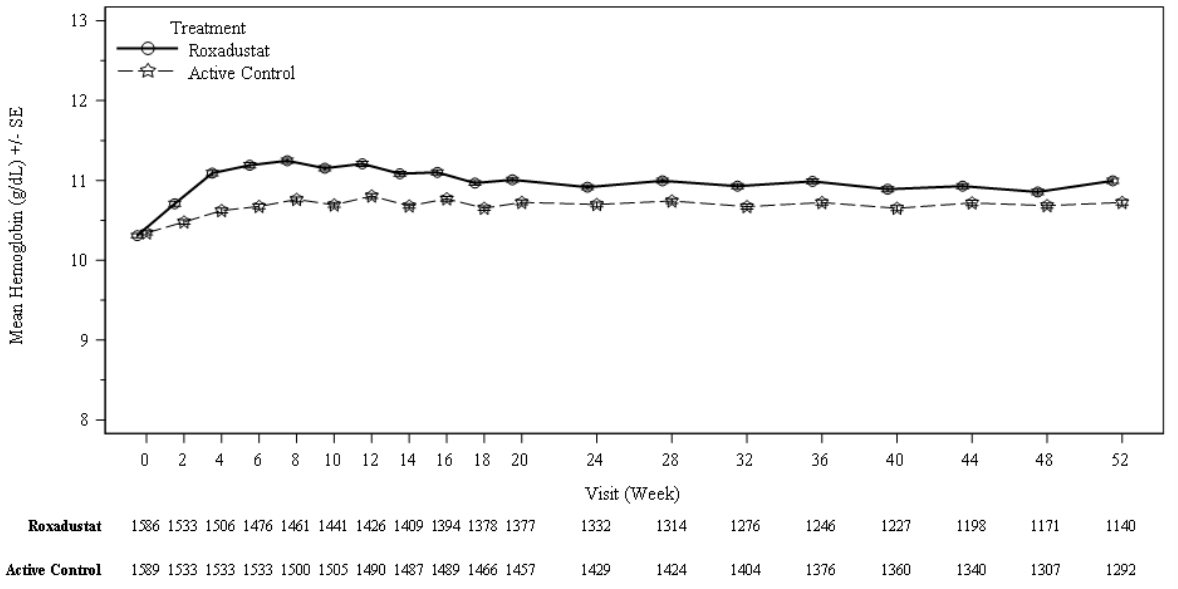
DD CKD patients
Course of Hb during treatment
In clinical studies, roxadustat was effective in achieving and maintaining target Hb levels (10-12 g/dL) in CKD patients on dialysis, irrespective of prior ESA treatment (see Figures 2 and 3).

Figure 2. Mean (SE) Hb up to week 52 (FAS); ID DD subpool (Hb correction)



DD: dialysis-dependent; FAS: full analysis set; Hb: haemoglobin; ID: incident; SE: standard error.

Figure 3. Mean (SE) Hb (g/dL) over time up to week 52 (FAS); stable DD subpool (ESA conversion)



DD: dialysis dependent; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; Hb: haemoglobin; SE: standard error.

Key Hb efficacy endpoints in DD CKD patients

In DD patients in need of anaemia treatment for Hb correction and those converted from ESA treatment, there was an increase in Hb from baseline to weeks 28 to 36 in the roxadustat group; this increase was comparable to that observed in the ESA group and was above the

prespecified noninferiority margin of -0.75 g/dL. The proportion of patients who achieved Hb response during the first 24 weeks was similar in the roxadustat and ESA groups (see Table 6).

Table 6. Key Hb efficacy endpoints (DD)

Population	**DD Patients**			
Setting	**Hb Correction**		**ESA Conversion**	
	ID DD pool (FAS/PPS)		**Stable DD Pool (PPS)**	
Endpoint/Parameter	**Roxadustat n = 756**	**ESA n = 759**	**Roxadustat n = 1379**	**ESA n = 1417**
Change from baseline in Hb (g/dL)				
Mean (SD) baseline	8.77 (1.20)	8.82 (1.20)	10.32 (0.99)	10.37 (0.99)
Mean (SD) CFB	2.37 (1.57)	2.12 (1.46)	0.65 (1.15)	0.36 (1.23)
LS mean	2.17	1.89	0.58	0.28
LS mean difference [95% CI]	0.28 [0.110, 0.451]		0.30 [0.228, 0.373]	
P value	0.0013		< 0.0001	
Proportion of patients who achieved Hb response [1,2]				
Responders, n (%) [95% CI]	453 (59.9) [56.3, 63.4]	452 (59.6) [56.0, 63.1]	978 (70.9) [68.4, 73.3]	959 (67.7) [65.2, 70.1]
Difference of proportions [95% CI]	0.3 [-4.5, 5.1]		2.7 [-0.7, 6.0]	
Odds ratio [95% CI]	ND		ND	
P value	ND		ND	

CFB: change from baseline; CI: confidence interval; CKD: chronic kidney disease; DD: dialysis dependent; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; Hb: haemoglobin; ID: incident; LS: Least squares; ND: not done; PPS: per protocol set; SD: standard deviation.

[1]Hb within the target range of 10.0 to 12.0 g/dL during weeks 28 to 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

[2]Data in the ID DD pool were only analysed for weeks 28 to 52.

Rescue therapy, RBC transfusion and intravenous iron

The effects of treatment with roxadustat on use of rescue therapy, RBC transfusion and intravenous iron are presented in Table 7 (NDD) and Table 8 (DD). In clinical studies, roxadustat reduced hepcidin (regulator of iron metabolism), reduced ferritin, increased serum iron while transferrin saturation was stable, all which were assessed over time as indicators of iron status.

Low-density lipoprotein (LDL) cholesterol

The effects of treatment with roxadustat on LDL cholesterol are presented in Tables 7 and 8. There was a reduction in mean LDL and high density lipoprotein (HDL) cholesterol levels in roxadustat-treated patients compared with placebo or ESA-treated patients. The effect on LDL cholesterol was more pronounced, leading to a reduction of the LDL/HDL ratio and was observed regardless of the use of statins.

Table 7. Other efficacy endpoints: use of rescue therapy, monthly intravenous iron use and change from baseline in LDL cholesterol (NDD)

Population	**NDD CKD patients**			
Intervention	**Correction**		**Correction**	
	NDD pool (FAS)		**DOLOMITES (1517-CL-0610)**	
Endpoint/Parameter	**Roxadustat n = 2368**	**Placebo n = 1865**	**Roxadustat n = 322**	**Darbepoetin alfa n = 292**
Number of patients with rescue therapy, n (%)[1]	211 (8.9)	580 (31.1)	ND	
RBC	118 (5.0)	240 (12.9)		
IV iron	50 (2.1)	90 (4.8)		
ESA	48 (2.0)	257 (13.8)		
IR	10.4	41.0		
Hazard ratio	0.19		ND	
95% CI	0.16, 0.23			
P value	<0.0001			
Number of Patients with IV Iron, n (%)[2]	ND		20 (6.2)	37 (12.7)
IR			9.9	21.2
Hazard ratio			0.45	
95% CI			0.26, 0.78	
P value			0.004	
Change from baseline in LDL cholesterol (mmol/L) to weeks 12 to 28[3]				
Analysis using ANCOVA				
LS mean	-0.446	0.066	-0.356	0.047
95% CI	-0.484, -0.409	0.017, 0.116	-0.432, -0.280	-0.033, 0.127
LS mean difference (R-comparator)	-0.513		-0.403	
95% CI	-0.573, -0.453		-0.510, -0.296	
P value	<0.0001		<0.001	

P values presented for the NDD pool are nominal p values.
ANCOVA: analysis of covariance; CI: confidence interval; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; IR: incidence rate (per 100 patient-years at risk); IV: intravenous; LDL: low density lipoprotein; LS: least squares; ND: not done; NDD: non-dialysis-dependent; R: roxadustat; RBC: red blood cell;
[1]For use of rescue therapy the NDD pool was analysed up to week 52.
[2]During weeks 1-36.
[3]Change from baseline in LDL cholesterol was assessed only through week 24 for study OLYMPUS (D5740C00001).

Table 8. Other efficacy endpoints: use of rescue therapy, monthly intravenous iron use and change from baseline in LDL cholesterol (DD)

Population	**DD CKD patients**			
Intervention	**Correction**		**Conversion**	
	ID DD pool (FAS)		**Stable DD pool (FAS)**	
Endpoint/ Parameter	**Roxadustat n = 756**	**ESA n = 759**	**Roxadustat n = 1586**	**ESA n = 1589**
Mean monthly IV iron over weeks 28 - 52 (mg)[1]				
n	606	621	1414	1486
Mean (SD)	53.57 (143.097)	70.22 (173.33)	42.45 (229.80)	61.99 (148.02)
Change from baseline in LDL cholesterol (mmol/L) to weeks 12 to 28				
Analysis using ANCOVA				
LS mean	-0.610	-0.157	-0.408	-0.035
95% CI	-0.700, -0.520	-0.245, -0.069	-0.449, -0.368	-0.074, 0.003
LS mean difference (R-comparator)	-0.453		-0.373	
95% CI	-0.575, -0.331		-0.418, -0.328	
P value	<0.0001		<0.0001	

P values presented for the ID DD and stable DD pools are nominal p values.
ANCOVA: analysis of covariance; CI: confidence interval; CKD: chronic kidney disease; DD: dialysis-dependent; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; ID: incident dialysis; IV: intravenous; LDL: low density lipoprotein; LS: least squares; R: roxadustat.
[1]Time period for PYRENEES (1517-CL-0613) study was up to week 36, and the time period for ROCKIES (D5740C0002) study was from week 36 through end of study.

In the dialysis study SIERRAS (FGCL-4592-064) a significantly lower proportion of patients received a red blood cell transfusion during treatment in the roxadustat group compared with the EPO-alfa group (12.5% versus 21.1%); the numerical reduction was not statistically significant in the ROCKIES (D5740C00002) study (9.8% versus 13.2%).

Patient reported outcomes not on dialysis
In the DOLOMITES study (1517-CL-0610) noninferiority of roxadustat to darbepoetin was established with regards to SF-36 PF and SF-36 VT.

Patient reported outcomes on dialysis
In the PYRENEES study (1517-CL-0613), non-inferiority of roxadustat to ESAs was established regarding SF-36 PF and SF-36 VT changes from baseline to weeks 12 to 28.

Clinical safety
Meta-analysis of pooled, adjudicated cardiovascular events
A meta-analysis, of adjudicated major adverse cardiovascular events (MACE; a composite of all-cause mortality [ACM], myocardial infarction, stroke) and MACE+ (a composite of ACM, myocardial infarction, stroke, and hospitalisation for either unstable angina or

congestive heart failure), from the phase 3 study program was conducted in 8984 patients.

MACE, MACE+ and ACM outcomes are presented for three datasets using the pooled hazard ratio (HR) and its 95% confidence interval (CI). The three datasets include:

- A pooled placebo-controlled Hb correction dataset in NDD patients [includes patients from studies OLYMPUS (D5740C00001), ANDES (FGCL-4592-060) and ALPS (1517-CL-0608); see Table 4]
- A pooled ESA-controlled Hb correction dataset in NDD and ID-DD patients [includes patients from studies DOLOMITES (1517-CL-0610), HIMALAYAS (FGCL-4592-063), and the ID-DD patients of studies SIERRAS (FGCL-4592-064) and ROCKIES (D5740C00002); see Table 4]
- A pooled ESA-controlled ESA conversion dataset in Stable DD patients [includes patients from study PYRENEES (1517-CL-0613) and Stable DD patients from studies ROCKIES (D5740C00002) and SIERRAS (FGCL-4592-064); see Table 4]

MACE, MACE+ and ACM in the placebo-controlled Hb correction set of non-dialysis-dependent CKD patients

In NDD patients the analysis for MACE, MACE+ and ACM of the on-treatment analyses included all data from the start of study treatment until 28 days of the end of treatment follow-up. The on-treatment analyses used a Cox model weighted inversely for the probability of censoring (IPCW method) which aims to correct for follow-up time differences between roxadustat and placebo including identified contributors to increased risk and early discontinuation, in particular estimated glomerular filtration rate (eGFR) determinants and Hb at baseline and over time. Whether any residual confounding is present with this model remains uncertain. The HRs for the on-treatment analyses were 1.26, 1.17 and 1.16 (see Table 9). The ITT analyses included all data from the start of study treatment until the end of posttreatment safety follow-up. The ITT analysis has been included to illustrate an imbalance in risk distribution favouring placebo in the on-treatment analysis, however, ITT analyses generally demonstrate a dilution of study drug treatment effect and in these ITT analyses bias cannot be completely excluded, especially as ESA rescue therapy was introduced after study

treatment discontinuation. The HRs were 1.10, 1.07 and 1.08, with upper limits of the 95% CIs of 1.27, 1.21 and 1.26, respectively.

Table 9. CV safety and mortality in placebo-controlled Hb correction NDD pool

	MACE		MACE+		ACM	
	Roxadustat n= 2386	Placebo n = 1884	Roxadustat n= 2386	Placebo n = 1884	Roxadustat n= 2386	Placebo n = 1884
On-treatment						
Number of patients with events (%)	344 (14.4)	166 (8.8)	448 (18.8)	242 (12.8)	260 (10.9)	122 (6.5)
FAIR	8.7	6.8	11.6	10.1	6.4	5.0
HR (95% CI)	1.26 (1.02, 1.55)		1.17 (0.99, 1.40)		1.16 (0.90, 1.50)	
ITT						
Number of patients with events (%)	480 (20.1)	350 (18.6)	578 (24.2)	432 (22.9)	400 (16.8)	301 (16)
FAIR	10.6	10.3	13.2	13.2	8.3	8.1
HR (95% CI)	1.10 (0.96, 1.27)		1.07 (0.94, 1.21)		1.08 (0.93, 1.26)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+. CI: confidence interval; FAIR: follow-up adjusted incidence rate (number of patients with event/100 patient years); HR: hazard ratio; ITT: intent-to-treat; MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

MACE, MACE+ and ACM in the ESA-controlled Hb correction set of non-dialysis-dependent and incident dialysis-dependent CKD patients

In the Hb correction setting of NDD and ID-DD patients baseline characteristics and treatment discontinuation rates were comparable between the pooled roxadustat and pooled ESA patients. The analysis for MACE, MACE+ and ACM observed on treatment showed HRs of 0.79, 0.78 and 0.78, with upper limits of the 95% CIs of 1.02, 0.98 and 1.05, respectively (see Table 10). The on-treatment analyses support no evidence of increased cardiovascular safety or mortality risk with roxadustat compared with ESA in CKD patients requiring Hb correction.

Table 10. CV safety and mortality in ESA-controlled Hb correction pool

	MACE		MACE+		ACM	
	Roxadustat n = 1083	ESA n = 1059	Roxadustat n = 1083	ESA n = 1059	Roxadustat n = 1083	ESA n = 1059

On-treatment						
Number of patients with events (%)	105 (9.7)	136 (12.8)	134 (12.4)	171 (16.1)	74 (6.8)	99 (9.3)
IR	6.5	8.2	8.3	10.3	4.6	6.0
HR (95% CI)	0.79 (0.61, 1.02)		0.78 (0.62, 0.98)		0.78 (0.57, 1.05)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+. CI: confidence interval; ESA: erythropoiesis-stimulating agent; HR: hazard ratio; IR: incidence rate (number of patients with event/100 patient years); MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

MACE, MACE+ and ACM in ESA-controlled ESA conversion set of stable dialysis-dependent CKD patients

In stable DD patients converting from ESA analysis results for MACE, MACE+ and ACM observed on treatment showed HRs of 1.18, 1.03 and 1.23, with upper limits of the 95% CIs for HRs of 1.38, 1.19 and 1.49, respectively (see Table 11). The results in Table 11 should be interpreted with caution as patients allocated to roxadustat were switched from ESA at the start of the study and the impact of an inherent risk in switching to any new treatment versus remaining on a treatment with a stabilised Hb may confound the observed results and thus any comparison of treatment effect estimates cannot be reliably established.

Table 11. CV safety and mortality in ESA-controlled ESA conversion stable DD pool

	MACE		**MACE+**		**ACM**	
	Roxadustat n=1594	**ESA n=1594**	**Roxadustat n=1594**	**ESA n=1594**	**Roxadustat n=1594**	**ESA n=1594**
On-treatment						
Number of patients with events (%)	297 (18.6)	301 (18.9)	357 (22.4)	403 (25.3)	212 (13.3)	207 (13.0)
IR	10.4	9.2	12.5	12.3	7.4	6.3
HR (95% CI)	1.18 (1.00, 1.38)		1.03 (0.90, 1.19)		1.23 (1.02, 1.49)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+. CI: confidence interval; ESA: erythropoiesis-stimulating agent; HR: hazard ratio; IR: incidence rate (number of patients with event/100 patient years); MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

5.2 Pharmacokinetic properties

Roxadustat plasma exposure (area under the plasma drug concentration over time curve [AUC] and maximum plasma concentrations [C_{max}]) is dose-proportional within the recommended therapeutic dose range. In a three times per week dosing regimen, steady-state

roxadustat plasma concentrations are achieved within one week (3 doses) with minimal accumulation. The pharmacokinetics of roxadustat do not change over time.

Absorption
Maximum plasma concentrations (C_{max}) are usually achieved at 2 hours post dose in the fasted state.
Administration of roxadustat with food decreased C_{max} by 25% but did not alter AUC as compared with the fasted state. Therefore, roxadustat can be taken with or without food (see section 4.2).

Distribution
Roxadustat is highly bound to human plasma proteins (approximately 99%), predominantly to albumin. The blood-to-plasma ratio of roxadustat is 0.6. The apparent volume of distribution at steady state is 24 L.

Biotransformation
Based on *in vitro data,* roxadustat is a substrate for CYP2C8 and UGT1A9 enzymes, as well as BCRP, OATP1B1, OAT1 and OAT3. Roxadustat is not a substrate for OATP1B3 or P-gp. Roxadustat is primarily metabolised to hydroxy-roxadustat and roxadustat-*O*-glucuronide. Unchanged roxadustat was the major circulating component in human plasma; no detectable metabolite in human plasma constituted more than 10% of total drug-related material exposure and no human specific metabolites were observed.

Elimination
The mean effective half-life ($t_{1/2}$) of roxadustat is approximately 15 hours in patients with CKD.
The apparent total body clearance (CL/F) of roxadustat is 1.1 L/h in patients with CKD not on dialysis and 1.4 L/h in patients with CKD on dialysis. Roxadustat and its metabolites are not significantly removed by haemodialysis.
When radiolabelled roxadustat was administered orally in healthy subjects, the mean recovery of radioactivity was 96% (50% in faeces, 46% in urine). In faeces, 28% of the dose was excreted as unchanged roxadustat. Less than 2% of the dose was recovered in urine as unchanged roxadustat.

Special Populations
Effects of age, sex, body weight, and race
No clinically relevant differences in the pharmacokinetics of roxadustat were observed based on age (≥18), sex, race, body weight, renal function (eGFR) or dialysis status in adult patients with anaemia due to CKD.

Haemodialysis
In dialysis-dependent CKD patients, no marked differences in pharmacokinetic parameter values were observed when roxadustat was administered 2 hours before or 1 hour after haemodialysis. Dialysis is a negligible route of overall clearance of roxadustat.

Hepatic impairment
Following a single dose of 100 mg roxadustat, mean roxadustat AUC was 23% higher and mean C_{max} was 16% lower in subjects with moderate hepatic impairment (Child-Pugh Class

B) and normal renal function compared to subjects with normal hepatic and renal functions. Subjects with moderate hepatic impairment (Child-Pugh Class B) and normal renal function showed an increase in unbound roxadustat AUC_{inf} (+70%) as compared to healthy subjects. The pharmacokinetics of roxadustat in subjects with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Drug-Drug Interactions
Based on *in vitro* data, roxadustat is an inhibitor of CYP2C8, BCRP, OATP1B1 and OAT3 (see section 4.5). The pharmacokinetics of rosiglitazone (moderate sensitive CYP2C8 substrate) were not affected by co-administration of roxadustat. Roxadustat may be an inhibitor of intestinal but not hepatic UGT1A1 and showed no inhibition of other CYP metabolising enzymes or transporters, or induction of CYP enzymes at clinically relevant concentrations. There is no clinically significant effect of oral adsorptive charcoal or omeprazole on roxadustat pharmacokinetics. Clopidogrel has no effect on roxadustat exposure in patients with CKD.

5.3 Preclinical safety data

Repeat-dose toxicity studies
In the 26-week intermittent repeat dose study in Sprague-Dawley or Fisher rats, roxadustat at approximately 4 to 6-fold the total AUC at Maximum Recommended Human Dose (MRHD) resulted in histopathological findings including aortic and atrioventricular valves (A-V) valvulopathies. These findings were present in surviving animals at the time of termination as well as in animals terminated early in a moribund state. Furthermore, the findings were not fully reversible as they were also present in animals at the end of a 30-day recovery period.

Exaggerated pharmacology resulting in excessive erythropoiesis has been observed in repeated-dose toxicity studies in healthy animals.

Haematological changes such as decreases in circulating platelets as well as increases in activated partial thromboplastin time and prothrombin time were noted in rats from approximately 2-fold the total AUC at MRHD. Thrombi were noted in the bone marrow (systemic exposures of approximately 7-fold the total AUC at MRHD in rats), kidneys (systemic exposures of approximately 5 to 6-fold total AUC at MRHD in rats), lungs (systemic exposures approximately 8- and 2-fold total AUC at MRHD in rats and cynomolgus monkeys, respectively), and the heart (systemic exposures of approximately 4 to 6-fold the total AUC at MRHD in rats).

Brain safety
In the 26-week intermittent repeat dose study in Sprague-Dawley rats, one animal, at approximately 6-fold the total AUC at MRHD showed a histologic finding of brain necrosis

and gliosis. In Fisher rats, treated for the same duration, brain/hippocampal necrosis was noted in a total of four animals at the approximately 3 to 5-fold the total AUC at MRHD.

Cynomolgus monkeys intermittently administered roxadustat for 22 or 52-weeks, did not show similar findings at systemic exposures up to approximately 2-fold the total AUC at MRHD.

Carcinogenicity and mutagenicity
Roxadustat was negative in the *in vitro* Ames mutagenicity test, *in vitro* chromosome aberration test in human peripheral blood lymphocytes and an *in vivo* micronucleus test in mice at 40-fold the MRHD based on a human equivalent dose.

In the mouse and rat carcinogenicity studies, animals were administered roxadustat with the clinical dosing regimen of three times per week. Due to the rapid clearance of roxadustat in rodents, systemic exposures were not continuous throughout the dosing period. As such, possible off-target carcinogenic effects may be underestimated.

In the 2-year mouse carcinogenicity study, significant increases in the incidence of lung bronchoalveolar carcinoma was noted in the low and high dose groups (systemic exposures approximately 1-fold and approximately 3-fold the total AUC at MRHD). A significant increase in subcutis fibrosarcoma was seen in females at the high dose group (systemic exposures approximately 3-fold total AUC at MRHD).

In the 2-year rat carcinogenicity study, a significant increase in the incidence of mammary gland adenoma was noted at the middle dose level (systemic exposure less than 1-fold the total AUC at MRHD). However, the finding was not dose related and the incidence of this tumour type was lower at the highest dose level tested (systemic exposure approximately 2-fold the total AUC at MRHD) and was therefore not considered test article related.

Similar findings from the mouse and rat carcinogenicity studies were not observed in the clinical studies.

Reproductive and developmental toxicity
Roxadustat had no effect on mating or fertility in treated male or female rats at approximately 4-fold the human exposure at the MRHD. However, at the NOAEL in male rats, there were decreases in weights of the epididymis and the seminal vesicles (with fluid) without effects on male fertility. The NOEL for any male reproductive organ related findings was 1.6-fold MRHD. In female rats there were increases in the number of non-viable embryos and post-implantation losses at this dose level compared to control animals.

Results from the reproductive and developmental toxicity studies in rats and rabbits demonstrated reduction of average foetal or pup body weight, average placental weight increase, abortion and pup mortalities.

Pregnant Sprague-Dawley rats administered roxadustat daily from implantation through the closure of the hard palate (Gestation Days 7 – 17) showed decreased foetal body weight and increased skeletal alterations at approximately 6-fold the total AUC at MRHD. Roxadustat had no effect on post-implant foetal survival.

Pregnant New Zealand rabbits were administered roxadustat daily from Gestation Day 7 through Gestation Day 19 and Caesarian sections were performed on Gestation Day 29. Roxadustat administration at systemic exposures up to approximately 3-fold the total AUC at MRHD showed no embryo-foetal findings. However, one doe aborted at approximately 1-fold the total AUC at MRHD and 2 does aborted at approximately 3-fold the total AUC at MRHD, the aborting females showed thin body condition.

In the perinatal/postnatal development study in Sprague-Dawley rats, pregnant dams were administered roxadustat daily from Gestation Day 7 to Lactation Day 20. During the lactation period, pups from dams administered roxadustat at approximately 2-fold the total C_{max} at MRHD showed high mortality during the preweaning period and were sacrificed at weaning. Pups from dams administered roxadustat at doses resulting in systemic exposures approximately 3-fold the human exposure at MRHD showed a significant decrease in 21-day survival after birth (lactation index) compared with pups from control litters.

In a cross-fostering study, the most pronounced effects on rat pup viability were noted in the pups exposed to roxadustat postnatally only, and the pup viability exposed to roxadustat until delivery was lower than that of unexposed pups.

The cross-fostering study in which pups from unexposed rats were cross fostered with dams treated with roxadustat (human equivalent dose approximately 2-fold MRHD), had roxadustat in pup plasma indicating transfer of drug via the milk. Milk from these dams had roxadustat present. The pups who were exposed to milk containing roxadustat showed a lower survival rate (85.1%) versus pups from untreated dams cross fostered with untreated dams (98.5% survival rate). The mean body weight of the surviving pups exposed to roxadustat during the lactation period was also less than the control pups (no *in utero* exposure – no exposure in milk).

Cardiovascular safety
A cardiovascular safety pharmacology study showed heart rate increases following a single administration of 100 mg/kg roxadustat to monkeys. There was no effect on hERG or ECG. Additional safety pharmacology studies in rats have shown that roxadustat reduced total peripheral resistance followed by a reflex increase in heart rate from approximately six times the exposure at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Cellulose, microcrystalline (E460 (i))
Croscarmellose sodium (E468)
Povidone (E1201)
Magnesium stearate (E470b)

Film-coating
Poly(vinyl alcohol) (E1203)
Talc (E553b)
Macrogol (E1521)
Allura Red AC aluminium lake (E129)
Titanium dioxide (E171)
Lecithin (soya) (E322)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium perforated unit dose blisters in a carton containing 12 x 1 film-coated tablet.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 20 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC aluminium lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew, break or crush the tablets.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 20 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 50 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC aluminium lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew, break or crush the tablets.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 50 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 70 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 70 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC aluminium lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew, break or crush the tablets.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 70 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 70 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 100 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC Aluminium Lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew, break or crush the tablets.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 100 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 150 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC Aluminium Lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Do not chew, break or crush the tablets.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 150 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Evrenzo 20 mg film-coated tablets
Evrenzo 50 mg film-coated tablets
Evrenzo 70 mg film-coated tablets
Evrenzo 100 mg film-coated tablets
Evrenzo 150 mg film-coated tablets
roxadustat

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Evrenzo is and what it is used for
2. What you need to know before you take Evrenzo
3. How to take Evrenzo
4. Possible side effects
5. How to store Evrenzo
6. Contents of the pack and other information

1. What Evrenzo is and what it is used for

What Evrenzo is
Evrenzo is a medicine that increases the number of red blood cells and haemoglobin level in your blood. It contains the active substance roxadustat.

What Evrenzo is used for
Evrenzo is used to treat adults with symptomatic anaemia that occurs in patients with chronic kidney disease. Anaemia is when you have too few red blood cells and your haemoglobin level is too low. As a result, your body might not receive enough oxygen. Anaemia can cause symptoms such as tiredness, weakness, or shortness of breath.

How Evrenzo works

Roxadustat, the active substance in Evrenzo, works by increasing the level of HIF, a substance in the body which increases the production of red blood cells when oxygen levels are low. By raising HIF levels, the medicine increases the production of red blood cells and raises the levels of haemoglobin (the oxygen-carrying protein in red blood cells). This improves the oxygen supply to your body and may reduce your symptoms of anaemia.

2. What you need to know before you take Evrenzo

Do not take Evrenzo

- if you are allergic to peanut or soya, do not use this medicine. Evrenzo contains soya lecithin.
- if you are allergic to roxadustat or any of the other ingredients of this medicine (listed in section 6).
- if you are more than 6 months pregnant, (It is also better to avoid this medicine in early pregnancy - see pregnancy section).
- if you are breast-feeding.

Warnings and precautions

Talk to your doctor, or pharmacist before taking Evrenzo:

- if you have epilepsy or have ever had convulsions or fits.
- if you have signs and symptoms of an infection, which may include fever, sweating or chills, sore throat, runny nose, shortness of breath, feeling weak, confusion, cough, vomiting, diarrhoea or stomach pain, feeling of burning when you pass urine, red or painful skin or sores on your body.
- if you have a liver disorder.

Chronic kidney disease and anaemia may increase the risk of cardiovascular events and death. Managing your anaemia is important. Your doctor will monitor your haemoglobin and also consider your treatment regimen as anaemia treatment and switching between anaemia treatments may also have a negative impact on your cardiovascular health.

Talk to your doctor, or pharmacist straight away:

- if you get blood clots:
  - in the veins of your legs (deep vein thrombosis or DVT), signs of which can include pain and/or swelling in the legs, cramping or a feeling of warmth in the affected leg;
  - in the lungs (pulmonary embolism or PE), signs of which can include sudden shortness of breath, chest pain (usually worse with breathing), feeling of anxiety, dizziness, light-headedness, or fainting; heart racing, coughing (sometimes with blood);
  - in your haemodialysis access (vascular access thrombosis or VAT) that stop the vascular access from working; signs of this can include swelling, redness,

hardening or thickening of the skin around your access, oozing at the access site, not feeling a vibration ("thrill") over the access area;

- if you have a seizure (convulsion or fit) or possible warning signs that a seizure may occur, such as headache, irritability, fear, confusion or unusual feelings;
- if you have signs and symptoms of an infection, which include fever, sweating or chills, sore throat, runny nose, shortness of breath, feeling weak or faint, confusion, cough, vomiting, diarrhoea, or stomach pain, burning when you pass urine, red or painful skin or sores on your body.

Misuse can lead to an increase in blood cells and consequently thicken the blood. This can cause life-threatening problems with the heart or blood vessels.

Children and adolescents
Do not give Evrenzo to children and adolescents aged under 18 years because there is not enough information about its use in this age group.

Other medicines and Evrenzo
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Evrenzo may affect the way these medicines work, or these medicines may affect how Evrenzo works.

In particular tell your doctor or pharmacist if you have, or are taking any of the following medicines:

- medicines to reduce phosphate levels in your blood (called phosphate binders) or other medicines or supplements that contain calcium, iron, magnesium or aluminium (called multivalent cations), such as sevelamer carbonate or calcium acetate. You must take Evrenzo at least 1 hour after these medicines or supplements. Otherwise roxadustat will not be properly absorbed by your body.
- a medicine to treat gout called probenecid.
- medicines used to lower cholesterol, such as simvastatin, atorvastatin, or rosuvastatin (also called "statins"), or gemfibrozil.
- other medicines used to treat anaemia such as erythropoiesis-stimulating agents (ESAs).

If you normally take any of these medicines, your doctor might change it and prescribe a different medicine for you during your treatment with Evrenzo.

Pregnancy, breast-feeding and fertility
If you are pregnant, think you may be pregnant or are planning to have a baby, contact your doctor.
Evrenzo may harm your unborn baby. Evrenzo is not recommended in the first 6 months of pregnancy and must not be taken in the last 3 months of pregnancy. Women taking Evrenzo who are able to become pregnant should use an effective method of contraception during treatment with Evrenzo and for at least one week after the last dose of Evrenzo. If you use a hormonal contraceptive, you must also use a barrier method, such as a condom, or a diaphragm.

Do not breastfeed if you are on treatment with Evrenzo. It is not known if Evrenzo passes into your breast milk and could harm your baby.

Driving and using machines
This medicine may affect your ability to drive or use machines. Seizures can occur as a side effect (see section 4).

Evrenzo contains lactose, soya lecithin and Allura Red AC aluminium lake
Evrenzo contains sugar (lactose), traces of peanut and soya (soya lecithin), and an azo colouring agent (Allura Red AC aluminium lake). If you have been told by your doctor that you have an intolerance to some sugars or are allergic to peanut, soya or azo colouring agents, contact your doctor before taking this medicine.

3. How to take Evrenzo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will tell you what dose of Evrenzo to take.

Your doctor will check your haemoglobin levels regularly and increase or lower your dose based on your haemoglobin levels.
Evrenzo is taken by mouth as tablets.

Taking Evrenzo

- Take your Evrenzo dose three times per week unless your doctor told you otherwise
- Never take Evrenzo on consecutive days
- Take Evrenzo on the same three days every week
- Evrenzo can be taken with food or between meals
- Swallow the tablets whole
- Do not chew, break or crush the tablets

Take Evrenzo at least 1 hour after you have taken medicines that reduce phosphate levels in your blood (called phosphate binders) or other medicines or supplements that contain calcium, iron, magnesium or aluminium (called multivalent cations) .

Dosing Schedule
3 times a week dosing schedule
Evrenzo comes in a blister pack containing medicine for 4 weeks (12 tablets), divided into 4 rows. Each row contains 1 week of medicine (3 tablets). Make sure you take tablets from the same row for each week.

Your dose ranges from 20 mg three times per week up to a maximum 400 mg three times per week.

Different dosing frequencies
In exceptional cases (based upon your haemoglobin levels), your doctor may decide to lower your Evrenzo dose to 20 mg two times or one time per week. In this case your doctor will explain which days week you need to take your dose.

More than 1 tablet needed to make up a dose
In most cases you will have 1 blister package per month. If your dose requires more than 1 blister package, you will need to take a tablet from each blister per dosing day. Your doctor will explain when and how many tablets to take.

Your doctor will monitor your haemoglobin level and may temporarily stop your treatment if your haemoglobin level becomes too high. Do not restart your treatment until your doctor tells you to. Your doctor will tell you what dose of Evrenzo to take and when to start taking it again.

If you take more Evrenzo than you should
If you take more tablets or a higher dose than you should, contact your doctor straight away.

If you forget to take Evrenzo

- Never take a double dose to make up for a forgotten dose.
- If more than 24 hours (1 day) remains before your next scheduled dose, take the missed dose as soon as possible and take the next dose on the next scheduled day.
- If less than 24 hours (1 day) remains before your next scheduled dose: skip the missed dose and take the next dose on the next scheduled day.

If you stop taking Evrenzo
Do not stop taking this medicine unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some possible side effects may be serious. Contact your doctor straight away if you get any of the following:

- blood clot in the veins of your legs (deep vein thrombosis or DVT) (may affect up to 1 in 10 people).
- blood clot in the lungs (pulmonary embolism) (may affect up to 1 in 100 people).
- blood clot in your haemodialysis access (vascular access thrombosis or VAT) that causes the vascular access to close up or stop working if you are using a fistula or graft for dialysis access (may affect more than 1 in 10 people).
- seizures and warning signs of seizures (convulsions or fits) (may affect up to 1 in 10 people).

- sepsis, a serious or in rare cases, life-threatening infection (may affect up to 1 in 10 people).

Other possible side effects

Very common (may affect more than 1 in 10 people)

- increased amount of potassium
- high blood pressure (hypertension)
- feeling sick (nausea)
- diarrhoea
- swelling due to fluid retention in the extremities (peripheral oedema)

Common (may affect up to 1 in 10 people):

- difficulty in sleeping (insomnia)
- headache
- vomiting
- constipation

Uncommon (may affect up to 1 in 100 people)

- increased amount of bilirubin in your blood

Reporting of side effects

If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Evrenzo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater, or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Evrenzo contains

Evrenzo 20 mg:
- The active substance is roxadustat. Each tablet contains 20 mg roxadustat

Evrenzo 50 mg:
- The active substance is roxadustat. Each tablet contains 50 mg roxadustat.

Evrenzo 70 mg:
- The active substance is roxadustat. Each tablet contains 70 mg roxadustat.

Evrenzo 100 mg:
- The active substance is roxadustat. Each tablet contains 100 mg roxadustat.

Evrenzo 150 mg:
- The active substance is roxadustat. Each tablet contains 150 mg roxadustat.

The other ingredients are:

- tablet core: lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone (E1201), magnesium stearate (E470b).

- film-coating: polyvinyl alcohol (E1203), talc (E553b), macrogol (E1521), Allura Red Aluminium Lake AC (E129), titanium dioxide (E171), lecithin (soya) (E322).

What Evrenzo looks like and contents of the pack
Evrenzo 20 mg are red, oval, film-coated tablets, debossed with "20" on one side.
Evrenzo 50 mg are red, oval, film-coated tablets, debossed with "50" on one side.
Evrenzo 70 mg are red, round, film-coated tablets, debossed with "70" on one side.
Evrenzo 100 mg are red, oval, film-coated tablets, debossed with "100" on one side.
Evrenzo 150 mg are red, almond-shaped, film-coated tablets, debossed with "150" on one side.

Each pack contains 12 x 1 film-coated tablet in PVC/aluminium perforated unit dose blisters.

Marketing Authorisation Holder and Manufacturer
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Sylviusweg 62
2333 BE Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site

Appendix D. Identification, selection and synthesis of clinical evidence

D.1 Identification and selection of relevant studies

A SLR was conducted to identify the clinical evidence (efficacy and safety) of roxadustat and standard of care in the management of anaemia associated with CKD. The SLR was conducted in two stages: an initial SLR in January 2019 and an update in January 2021. The same search strategy was used in the original SLR and update.

D.1.1 Search strategy

The following electronic databases were searched via the given platforms for resource use data:

- MEDLINE
- Pubmed
- Embase
- EconLit (via OvidSP)
- PsycInfo
- ScHARRHud
- PubMed
- Cost-Effectiveness Analysis (CEA) Registry
- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment
- NHS Economic Evaluation Database (NHS EED)

Additional studies were identified by searching the following sources:

- The organisational website of NICE
- European Renal Association - European dialysis and Transplant Association (ERA EDTA) Congress

- American Society of Nephrology (ASN) Kidney Week
- International Society of Pharmacoeconomics and Outcomes Research (ISPOR) conference

D.1.1.1 Source: MedlineALL

Table 76. Clinical SLR search details (MedlineALL)

	Original SLR	Original SLR
Interface / URL:	Ovid Medline	Ovid Medline
Database coverage dates:	1946 to April 15, 2019	2019 to January 27, 2021
Search date:	29/04/2019	27/01/2017
Retrieved records:	50	87

Table 77. Clinical SLR search strategy (MedlineALL)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kf,rn,nm.	32	100
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kf,rn,nm.	46	103
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kf,rn,nm.	0	0
4	1 or 2 or 3	57	145
5	exp Animals/ not Humans/	4574312	4780931
6	4 not 5	50	125
7	limit 6 to yr="2019-current"	NA	87

B.5.1.1.1 Source: Embase

Table 78. Clinical SLR search details (Embase)

	Original SLR	SLR Update
Interface / URL:	Ovid SP	Ovid SP
Database coverage dates:	1974 to April 25, 2019	2019 to January 27, 2021
Search date:	29/04/2019	27/01/2017
Retrieved records:	24	169

Table 79. Clinical SLR search strategy (Embase)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kf,rn,nm.	113	305
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kf,rn,nm.	105	176
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kf,rn,nm.	99	260
4	1 or 2 or 3	146	341
5	exp Animals/ not Humans/	5715131	6179050
6	4 not 5	120	285

#	Searches	Hits (Original SLR)	Hits (SLR Update)
7	limit 6 to yr="2019-current"	NA	169

B.5.1.1.2 Source: DARE

Table 80. Clinical SLR search details (DARE)

	Original SLR	SLR Update
Interface / URL:	Ovid SP	Ovid SP
Database coverage dates:	1974 to April 25, 2019	2019 to January 27, 2021
Search date:	29/04/2019	27/01/2017
Retrieved records:	0	169

Table 81. Clinical SLR search strategy (DARE)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kf,rn,nm.	0	0
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kf,rn,nm.	0	0
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kf,rn,nm.	0	0
4	1 or 2 or 3	0	0

B.5.1.1.3 Source: HTA Database

Table 82. Clinical SLR search details (HTA database)

	Original SLR	SLR Update
Interface / URL:	Ovid SP	Ovid SP
Database coverage dates:	From 31 March 2018, the HTA database remains available, but CRD are no longer adding new records to it.	
Search date:	29/04/2019	27/01/2017
Retrieved records:	0	0

Table 83 Clinical SLR search strategy (HTA database)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kf,rn,nm.	0	0
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kf,rn,nm.	0	0
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kf,rn,nm.	0	0
4	1 or 2 or 3	0	0

B.5.1.1.4 Source: NHS EED

Table 84 Clinical SLR search details (NHS EED)

	Original SLR	SLR Update
Interface / URL:	CRD	CRD

Database coverage dates:	Bibliographic records were published on NHS EED until 31st March 2015	
Search date:	29/04/2019	27/01/2017
Retrieved records:	0	0

Table 85 Clinical SLR search strategy (NHS EED)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kf,rn,nm.	0	0
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kf,rn,nm.	0	0
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kf,rn,nm.	0	0
4	1 or 2 or 3	0	0

B.5.1.1.5 Source: CRD Central

Table 86 Clinical SLR search details (CRD Central)

	Original SLR	SLR Update
Interface / URL:	The Cochrane Library	The Cochrane Library
Database coverage dates:	May 2019	March 2021
Search date:	29/04/2019	19/03/2021
Retrieved records:	63	52

Table 87 Clinical SLR search strategy (CRD Central)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kf,rn,nm.	30	81
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kf,rn,nm.	49	59
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kf,rn,nm.	5	6
4	1 or 2 or 3	63	NA
7	1 or 2 or 3, limit yr="2019-current"	NA	52

B.5.1.1.6 Source: Econlit

Table 88 Clinical SLR search details (Econlit)

	Original SLR	SLR Update
Interface / URL:	Ovid SP	Ovid SP
Database coverage dates:	1886 to April 20, 2019	1886 to March 2, 2021
Search date:	29/04/2019	02/03/2021
Retrieved records:	0	0

Table 89 Clinical SLR search strategy (Econlit)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kf,rn,nm.	0	0

#	Searches	Hits (Original SLR)	Hits (SLR Update)
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kf,rn,nm.	0	0
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kf,rn,nm.	0	0
4	1 or 2 or 3	0	0

B.5.1.1.7 Source: Pubmed

Table 90 Clinical SLR search details (Pubmed)

	Original SLR
Interface / URL:	https://www.ncbi.nlm.nih.gov/pubmed
Database coverage dates:	Information not found
Search date:	29/04/2019
Retrieved records:	19

Table 91 Clinical SLR search strategy (Pubmed)

#	Searches	Hits (Original SLR)
1	Search ((roxadustat*[tiab] OR roxadustat*[rn] OR roxadustat*[nm]))	32
2	Search (((asp1517*[tiab] OR asp1517*[rn] OR asp1517*[nm]) OR (asp-1517*[tiab] OR asp-1517*[rn] OR asp-1517*[nm]) OR ("asp 1517"[tiab] OR "asp 1517"[rn] OR "asp 1517"[nm]) OR (fg4592*[tiab] OR fg4592*[rn] OR fg4592*[nm]) OR (fg-4592*[tiab] OR fg-4592*[rn] OR fg-4592*[nm]) OR (sp1517*[tiab] OR sp1517*[rn] OR sp1517*[nm]) OR (sp-1517*[tiab] OR sp-1517*[rn] OR sp-1517*[nm]) OR (azd9941*[tiab] OR azd9941*[rn] OR azd9941*[nm]) OR (azd-9941*[tiab] OR azd-9941*[rn] OR azd-9941*[nm])))	46
3	Search ((("808118-40-3"[tiab] OR "808118-40-3"[rn] OR "808118-40-3"[nm]) OR ("808118403"[tiab] OR "808118403"[rn] OR "808118403"[nm]) OR ("x3o30d9ymx"[tiab] OR "x3o30d9ymx"[rn] OR "x3o30d9ymx"[nm])))	0
4	Search (#1 or #2 or #3)	57
5	Search (animals [mh] NOT humans[mh:noexp])	4574539
6	Search (#4 not #5)	50
7	Search medline[sb]	25776790
8	Search (#6 not #7)	19

B.5.1.1.8 Hand Searches

#	Conference, website, search terms	Hits (Original SLR)	Hits (SLR Update)
1	American Society of Nephrology (ASN), 2016, 2017, 2018, 2019, 2020 Search dates: April 30, 2019; February 26, 2021 Search terms: Roxadustat; asp1517; asp-1517; asp 1517; fg4592; fg-4592; sp1517; sp-1517; azd9941; azd-9941; 808118-40-3; "808118403"; x3o30d9ymx	7	50
2	European Renal Association- European dialysis and Transplant Association (ERA EDTA), 2016, 2017, 2018, 2019, 2020 Search dates: April 30, 2019; February 26, 2021	0	1

#	Conference, website, search terms	Hits (Original SLR)	Hits (SLR Update)
	Search terms: Roxadustat; asp1517; asp-1517; asp 1517; fg4592; fg-4592; sp1517; sp-1517; azd9941; azd-9941; 808118-40-3; "808118403"; x3o30d9ymx		
3	International Society of Nephrology (ISN), 2016, 2017, 2018, 2019, 2020 Search dates: April 30, 2019; February 26, 2021 Search terms: Roxadustat; asp1517; asp-1517; asp 1517; fg4592; fg-4592; sp1517; sp-1517; azd9941; azd-9941; 808118-40-3; "808118403"; x3o30d9ymx	0	0
4	Clinicaltrials.gov to 2021 Search dates: April 30, 2019; February 26, 2021 Search terms: Roxadustat; asp1517; asp-1517; asp 1517; fg4592; fg-4592; sp1517; sp-1517; azd9941; azd-9941; 808118-40-3; "808118403"; x3o30d9ymx	39	26
5	International Clinical Trials Registry Platform (ICTRP), to 2021 Search dates: April 30, 2019; February 26, 2021 Search terms: Roxadustat; asp1517; asp-1517; asp 1517; fg4592; fg-4592; sp1517; sp-1517; azd9941; azd-9941; 808118-40-3; "808118403"; x3o30d9ymx	55	45

D.1.2 Study selection

The eligibility criteria for the utility review is outlined in

Table 92. Eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years of age) with CKD (stage 3-5) and anaemia.	Studies conducted in wholly Chinese or Japanese populations
Interventions and comparators	Roxadustat Best supportive care Placebo	
Outcomes	Life years gained Time to dialysis (in non-dialysis patients) Proportion of patients with subsequent transplant Change from baseline in the following parameters: Blood pressure Cholesterol Serum hepcidin Serum ferritin Transferrin Saturation (TSAT) Glycated haemoglobin (HbA1c) CRP HRQoL: Patients' Global Impression of Change EQ-5D-5L SF-36 FACT-An FACT-fatigue Adverse events (AEs):	

	Inclusion criteria	Exclusion criteria
	Proportion of patients with grade 3 or higher AEs Proportion of patients with Serious AEs (SAEs) Specific cardiac adverse events including: Ischaemic heart disease Stroke Myocardial infarction Pulmonary embolism Withdrawal due to AEs Discontinuation due to any cause	
Study design	RCTs of any size and duration were eligible for inclusion. Cross-over RCTs were included if data are presented at cross-over	Non-systematic reviews Editorials News stories
Limits	No language or date limits were applied	

Abbreviations: AEs: adverse events; SAEs: serious adverse events, RCT: randomised controlled trial, TSAT:tTransferrin Saturation, HbA1c: Glycated haemoglobin; CKD: Chronic Kidney disease,

D.2 Results

The PRISMA diagram below in shows the number of articles screened at abstract and full text stage, and the number of included and excluded articles based on the PICOS criteria.

Figure 16. PRISMA diagram (original SLR)

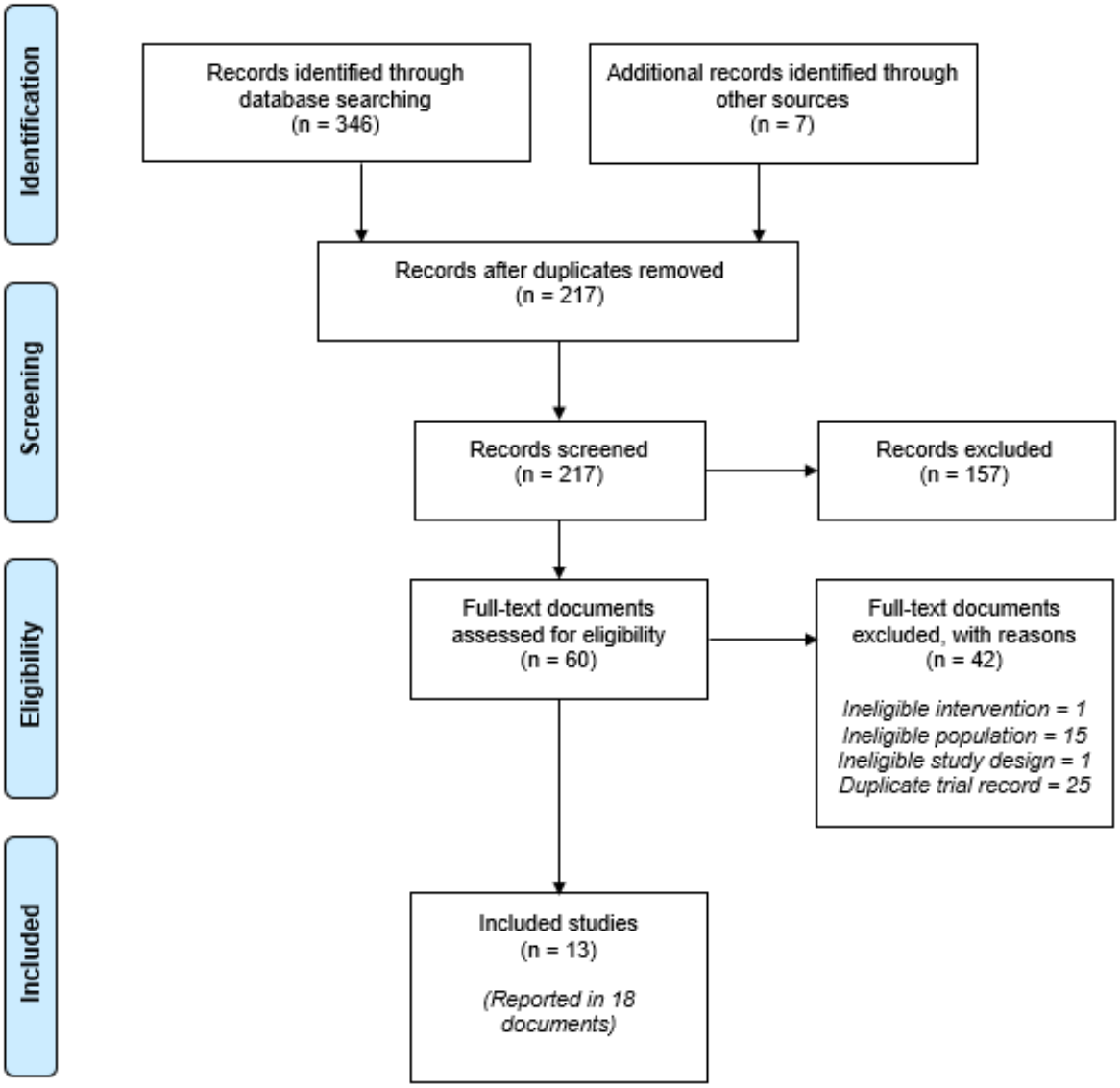
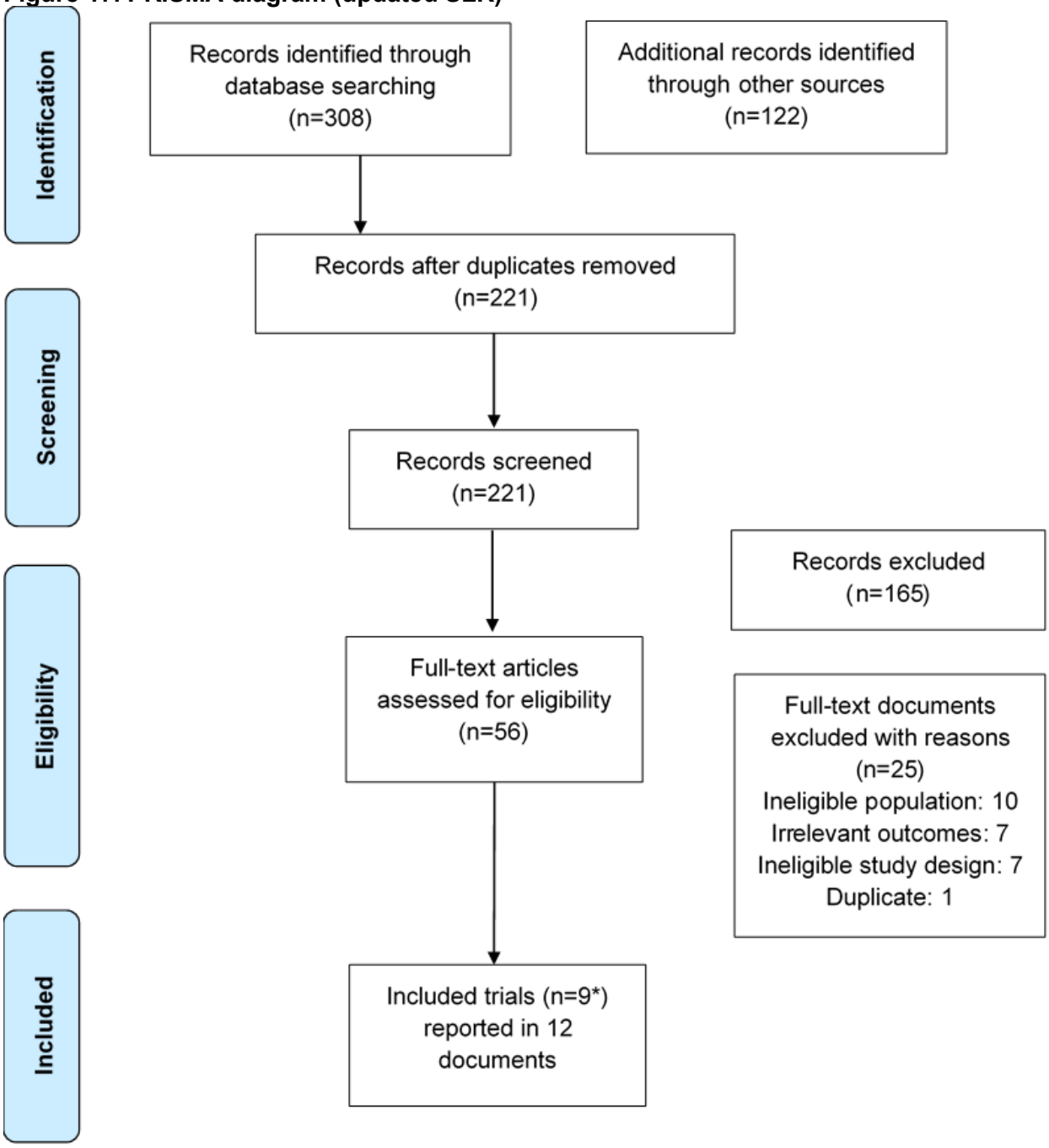


Figure 17. PRISMA diagram (updated SLR)



Thirteen trials were identified that assessed Roxadustat in patients with anaemia and CKD:

- One Phase Ib/II trial
- Four Phase II trials
- One Phase II/III extension trial
- Eight Phase III trials

The following tables provide the trial identifier, full reference (primary and associated references) and a summary of the treatment arms assessed in each trial.

Table 93. Phase Ib/ II trials

Identifier	References	Arms
FGCL-4592-039 (112)	Provenzano, R., et al., Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor Roxadustat (FG-4592) for Treatment of Anemia in Chronic Kidney Disease: A Placebo-Controlled Study of Pharmacokinetic and Pharmacodynamic Profiles in Hemodialysis Patients. Journal of Clinical Pharmacology, 2020. 60(11): p. 1432-1440.	Roxadustat Placebo
NCT00761657 FGCL-SM4592-017 (113, 114)	Besarab A, Provenzano R, Hertel J, Zabaneh R, Klaus SJ, Lee T, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. Nephrol Dial Transplant. 2015;30(10):1665-73.	Roxadustat Placebo
	Besarab A, Belo D, Diamond S, Martin E, Sun C, Lee T, et al. Evaluation of hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for hemoglobin correction and maintenance in nondialysis chronic kidney disease patients for 16 and 24 weeks. Nephrol Dial Transplant. 2012;27(Suppl 2):ii133–ii45.	
	Phase 2 Study of FG-4592 in Subjects With Anemia and Chronic Kidney Disease Not Requiring Dialysis. Identifier: NCT00761657. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2008. Available from https://clinicaltrials.gov/show/NCT00761657.	
NCT01244763 FGCL-4592-041 (115)	Provenzano R, Besarab A, Sun CH, Diamond SA, Durham JH, Cangiano JL, et al. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. Clin J Am Soc Nephrol. 2016;11(6):982-91.	Roxadustat at various doses
	Study of FG-4592 in Non-Dialysis Chronic Kidney Disease Patients With Anemia. Identifier: NCT01244763. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://clinicaltrials.gov/show/nct01244763.	
NCT01147666 FGCL-4592-040 (116, 117)	Provenzano R, Besarab A, Wright S, Dua S, Zeig S, Nguyen P, et al. Roxadustat (FG-4592) versus epoetin alfa for anemia in patients receiving maintenance hemodialysis: A phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study. Am J Kidney Dis. 2016;67(6):912-24.	Roxadustat Epoetin alfa
	Study of FG-4592 in Subjects With End-Stage Renal Disease Receiving Maintenance Hemodialysis. Identifier: NCT01147666. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://clinicaltrials.gov/show/nct01147666.	
	Provenzano R, Goodkin D, Klaus S, Linde P, Kazazi F, Lee T, et al. Evaluation of FG-4592, a novel oral hypoxiainducible factor prolyl hydroxylase inhibitor, to treat anemia in hemodialysis patients. Am J Kidney Dis. 2011;57(4):A80. [Interim results]	
NCT01414075 FGCL-4592-053	Study of FG-4592 to Correct Anemia in New Dialysis Patients. Identifier: NCT01414075. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://clinicaltrials.gov/show/nct01414075.	Roxadustat at various doses

Table 94. Phase II/III trials

Identifier	References	Arms
NCT01630889 (open label extension study) FGCL-4592-059	Open Label Extension Study for the Long-term Efficacy and Safety of FG-4592 in Dialysis and Non-dialysis Chronic Kidney Disease Patients. Identifier: NCT01630889. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2012. Available from https://clinicaltrials.gov/show/NCT01630889.	Roxadustat at various doses

Table 95. Phase III trials

Identifier	References	Arms
DOLOMITES NCT02021318 1517-CL-0610 2013-000951-42 (118, 119)	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa. Identifier: NCT02021318. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://clinicaltrials.gov/show/nct02021318.	Roxadustat Darbepoetin alfa
	Barratt, J., et al., Roxadustat for the treatment of anemia in CKD patients not on dialysis (NDD): A phase 3, randomized, open-label, active-controlled study. Journal of the American Society of Nephrology, 2020. 31: p. 1.	
	Barratt, J., et al., Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: A phase 3, randomised, open-label, active controlled study. Nephrology Dialysis Transplantation, 2020. 35(SUPPL 3).	
OLYMPUS NCT02174627 CTRI/2015/12/006412 D5740C00001 PERU 068-14 (54, 120, 121)	Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease (CKD), Not on Dialysis. Identifier: NCT02174627. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02174627.	Roxadustat Placebo
	Fishbane, S., et al., Olympus: A phase 3, randomized, double-blind, placebo-controlled, international study of roxadustat efficacy in patients with non-dialysis-dependent (NDD) CKD and anemia. Journal of the American Society of Nephrology, 2019. 30: p. 6.	
	Pecoits-Filho, R., et al., Roxadustat treatment results in consistent improvements in hemoglobin (Hb) vs. placebo: An analysis of three multinational randomized clinical trials in patients with non-dialysis-dependent CKD (NDD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 2.	
	Provenzano, R., et al., Roxadustat treatment of anemia in non-dialysis-dependent CKD is not influenced by iron status. Journal of the American Society of Nephrology, 2020. 31: p. 1.	
ANDES NCT01750190 FGCL-4592-060 KCT0001690 PERU 041-14 (120, 122, 123)	A Study of FG-4592 for the Treatment of Anemia in Chronic Kidney Disease Patients Not Receiving Dialysis. Identifier: NCT01750190. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2012. Available from https://clinicaltrials.gov/ct2/show/nct01750190.	Roxadustat Placebo
	Coyne, D.W., et al., Andes: A phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of roxadustat for the treatment of anemia in CKD patients not on dialysis. Journal of the American Society of Nephrology, 2019. 30: p. 822-823.	

Identifier	References	Arms
	Coyne, D.W., et al., Roxadustat favorably modifies iron indices in patients with non-dialysis-dependent CKD-related anemia. Journal of the American Society of Nephrology, 2020. 31: p. 132.	
	Pecoits-Filho, R., et al., Roxadustat treatment results in consistent improvements in hemoglobin (Hb) vs. placebo: An analysis of three multinational randomized clinical trials in patients with non-dialysis-dependent CKD (NDD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 2.	
	Provenzano, R., et al., Roxadustat treatment of anemia in non-dialysis-dependent CKD is not influenced by iron status. Journal of the American Society of Nephrology, 2020. 31: p. 1.	
ALPS NCT01887600 1517-CL-0608 2012-005180-27 PERU 058-15 (120, 121, 124)	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis. Identifier: NCT01887600. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://clinicaltrials.gov/show/nct01887600.	Roxadustat Placebo
	Pecoits-Filho, R., et al., Roxadustat treatment results in consistent improvements in hemoglobin (Hb) vs. placebo: An analysis of three multinational randomized clinical trials in patients with non-dialysis-dependent CKD (NDD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 2.	
	Provenzano, R., et al., Roxadustat treatment of anemia in non-dialysis-dependent CKD is not influenced by iron status. Journal of the American Society of Nephrology, 2020. 31: p. 1.	
	Esposito, C., et al., Two phase 3, multicenter, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis. Journal of the American Society of Nephrology, 2019. 30: p. 822.	
HIMALAYAS NCT02052310 2013-002753-30 FGCL-4592-063/CFG13001 PERU 038-14 (125)	Safety and Efficacy Study for Treatment of Anemia in ESRD Newly Initiated Dialysis Patients. Identifier: NCT02052310. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02052310.	Roxadustat Epoetin alfa
	Provenzano, R., et al., Himalayas: A phase 3, randomized, open-label, active-controlled study of the efficacy and safety of roxadustat in the treatment of anemia in incident-dialysis patients. Journal of the American Society of Nephrology, 2019. 30: p. 5.	
ROCKIES NCT02174731 D5740C00002 PERU 067-14 (126)	Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease, on Dialysis. Identifier: NCT02174731. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/NCT02174731	Roxadustat Epoetin alfa
	Fishbane, S., et al., Rockies: An international, phase 3, randomized, open-label, active-controlled study of roxadustat for anemia in dialysis-dependent CKD patients. Journal of the American Society of Nephrology, 2019. 30: p. 6.	
SIERRAS NCT02273726	Evaluation of Efficacy and Safety of Roxadustat in the Treatment of Anemia in Stable Dialysis Subjects. Identifier: NCT02273726. In: ClinicalTrials.gov [internet]. Bethesda: US	Roxadustat Epoetin alfa

Identifier	References	Arms
FGCL-4592-064 (127)	National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02273726. Charytan, C., et al., Sierras: A phase 3, open-label, randomized, active-controlled study of the efficacy and safety of roxadustat in the maintenance treatment of anemia in subjects with ESRD on stable dialysis. Journal of the American Society of Nephrology, 2019. 30: p. 822.	
PYRENEES NCT02278341 EUCTR2013-001497-16-GB (124)	Roxadustat in the Treatment of Anemia in End Stage Renal Disease (ESRD) Patients on Stable Dialysis. Identifier: NCT02278341. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02278341. Esposito, C., et al., Two phase 3, multicenter, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis. Journal of the American Society of Nephrology, 2019. 30: p. 822.	Roxadustat Epoetin alfa / Darbepoetin alfa

Table 96. Additional publications reporting pooled data from phase III trials

Identifier	References	Arms
Roger 2020(128)	Roger, S.D., et al., Efficacy and safety of roxadustat in patients with non-dialysis-dependent CKD, anemia, and heart failure. Journal of the American Society of Nephrology, 2020. 31: p. 648.	Roxadustat Placebo
Pollock 2020 (129)	Pollock, C.A., et al., Roxadustat increases hemoglobin in anemic non-dialysis-dependent (NDD) CKD patients independent of inflammation. Journal of the American Society of Nephrology, 2020. 31: p. 132-133.	Roxadustat at various doses
Fishbane 2020 (130)	Fishbane, S., et al., Hemoglobin (HB) correction with roxadustat is associated with improved iron homeostasis in patients with non-dialysis-dependent CKD (NDD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 130.	Roxadustat Placebo
Fishbane 2020 (131)	Fishbane, S., et al., Associations between achieved hemoglobin and cardiovascular outcomes in the pooled phase 3 roxadustat studies of non-dialysis-dependent patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. B4.	Roxadustat
Coyne 2020 (132)	Coyne, D.W., et al., Subgroup analyses of efficacy of roxadustat for treatment of anemia in patients with non-dialysis-dependent CKD. Journal of the American Society of Nephrology, 2020. 31: p. 131-132.	Roxadustat Placebo
Coyne 2020 (133)	Coyne, D.W., et al., Health-related quality of life in roxadustat-treated patients with anemia and non-dialysis-dependent CKD. Journal of the American Society of Nephrology, 2020. 31: p. 131.	Roxadustat Placebo
Roger 2020 (134)	Roger, S.D., et al., Efficacy and safety of roxadustat in patients with non-dialysis-dependent CKD, anemia, and diabetes mellitus. Journal of the American Society of Nephrology, 2020. 31: p. 352.	Roxadustat Placebo
Provenzano 2020 (135)	Provenzano, R., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD and anemia on hemodialysis. Journal of the American Society of Nephrology, 2020. 31: p. 23.	Roxadustat Epoetin alfa
Pergola 2020 (136)	Pergola, P.E., et al., Hemoglobin (HB) correction with roxadustat is associated with improved iron homeostasis in patients with dialysis-dependent CKD (DD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 2.	Roxadustat Epoetin alfa

Identifier	References	Arms
Coyne 2020 (137)	Coyne, D.W., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD, anemia, and heart failure. Journal of the American Society of Nephrology, 2020. 31: p. 648.	Roxadustat Epoetin alfa
Chan 2020 (138)	Chan, T.M.D., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD and anemia on peritoneal dialysis. Journal of the American Society of Nephrology, 2020. 31: p. 51.	Roxadustat Epoetin alfa
El-Shahawy 2020 (139)	El-Shahawy, M.A., et al., Roxadustat increases hemoglobin in anemic dialysis-dependent (DD) CKD patients independent of inflammation. Journal of the American Society of Nephrology, 2020. 31: p. 133	Roxadustat at various doses
Provenzano 2020 (140)	Provenzano, R., et al., Associations between achieved hemoglobin and cardiovascular outcomes in the pooled phase 3 trials of roxadustat in dialysis-dependent patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. B4-B5.	Roxadustat
Provenzano 2020 (141)	Provenzano, R., et al., Subgroup analyses of efficacy of roxadustat for treatment of anemia in patients with incident dialysis-dependent CKD. Journal of the American Society of Nephrology, 2020. 31: p. 131.	Roxadustat Epoetin alfa
Chan 2020 (142)	Chan, T.M.D., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD, anemia, and diabetes mellitus. Journal of the American Society of Nephrology, 2020. 31: p. 352.	Roxadustat Epoetin alfa
Coyne 2020 (143)	Coyne, D.W., et al., Roxadustat is not associated with an increased risk of neoplasm in patients with CKD and anemia. Journal of the American Society of Nephrology, 2020. 31: p. 1-2.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa
Provenzano 2020 (144)	Provenzano, R., et al., Pooled analyses of the phase 3 roxadustat studies: Congestive heart failure hospitalization rates in dialysis and non-dialysis patients with anemia treated with roxadustat vs. comparators. Journal of the American Society of Nephrology, 2020. 31: p. 41-42.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa
Chan 2020 (145)	Chan, T.M.D., et al., Roxadustat vs. Placebo or epoetin alfa has no clinically meaningful effect on blood pressure in patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. 649.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa
Roger 2020 (146)	Roger, S.D., et al., Roxadustat lowers low-density lipoprotein cholesterol in patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. 648-649.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa

D.3 Participant flow

D.3.1 NDD population trials

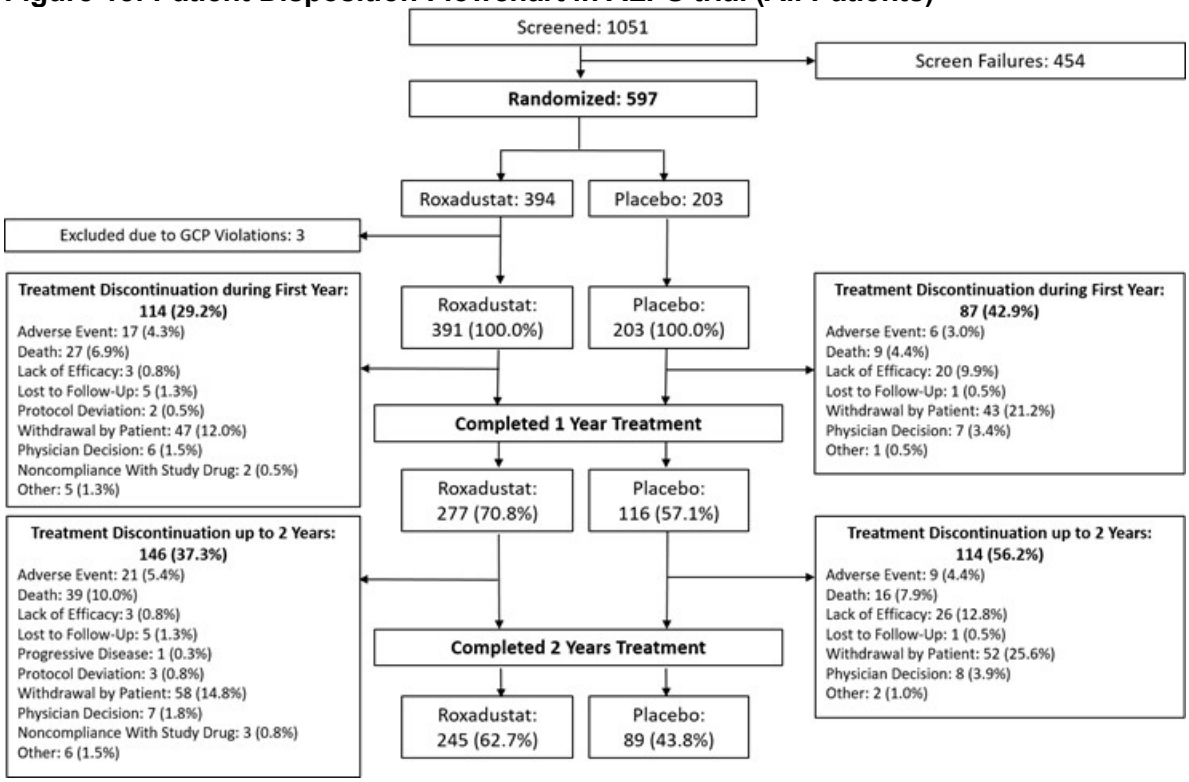
D.3.1.1 ALPS

In ALPS (43), a total of 1051 patients signed the informed consent form and were screened, of these patients, 597 were randomised to receive treatment. All data from

site 70051 (3 randomised patients) were excluded due to GCP violations; therefore, a total of 594 patients were considered randomised for statistical analysis, 391 to the roxadustat group and 203 to the placebo group. Patients were evenly distributed according to prespecified stratification criteria.

A total of 334 (56.2%) patients received study treatment up to 2 years, 245 (62.7%) in the roxadustat group and 89 (43.8%) in the placebo group. Patients could discontinue treatment but continue within the trial for safety follow-up or discontinue from the study completely. Premature withdrawal from the study overall was comparable between the treatment groups (30.4% of patients in the roxadustat group vs 35.0% of patients in the placebo group); the most common reason was withdrawal by patient in both groups (12.3% vs 20.2%). A CONSORT diagram showing the flow of participants through the ALPS trial is shown in Figure 18.

Figure 18: Patient Disposition Flowchart in ALPS trial (All Patients)



Notes: Discontinuations at up to 2 years are cumulative.

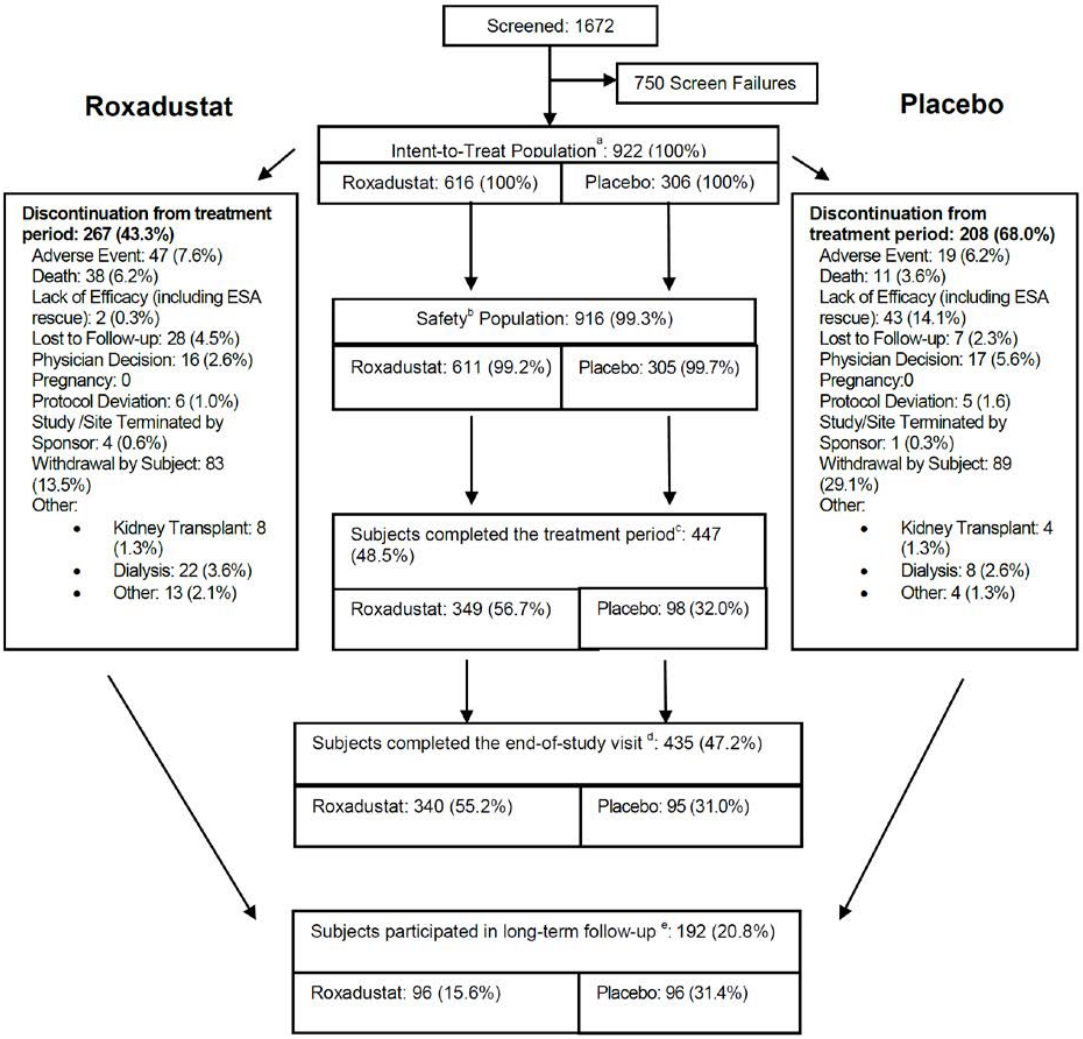
D.3.1.2 ANDES

In ANDES (46), a total of 1672 subjects were screened from 163 clinical sites (only 140 clinical sites with actual subject enrolment). Of these, 750 subjects had screen failures, 922 subjects were randomised (616 to roxadustat and 306 to placebo), and

916 subjects (611 [99.2%] roxadustat vs. 305 [99.7%] placebo) received at least one dose of study treatment. A total of 349 (56.7%) roxadustat-treated subjects vs. 98 (32.0%) placebo-treated subjects completed the treatment period. The median duration of study drug exposure was 95.6 weeks for roxadustat-treated subjects vs. 52.1 weeks for placebo-treated subjects. Two hundred and sixty-seven (43.3%) subjects in roxadustat arm and 208 (68.0%) in placebo arm prematurely discontinued treatment.

Among those subjects who prematurely discontinued treatment, 96 (15.6%) roxadustat and 96 (31.4%) placebo subjects participated in the LTFU for CV events of interest, vital status, and hospitalisations after early termination until study closure. The primary reasons for discontinuation in roxadustat-treated subjects were withdrawal by subject, adverse event, and death (83 [13.5%], 47 [7.6%], 38 [6.2%] subjects, respectively). The primary reasons for discontinuation for placebo-treated subjects were withdrawal by subject, lack of efficacy, and adverse event (89 [29.1%], 43 [14.1%], 19 [6.2%] subjects, respectively). A CONSORT diagram showing the flow of participants through the ANDES trial is shown in Figure 19.

Figure 19: Patient Disposition Flowchart in ANDES trial (All Patients)



Notes: The percentage is calculated based on the number of randomised subjects.; [a] The Intent-to-Treat Population (ITT) included all randomised/enrolled subjects.; [b] The Safety Population included all subjects who took any dose of study medication.; [c] Completed the treatment period (EOT): Subjects who completed the treatment period per protocol version; [d] Completed end-of-study visit (EOS): Subjects who completed the end-of-study visit; [e] Subjects who discontinued from study and participated in long-term follow-up (LTFU) were followed for; cardiovascular events of interest, vital status, and hospitalisations after EOS until study closure.

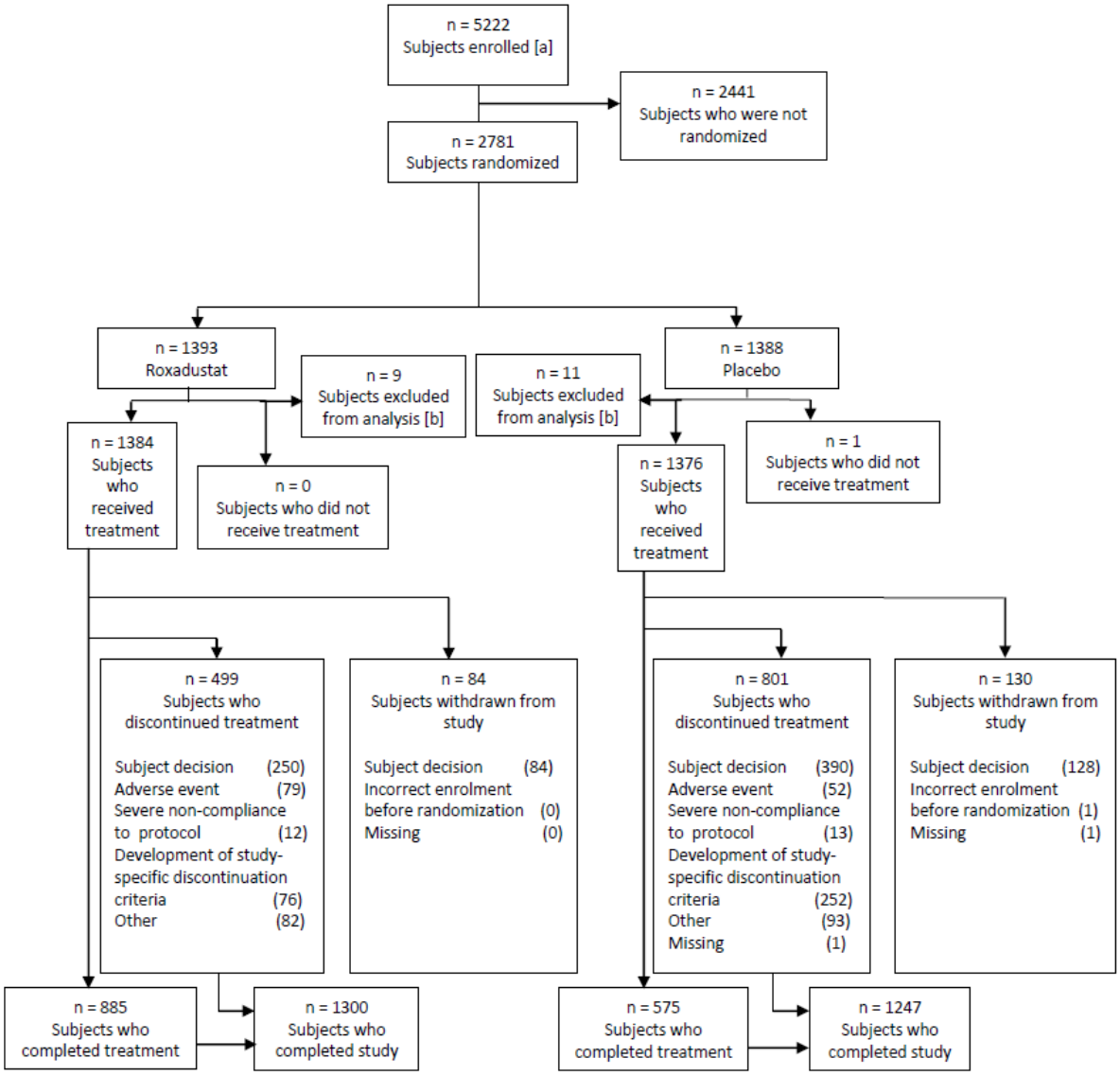
D.3.1.3 OLYMPUS

In OLYMPUS (45), 5222 subjects were enrolled in the study (informed consent obtained), 2781 subjects were randomised (1393 [26.7%] to roxadustat and 1388 [26.6%] to placebo). Twenty subjects were excluded from analysis due to system technical issues/errors and major GCP violations. Of the subjects who were randomised to treatment and not excluded from the analysis, 2760 (>99.9%) received the IP.

A total of 2547 (92.2%) randomised subjects completed the study (1300 [93.9%] in the roxadustat group and 1247 [90.6%] in the placebo group). A total of 214 (7.8%)

subjects withdrew from the study (84 [6.1%] in the roxadustat group and 130 [9.4%] in the placebo group). The main reason for study withdrawal was subject decision (i.e., withdrawal of consent) for 212 (7.7%) subjects (84 [6.1%] in the roxadustat group and 128 [9.3%] in the placebo group). A CONSORT diagram showing the flow of participants through the OLYMPUS trial is shown in Figure 20.

Figure 20: Patient Disposition Flowchart in OLYMPUS trial (All Patients)



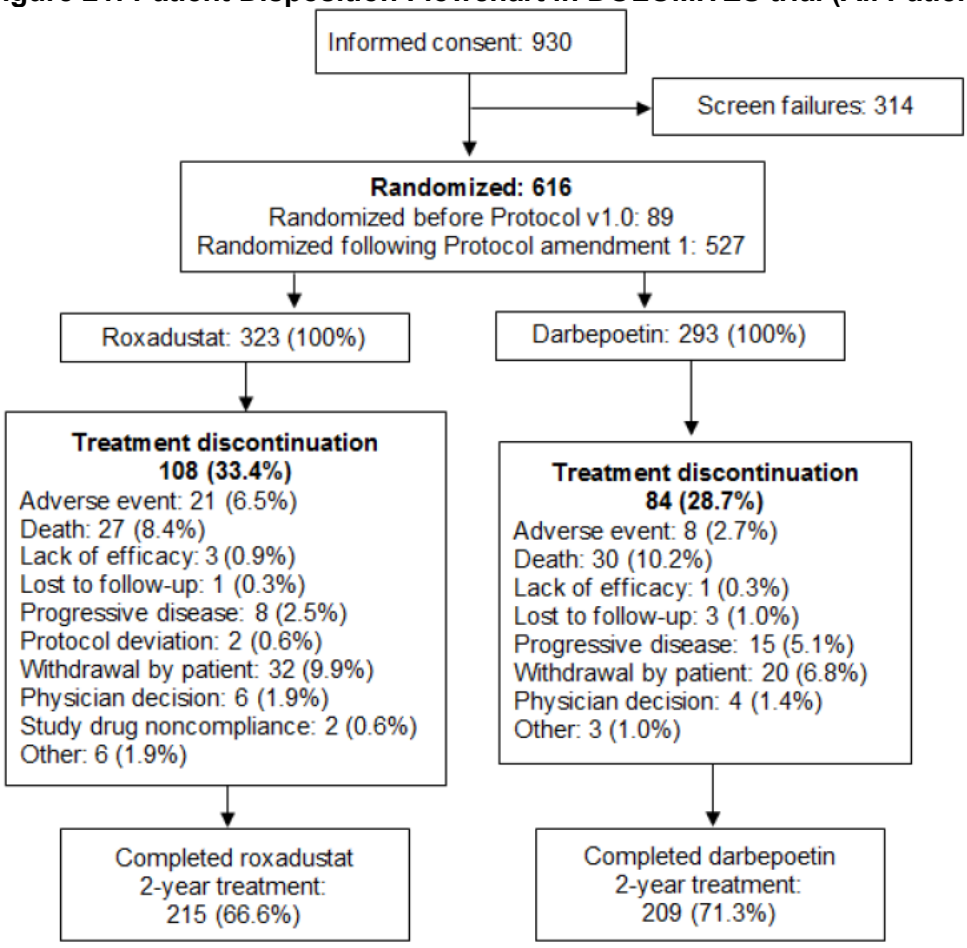
Notes: [a] Informed consent received; [b] Twenty subjects were excluded from the analysis due to major GCP violations or being phantom subjects due to system technical issues.

D.3.1.4 DOLOMITES

In DOLOMITES (42), a total of 930 patients signed the informed consent form and were screened, of these 616 were randomised to receive treatment: 323 to the roxadustat group and 293 to the darbepoetin alfa group. A total of 424 (68.8%)

patients completed the 2-year treatment, 215 (66.6%) in the roxadustat group and 209 (71.3%) in the darbepoetin alfa group. Study discontinuation was comparable between the randomised treatment groups (22.6% of patients in the roxadustat group vs 21.5% in the darbepoetin alfa group); the most common reason was death for both groups (10.2% vs 11.6%). Premature withdrawal from the study treatment was comparable between the treatment groups (33.4% of patients in the roxadustat group vs 28.7% in the darbepoetin alfa group); the most common reasons given were “withdrawal by patient” (9.9% vs 6.8%) and withdrawal due to death (8.4% vs 10.2%). Overall, 4.7% of patients withdrew due to AEs (6.5% roxadustat vs 2.7% darbepoetin alfa). A CONSORT diagram showing the flow of participants through the DOLOMITES trial is shown in Figure 21.

Figure 21: Patient Disposition Flowchart in DOLOMITES trial (All Patients)



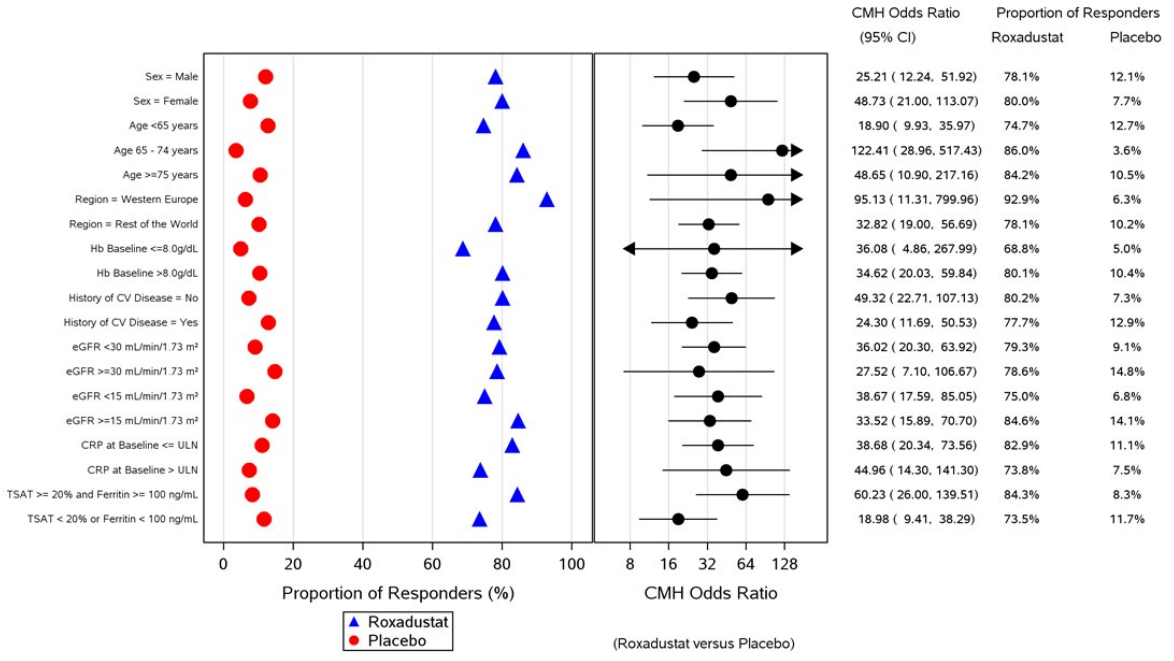
Appendix E. Subgroup analysis

Subgroup analysis have been conducted in roxadustat clinical trial programme around demographic characteristics (age, gender, geographic region, etc.) and disease characteristics (cardiovascular history, baseline Hb levels, iron repletion status, etc.) (as described in the trial methodology section in B.2.3). The subgroup analysis results from NDD population trials are presented below.

E.1 ALPS

The results of all the subgroup analyses were consistent with the results for primary analysis (Figure 22) (43). Subgroups were predefined on the basis of key baseline demographic and disease characteristics (including factors used in stratification for randomisation. It should be noted that some subgroups were relatively small, including age ≥ 75 years, Western Europe, Hb ≤ 8.0g/dL and baseline eGFR ≥ 30 mL/min/1.73 m^2) (43).

Figure 22: Summary of Subgroup Analyses of the Primary Efficacy Analysis (Full Analysis Set)

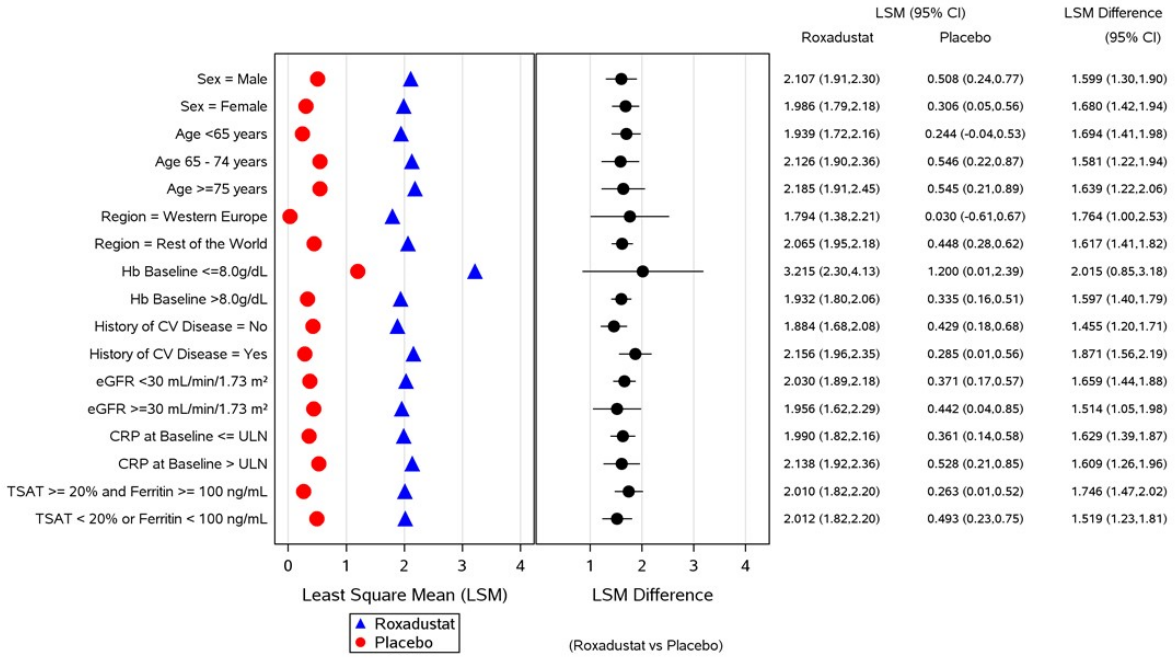


Abbreviations: CMH: Cochran-Mantel-Haenszel; CV: cardiovascular; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HB: haemoglobin; TSAT: transferrin saturation.

For all subgroups assessed (sex, age, region, baseline Hb, baseline cardiovascular disease history, baseline eGFR, baseline CRP and baseline TSAT and ferritin; P <

0.001 for all subgroups) (Figure 23) were consistent with the analysis of first key secondary endpoint (43).

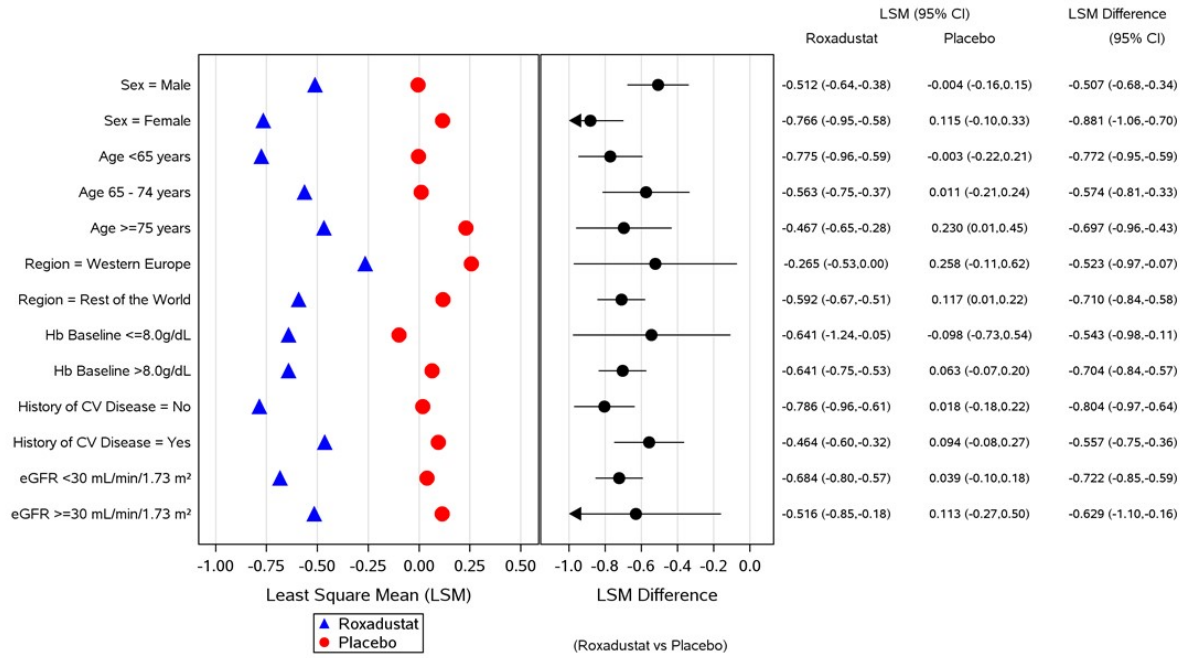
Figure 23: Subgroup Analysis of Change from Baseline to the Average Hb in Weeks 28 to 36 without Rescue Therapy (Full Analysis Set



Abbreviations: CV: cardiovascular; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; LSM: least squares means; TSAT: transferrin saturation.

For all subgroups assessed (sex, age, region, baseline Hb, baseline cardiovascular disease history and baseline eGFR; $P < 0.05$ for all subgroups) (Figure 24) were consistent with the analysis of the second key secondary endpoint (43).

Figure 24: Subgroup Analysis of Change from Baseline in LDL Cholesterol (Full Analysis Set)



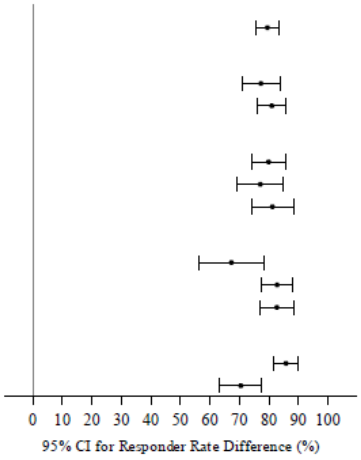
Abbreviations: CV: cardiovascular; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; LSM: lease squares means; TSAT: transferrin saturation.

E.2 ANDES

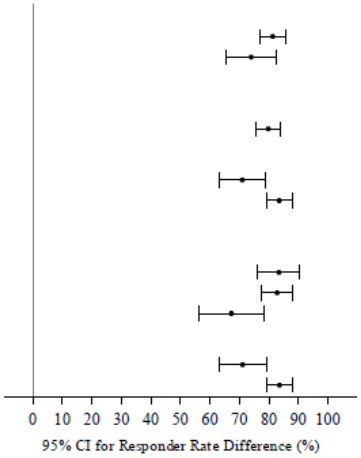
The subgroup analyses results were consistent with the main analysis (46). The subgroup analyses for both primary efficacy endpoints also demonstrated that roxadustat significantly increases Hb compared to placebo irrespective of sex, age, baseline eGFR and CKD stage, as well as baseline Hb, cardiovascular disease history, iron repletion status, and inflammation status as indicated by baseline CRP level. The treatment effect magnitude in each of these subgroups was consistent with the observed treatment effect for the overall population (Figure 25) (46).

Figure 25: Subgroup Analyses of the Primary Efficacy Endpoint (FAS Population)

Subgroup/ Value	Pooled Roxadustat n/ N (%) [1]	Placebo n/ N (%)	Responder Rate Difference 95% CI [2]
Overall	523/ 608 (86.0)	20/ 305 (6.6)	79.5 (75.55, 83.38)
Sex			
Male	204/ 240 (85.0)	10/ 130 (7.7)	77.3 (70.87, 83.74)
Female	319/ 368 (86.7)	10/ 175 (5.7)	81.0 (76.08, 85.86)
Age Group			
18 - 64	231/ 266 (86.8)	10/ 145 (6.9)	79.9 (74.16, 85.73)
65 - 74	161/ 190 (84.7)	6/ 79 (7.6)	77.1 (69.38, 84.91)
>=75	131/ 152 (86.2)	4/ 81 (4.9)	81.2 (74.01, 88.48)
CKD Stage			
Stage 3	107/ 127 (84.3)	11/ 65 (16.9)	67.3 (56.23, 78.43)
Stage 4	254/ 290 (87.6)	7/ 146 (4.8)	82.8 (77.65, 87.93)
Stage 5	162/ 191 (84.8)	2/ 94 (2.1)	82.7 (76.82, 88.56)
Iron Repletion Status			
ferritin>=100 ng/mL and TSAT>=20%	327/ 366 (89.3)	6/ 170 (3.5)	85.8 (81.61, 90.02)
ferritin<100 ng/mL or TSAT<20%	195/ 241 (80.9)	14/ 134 (10.4)	70.5 (63.29, 77.64)



Subgroup/ Value	Pooled Roxadustat n/ N (%) [1]	Placebo n/ N (%)	Responder Rate Difference 95% CI [2]
CRP Category			
<=ULN	394/ 450 (87.6)	14/ 223 (6.3)	81.3 (76.87, 85.69)
>ULN	127/ 156 (81.4)	6/ 81 (7.4)	74.0 (65.65, 82.36)
Hb Category			
<=8	39/ 66 (76.5)	0/ 25 (0.0)	
>8	484/ 542 (86.9)	20/ 280 (7.1)	79.8 (75.70, 83.90)
Cardiovascular History			
Yes	157/ 196 (80.1)	9/ 99 (9.1)	71.0 (63.05, 78.97)
No	366/ 412 (88.8)	11/ 206 (5.3)	83.5 (79.17, 87.82)
eGFR Category			
<10	57/ 69 (82.6)	0/ 19 (0.0)	
10-<15	105/ 122 (86.1)	2/ 75 (2.7)	83.4 (76.25, 90.54)
15-<30	254/ 290 (87.6)	7/ 146 (4.8)	82.8 (77.65, 87.93)
>=30	107/ 127 (84.3)	11/ 65 (16.9)	67.3 (56.23, 78.43)
Geographic Region			
US	171/ 206 (83.0)	12/ 101 (11.9)	71.1 (63.00, 79.26)
EX-US	352/ 402 (87.6)	8/ 204 (3.9)	83.6 (79.46, 87.82)



Abbreviations: CI: confidence interval; CKD: chronic kidney disease; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; TSAT: transferrin saturation; ULN: upper limit of normal; US: United States.

E.3 OLYMPUS

The subgroup analyses results were consistent with the main analysis (Table 97) (45).

Table 97: Subgroup Analyses Results from OLYMPUS trial

						Difference between groups (Roxadustat-placebo)			
Sub-group	**Planned group**	**n**	**Mean baseline**	**Adjusted LS mean change (SE)**	**95% CI**	**Differences (SE) in LS mean changes**	**95% CI**	**p-value**	**Treatment by subgroup interaction [a] p-value**
Age (years)									
<65	Roxadustat (N=796)	766	9.06	1.68 (0.042)	(1.60, 1.77)	1.26 (0.054)	(1.15, 1.36)	<0.001	0.107
	Placebo (N=730)	705	9.04	0.43 (0.046)	(0.34, 0.52)				
>=65	Roxadustat (N=588)	568	9.23	1.79 (0.045)	(1.70, 1.88)	1.41 (0.060)	(1.30, 1.53)	<0.001	
	Placebo (N=647)	625	9.21	0.38 (0.044)	(0.29, 0.47)				
<75	Roxadustat (N=1117)	1073	9.09	1.71 (0.037)	(1.64, 1.78)	1.30 (0.045)	(1.22, 1.39)	<0.001	0.481
	Placebo (N=1080)	1044	9.09	0.41 (0.038)	(0.34, 0.48)				
>=75	Roxadustat (N=267)	261	9.29	1.80 (0.064)	(1.68, 1.93)	1.42 (0.088)	(1.25, 1.59)	<0.001	
	Placebo (N=297)	286	9.23	0.39 (0.064)	(0.26, 0.51)				
Gender									
Male	Roxadustat (N=564)	540	9.14	1.74 (0.047)	(1.65, 1.84)	1.26 (0.062)	(1.14, 1.38)	<0.001	0.315
	Placebo (N=603)	578	9.11	0.48 (0.047)	(0.39, 0.58)				
Female	Roxadustat (N=820)	794	9.13	1.72 (0.040)	(1.64, 1.80)	1.37 (0.052)	(1.27, 1.47)	<0.001	
	Placebo (N=774)	752	9.12	0.35 (0.042)	(0.26, 0.43)				
Race									
White	Roxadustat (N=623)	595	9.23	1.78 (0.044)	(1.70, 1.87)	1.24 (0.060)	(1.13, 1.36)	<0.001	0.765
	Placebo (N=611)	586	9.20	0.54 (0.045)	(0.45, 0.63)				
Black or African American	Roxadustat (N=112)	110	9.25	1.65 (0.100)	(1.45, 1.85)	1.44 (0.137)	(1.17, 1.70)	<0.001	
	Placebo (N=115)	113	9.32	0.22 (0.100)	(0.02, 0.41)				
Asian	Roxadustat (N=544)	528	8.99	1.65 (0.056)	(1.54, 1.76)	1.38 (0.063)	(1.26, 1.51)	<0.001	
	Placebo (N=538)	524	8.96	0.27 (0.056)	(0.16, 0.38)				
American Indian or Alaska Native	Roxadustat (N=24)	23	9.23	1.51 (0.203)	(1.11, 1.91)	1.36 (0.284)	(0.80, 1.91)	<0.001	
	Placebo (N=29)	27	9.27	0.15 (0.204)	(-0.25, 0.55)				
Other and Native Hawaiian or another Pacific Islander	Roxadustat (N=81)	78	9.14	1.71 (0.116)	(1.49, 1.94)	1.38 (0.157)	(1.07, 1.69)	<0.001	
	Placebo (N=84)	80	9.17	0.33 (0.118)	(0.10, 0.56)				
Baseline Weight (kg)									
<70	Roxadustat (N=781)	755	9.07	1.69 (0.045)	(1.60, 1.78)	1.36 (0.053)	(1.26, 1.47)	<0.001	0.756
	Placebo (N=742)	716	9.02	0.33 (0.046)	(0.24, 0.42)				
>=70	Roxadustat (N=603)	579	9.21	1.76 (0.044)	(1.67, 1.84)	1.29 (0.059)	(1.17, 1.41)	<0.001	
	Placebo (N=635)	614	9.24	0.47 (0.043)	(0.38, 0.55)				
Baseline Weight (kg)									

						Difference between groups (Roxadustat-placebo)			
Sub-group	**Planned group**	**n**	**Mean baseline**	**Adjusted LS mean change (SE)**	**95% CI**	**Differences (SE) in LS mean changes**	**95% CI**	**p-value**	**Treatment by subgroup interaction [a] p-value**
<100	Roxadustat (N=1292)	1246	9.12	1.74 (0.035)	(1.67, 1.81)	1.32 (0.041)	(1.24, 1.40)	<0.001	0.710
	Placebo (N=1277)	1230	9.11	0.42 (0.036)	(0.35, 0.49)				
>=100	Roxadustat (N=92)	88	9.25	1.68 (0.110)	(1.46, 1.89)	1.38 (0.151)	(1.09, 1.68)	<0.001	
	Placebo (N=100)	100	9.24	0.29 (0.105)	(0.09, 0.50)				
Baseline Weight by gender-specific median									
<73 kg (median weight for males)	Roxadustat (N=284)	277	9.04	1.64 (0.066)	(1.51, 1.77)	1.28 (0.086)	(1.11, 1.45)	<0.001	0.862
	Placebo (N=300)	288	8.97	0.36 (0.066)	(0.23, 0.49)				
>=73 kg (median weight for males)	Roxadustat (N=280)	263	9.24	1.83 (0.064)	(1.70, 1.95)	1.24 (0.089)	(1.07, 1.42)	<0.001	
	Placebo (N=303)	290	9.25	0.58 (0.063)	(0.46, 0.71)				
<63 kg (median weight for females)	Roxadustat (N=412)	397	9.07	1.71 (0.056)	(1.60, 1.82)	1.40 (0.074)	(1.26, 1.55)	<0.001	
	Placebo (N=373)	360	8.99	0.31 (0.061)	(0.19, 0.43)				
>=63 kg (median weight for females)	Roxadustat (N=408)	397	9.18	1.70 (0.053)	(1.60, 1.80)	1.34 (0.072)	(1.20, 1.49)	<0.001	
	Placebo (N=401)	392	9.25	0.36 (0.054)	(0.25, 0.46)				
Baseline Body mass index (BMI (kg/m2))									
<30	Roxadustat (N=1061)	1020	9.10	1.74 (0.038)	(1.66, 1.81)	1.30 (0.046)	(1.21, 1.39)	<0.001	0.661
	Placebo (N=1045)	1006	9.07	0.44 (0.039)	(0.36, 0.51)				
>=30	Roxadustat (N=319)	310	9.24	1.73 (0.059)	(1.61, 1.85)	1.40 (0.083)	(1.23, 1.56)	<0.001	
	Placebo (N=329)	321	9.26	0.34 (0.059)	(0.22, 0.45)				
Geographical region									
US	Roxadustat (N=343)	334	9.21	1.82 (0.058)	(1.71, 1.93)	1.43 (0.080)	(1.28, 1.59)	<0.001	0.251
	Placebo (N=340)	335	9.29	0.38 (0.059)	(0.27, 0.50)				
Ex-US	Roxadustat (N=1041)	1000	9.10	1.69 (0.036)	(1.62, 1.76)	1.29 (0.046)	(1.20, 1.38)	<0.001	
	Placebo (N=1037)	995	9.06	0.39 (0.036)	(0.32, 0.46)				
North America	Roxadustat (N=369)	360	9.22	1.79 (0.055)	(1.68, 1.90)	1.41 (0.077)	(1.25, 1.56)	<0.001	0.138
	Placebo (N=364)	359	9.30	0.39 (0.056)	(0.28, 0.50)				
Latin America	Roxadustat (N=206)	194	9.23	1.48 (0.073)	(1.34, 1.63)	1.14 (0.102)	(0.94, 1.34)	<0.001	
	Placebo (N=205)	193	9.16	0.34 (0.076)	(0.19, 0.49)				
Asia and Australia	Roxadustat (N=522)	506	9.00	1.62 (0.049)	(1.52, 1.72)	1.39 (0.064)	(1.27, 1.52)	<0.001	
	Placebo (N=521)	508	8.95	0.23 (0.050)	(0.13, 0.33)				
Europe	Roxadustat (N=287)	274	9.18	1.87 (0.061)	(1.75, 1.99)	1.24 (0.087)	(1.07, 1.41)	<0.001	
	Placebo (N=287)	270	9.16	0.63 (0.063)	(0.51, 0.75)				

						Difference between groups (Roxadustat-placebo)				
Sub-group	**Planned group**	**n**	**Mean baseline**	**Adjusted LS mean change (SE)**	**95% CI**	**Differences (SE) in LS mean changes**	**95% CI**	**p-value**	**Treatment by subgroup interaction [a] p-value**	
Cardiovascular/cerebrovascular/thromboembolic history [b]										
Yes	Roxadustat (N=278)	268	9.22	1.73 (0.063)	(1.61, 1.86)	1.23 (0.087)	(1.06, 1.40)	<0.001	0.384	
	Placebo (N=305)	292	9.20	0.51 (0.061)	(0.39, 0.63)					
No	Roxadustat (N=1106)	1066	9.11	1.69 (0.034)	(1.63, 1.76)	1.35 (0.045)	(1.27, 1.44)	<0.001		
	Placebo (N=1072)	1038	9.09	0.34 (0.035)	(0.27, 0.41)					
Baseline Hb (g/dL)										
<=8	Roxadustat (N=129)	112	7.51	2.95 (0.105)	(2.75, 3.16)	1.65 (0.149)	(1.36, 1.94)	<0.001	0.042	
	Placebo (N=131)	120	7.53	1.30 (0.108)	(1.09, 1.51)					
>8	Roxadustat (N=1255)	1222	9.28	1.61 (0.036)	(1.54, 1.68)	1.30 (0.043)	(1.21, 1.38)	<0.001		
	Placebo (N=1246)	1210	9.27	0.31 (0.036)	(0.24, 0.38)					
<=9	Roxadustat (N=515)	481	8.37	2.29 (0.053)	(2.18, 2.39)	1.46 (0.069)	(1.33, 1.60)	<0.001	0.040	
	Placebo (N=533)	508	8.36	0.82 (0.053)	(0.72, 0.93)					
>9	Roxadustat (N=869)	853	9.56	1.40 (0.040)	(1.32, 1.48)	1.26 (0.052)	(1.16, 1.36)	<0.001		
	Placebo (N=844)	822	9.59	0.14 (0.041)	(0.06, 0.22)					
Baseline eGFR (mL/min/1.73m2)										
<10	Roxadustat (N=291)	264	8.74	1.64 (0.069)	(1.51, 1.78)	1.34 (0.093)	(1.16, 1.53)	<0.001	0.650	
	Placebo (N=283)	265	8.72	0.30 (0.072)	(0.15, 0.44)					
>=10	Roxadustat (N=1093)	1070	9.23	1.77 (0.036)	(1.70, 1.84)	1.32 (0.044)	(1.23, 1.40)	<0.001		
	Placebo (N=1094)	1065	9.22	0.45 (0.036)	(0.38, 0.52)					
<15	Roxadustat (N=591)	558	8.94	1.63 (0.049)	(1.54, 1.73)	1.33 (0.063)	(1.21, 1.46)	<0.001	0.627	
	Placebo (N=598)	570	8.90	0.30 (0.051)	(0.20, 0.40)					
>=15	Roxadustat (N=793)	776	9.27	1.81 (0.040)	(1.73, 1.89)	1.31 (0.052)	(1.21, 1.41)	<0.001		
	Placebo (N=779)	760	9.28	0.50 (0.040)	(0.42, 0.58)					
<30	Roxadustat (N=1125)	1080	9.08	1.68 (0.037)	(1.61, 1.75)	1.32 (0.044)	(1.23, 1.40)	<0.001	0.579	
	Placebo (N=1118)	1079	9.06	0.37 (0.036)	(0.29, 0.44)					
>=30	Roxadustat (N=259)	254	9.33	1.99 (0.065)	(1.86, 2.12)	1.35 (0.090)	(1.17, 1.52)	<0.001		
	Placebo (N=259)	251	9.37	0.65 (0.067)	(0.51, 0.78)					
Diabetes										
Yes	Roxadustat (N=793)	755	9.16	1.69 (0.040)	(1.62, 1.77)	1.35 (0.053)	(1.24, 1.45)	<0.001	0.932	
	Placebo (N=807)	777	9.13	0.35 (0.041)	(0.27, 0.43)					

						Difference between groups (Roxadustat-placebo)				
Sub-group	**Planned group**	**n**	**Mean baseline**	**Adjusted LS mean change (SE)**	**95% CI**	**Differences (SE) in LS mean changes**	**95% CI**	**p-value**	**Treatment by subgroup interaction [a] p-value**	
No	Roxadustat (N=591)	579	9.09	1.80 (0.048)	(1.71, 1.89)	1.30 (0.061)	(1.18, 1.42)	<0.001		
	Placebo (N=570)	553	9.10	0.51 (0.049)	(0.41, 0.60)					
Baseline hsCRP										
<=ULN	Roxadustat (N=520)	503	9.18	1.82 (0.052)	(1.72, 1.92)	1.35 (0.066)	(1.22, 1.48)	<0.001	0.076	
	Placebo (N=497)	478	9.18	0.47 (0.054)	(0.37, 0.58)					
>ULN	Roxadustat (N=227)	213	9.06	1.73 (0.072)	(1.58, 1.87)	1.10 (0.102)	(0.90, 1.30)	<0.001		
	Placebo (N=209)	198	9.06	0.62 (0.076)	(0.47, 0.77)					
Iron replete at baseline										
Yes	Roxadustat (N=809)	782	9.10	1.71 (0.040)	(1.63, 1.79)	1.33 (0.052)	(1.22, 1.43)	<0.001	0.484	
	Placebo (N=799)	770	9.08	0.39 (0.042)	(0.30, 0.47)					
No	Roxadustat (N=575)	552	9.17	1.76 (0.046)	(1.67, 1.85)	1.33 (0.061)	(1.21, 1.45)	<0.001		
	Placebo (N=578)	560	9.18	0.43 (0.047)	(0.34, 0.53)					

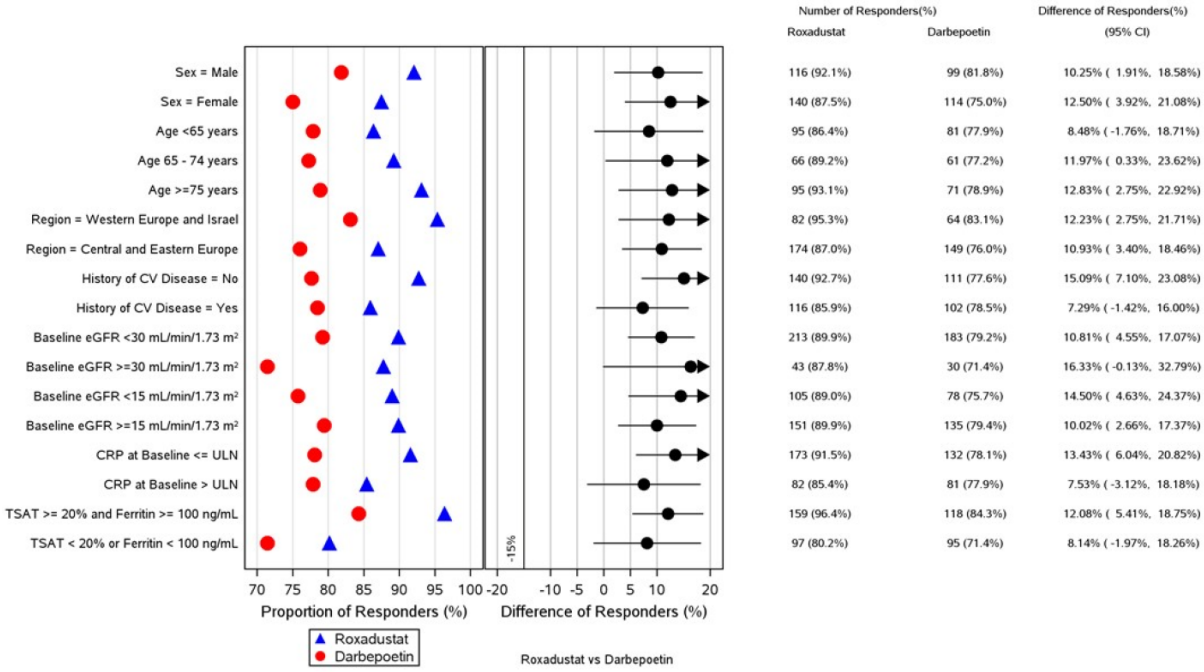
Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; hsCRP: high-sensitivity C-reactive protein; LS: least square; SE: standard error; ULN: upper limit of normal; US: United States

E.4 DOLOMITES

The results for the subgroup analyses conducted in DOLOMITES trial are presented in Figure 26 to Figure 32 (42). Notes:

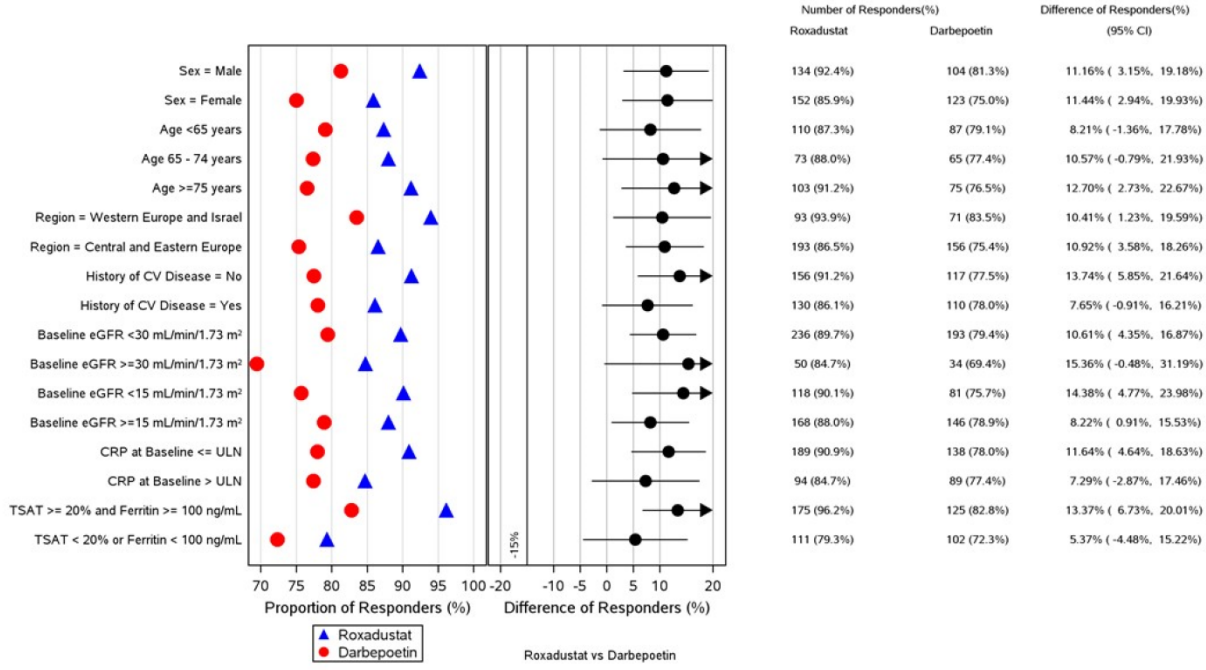
- The results of all subgroup analyses in patients' Hb response rate without rescue therapy (Figure 26) and regardless of rescue therapy use (Figure 27) were consistent with the primary analysis (42).
- The results for the subgroup analysis for haemoglobin change from baseline were consistent for all subgroups assessed (sex, age, region, baseline cardiovascular disease history, baseline eGFR, baseline CRP and baseline TSAT and ferritin) (Figure 28) with 95% CIs crossing 0 for all subgroups. Except for the subgroup of patients with baseline eGFR ≥ 30 mL/min/1.73 m^2, changes favoured roxadustat versus darbepoetin alfa (42).
- The results for all subgroups assessed for the change in LDL cholesterol from baseline (sex, age, region, baseline cardiovascular disease history, baseline eGFR, baseline CRP and baseline TSAT and ferritin) (Figure 29) were consistent with analysis of the key secondary endpoint (42).
- The results for the subgroup analysis for time to first IV iron use were consistent with analysis of the key secondary endpoint (Figure 30). While there were apparent differences in some subgroups, notably gender and randomisation by region, patient numbers are small, and results should be interpreted with care. This difference was particularly noticeable in the subgroup of patients who were not iron-replete at baseline (TSAT < 20% or ferritin < 100 ng/mL) (42).
- The results for the subgroup analysis for SF-36 physical functioning change (Figure 31) and SF-36 vitality sub-score change (Figure 32) from baseline were consistent with analysis of the key secondary endpoint (42).

Figure 26: Summary of Subgroup Analyses of the Primary Efficacy Endpoint Without Rescue Therapy (Per Protocol Set)



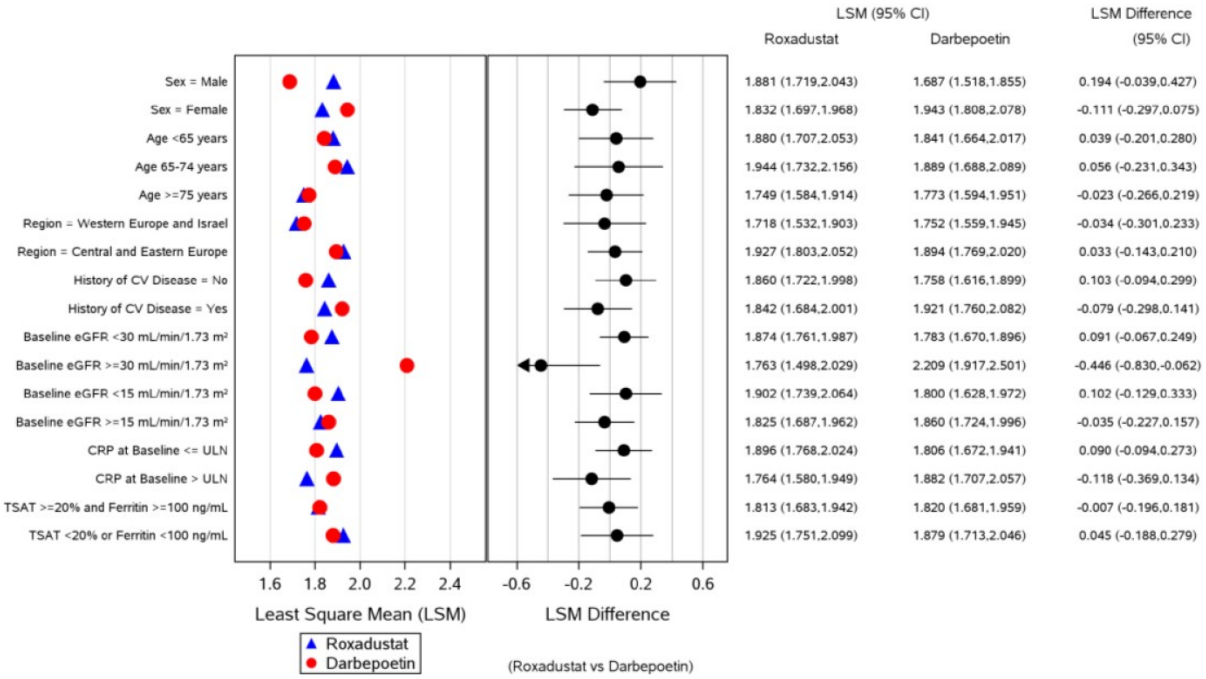
Abbreviations: CI: confidence interval; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; PPS: Per Protocol Set; TSAT: transferrin saturation.

Figure 27: Summary of Subgroup Analyses of the Primary Efficacy Endpoint Regardless of Rescue Therapy (Full Analysis Set)



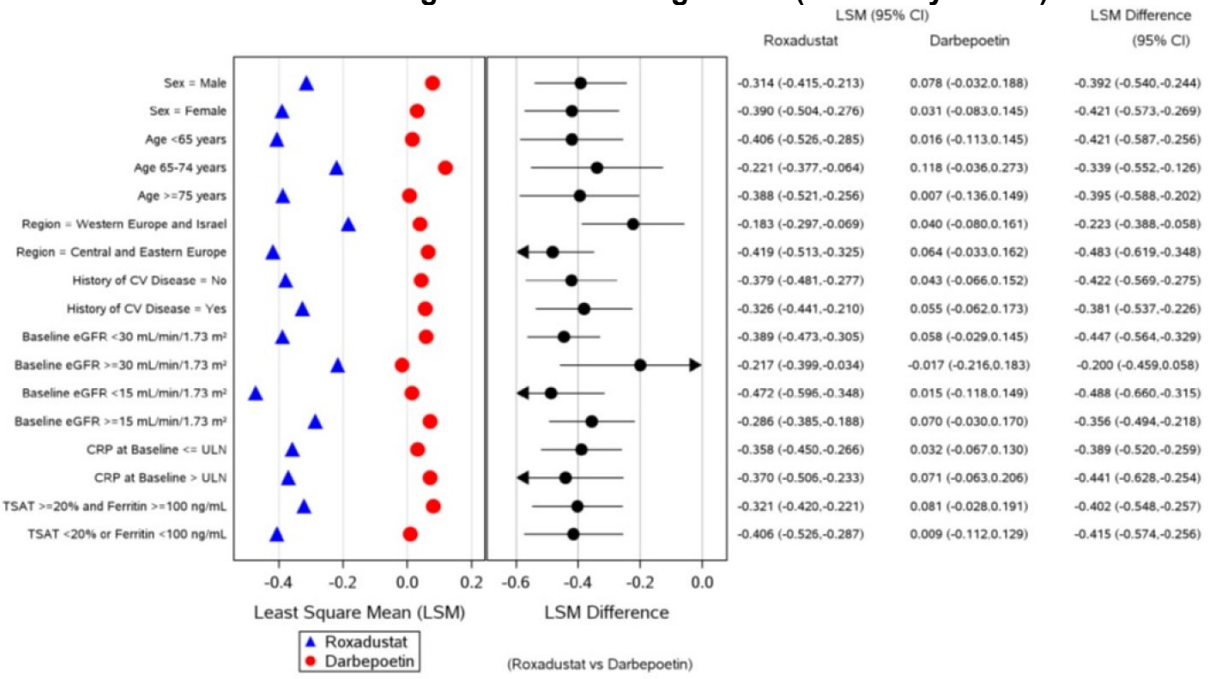
Abbreviations: CI: confidence interval; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; Hb: haemoglobin; TSAT: transferrin saturation.

Figure 28: Summary of Subgroup Analyses for Haemoglobin Change from Baseline in Weeks 28 to 36 Without Rescue Therapy (Per Protocol Set)



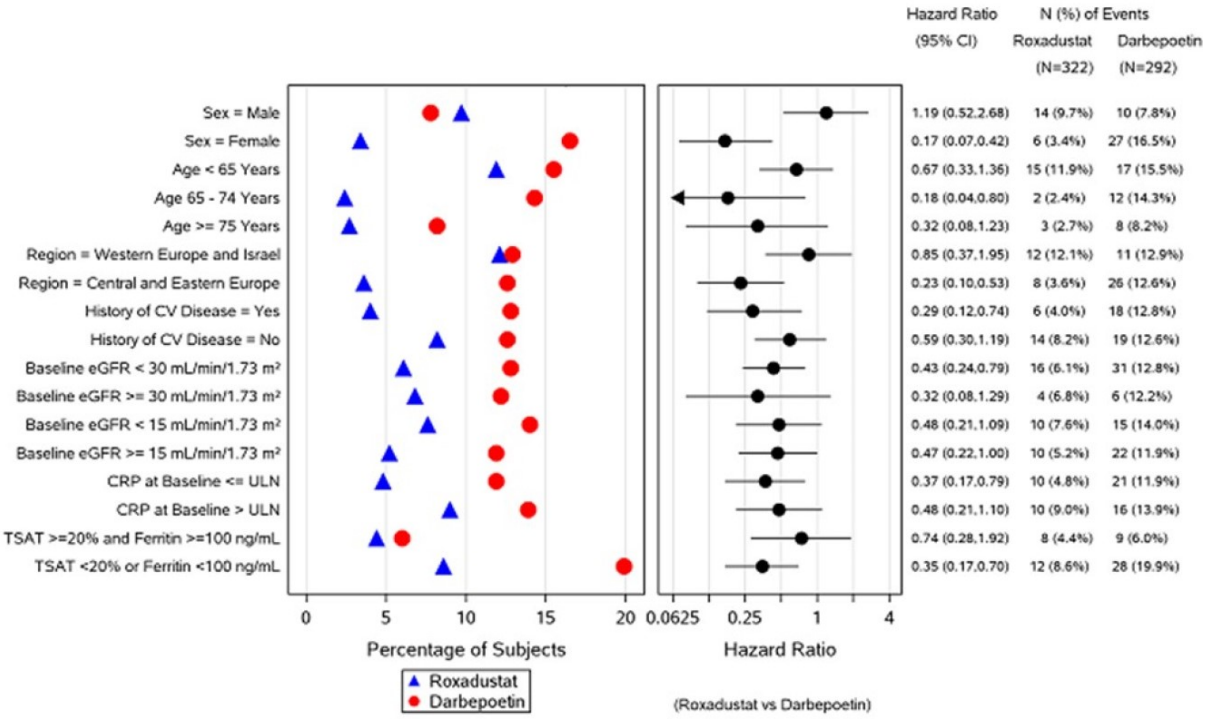
Abbreviations: CI; confidence interval; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; LSM: least squares mean; PPS: Per Protocol Set; TSAT: transferrin saturation; ULN: upper limit of normal.

Figure 29: Summary of Subgroup Analyses for Change in LDL Cholesterol from Baseline to Weeks 12 to 28 Regardless of Fasting Status (Full Analysis Set)



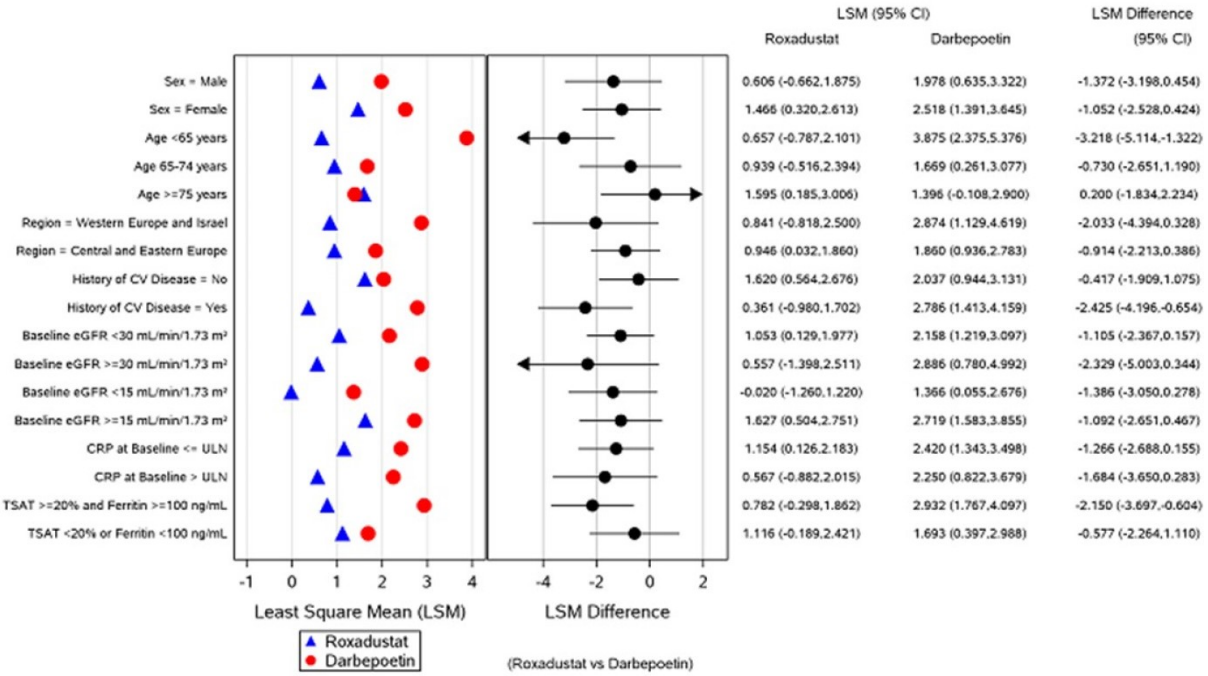
Abbreviations: CI: Confidence interval; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; Hb: haemoglobin; LDL: low density lipoprotein; TSAT: transferrin saturation; ULN: upper limit of normal.

Figure 30: Summary of Subgroup Analyses for Time to First Intravenous Iron Use (Full Analysis Set)



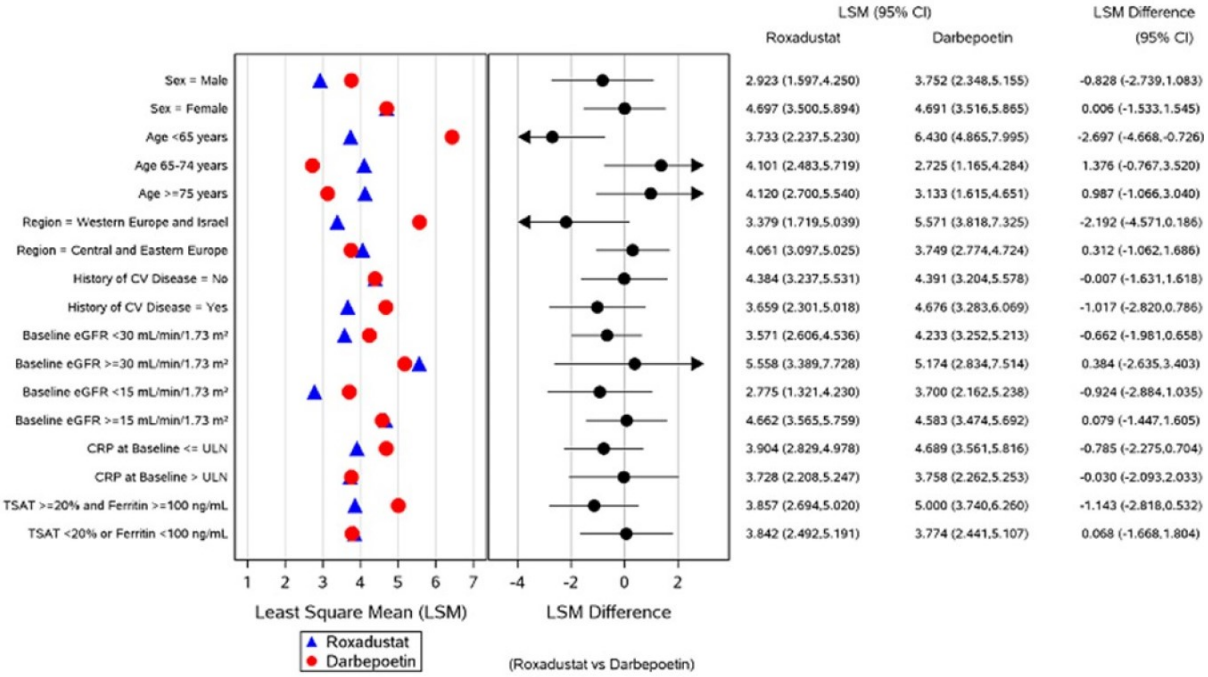
Abbreviations: CI: confidence interval; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; Hb: haemoglobin; TSAT: transferrin saturation; ULN: upper limit of normal.

Figure 31: Summary of Subgroup Analyses for SF-36 Physical Functioning Change from Baseline to the Average in Weeks 12 to 28 (Per Protocol Set)



Abbreviations: CI: confidence interval; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; LSM: least squares mean; PPS: Per Protocol Set; SF-36: short form-36 questionnaire; TSAT: transferrin saturation; ULN: upper limit of normal.

Figure 32: Summary of Subgroup Analyses for the SF-36 Vitality Subscore Change From Baseline to the Average in Weeks 12 to 28 by Subgroup (Per Protocol Set)



Abbreviations: CI: confidence interval; CRP: C-reactive protein; CV: cardiovascular; eGFR: estimated glomerular filtration rate; FAS: Full Analysis Set; LSM: least squares mean; PPS: Per Protocol Set; SF-36: short form-36 questionnaire; TSAT: transferrin saturation; ULN: upper limit of normal.

Appendix F. Adverse reactions

This section provides safety data from the relevant roxadustat clinical trials. Unless stated otherwise, all data in this section originate from the ALPS, ANDES and OLYMPUS, and DOLOMITES clinical study reports (42, 43, 45, 46).

F.1 ALPS

Overall, more patients in the placebo group (56.2%) than the roxadustat group (37.3%) discontinued study treatment, with the majority of discontinuations in both treatment groups occurring in the first year of the study. Lack of efficacy and withdrawal by patient were the reasons for discontinuation responsible for the difference between the treatment groups (Table 98) (43).

Table 98. Early Treatment Discontinuation (All Randomised Patients)

Parameter	Category	Roxadustat (n=391)	Placebo (n=203)	Total (n=594)
Early treatment discontinuation up to two years	Yes	146 (37.3%)	114 (56.2%)	260 (43.8%)
	No	245 (62.7%)	89 (43.8%)	334 (56.2%)
Primary reason for discontinuation†	Randomised/registered but never received/ dispensed study drug	0	0	0
	Adverse event	21 (5.4%)	9 (4.4%)	30 (5.1%)
	Death	39 (10.0%)	16 (7.9%)	55 (9.3%)
	Lack of efficacy	3 (0.8%)	26 (12.8%)	29 (4.9%)
	Lost to follow-up	5 (1.3%)	1 (0.5%)	6 (1.0%)
	Progressive disease	1 (0.3%)	0	1 (0.2%)
	Protocol deviation	3 (0.8%) 0	0	3 (0.5%)
	Withdrawal by patient	58 (14.8%)	52 (25.6%)	110 (18.5%)
	Study terminated by sponsor	0	0	0
	Physician decision	7 (1.8%)	8 (3.9%)	15 (2.5%)
	Noncompliance with study drug	3 (0.8%)	0	3 (0.5%)
	Pregnancy	0	0	0
	Other	6 (1.5%)	2 (1.0%)	8 (1.3%)

Notes: †Patients who discontinued during the first year are also counted.

The overall incidence of TEAEs was comparable between treatment groups: 87.7% of patients in the roxadustat group and 86.7% of patients in the placebo group were reported to have experienced TEAEs. In addition, a comparable proportion of patients in both treatment groups (47.3% roxadustat and 43.3% placebo) had TEAEs ≥Grade 3 in severity although a greater proportion of patients in the roxadustat treatment group (20.7%) experienced TEAEs considered related to treatment by the investigator compared with the placebo group (13.3%). Overall, 61.6% of patients in the roxadustat treatment group compared with 56.7% in the placebo group had

serious TEAEs; 6.4% and 2.0% of patients respectively had serious TEAEs considered related to treatment by the investigator (Table 99) (43).

Overall, 45 (11.5%) patients in the roxadustat treatment group and 20 (9.9%) in the placebo group died due to any cause following study drug administration; of these, 37 (9.5%) and 16 (7.9%) patients respectively died of any cause during the safety emergent period, i.e., within the 28 day period after last study drug administration. In addition, 23 (5.9%) patients in the roxadustat treatment group and 8 (3.9%) in the placebo group experienced a TEAE which led to withdrawal of treatment (Table 99) (43).

Table 99. Overview of TEAEs and death (SAF population)

	Roxadustat (N=391)	Placebo (N=203)
TEAE	343 (87.7%)	176 (86.7%)
Drug-related TEAE	81 (20.7%)	27 (13.3%)
Serious TEAE	241 (61.6%)	115 (56.7%)
Drug-related serious TEAE	25 (6.4%)	4 (2.0%)
TEAE leading to death	40 (10.2%)	19 (9.4%)
Drug-related TEAE leading to death	5 (1.3%)	0
TEAE leading to withdrawal of treatment	23 (5.9%)	8 (3.9%)
Drug-related TEAE leading to withdrawal of treatment	8 (2.0%)	1 (0.5%)
TEAE NCI CTC grades ≥3	185 (47.3%)	88 (43.3%)
Death during the safety emergent period	37 (9.5%)	16 (7.9%)
Death (overall)	45 (11.5%)	20 (9.9%)

Abbreviations: BL: baseline; Hb: haemoglobin; TEAE: treatment-emergent adverse event; NCI CTC: National Cancer Institute - common terminology criteria for adverse events

The most common TEAEs in roxadustat and placebo treatment groups were ESRD (34.5% versus 30.5% respectively), hypertension (22.3% and 13.8% respectively), peripheral oedema (11.5% and 10.3% respectively), and a decrease in the glomerular filtration rate (11.0% and 11.3% respectively) (Table 100) (43).

Table 100. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population)

	Roxadustat (N=391)		Placebo (N=203)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Overall	373 (87.7%)	476.7	176 (86.7%)	514.7
End-stage renal disease	135 (34.5%)	27.2	62 (30.5%)	30.0
Hypertension	87 (22.3%)	28.6	28 (13.8%)	21.9
Oedema peripheral	45 (11.5%)	10.9	21 (10.3%)	10.5
Glomerular filtration rate decreased	43 (11.0%)	9.7	23 (11.3%)	13.3
Hyperkalaemia	39 (10.0%)	10.5	15 (7.4%)	10.0
Viral upper respiratory tract infection	38 (9.7%)	10.1	9 (4.4%)	7.1
Nausea	37 (9.5%)	9.5	6 (3.0%)	2.9
Diarrhoea	33 (8.4%)	8.3	7 (3.4%)	4.8

	Roxadustat (N=391)		Placebo (N=203)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Pneumonia	28 (7.2%)	7.0	14 (6.9%)	8.1
Iron deficiency	26 (6.6%)	5.2	8 (3.9%)	4.8
Anaemia	24 (6.1%)	5.4	37 (18.2%)	25.7
Headache	21 (5.4%)	4.4	11 (5.4%)	5.7
Arteriovenous fistula thrombosis	20 (5.1%)	5.4	2 (1.0%)	1.4
Pruritus	20 (5.1%)	4.4	2 (1.0%)	1.0
Asthenia	19 (4.9%)	4.6	12 (5.9%)	7.1
Hyperuricaemia	9 (2.3%)	1.8	11 (5.4%)	5.2

Abbreviations:PEY: patient exposure years; TEAE: treatment-emergent adverse event; SAF: safety analysis set.

F.2 ANDES

A total of 267 (43.3%) patients in roxadustat arm and 208 (68.0%) in placebo arm prematurely discontinued treatment. The primary reasons for discontinuation in roxadustat-treated patients were withdrawal by patient, adverse event, and death (83 [13.5%], 47 [7.6%], 38 [6.2%] patients, respectively). The primary reasons for discontinuation for placebo-treated patients were withdrawal by patient, lack of efficacy, and adverse event (89 [29.1%], 43 [14.1%], 19 [6.2%] patients, respectively) (Table 101) (46).

Table 101. Early Treatment Discontinuation

	Roxadustat (n=616)	Placebo (n=306)
Completed through End of Treatment		
Yes	349 (56.7)	98 (32.0)
No	267 (43.3)	208 (68.0)
Completed the End of Study Visit		
Yes	340 (55.2)	95 (31.0)
No	276 (44.8)	211 (69.0)
Reasons for discontinuation from treatment period		
Adverse Event	47 (7.6)	19 (6.2)
Death	38 (6.2)	11 (3.6)
Lack of efficacy (including ESA rescue)	2 (0.3)	43 (14.1)
Lost to follow-up	28 (4.5)	7 (2.3)
Physician decision	16 (2.6)	17 (5.6)
Pregnancy	0	0
Protocol deviation	6 (1.0)	5 (1.6)
Study/site terminated by sponsor	4 (0.6)	1 (0.3)
Withdrawal by patient	83 (13.5)	89 (29.1)
Other		
Kidney transplant	8 (1.3)	4 (1.3)
Dialysis	22 (3.6)	8 (2.6)
Other	13 (2.1)	4 (1.3)

Abbreviations: ESA: erythropoietin stimulating agent; ITT: intention-to-treat

Overall, the incidence of any TEAEs was slightly higher in the roxadustat group (92.3%) compared with the placebo group (89.5%). A total of 43 (7.0%) patients in

the roxadustat group died during the treatment period due to an AE compared with 11 (3.6%) patients in the placebo group (Table 102) (46).

Table 102. Adverse events in the ANDES trial (OT+28)

	Roxadustat (N=611)	Placebo (N=305)
Any TEAE	564 (92.3%)	273 (89.5%)
AE leading to withdrawal of treatment	50 (8.2%)	22 (7.2%)
AE directly related to treatment	95 (15.5%)	39 (12.8%)
TESAEs leading to death	43 (7.0%)	11 (3.6%)
Any TESAEs	321 (52.5%)	120 (39.3%)

Abbreviations: AE: adverse event; OT+28: On treatment plus 28 days; TEAE: treament-emergent adverse event; TESAE: treatment-emergent serious adverse event

The most common TEAE for the roxadustat and placebo treatment groups were hyperkalaemia (18.2% versus 13.4% respectively), constipation (17.2% versus 11.1% respectively), viral upper respiratory tract infection (16.0% versus 13.1% respectively), upper respiratory tract infection (12.9% versus 15.7% respectively), hypertension (15.5% versus 8.9% respectively), nausea (13.9% versus 9.5% respectively) and peripheral oedema (14.6% and 9.2% respectively) (Table 103) (46).

Table 103. Summary of most common TEAEs occurring in ≥5% of patients in both treatment arms (OT+28)

	Roxadustat (N=611)		Placebo (N=305)	
	n (%)	Events (Event rate per 100 PEY)	n (%)	Event rate per 100 PEY
Overall	490 (80.2)	2801 (246.8)	224 (73.4)	1001 (265.3)
Anaemia	17 (2.8)	19 (1.7)	44 (14.4)	58 (15.4)
Constipation	105 (17.2)	139 (12.2)	34 (11.1)	39 (10.3)
Nausea	85 (13.9)	110 (9.7)	29 (9.5)	35 (9.3)
Diarrhoea	78 (12.8)	106 (9.3)	31 (10.2)	39 (10.3)
Vomiting	54 (8.8)	65 (5.7)	20 (6.6)	22 (5.8)
Dyspepsia	39 (6.4)	45 (4.0)	12 (3.9)	12 (3.2)
Abdominal pain	35 (5.7)	44 (3.9)	13 (4.3)	14 (3.7)
Oedema peripheral	89 (14.6)	128 (11.3)	28 (9.2)	38 (10.1)
Oedema	48 (7.9)	62 (5.5)	9 (3.0)	12 (3.2)
Pyrexia	39 (6.4)	61 (5.4)	9 (3.0)	12 (3.2)
Asthenia	31 (5.1)	35 (3.1)	11 (3.6)	11 (2.9)
Viral upper respiratory tract infection	98 (16.0)	192 (16.9)	40 (13.1)	58 (15.4)
Upper respiratory tract infection	79 (12.9)	145 (12.8)	48 (15.7)	68 (18.0)
Urinary tract infection	68 (11.1)	103 (9.1)	29 (9.5)	56 (14.8)
Pneumonia	44 (7.2)	52 (4.6)	18 (5.9)	21 (5.6)
Bronchitis	34 (5.6)	44 (3.9)	13 (4.3)	16 (4.2)
Cellulitis	32 (5.2)	37 (3.3)	7 (2.3)	22 (5.8)
Hyperkalaemia	111 (18.2)	154 (13.6)	41 (13.4)	47 (12.5)
Hypoglycaemia	53 (8.7)	69 (6.1)	15 (49)	17 (4.5)
Decreased appetite	41 (6.7)	51 (4.5)	8 (2.6)	8 (2.1)
Hyperphosphataemia	40 (6.5)	46 (4.1)	10 (3.3)	10 (2.7)
Gout	32 (5.2)	46 (4.1)	20 (6.6)	33 (8.7)

Metabolic acidosis	29 (4.7)	31 (2.7)	18 (5.9)	20 (5.3)
Back pain	55 (9.0)	66 (5.8)	18 (5.9)	20 (5.3)
Arthralgia	45 (7.4)	50 (4.4)	24 (7.9)	27 (7.2)
Muscle spasms	41 (6.7)	53 (4.7)	9 (3.0)	10 (2.7)
Pain in extremity	39 (6.4)	42 (3.7)	14 (4.6)	14 (3.7)
Headache	66 (10.8)	99 (8.7)	26 (8.5)	31 (8.2)
Dizziness	58 (9.5)	85 (7.5)	32 (10.5)	35 (9.3)
Insomnia	63 (10.3)	75 (6.6)	9 (3.0)	10 (2.7)
End-stage renal disease	67 (11.0)	74 (6.5)	18 (5.9)	18 (4.8)
Chronic kidney disease	54 (8.8)	61 (5.4)	21 (6.9)	22 (5.8)
Acute kidney injury	49 (8.0)	55 (4.8)	11 (3.6)	13 (3.4)
Cough	57 (9.3)	71 (6.3)	28 (9.2)	33 (8.7)
Dyspnoea	34 (5.6)	49 (4.3)	23 (7.5)	28 (7.4)
Pruritus	54 (8.8)	72 (6.3)	19 (6.2)	24 (6.4)
Hypertension	95 (15.5)	128 (11.3)	27 (8.9)	38 (10.1)
Hypotension	31 (5.1)	37 (3.3)	10 (3.3)	10 (2.7)

Abbreviations: AE: adverse event; PEY: patient exposure years; OT+28: On-treatment plus 28 days

F.3 OLYMPUS

A total of 2547 (92.2%) randomised patients completed the study (1300 [93.9%] in the roxadustat group and 1247 [90.6%] in the placebo group). A total of 214 (7.8%) patients withdrew from the study (84 [6.1%] in the roxadustat group and 130 [9.4%] in the placebo group). The main reason for study withdrawal was patient decision (i.e., withdrawal of consent) for 212 (7.7%) patients (84 [6.1%] in the roxadustat group and 128 [9.3%] in the placebo group) (Table 104) (45).

Table 104. Early Treatment Discontinuation (All randomised patients)

	Roxadustat (n=1,393)	**Placebo (n=1,388)**
Patients who discontinued treatment	499 (36.1)	801 (58.2)
Patient decision	250 (18.1)	390 (28.3)
Adverse event	79 (5.7)	52 (3.8)
Severe non-compliance to protocol	12 (0.9)	13 (0.9)
Development of study-specific discontinuation criteria	76 (5.5)	252 (18.3)
Other	82 (5.9)	93 (6.8)
Missing	0	1 (<0.1)

The incidence of any AEs was slightly higher in the roxadustat group (88.5%) compared with the placebo group (84.2%). A total of 297 (10.8%) patients died during the treatment period due to an AE: 193 (13.9%) patients (8.22 events per 100 patient years) in the roxadustat group compared with 104 (7.6%) patients (5.65 events per 100 patient years) in the placebo group) (Table 105). A higher proportion of patients in the roxadustat treatment group experienced SAEs in comparison with the placebo group (53.9% vs. 44.3% respectively). The overall

incidence of AEs leading to discontinuation was comparable between treatment groups: 5.5% of patients in the roxadustat group and 4.1% of patients in the placebo group (Table 105) (45).

Table 105. Adverse events in the OLYMPUS trial (OT+28)

	Roxadustat (N=1,384)	Placebo (N=1,376)
Any AE	1225 (88.5%)	1159 (84.2%)
AE leading to death	193 (13.9%)	104 (7.6%)
SAE (including events leading to death)	746 (53.9%)	610 (44.3%)
AE leading to withdrawal of treatment	76 (5.5%)	57 (4.1%)
AE leading to dose interruption	123 (8.9%)	104 (7.6%)
AE leading to dose reduction	10 (0.7%)	6 (0.4%)
AE leading to dose increase	13 (0.9%)	4 (0.3%)
AE directly related to treatment	125 (9.0%)	87 (6.3%)

Abbreviations: AE: adverse event; OT+28: On-treatment plus 28 days; SAE: serious adverse event.

The most common AEs for the roxadustat group were ESRD, urinary tract infection and hypertension, in the placebo group the most common AEs were ESRD, hypertension and oedema peripheral. For both groups, similar event rates were observed for ESRD and hypertension (Table 106) (45).

Table 106. Summary of most common AEs occurring in ≥5% of patients in both treatment arms (OT+28)

	Roxadustat (N=1,384)		Placebo (N=1,376)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Overall	1225 (88.5%)	199.90	1159 (84.2%)	191.52
End-stage renal disease	271 (19.6)	12.72	202 (14.7)	11.59
Hypertension	147 (10.6)	6.76	98 (7.1)	5.57
Urinary tract infection	164 (11.8)	7.48	81 (5.9)	4.59
Oedema peripheral	145 (10.5)	6.67	94 (6.8)	5.34
Diarrhoea	137 (9.9)	6.23	91 (6.6)	5.18
Pneumonia	140 (10.1)	6.23	86 (6.3)	4.79
Nausea	121 (8.7)	5.51	84 (6.1)	4.77
Hyperkalaemia	111 (8.0)	4.96	77 (5.6)	4.35
Viral upper respiratory tract infection	92 (6.6)	4.16	88 (6.4)	5.07
Headache	91 (6.6)	4.09	66 (4.8)	3.72
Cough	101 (7.3)	4.52	54 (3.9)	3.01
Dizziness	76 (5.5)	3.37	76 (5.5)	4.29
Constipation	86 (6.2)	3.83	64 (4.7)	3.58
Upper respiratory tract infection	94 (6.8)	4.21	56 (4.1)	3.14
Hypoglycaemia	83 (6.0)	3.67	57 (4.1)	3.17
Azotaemia	73 (5.3)	3.20	63 (4.6)	3.48
Dyspnoea	73 (5.3)	3.18	60 (4.4)	3.34
Gastritis	72 (5.2)	3.17	59 (4.3)	3.29
Vomiting	76 (5.5)	3.36	52 (3.8)	2.89
Acute kidney injury	71 (5.1)	3.09	40 (2.9)	2.20

Abbreviations: PEY: patient exposure years; OT+28: On-treatment plus 28 days

F.4 DOLOMITES

Study discontinuation was comparable between the randomised treatment groups (22.6% of patients in the roxadustat group versus 21.5% in the darbepoetin alfa group); the most common reason was death for both groups (10.2% vs 11.6% respectively) (Table 107) (42).

Table 107. Early treatment discontinuation (ITT population)

	Roxadustat (n=323)	Darbepoetin alfa (n=293)	Total (n=616)
Early treatment discontinuation up to two years			
Yes	73 (22.6%)	63 (21.5%)	136 (22.1%)
No	250 (77.4%)	230 (78.5%)	480 (77.9%)
Primary reason for discontinuation			
Completed	250 (77.4%)	230 (78.5%)	480 (77.9%)
Adverse event	2 (0.6%)	1 (0.3%)	3 (0.5%)
Death	33 (10.2%)	34 (11.6%)	67 (10.9%)
Lost to follow-up	3 (0.9%)	3 (1.0%)	6 (1.0%)
Progressive disease	0	1 (0.3%)	1 (0.2%)
Withdrawal by patient	30 (9.3%)	18 (6.1%)	48 (7.8%)
Study terminated by sponsor	0	0	0
Physician decision	3 (0.9%)	3 (1.0%)	6 (1.0%)
Pregnancy	0	0	0
Other	2 (0.6%)	3 (1.0%)	5 (0.8%)

Abbreviations: ITT: intention-to-treat.

The overall incidence of TEAEs seen in this study was comparable between treatment groups; 91.6% of patients in the roxadustat group and 92.5% of patients in the darbepoetin alfa group experienced TEAEs. In both the roxadustat group and the darbepoetin alfa group 56.0% of patients had TEAEs ≥Grade 3 in severity. A comparable proportion of patients in the roxadustat group (24.1%) and darbepoetin alfa groups (22.5%) experienced TEAEs considered related to treatment by the investigator (Table 108) (42).

More patients in the roxadustat group (64.7%) compared with the darbepoetin alfa group (61.8%) had serious TEAEs; 5.6% and 3.1% of patients, respectively, had serious TEAEs considered related to treatment by the investigator (Table 108) (42).

Table 108. Overview of TEAEs and death (SAF population)

	Roxadustat (n=323)	Darbepoetin alfa (n=293)
TEAE	296 (91.6%)	271 (92.5%)
Drug-related TEAE	78 (24.1%)	66 (22.5%)
Serious TEAE	209 (64.7%)	181 (61.8%)
Drug-related serious TEAE	18 (5.6%)	9 (3.1%)

	Roxadustat (n=323)	Darbepoetin alfa (n=293)
TEAE leading to death	34 (10.5%)	34 (11.6%)
Drug-related TEAE leading to death	2 (0.6%)	0
TEAE leading to withdrawal of treatment	25 (7.7%)	11 (3.8%)
Drug-related TEAE leading to withdrawal of treatment	7 (2.2%)	1 (0.3%)
TEAE NCI-CTCAE Grades 3 or Higher	181 (56.0%)	164 (56.0%)
Death during the Safety Emergent Period	30 (9.3%)	31 (10.6%)
Death (Overall)	40 (12.4%)	37 (12.6%)

Abbreviations: TEAE: treatment-emergent adverse event; NCI CTCAE: National Cancer Institute - common terminology criteria for adverse events; SAF: safety analysis set.

The most common TEAE in roxadustat and darbepoetin alfa treatment groups were ESRD (33.4% versus 36.2% respectively), hypertension (29.7% versus 33.8% respectively), decreased glomerular filtration rate (17.0% versus 16.7% respectively), peripheral oedema (15.2% versus 12.3% respectively) and hyperkalaemia (11.8% versus 14.3% respectively) (Table 109) (42).

Table 109. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population)

	Roxadustat (n=323)		Darbepoetin alfa (n=293)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Overall	296 (91.6)	2730 (505.0)	271 (92.5)	2498 (495.4)
End-stage renal disease	108 (33.4)	108 (20.0)	106 (36.2)	106 (21.0)
Hypertension	96 (29.7)	140 (25.9)	99 (33.8)	155 (30.7)
Glomerular filtration rate decreased	55 (17.0)	63 (11.7)	49 (16.7)	67 (13.3)
Oedema peripheral	49 (15.2)	61 (11.3)	36 (12.3)	52 (10.3)
Hyperkalaemia	38 (11.8)	45 (8.3)	42 (14.3)	50 (9.9)
Nausea	35 (10.8)	40 (7.4)	25 (8.5)	27 (5.4)
Viral upper respiratory tract infection	29 (9.0)	33 (6.1)	25 (8.5)	30 (5.9)
Diarrhoea	28 (8.7)	41 (7.6)	30 (10.2)	38 (7.5)
Hyperphosphataemia	28 (8.7)	29 (5.4)	15 (5.1)	18 (3.6)
Muscle spasms	25 (7.7)	33 (6.1)	15 (5.1)	20 (4.0)
Pneumonia	25 (7.7)	30 (5.5)	22 (7.5)	27 (5.4)
Dyspnoea	24 (7.4)	26 (4.8)	12 (4.1)	13 (2.6)
Bronchitis	22 (6.8)	28 (5.2)	18 (6.1)	23 (4.6)
Constipation	21 (6.5)	24 (4.4)	15 (5.1)	18 (3.6)
Headache	21 (6.5)	24 (4.4)	12 (4.1)	13 (2.6)
Iron deficiency	21 (6.5)	25 (4.6)	25 (8.5)	34 (6.7)
Urinary tract infection	21 (6.5)	31 (5.7)	27 (9.2)	33 (6.5)
Vomiting	21 (6.5)	32 (5.9)	19 (6.5)	22 (4.4)
Back pain	20 (6.2)	22 (4.1)	17 (5.8)	20 (4.0)
Pruritus	20 (6.2)	27 (5.0)	13 (4.4)	13 (2.6)
Insomnia	19 (5.9)	19 (3.5)	8 (2.7)	9 (1.8)
Arthralgia	18 (5.6)	21 (3.9)	14 (4.8)	19 (3.8)

	Roxadustat (n=323)		Darbepoetin alfa (n=293)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Atrial fibrillation	18 (5.6)	21 (3.9)	12 (4.1)	16 (3.2)
Cardiac failure	18 (5.6)	27 (5.0)	18 (6.1)	27 (5.4)
Arteriovenous fistula thrombosis	16 (5.0)	17 (3.1)	10 (3.4)	16 (3.2)
Dizziness	16 (5.0)	20 (3.7)	15 (5.1)	17 (3.4)
Anaemia	14 (4.3)	15 (2.8)	19 (6.5)	21 (4.2)

Abbreviations: PEY: Patient exposure years; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

Appendix G. Published cost-effectiveness studies

Studies included in the Cost and Healthcare Resource use SLR and Health-related quality of life SLR detailed in Cost and healthcare resource identification, measurement and valuation and Health-related quality of life studies were screened to identify cost-effectiveness models relevant for this submission. Four studies were identified (147-150). As well, a model used in the cost-effectiveness model to inform inputs (76), and a model assessing the cost-effectiveness of roxadustat (63) were targeted and included.

Additionally, a published systematic literature review of cost-effectiveness evidence in anaemia associated with CKD (151) was targeted and the evidence evaluated, a total of seven studies (152-157), were added to the above mentioned studies.

G.1 Identified studies

Table 110 shows the studies identified as relevant to this submission. In total 13 models were included in the review (63, 76, 147-150, 152-157).

Table 110: Cost-effectiveness models relevant for this submission

Reference
Clement FM, Klarenbach S, Tonelli M, Wiebe N, Hemmelgarn B, Manns BJ: An economic evaluation of erythropoiesis-stimulating agents in CKD. Am J Kidney Dis 2010; 56:1050–1061.
Glenngård AH, Persson U, Schön S: Cost-effectiveness analysis of treatment with epoietin-alpha for patients with anaemia due to renal failure: the case of Sweden. Scand J Urol Nephrol 2008; 42: 66–73
Hu Z, Tao H, Shi A, Pan J. The efficacy and economic evaluation of roxadustat treatment for anemia in patients with kidney disease not receiving dialysis. Expert review of pharmacoeconomics & outcomes research. 2020;20(4):411-8
Kourlaba G, Boletis I, Goumenos D, Iatrou C, Papagiannopoulou V, Tritaki G, et al. Cost consequence analysis of darbepoetin alfa for the treatment of anemia due to chronic kidney disease (CKD) in Greece. Value Health. 2014;17(7):A468-9.
Krysanov I, Vaskova LB, Tiapkina M, Ermakova V, Glad'ko OV. Pharmacoeconomic evaluation of biosimilar recombinant alpha-epoetin in the treatment of anemia in hemodialysis patients. Value Health. 2018;21(Suppl 3):S455.
Leese B, Hutton J, Maynard A: A comparison of the costs and benefits of recombinant human erythropoietin (epoetin) in the treatment of chronic renal failure in 5 European countries. Pharmacoeconomics 1992; 1: 346–356.
Maoujoud O, Ahid S, Cherrah Y. The cost-utility of treating anemia with continuous erythropoietin receptor activator or Epoetin versus routine blood transfusions among chronic hemodialysis patients. Int J Nephrol Renovascular Dis. 2016;9:35-43.
Naci H, de Lissovoy G, Hollenbeak C, et al: Historical clinical and economic consequences of anemia management in patients with end-stage renal disease on dialysis using erythropoietin stimulating agents versus routine blood transfusions: a retrospective costeffectiveness analysis. J Med Econ 2012; 15: 293–304.
Oliver, Modelling the Clinical and Economic Burden of Anaemia in Patients with CKD. Journal of American Society of Nephrology, 2020.
Quon P, Gitlin M, Isitt J, et al: Cost-effectiveness of treating chronic anemia with epoetin alfa among hemodialysis patients in the United States. Health Outcomes Res Med 2012; 3:e79–e89
Remák E, Hutton J, Jones M, Zagari M: Changes in cost-effectiveness over time. The case of epoetin alfa for renal replacement therapy patients in the UK. Eur J Health Econ 2003; 4: 115–121
Tonelli M, Winkelmayer WC, Jindal KK, Owen WF, Manns BJ: The cost-effectiveness of maintaining higher hemoglobin targets with erythropoietin in hemodialysis patients. Kidney Int 2003; 64: 295–304.
Yarnoff, Benjamin O., et al. "The cost-effectiveness of anemia treatment for persons with chronic kidney disease." PloS one 11.7 (2016): e0157323.

G.2 Description of identified studies

Thirteen cost-effectiveness studies (63, 76, 147-150, 152-157), were identified and are described below.

CLEMENT F. ET AL., 2010 (158)

A lifetime Markov model with yearly cycles was developed in order to determine the cost-effectiveness of treating anaemia associated with CKD NDD and dialysis-

dependent patients with ESA. The strategies evaluated were ESA treatment targeting an Hb level of 9-10.9, 11-12 or >12 g/dL, compared to managing anaemia without ESA.

The model considered a flow allowing patients to transition in 4 states: non-dialysis, dialysis, transplanted, and dead. Patient baseline characteristics and clinical inputs were derived from two large dialysis and non-dialysis Canadian CKD cohorts. Other outcome of interest was the risk of hospitalization. Utility estimates were obtained from observational studies and published literature. It was assumed patients treated to a low and intermediate hemoglobin targets had the same utility, being this higher than for patients treated with no ESA.

Costs included were those related to the annual management of NDD CKD patients, annual cost of hemodialysis, transplant, and RBC transfusion.

Anaemia management with ESA compared to not using ESA in dialysis patients to target an Hb level of 9-10.9 g/dL was associated with a cost per QALY of $96,270 Canadian dollars. Targeting the intermediate level resulted in less costs and less QALYs but a higher ICER, and the >12 g/dL target strategy was dominated with more costs and less QALYs by the lower level target strategy. Results were similar in anaemia associated with CKD non–dialysis patients, with a cost per QALY for a low target compared with no ESA of $147,980 Canadian dollars.

GLENNGARD A. ET AL., 2008 (156)

By using a Markov model, this study aimed to explore the cost-effectiveness of EPO combined with RBCT versus RBCT alone in Sweden from a provider perspective.

This model allowed patients to transition in 4 weeks cycles among different Hb stages: <8, 8-9, 9-10, 10-11, 11-12, 12-13, and >13 g/dL. Patient baseline characteristics and clinical practice regarding dosage and use of EPO and iron supplementation were informed from national databases and pharmacy specialists. Information about changes in blood transfusion was based on the meta-analysis performed by Remak et al., 2002 (155). Quality of life was obtained from published literature. Other outcomes of interest are hospitalisations, and laboratory tests. Costs included EPO drug, costs related to complications and administration of EPO, iron supplementation, blood transfusions

The estimated cost per QALY derived from the administration of EPO in combination with RBCT vs. RBCT alone was €63,665 and €28,875 for haemodialysis and peritoneal dialysis patients respectively. These values fall under the maximum acceptable threshold in Sweden.

HU ET AL., 2020 (63)

Hu et al. 2020 (63) explored the efficacy, tolerance, and cost-effectiveness of roxadustat treatment for anaemia in patients with CKD not receiving dialysis. The authors conducted a meta-analysis to evaluate the clinical efficacy and tolerance of roxadustat for the correction of anaemia associated with CKD and developed a Markov model to evaluate the cost-effectiveness of roxadustat against placebo. The disease development of the study subjects was classified by three disease states: Hb 10–12 g/dL (target), Hb < 10 g/dL (below target), or dead. The patients could remain at the same Hb level, transition to another Hb level, or die. The cycle length of the Markov model was set to 3 months with a time horizon of 5 years. Given the focus of this model in patients not receiving dialysis, the time horizon was selected based on the average time non-dialysis patients take to progress to dialysis. Only direct medical costs, including the cost of drugs, routine blood and blood biochemical examinations, management of adverse events, and blood transfusion, were considered in the Markov model. The utility associated with different Hb target levels was based on the literature.

In comparison with placebo, the use of oral roxadustat to treat anaemia in patients with CKD not on dialysis was more effective (3.36 QALYs vs 2.87 QALYs), and costly ($14,282 vs $1756 USD) over a 5-year interval. The incremental QALY and incremental cost value for roxadustat treatment in comparison with a placebo were 0.49 QALYs and 12,526 USD, respectively, resulting in an ICER of $25,563 USD per QALY.

KOURLABA G. ET AL., 2014 (147)

Kourlaba et al. (147) conducted a study with the aim of assessing the cost-effectiveness of darbepoetin alfa for the treatment of anaemia due to CKD compared to other ESA in patients on haemodialysis or peritoneal dialysis in Greece.

This model took the form of a decision tree, with a duration of 1 year, and from the perspective of a public third-party payer perspective. The efficacy was defined as "% patients under anaemia control", meaning these patients alive, not hospitalized of transfused during the treatment period. The costs included were those related to drug acquisition, administration and clinical event costs, and the last comprising hospitalization and blood transfusion costs.

In terms of efficacy, the results of this model considered all included interventions as equal. Given this, total costs per patient were mainly affected by drug acquisition costs and by ESA dose.

Darbepoetin alfa was associated with the lowest overall costs per patient in control at €8,210 and €6,689, for patients on haemodialysis or peritoneal dialysis, respectively, followed by short-acting ESA, pegylated epoetin beta and short-acting biosimilar ESA.

KRYSANOV I. ET AL., 2018 (148)

A decision tree model for cost-minimization analysis was developed to compare the costs for IV treatment with epoetin alfa biosimilars 33.3 ME/kg three times-weekly, darbepoetin alfa 0.5 mcg/kg once weekly, and continuous erythropoiesis receptor activator (CERA) 60 mcg every two weeks or 120 mcg per month.

Under the assumption of similar effectiveness among ESA, the total annual costs for epoetin alfa was €2,180, followed by darbepoetin alfa €2,283-€ 3,085, and CERA €2,267- €2,945. Subcutaneously biosimilar epoetin alfa under the same assumptions was associated with a higher cost-saving of 36-53%. Results are detailed in Table 111.

Table 111 Cost-minimization results for Krysanov I. et al.

Drug name	Total cost, EUR	Δ cost, EUR	Δ cost, EUR
Cost-minimization analysis for intravenous maintenance dose of biosimilar epoetin alfa 2500 ME			
Biosimilar Epo A 2500 ME	2,180	-	-
CERA 50 mkg +75 mkg	2,267	- 87	- 4%
CERA 75 mkg	2,945	- 765	- 26%
DARB 20 mkg	3,085	-905	- 29%
DARB 30 mkg	2,283	- 103	- 5%
Cost-minimization analysis for subcutaneously maintenance dose of biosimilar epoetin alfa 2500 ME			
Biosimilar epoetin alfa 2500 ME	1,454	-	-

CERA 50 mkg +75 mkg = 125 mkg	2,267	- 813	- 36%
CERA 75 mkg	2,945	-1,491	- 51%
DARB 20 mkg	3,085	-1,631	- 53%
DARB 30 mkg	2,283	- 829	- 36%

Abbreviations: Darb; darbepoietin alpha; CERA, continuous erythropoietin receptor activator; mkg, microgram.

LEESE B. ET AL., 1992 (157)

The aim of this paper was to estimate costs and benefits associated to the treatment of anaemia associated with CKD with EPO vs. RBCT in dialysis patients. To do so, a study was carried out in 5 European countries; Spain, Italy, UK, Germany and France, were information related to costs and efficacy was collected to inform a Markov model.

The data informing this model was based on secondary data collected from a variety of source sin each country including published literature, retrospective studies and data from healthcare funding organisations. QoL effects of EPO were produced prospectively in Spain and Italy and reinforced with assessments of patients' QoL by medical staff in Germany, France and the UK. Costs were limited to those relative to EPO and blood transfusion interventions, adverse events related to EPO and blood transfusions.

Results were reported in USD and oscillated from $173,271 USD in France to $677,749 USD in Spain.

MAOUJOUD O. ET AL., 2016 (149)

Majoud et al. conducted a study to determine the cost-utility of treating dialysis patients with three interventions: CERA once monthly, epoetin beta thrice weekly, or a strategy not using ESA based on RBCT.

A decision analytical model from the healthcare payer perspective and a duration of 1 year was implemented to model a cohort of Moroccan chronic haemodialysis patients. Key model inputs included the clinical success rate of treatment which was defined as the proportion of patients successfully maintaining Hb within the range of 10.5–12 g/dL, iron use, RBC transfusion requirements, survival, hospitalizations, and drug acquisition costs. Three ranges of Hb level were determined: Low Hb range (9-10.5 g/dL),

intermediate Hb range (10.5-12 g/dL), and high Hb range (>12 g/dL). Both costs and utilities were discounted at a rate of 3%.

Results have been detailed in Table 112. The incremental cost-utility ratio of CERA and epoetin beta in relation to RBCT was 19,606 and 22,466 $/QALY respectively.

Table 112 Cost-utility results for Maoujoud O. et al.

Intervention	Average cost ($)	Incremental cost ($)	Average QALY	Incremental QALY	Cost-utility ratio	ICUR ($/QALY)
RBCT	2,176.37	–	0.491	–	4,423.52	–
CERA	4,107.01	1,930.64	0.591	0.1	6,955.50	19,606.4
Epo B	4,365.69	2,189.32	0.591	0.1	7,406.38	22,466.09

Abbreviations: RBCT, red blood cell transfusion; CERA, methoxy polyethylene glycol-Epoetin beta; B, beta; ICUR, incremental cost-utility ratio; QALY, quality adjusted life year.

NACI H. ET AL., 2012 (153)

A Markov cohort model was developed to analyse retrospectively the cost-effectiveness of ESA versus routine RBCT for the management of anaemia in a cohort of ESRD patients.

A simulated cohort of patients was derived from a sample of patients receiving ESA between 1995 and 2004. The model paralleled the natural course of ESRD by establishing three stages: dialysis without a transplant, renal transplant, and dead. Then, Hb level was analysed. Other outcomes of interest were hospitalizations, transplantation and acute graft failure, blood transfusions and related adverse events.

Both clinical and economic inputs were informed by summary statistics from a cohort of ESRD patients receiving ESA between 1995 and 2004. Regarding quality of life, departing from an assigned utility assigned to each health state, utility decrements associated to Hb ranges of <11 g/dL and 11 to 12 g/dL were applied.

Results reported an estimated ICER of ESA compared to routine blood transfusions of $873 USD per QALY gained. The model was sensitive to several parameters according to one-way and probabilistic sensitivity analyses.

OLIVER T. ET AL., 2020 (150)

To characterize the consequences of anaemia in patients with CKD, a lifetime Markov model was developed. The outcomes of interest were differences in life expectancy, QALY and event incidence.

The modelled population were patients aged 58 years old, CKD stage 3b, with anaemia (Hb 9-10 g/dL) and without anaemia (Hb >12 g/dL). Anaemia status was linked to CKD progression, CV hospitalizations and mortality by using published data. Published direct costs and utility estimates were incorporated and treatment costs were not considered. A discount rate of 3% was applied.

The results of the model stated a reduction in life expectancy of 2.15 years and 2.18 fewer QALYs for patients with anaemia compared with those without. Patients with anaemia also experienced a shorter time to end stage renal disease and additional CV related hospitalizations. Regarding lifetime costs, these were higher in the non-anaemic group due to improved life expectancy. Still, annual costs were lower due to reduced CV events and CKD management costs.

QUON P. ET AL., 2012 (154)

A study was conducted with the aim of assessing Hb level targets of 10.0-11.0 g/dL and 9.0-10.0 g/dL for the treatment of anaemia associated with CKD in haemodialysis patients with epoetin alfa.

A Markov model with a duration of 5 years was developed and recorded three states: haemodialysis, transplant and acute graft failure. A curve for estimating epoetin alfa dose dependent on targeted Hb was extracted from published literature. Other outcomes of interest were hospitalizations and mortality. Only direct costs were included and cost for epoetin alfa and iron were calculated separately.

Results suggested that epoetin alfa use targeting Hb levels of 10.0 to 11.0 g/dL relative to 9.0 to 10.0 g/dL may result in better patient outcomes and lower costs.

REMAK E. ET AL., 2002 (155)

The aim of this paper was to analyse the factors influencing the cost-effectiveness of a health care intervention over time. In order to do so, an already existing economic

evaluation (157) comparing epoetin alfa versus red blood cells transfusions was updated with recent inputs.

The modelled population was a sample of dialysis patients simulated based on data from the UK Renal Registry. Efficacy was informed by a meta-analysis performed to estimate response to epoetin alfa therapy in terms of hospitalisation and iron transfusions requirements. Quality of life estimates were extracted from published literature. Only direct costs were considered, and these were discounted at a 6% rate yearly. Health benefits were discounted at a 1.5% rate yearly.

Results reported an average survival on dialysis in the UK of 6.75 years and concluded an ICER of €35,434 per QALY for epoetin alfa versus red blood cell transfusions.

TONELLI M. ET AL., 2003 (152)

Tonelli M. et al. (152) conducted a study with the aim of determining the cost-effectiveness of prescribing EPO to maintain different target Hb levels in haemodialysis patients.

The Hb levels of interest were 11-12 g/dL, 12-12,5 g/dL, and 14.0 g/dL versus maintaining a more conservative level of 9.5-10.5 g/dL. The population was simulated based on a typical dialysis centre in the United States.

Adopting the perspective of the healthcare purchaser over a patient lifetime, a Markov model with three states; alive on haemodialysis, alive with a renal transplant, and dead; was developed. Only direct costs were included and data from randomized clinical trials was used to inform the efficacy. Regarding quality of life, information derived from clinical trials and published studies was applied. Other outcomes of interest were risk of hospitalization, and vascular access failure.

The cost per QALY of maintaining an Hb level of 11.0 to 12.0 g/dL vs. 9.5 to 10.5 g/dL was $55,295. For the level 12.0 to 12.5 g/dL vs. 11.0 to 12.0 g/dL and 14.0 g/dL vs. 12.0 to 12.5 g/dL the cost per QALY gained were $613,015 and $828,215 USD respectively.

YARNOFF B. O. ET AL., 2016 (76)

This study aimed to explore the most cost-effective Hb target for anaemia treatment in patients with CKD stages 3-4 not on dialysis. Incremental costs and QALYs were assessed for Hb targets of 10-13 g/dL at 0.5 g/dL increments. The intervention of interest was epoetin alfa, being darbepoetin alpha considered an equivalent alternative.

Based on an already existing microsimulation model of CKD progression, an adaptation was carried out to simulate 1) decline of Hb levels; 2) complications associated with both Hb levels and anaemia treatment such as stroke, myocardial infarction, hypertension, blood transfusion, and non-CVD mortality, and 3) quality of life reductions related to lower Hb levels.

The model includes seven states related to CKD defined by eGFR and albuminuria levels: no CKD, CKD 1-5, and death. Regarding the modelling of anaemia treatment, patients receive ESA treatment once Hb levels falls below 10 g/d receiving incremental doses to restore Hb level to a pre-set target level. All persons receiving treatment for anaemia also received a monthly dose of iron once they become anaemic and continue to receive iron once they begin ESA treatment to improve their response to ESA.

In terms of costs, the model included those related with CKD progression and its complications and anaemia treatment such as ESA treatment, IV iron, and blood transfusion. Costs were discounted 3% annually. Regarding quality of life, disutilities were applied to each event in the model and each 1 g/dL decrease in Hb below 13 g/dL.

Model results concluded targeting a Hb of 10 g/dL has an ICER of $32,111 USD compared with no treatment and targeting a Hb of 10.5 g/dL results in an ICER of $32,475 compared with a Hb target of 10 g/dL. Any treatment target above 11 g/dL increased medical costs and decreased QALYs.

G.3 Discussion of included studies

In total, 13 studies were assessed (63, 76, 147-150, 152-157). A summary of the study characteristics, model inputs and outcomes are described in Table 113 and summarised below.

Model structure:

In total, two studies (147, 148) used decision trees models rather than cohort models. Given its simplicity, these models are more limited when it comes to modelling recurrent events and more complex decision problems. Nine studies (63, 150, 152-158)were based on a Markov health state transition model structure using patient cohorts, another used a microsimulation approach (76), and a last one was defined as a decision analytic model(149). According to the SLR performed by Ferguson et al. (151) cost-utility Markov models are the preferred option when modelling anaemia treatment on CKD dialysis patients.

Ten studies modelled QALYs and clinical benefits (76, 149, 150, 152-158), while other two assumed clinical parity among interventions and focused only on costs (147, 148).

Health states:

Regarding the strategy used to model anaemia progression, there were two main streams with some studies emphasizing the modelling of CKD and others focusing on the modelling of Hb progression and specific Hb states.

A first group of studies (76, 147, 152, 154, 158) focused on the modelling of CKD progression defining disease specific states, and then analysed the performance of setting different Hb level targets for the interventions of interest. Efficacy and outcomes were modelled related to each Hb level strategy. Similarly, one study modelled CKD progression and analysed parallelly the progression of Hb level (153).

A second group of studies modelled Hb progression through different Hb states with more or less granularity. One study focused on seven different Hb level categories (156), two studies focused on three (63, 149), and a last one on two (150).

This information was not reported in 3 studies (148, 155, 157).

Time horizon:

In total, 5 models reported a lifetime model time horizon (76, 150, 152, 155, 158), one model a 10 years horizon (153), two models a 5 years horizon (63, 154), and lastly 2 models reported a yearly time horizon (147, 149). When assuming clinical similarity among interventions, shorter time horizons allow performing a simpler approach

compared to lifetime models that usually require long-term model extrapolations. One model did not report time horizon (148, 156, 157).

Costs:

The resource use concepts and costs modelled differed across the identified studies. The most relevant resources were those associated with drug acquisition costs, clinical events, dialysis, hospitalizations, supplementary iron costs, and blood transfusion costs.

Table 113 Summary of the study characteristics of included studies

Author, Year	Model type	Health States	Time horizon	Intervention, Setting	Cycle length	Threshold	Currency	Discount rate	Sensitivity analysis
Clement F. et al., 2010 (158)	Markov model	Four states: non-dialysis, dialysis, transplant, and death	Lifetime	ESA for Hb targets of 9-10.9, 11-12 or >12 g/dL, vs no ESA.	Yearly	$50,000	Canadian dollars	5%	Scenario analysis and PSA
Glenngard A. Et al., 2008 (156)	Markov model	Hb categories: <8, 8-9, 9-10, 10-11, 11-12, 12-13, and >13 g/dL	NA	EPO+ RBCT vs. RBCT	4 weeks	Not adpted	EUR/SEK	3%	Different scenarios: Discount rates, length of hospital stay, costs of blood transfusion and EPO administration
Hu et al., 2020 (63)	Markov model	Three states: Hb 10–12 g/dL (target), Hb < 10 g/dL (below target), or dead	5 years	Roxadustat vs. placebo	3 months	$29,295	USD	5%	OWSA and PSA
Kourlaba et al. 2014 (147)	Decision tree	% patients under anaemia control, Hb level	1 year	Darbepoetin alpha, short acting ESA, pegylated epoetin beta, short acting biosimilar ESA	NA	NA	Eur	NA	NA
Krysanov I et al. 2018 (148)	Decision tree, cost-minimization analysis	NA	NA	Epoetin alpha, darbepoetin alpha, pegylated epoetin beta	NA	NA	Eur	NA	OWSA
Leese B. Et al.,	Markov model	NA	NA	EPO vs. RBCT	NA	NA	USD	NA	Various scenario

Author, Year	Model type	Health States	Time horizon	Intervention, Setting	Cycle length	Threshold	Currency	Discount rate	Sensitivity analysis
1992 (157)									analyses per country
Maoujoud O. et al., 2016 (149)	Decision analytical model	Three health states based on Hb levels: Low Hb range (9-10.5 g/dL), intermediate Hb range (10.5-12 g/dL) and high Hb range (>12 g/dL).	1 year	CERA once monthly, epoetin beta thrice weekly, RBCT	NA	NA	USD	3%	OWSA, PSA. The model was most sensitive to hospitalization cost, hospital stay, and annual number of RBCT
Naci H. Et al., 2012 (153)	Markov model	Three states: Alive on haemodialysis, alive with a renal transplant, and dead	10 years	ESA vs. blood transfusion	1 year	$10,000 and $20,000	USD	NA	Scenario analysis and PSA
Oliver T. et al. 2020 (150)	Markov model	Based on Hb levels	Lifetime	Anaemia (Hb 9-10 g/dL), and non-anaemia (Hb >12 g/dL)	NA	NA	USD	3%	NA
Quon P. Et al., 2012 (154)	Markov model	Three states: haemodialysis, transplant and acute graft failure	5 years	ESA (epoetin alfa) for Hb targets of 10.0 to 11 g/dL and 10.0 to 11.0 g/dL	NA	$50,000 and $100,000	USD	3.5%	Scenario analysis and PSA
Remak et al., 2002 (155)	Markov model	NR	Lifetime	Epoetin alfa vs. RBCT	NA	NA	Euro	Costs 6% and benefits 1.5%	Sensitivity analyses were carried out to assess the

Author, Year	Model type	Health States	Time horizon	Intervention, Setting	Cycle length	Threshold	Currency	Discount rate	Sensitivity analysis
									impact of uncertainty surrounding key variables
Tonelli M. et al., 2003 (152)	Markov model	Three states: Alive on haemodialysis, alive with a renal transplant, and dead	Lifetime	EPO treatment target of 11 to 12 g/dL, 12 to 12,5 g/dL, and 14.0 g/dL	NA	NA	USD	3%	Focused on EPO dose and HRQoL for each strategy
Yarnoff B. O. et al., 2016 (76)	Microsimulation level	CKD stages and Hb level target	Lifetime	No ESA treatment, ESA treatment targetting 10.0 to 13.0	NA	NA	USD	3% costs	OWSA and PSA varying key model parameters

Abbreviations: CERA: continuous erythropoietin receptor activator; CKD: chronic kidney disease; ESA, erythropoietin stimulating agent; EPO: erythropoietin; HRQoL: health-related quality of life; Hb: haemoglobin NA, not available; OWSA, one-way sensitivity analysis; RBCT, red blod cell transfusion; PSA, probabilistic sensitivity analysis; USD: united states dollar.

Appendix H. Health-related quality of life studies

H.1 Identification of studies

A systematic literature review was undertaken to identify, and review published health utilities data in patients with anaemia in CKD. Literature searches were conducted by an information specialist between 22 January 2019 and 10 February 2019.
An update to the SLR was conducted to cover the time period between February 2019 and March 2021.

H.1.1 Search Strategy

The following electronic databases were searched via the given platforms for HRQoL/utility SLR:

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily – via OvidSP
- Embase via OvidSP
- PubMed
- EconLit via OvidSP
- PsycInfo via OvidSP
- The Cochrane library incorporating-
- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment Database (HTA Database)
- NHS Economic Evaluation Database (NHS EED)
- Cost-Effectiveness Analysis (CEA) Registry
- ScHARRHud
- NICE website

Additional studies were identified by searching the following sources:

- European Renal Association - European dialysis and Transplant Association (ERA EDTA) Congress [2016, 2017, 2018, 2019, 2020]
- American Society of Nephrology (ASN) Kidney Week [2016, 2017, 2018, 2019, 2020]
- International Society of Pharmacoeconomics and Outcomes Research (ISPOR) conference [2016, 2017, 2018, 2019, 2020]

H.1.1.1 Source: Ovid MEDLINE(R)

Table 114 HRQoL SLR search details (Ovid MEDLINE®)

	Original SLR	SLR Update
Interface / URL:	OvidSP	OvidSP
Database coverage dates:	1946 to January 28, 2019	2019 to January 27, 2021
Search date:	30/01/19	07/01/21
Retrieved records:	1382	410

Table 115 HRQoL SLR search strategy (Ovid MEDLINE®)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	exp Renal Insufficiency/	159109	176735
2	kidney diseases/ and (chronic or end-stage$ or endstage$ or final stage$).ti,ab,kf.	12991	13838
3	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	93865	108145
4	((kidney$ or renal$ or nephropath$) adj3 fail$).ti,ab,kf.	98257	104808
5	((kidney$ or renal$ or nephropath$) adj3 insufficien$).ti,ab,kf.	23621	25051
6	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).ti,ab,kf.	40274	46114
7	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	59	67
8	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5(kidney$ or renal$ or nephropath$)).ti,ab,kf.	2225	2778
9	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	2	4
10	(early adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	14420	16030
11	((kidney$ or renal$ or nephropath$) adj3 injur$).ti,ab,kf.	37563	48080
12	(CKF or CKD or CRF or CRD).ti,ab,kf.	41526	50075
13	(ESKD or ESRD or ESKF or ESRF).ti,ab,kf.	16852	19540

#	Searches	Hits (Original SLR)	Hits (SLR Update)
14	exp Renal Replacement Therapy/	194449	213627
15	Dialysis/	12513	12642
16	Hemodialysis Units, Hospital/	1362	1427
17	Kidneys, Artificial/	4302	4347
18	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).ti,ab,kf.	116762	126127
19	(hemodialy$ or haemodialy$).ti,ab,kf.	74064	80664
20	(prehemodialy$ or prehaemodialy$).ti,ab,kf.	81	86
21	exp Hemofiltration/	6491	6847
22	Ultrafiltration/	9780	10185
23	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemo-filtra$ or haemodiafiltra$ or haemo-diafiltra$).ti,ab,kf.	6611	7098
24	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).ti,ab,kf.	18114	19654
25	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).ti,ab,kf.	104075	114405
26	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).ti,ab,kf.	2888	3021
27	(CAPD or CCPD or APD).ti,ab,kf.	11227	11899
28	glomerular filtration rate/	40810	45131
29	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).ti,ab,kf.	7268	8288
30	diabetic nephropathies/	23693	25814
31	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).ti,ab,kf.	19096	22120
32	or/1-31	534791	589645
33	exp Anemia/	154557	162737
34	(anemi$ or anaemi$).ti,ab,kf.	146500	158647
35	or/33-34	217009	232631
36	32 and 35	19228	20954
37	Economics/	26992	27278
38	exp "costs and cost analysis"/	221598	241333
39	Economics, Dental/	1901	1915
40	exp economics, hospital/	23325	24878
41	Economics, Medical/	8993	9116
42	Economics, Nursing/	3986	4002
43	Economics, Pharmaceutical/	2837	2963
44	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	707933	833445
45	(expenditure$ not energy).ti,ab.	27049	30983
46	value for money.ti,ab.	1527	1771
47	budget$.ti,ab.	26896	30300

#	Searches	Hits (Original SLR)	Hits (SLR Update)
48	or/37-47	853515	987618
49	((energy or oxygen) adj cost).ti,ab.	3830	4191
50	(metabolic adj cost).ti,ab.	1286	1466
51	((energy or oxygen) adj expenditure).ti,ab.	23265	25716
52	or/49-51	27448	30381
53	48 not 52	847224	980651
54	(burden or resource$1).ti.	62318	74910
55	(burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kf.	32554	41367
56	(resource$1 adj4 (use$1 or usage or utilit$ or utilis$ or utiliz$)).ti,ab,kf.	40600	48735
57	[Office Visits/sn, td, ut]	0	0
58	(visit or visits or visited).ti,ab,kf.	183971	218115
59	appointment$.ti,ab,kf.	20817	25080
60	Hospitalisation/	96654	111902
61	(hospitalisation$1 or hospitalisation$1 or hospitalised or hospitalised).ti,ab,kf.	219027	258835
62	(admission$1 or readmission$1 or admitted or readmitted).ti,ab,kf.	349003	405948
63	"length of stay"/ or los.ti,ab,kf.	107580	129193
64	hospital stay$1.ti,ab,kf.	74273	86708
65	(bed adj3 day$1).ti,ab,kf.	3260	3644
66	((days or time or length or duration$1) adj3 hospital$).ti,ab,kf.	80082	95013
67	((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kf.	88628	107030
68	((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kf.	20863	24954
69	or/54-68	959148	1124990
70	Quality-Adjusted Life Years/	10685	12737
71	(quality adjusted or adjusted life year$).ti,ab,kf.	14550	17915
72	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	9370	11373
73	(illness state$1 or health state$1).ti,ab,kf.	5850	6803
74	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1354	1595
75	(multiattribute$ or multi attribute$).ti,ab,kf.	816	958
76	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	13453	16016
77	utilities.ti,ab,kf.	6394	7505
78	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	9600	51261
79	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	3332	4419

#	Searches	Hits (Original SLR)	Hits (SLR Update)
80	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	20381	22895
81	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	1744	1962
82	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	10482	12115
83	quality of life/ and ec.fs.	9245	10339
84	quality of life/ and (health adj3 status).ti,ab,kf.	8059	9331
85	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	11043	13223
86	((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	32293	40066
87	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	2972	3713
88	*quality of life/ and (quality of life or qol).ti.	48368	55609
89	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	23719	28793
90	quality of life/ and health-related quality of life.ti,ab,kf.	27641	33527
91	models,economic/	9156	10372
92	or/70-91	146529	185788
93	(utility loss$ or disutilit$ or short form$ or shortform$ or SF-12 or SF12).ti,ab,kf.	32444	38665
94	(15-D or 15D or SF-6 or SF6 or SF-6D or SF6D).ti,ab,kf.	7397	8262
95	discrete choice$.ti,ab,kf. (1712)87 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	2972	2277
96	choice experiment$1.ti,ab,kf.	2438	3118
97	(dce or dces).ti,ab,kf.	5187	6282
98	standard gamble$.ti,ab,kf.	816	869
99	sg.ti,ab,kf.	8952	10751
100	92 or 93 or 94 or 95 or 96 or 97 or 98 or 99	184003	229914
101	36 and (53 or 69)	2963	3414
102	36 and 100	336	387
103	101 or 102	3176	3656
104	exp animals/ not humans/	4541167	4772383
105	(news or editorial or case reports).pt. or case report.ti.	2654121	2947045
106	103 not (104 or 105)	2551	2894
107	remove duplicates from 106	2535	2882
108	limit 107 to yr="2009 -Current" / "2019 -Current"	1382	410

H.1.1.2 Source: Embase via OvidSP

Table 116 HRQoL SLR search details (OvidSP)

	Original SLR	SLR Update

Interface / URL:	OvidSP	OvidSP
Database coverage dates:	1946 to January 28, 2019	2019 to January 29, 2021
Search date:	30/01/19	29/01/21
Retrieved records:	6389	2292

Table 117 HRQoL SLR search strategy (OvidSP)

#	Searches	Results	Updated results
1	exp kidney failure/	318810	384163
2	kidney disease/ and (chronic or end-stage$ or endstage$ or final stage$).ti,ab,kw,dj.	22657	24823
3	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	135076	163890
4	((kidney$ or renal$ or nephropath$) adj3 fail$).ti,ab,kw,dj.	140452	155517
5	((kidney$ or renal$ or nephropath$) adj3 insufficien$).ti,ab,kw,dj.	31557	34416
6	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).ti,ab,kw,dj.	57268	69265
7	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	94	107
8	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	4218	5524
9	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	19	23
10	(early adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	20825	24312
11	((kidney$ or renal$ or nephropath$) adj3 injur$).ti,ab,kw,dj.	55922	75985
12	(CKF or CKD or CRF or CRD).ti,ab,kw,dj.	64951	85168
13	(ESKD or ESRD or ESKF or ESRF).ti,ab,kw,dj.	26768	34379
14	exp renal replacement therapy/ or exp kidney transplantation/	296532	334705
15	dialysis/	45600	52110
16	dialyzer/	484	1091
17	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).ti,ab,kw,dj.	155796	178876
18	(hemodialy$ or haemodialy$).ti,ab,kw,dj.	101298	117325
19	(prehemodialy$ or prehaemodialy$).ti,ab,kw,dj.	96	103
20	ultrafiltration/	20078	22789
21	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemofiltra$ or haemodiafiltra$ or haemo-diafiltra$).ti,ab,kw,dj.	9672	10756
22	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).ti,ab,kw,dj.	24828	27546
23	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).ti,ab,kw,dj.	153296	177009
24	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).ti,ab,kw,dj.	1803	1992
25	(CAPD or CCPD or APD).ti,ab,kw,dj.	14765	16411

#	Searches	Results	Updated results
26	exp glomerulus filtration rate/ (86886)	86886	110861
27	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).ti,ab,kw,dj.	10890	13145
28	diabetic nephropathy/	37802	44031
29	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).ti,ab,kw,dj.	27161	32764
30	or/1-29	795812	924857
31	exp anemia/	325762	369291
32	(anemi$ or anaemi$).ti,ab,kw,dj.	191386	218614
33	or/31-32	363514	411161
34	30 and 33	46556	54575
35	Health Economics/	31687	33336
36	exp Economic Evaluation/	284834	314329
37	exp Health Care Cost/	272276	298702
38	pharmacoeconomics/	6988	7471
39	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	933299	1122862
40	(expenditure$ not energy).ti,ab.	35987	42207
41	(value adj2 money).ti,ab.	2205	2527
42	budget$.ti,ab.	34668	40202
43	or/35-42	1180769	1388311
44	(metabolic adj cost).ti,ab.	1364	1586
45	((energy or oxygen) adj cost).ti,ab.	3952	4490
46	((energy or oxygen) adj expenditure).ti,ab.	29152	32831
47	or/44-46	33434	37775
48	43 not 47	1173974	1380553
49	disease burden/	7595	21583
50	cost/	56200	59242
51	(burden or resource$1.ti	80947	101207
52	(burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$.ti,ab,kw,dj.	49372	64335
53	(resource$1 adj4 (use$1 or usage or utilit$ or utilis$ or utiliz$.ti,ab,kw,dj.	59735	73598
54	(visit or visits or visited).ti,ab,kw,dj.	292303	359967
55	appointment$.ti,ab,kw,dj.	34446	43669
56	hospitalisation/ or hospital admission/	472947	571338
57	(hospitalisation$1 or hospitalisation$1 or hospitalised or hospitalised).ti,ab,kw,dj.	345568	421367
58	(admission$1 or readmission$1 or admitted or readmitted).ti,ab,kw,dj.	576843	694122
59	"length of stay"/ or los.ti,ab,kw,dj.	186356	230854
60	hospital stay$1.ti,ab,kw,dj.	120635	144299
61	(bed adj3 day$1).ti,ab,kw,dj.	5180	6004

#	Searches	Results	Updated results
62	((days or time or length or duration$1) adj3 hospital$).ti,ab,kw,dj.	131473	160838
63	((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kw,dj.	153335	191057
64	((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kw,dj.	36637	45298
65	or/49-64	1625690	1957881
66	quality adjusted life year/	23089	28057
67	(quality adjusted or adjusted life year$).ti,ab,kw,dj.	21309	26502
68	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw,dj.	17654	21586
69	(illness state$1 or health state$1).ti,ab,kw,dj.	10008	11924
70	(hui or hui1 or hui2 or hui3).ti,ab,kw,dj.	2032	2440
71	(multiattribute$ or multi attribute$).ti,ab,kw,dj.	1045	1241
72	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw,dj.	21345	25720
73	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw,dj.	21345	25720
74	utilities.ti,ab,kw,dj.	10336	12389
75	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw,dj.	17652	22981
76	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw,dj.	5142	6762
77	short form 36/	24638	30722
78	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw,dj.	34477	39570
79	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw,dj.	2516	2917
80	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw,dj.	22218	26703
81	quality of life/ and ec.fs.	37656	44636
82	quality of life/ and (health adj3 status).ti,ab,kw,dj.	14258	16956
83	(quality of life or qol).ti,ab,kw,dj. and cost benefit analysis/	5037	5724
84	((qol or hrqol or quality of life).ti,kw,dj. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	49435	60513
85	cost benefit analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kw,dj.	725	878
86	*quality of life/ and (quality of life or qol).ti.	74274	89958
87	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw,dj.	65781	79792
88	quality of life/ and health-related quality of life.ti,ab,kw,dj.	50075	61610
89	economic model/	1524	2296
90	or/66-89	275093	332033

#	Searches	Results	Updated results
91	(utility loss$ or disutilit$ or short form$ or shortform$ or SF-12 or SF12).ti,ab,kw,dj.	45269	54949
92	(15-D or 15D or SF-6 or SF6 or SF-6D or SF6D).ti,ab,kw,dj.	9329	10666
93	discrete choice$.ti,ab,kw,dj.	2470	3327
94	choice experiment$1.ti,ab,kw,dj.	3029	4002
95	(dce or dces).ti,ab,kw,dj.	7943	9698
96	standard gamble$.ti,ab,kw,dj.	1069	1150
97	sg.ti,ab,kw,dj.	13006	16244
98	90 or 91 or 92 or 93 or 94 or 95 or 96 or 97	323112	390735
99	34 and (48 or 65)	10343	12975
100	34 and 98	1587	1807
101	99 or 100	11340	14115
102	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	5655240	6186723
103	editorial.pt. or case report.ti.	860137	990174
104	101 not (102 or 103)	10710	13268
105	conference abstract.pt. and 104	3307	4575
106	104 not 105	7403	8693
107	limit 105 to yr="2014 -Current" / yr="2019 -Current"	1930	980
108	limit 106 to yr="2009 -Current" / yr="2019 -Current"	4550	1329
109	remove duplicates from 107	1924	976
110	remove duplicates from 108	4465	1316
111	109 or 110	6389	2292

H.1.1.3 Source: Health Technology Assessment Database (HTA)

Table 118 HRQoL SLR search details (Health Technology Assessment Database)

	Original SLR
Interface / URL:	CRD database
Database coverage dates:	From 31 March 2018, the HTA database remains available, but CRD are no longer adding new records to it.
Search date:	30/01/19
Retrieved records:	19

Table 119 HRQoL SLR search strategy (Health Technology Assessment Database)

#	Searches	Results
1	((MeSH DESCRIPTOR Renal Insufficiency EXPLODE ALL TREES))	729
2	(((MeSH DESCRIPTOR kidney diseases) AND ((chronic or end-stage* or endstage* or final stage*))))	86
3	(((((chronic* or progressiv*) adj5 (kidney* or renal* or nephropath*)))))	571
4	(((((kidney* or renal* or nephropath*) adj5 (chronic* or progressiv*)))))	588

#	Searches	Results
5	(((((kidney* or renal* or nephropath*) adj3 fail*))))	859
6	((((fail* adj3 (kidney* or renal* or nephropath*)))))	171
7	(((((kidney* or renal* or nephropath*) adj3 insufficien*))))	326
8	((((insufficien* adj3 (kidney* or renal* or nephropath*)))))	18
9	(((((endstage* or end-stage*) adj5 (kidney* or renal or nephropath*)))))	357
10	(((((kidney* or renal or nephropath*) adj5 (endstage* or end-stage*)))))	43
11	((((final stage* adj5 (kidney* or renal* or nephropath*)))))	0
12	(((((kidney* or renal* or nephropath*) adj5 final stage*))))	0
13	(((((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney* or renal* or nephropath*)))))	12
14	(((((kidney* or renal* or nephropath*) adj5 (stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five)))))	11
15	(((((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney* or renal* or nephropath*)))))	0
16	(((((kidney* or renal* or nephropath*) adj5 (stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev)))))	0
17	((((early adj5 (kidney* or renal* or nephropath*)))))	49
18	(((((kidney* or renal* or nephropath*) adj5 early))))	17
19	(((((kidney* or renal* or nephropath*) adj3 injur*))))	192
20	((((injur* adj3 (kidney* or renal* or nephropath*)))))	15
21	((((CKF or CKD or CRF)) OR (CRD):TI))	114
22	((((ESKD or ESRD or ESKF or ESRF))))	158
23	((MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES))	881
24	((MeSH DESCRIPTOR Dialysis))	14
25	(MeSH DESCRIPTOR Hemodialysis Units, Hospital)	14
26	(MeSH DESCRIPTOR Kidneys, Artificial)	3
27	((((dialys* or predialys* or dialyz* or predialyz* or dialytic* or predialytic* or dopps*))))	920
28	((((hemodialy* or haemodialy*))))	456
29	((((prehemodialy* or prehaemodialy*))))	0
30	(MeSH DESCRIPTOR Hemofiltration EXPLODE ALL TREES)	50
31	(MeSH DESCRIPTOR Ultrafiltration)	15
32	((((hemofiltra* or hemo-filtra* or hemodiafiltra* or hemo-diafiltra* or haemofiltra* or haemo-filtra* or haemodiafiltra* or haemo-diafiltra*))))	73
33	((((ultrafiltra* or ultra-filtra* or biofiltra* or bio-filtra*))))	30
34	(((((kidney* or renal*) adj4 (transplant* or graft* or allograft* or replac*)))))	702
35	(((((transplant* or graft* or allograft* or replac*) adj4 (kidney* or renal*)))))	181
36	(((((artificial* or extracorporeal or extra-corporeal) adj3 (renal* or kidney*)))))	11
37	(((((renal* or kidney*) adj3 (artificial* or extracorporeal or extra-corporeal)))))	6
38	((((CAPD or CCPD or APD))))	29
39	(MeSH DESCRIPTOR glomerular filtration rate)	92

#	Searches	Results
40	(((((low or reduc*) adj4 (gfr or egfr or glomerular filtration rate*)))))	17
41	(((((gfr or egfr or glomerular filtration rate*) adj4 (low or reduc*)))))	4
42	((MeSH DESCRIPTOR diabetic nephropathies))	113
43	((((diabetic kidney disease* or diabetic renal disease* or diabetic nephropath*))))	150
44	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43))	2450
45	(MeSH DESCRIPTOR Anemia EXPLODE ALL TREES)	380
46	((((anemi* or anaemi*))))	731
47	(#45 OR #46)	791
48	(#44 AND #47)	138
49	(#48) IN DARE FROM 2009 TO 2019	43
50	(#48) IN NHSEED FROM 2009 TO 2019	12
51	(#48) IN HTA FROM 2009 TO 2019	19

H.1.1.4 Source: NHS Economic Evaluation Database (NHS EED)

Table 120 HRQoL SLR search details (NHS EED)

	Original SLR
Interface / URL:	CRD database
Database coverage dates:	Bibliographic records were published on NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014
Search date:	30/01/19
Retrieved records:	12

Table 121 HRQoL SLR search strategy (NHS EED)

#	Searches	Results
1	((MeSH DESCRIPTOR Renal Insufficiency EXPLODE ALL TREES	729
2	(((MeSH DESCRIPTOR kidney diseases) AND ((chronic or end-stage* or endstage* or final stage*))))	86
3	(((((chronic* or progressiv*) adj5 (kidney* or renal* or nephropath*)))))	571
4	(((((kidney* or renal* or nephropath*) adj5 (chronic* or progressiv*)))))	588
5	(((((kidney* or renal* or nephropath*) adj3 fail*))))	859
6	((((fail* adj3 (kidney* or renal* or nephropath*)))))	171
7	(((((kidney* or renal* or nephropath*) adj3 insufficien*))))	326
8	((((insufficien* adj3 (kidney* or renal* or nephropath*)))))	18
9	(((((endstage* or end-stage*) adj5 (kidney* or renal or nephropath*)))))	357
10	(((((kidney* or renal or nephropath*) adj5 (endstage* or end-stage*)))))	43
11	((((final stage* adj5 (kidney* or renal* or nephropath*)))))	0

#	Searches	Results
12	(((((kidney* or renal* or nephropath*) adj5 final stage*))))	0
13	(((((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney* or renal* or nephropath*)))))	12
14	(((((kidney* or renal* or nephropath*) adj5 (stage 3 or stage iii or stage three or stage3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage ivor stage 1v or stage four or stage 5 or stage v or stage five)))))	11
15	(((((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney* or renal* or nephropath*)))))	0
16	(((((kidney* or renal* or nephropath*) adj5 (stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev)))))	0
17	((((early adj5 (kidney* or renal* or nephropath*)))))	49
18	(((((kidney* or renal* or nephropath*) adj5 early))))	17
19	(((((kidney* or renal* or nephropath*) adj3 injur*))))	192
20	((((injur* adj3 (kidney* or renal* or nephropath*)))))	15
21	((((CKF or CKD or CRF)) OR (CRD):TI))	114
22	((((ESKD or ESRD or ESKF or ESRF))))	158
23	((MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES))	881
24	((MeSH DESCRIPTOR Dialysis))	14
25	(MeSH DESCRIPTOR Hemodialysis Units, Hospital)	14
26	(MeSH DESCRIPTOR Kidneys, Artificial)	3
27	((((dialys* or predialys* or dialyz* or predialyz* or dialytic* or predialytic* or dopps*))))	920
28	((((hemodialy* or haemodialy*))))	456
29	((((prehemodialy* or prehaemodialy*))))	0
30	(MeSH DESCRIPTOR Hemofiltration EXPLODE ALL TREES)	50
31	(MeSH DESCRIPTOR Ultrafiltration)	15
32	((((hemofiltra* or hemo-filtra* or hemodiafiltra* or hemo-diafiltra* or haemofiltra* or haemo-filtra* or haemodiafiltra* or haemo-diafiltra*))))	73
33	((((ultrafiltra* or ultra-filtra* or biofiltra* or bio-filtra*))))	30
34	(((((kidney* or renal*) adj4 (transplant* or graft* or allograft* or replac*)))))	702
35	(((((transplant* or graft* or allograft* or replac*) adj4 (kidney* or renal*)))))	181
36	(((((artificial* or extracorporeal or extra-corporeal) adj3 (renal* or kidney*)))))	11
37	(((((renal* or kidney*) adj3 (artificial* or extracorporeal or extra-corporeal)))))	6
38	((((CAPD or CCPD or APD))))	29
39	(MeSH DESCRIPTOR glomerular filtration rate)	92
40	(((((low or reduc*) adj4 (gfr or egfr or glomerular filtration rate*)))))	17
41	(((((gfr or egfr or glomerular filtration rate*) adj4 (low or reduc*)))))	4
42	((MeSH DESCRIPTOR diabetic nephropathies))	113
43	((((diabetic kidney disease* or diabetic renal disease* or diabetic nephropath*))))	150

#	Searches	Results
44	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43))	2450
45	(MeSH DESCRIPTOR Anemia EXPLODE ALL TREES)	380
46	((((anemi* or anaemi*))))	731
47	(#45 OR #46)	791
48	(#44 AND #47)	138
49	(#48) IN DARE FROM 2009 TO 2019	43
50	(#48) IN NHSEED FROM 2009 TO 2019	12

H.1.1.5 Source: Database of Abstracts of Reviews of Effects (DARE)

Table 122 HRQoL SLR search details (DARE)

	Original SLR
Interface / URL:	CRD database
Database coverage dates:	Bibliographic records were published on DARE until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014
Search date:	30/01/19
Retrieved records:	43

Table 123 HRQoL SLR search strategy (DARE)

#	Searches	Results
1	((MeSH DESCRIPTOR Renal Insufficiency EXPLODE ALL TREES))	**729**
2	(((MeSH DESCRIPTOR kidney diseases) AND ((chronic or end-stage* or endstage*or final stage*))))	86
3	(((((chronic* or progressiv*) adj5 (kidney* or renal* or nephropath*)))))	571
4	(((((kidney* or renal* or nephropath*) adj5 (chronic* or progressiv*)))))	588
5	(((((kidney* or renal* or nephropath*) adj3 fail*))))	859
6	((((fail* adj3 (kidney* or renal* or nephropath*)))))	171
7	(((((kidney* or renal* or nephropath*) adj3 insufficien*))))	326
8	((((insufficien* adj3 (kidney* or renal* or nephropath*)))))	18
9	(((((endstage* or end-stage*) adj5 (kidney* or renal or nephropath*)))))	357
10	(((((kidney* or renal or nephropath*) adj5 (endstage* or end-stage*)))))	43
11	((((final stage* adj5 (kidney* or renal* or nephropath*)))))	0
12	(((((kidney* or renal* or nephropath*) adj5 final stage*))))	0
13	(((((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney* or renal* or nephropath*)))))	12
14	(((((kidney* or renal* or nephropath*) adj5 (stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb	11

#	Searches	Results
	or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five)))))	
15	(((((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney* or renal* or nephropath*)))))	0
16	(((((kidney* or renal* or nephropath*) adj5 (stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev)))))	0
17	((((early adj5 (kidney* or renal* or nephropath*)))))	49
18	((((kidney* or renal* or nephropath*) adj5 early))))	17
19	((((kidney* or renal* or nephropath*) adj3 injur*))))	192
20	((((injur* adj3 (kidney* or renal* or nephropath*)))))	15
21	((((CKF or CKD or CRF)) OR (CRD):TI))	114
22	((((ESKD or ESRD or ESKF or ESRF))))	158
23	((MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES))	881
24	((MeSH DESCRIPTOR Dialysis))	14
25	(MeSH DESCRIPTOR Hemodialysis Units, Hospital)	14
26	(MeSH DESCRIPTOR Kidneys, Artificial)	3
27	((((dialys* or predialys* or dialyz* or predialyz* or dialytic* or predialytic* or dopps*))))	920
28	((((hemodialy* or haemodialy*))))	456
29	((((prehemodialy* or prehaemodialy*))))	0
30	(MeSH DESCRIPTOR Hemofiltration EXPLODE ALL TREES)	50
31	(MeSH DESCRIPTOR Ultrafiltration)	15
32	((((hemofiltra* or hemo-filtra* or hemodiafiltra* or hemo-diafiltra* or haemofiltra* or haemo-filtra* or haemodiafiltra* or haemo-diafiltra*))))	73
33	((((ultrafiltra* or ultra-filtra* or biofiltra* or bio-filtra*))))	30
34	(((((kidney* or renal*) adj4 (transplant* or graft* or allograft* or replac*)))))	702
35	(((((transplant* or graft* or allograft* or replac*) adj4 (kidney* or renal*)))))	181
36	(((((artificial* or extracorporeal or extra-corporeal) adj3 (renal* or kidney*)))))	11
37	(((((renal* or kidney*) adj3 (artificial* or extracorporeal or extra-corporeal)))))	6
38	((((CAPD or CCPD or APD))))	29
39	(MeSH DESCRIPTOR glomerular filtration rate)	92
40	(((((low or reduc*) adj4 (gfr or egfr or glomerular filtration rate*)))))	17
41	(((((gfr or egfr or glomerular filtration rate*) adj4 (low or reduc*)))))	4
42	((MeSH DESCRIPTOR diabetic nephropathies))	113
43	((((diabetic kidney disease* or diabetic renal disease* or diabetic nephropath*))))	150
44	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43))	2450
45	(MeSH DESCRIPTOR Anemia EXPLODE ALL TREES)	380

#	Searches	Results
46	((((anemi* or anaemi*))))	731
47	(#45 OR #46)	791
48	(#44 AND #47)	138
49	(#48) IN DARE FROM 2009 TO 2019	43

H.1.1.6 Source: Econlit

Table 124 HRQoL SLR search details (Econlit)

	Original SLR	SLR Update
Interface / URL:	OvidSP	OvidSP
Database coverage dates:	1946 to January 28, 2019	2019 to March 2, 2021
Search date:	30/01/19	02/03/21
Retrieved records:	7	0

Table 125 HRQoL SLR search strategy (Econlit)

#	Searches	Results	Updated results
1	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).af.	21	21
2	((kidney$ or renal$ or nephropath$) adj3 fail$).af.	35	35
3	((kidney$ or renal$ or nephropath$) adj3 insufficien$).af.	3	3
4	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).af.	52	52
5	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).af.	0	0
6	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney$ or renal$ or nephropath$)).af.	0	0
7	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).af.	0	0
8	(early adj5 (kidney$ or renal$ or nephropath$)).af.	1	1
9	((kidney$ or renal$ or nephropath$) adj3 injur$).af.	3	3
10	(CKF or CKD or CRF or CRD).af.	66	66
11	(ESKD or ESRD or ESKF or ESRF).af.	33	33
12	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).af.	89	89
13	(hemodialy$ or haemodialy$).af.	31	31
14	(prehemodialy$ or prehaemodialy$).af.	0	0
15	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemofiltra$ or haemodiafiltra$ or haemo-diafiltra$).af.	1	1
16	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).af.	6	6
17	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).af.	101	101

#	Searches	Results	Updated results
18	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).af.	0	0
19	(CAPD or CCPD or APD).af.	14	14
20	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).af.	1	1
21	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).af.	3	3
22	or/1-21	321	321
23	(anemi$ or anaemi$).af.	195	195
24	22 and 23	10	10
25	limit 24 to yr="2009 -Current"	7	0

H.1.1.7 Source: PsycINFO

Table 126 HRQoL SLR search details (PsycINFO)

	Original SLR	SLR Update
Interface / URL:	OvidSP	OvidSP
Database coverage dates:	1806 to January Week 3 2019	2019 to January 29, 2021
Search date:	30/01/19	29/01/21
Retrieved records:	81	10

Table 127 HRQoL SLR search strategy (PsycINFO)

#	Searches	Results	Updated results
1	Kidney Diseases/	2016	2235
2	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	1412	1615
3	((kidney$ or renal$ or nephropath$) adj3 fail$).ti,ab,id.	1256	1349
4	((kidney$ or renal$ or nephropath$) adj3 insufficien$).ti,ab,id.	262	281
5	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).ti,ab,id.	1082	1206
6	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	0	0
7	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	32	35
8	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	0	0
9	(early adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	76	82
10	((kidney$ or renal$ or nephropath$) adj3 injur$).ti,ab,id.	181	206
11	(CKF or CKD or CRF or CRD).ti,ab,id.	3317	3629
12	(ESKD or ESRD or ESKF or ESRF).ti,ab,id.	464	523
13	hemodialysis/ or dialysis/	1758	1947
14	[Organ Transplantation/ and (Kidneys/ or (kidney$ or renal$ or nephropath$)).ti,ab,id.]	0	0

#	Searches	Results	Updated results
15	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).ti,ab,id.	2511	2695
16	(hemodialy$ or haemodialy$).ti,ab,id.	1504	1670
17	(prehemodialy$ or prehaemodialy$).ti,ab,id.	2	3
18	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemofiltra$ or haemodiafiltra$ or haemo-diafiltra$).ti,ab,id.	14	15
19	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).ti,ab,id.	48	51
20	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).ti,ab,id.	1004	1105
21	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).ti,ab,id.	19	19
22	(CAPD or CCPD or APD).ti,ab,id.	1014	1097
23	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).ti,ab,id.	69	71
24	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).ti,ab,id.	79	87
25	or/1-24	10310	11202
26	anemia/	665	733
27	(anemi$ or anaemi$).ti,ab,id.	2052	2231
28	or/26-27	2103	2284
29	25 and 28	117	130
30	remove duplicates from 29	117	130
31	limit 30 to yr="2009 -Current"	81	10

H.1.1.8 Source: PubMed

Table 128 HRQoL SLR search details (PubMed)

	Original SLR
Interface / URL:	https://www.ncbi.nlm.nih.gov/pubmed/
Database coverage dates:	Information not found
Search date:	23/01/19
Retrieved records:	421

Table 129 HRQoL SLR search strategy (PubMed)

#	Searches	Results
1	Search Renal Insufficiency[mh]	158910
2	Search kidney diseases [mh:noexp] AND (chronic[tiab] OR end-stage*[tiab] OR endstage*[tiab] OR final stage*[tiab])	12986
3	Search ((chronic*[tiab] OR progressiv*[tiab]) AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	143138
4	Search ((kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]) AND fail*[tiab])	137828
5	Search ((kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]) AND insufficien*[tiab])	30037
6	Search ((endstage*[tiab] OR end-stage*[tiab]) AND (kidney*[tiab] OR renal[tiab] OR nephropath*[tiab]))	41880

#	Searches	Results
7	Search (final stage*[tiab] AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	192
8	Search ((stage 3[tiab] OR stage iii[tiab] OR stage three[tiab] OR stage 3a[tiab] OR stage iiia[tiab] OR (stage[tiab] AND threea[tiab]) OR stage 3b[tiab] OR stage iiib[tiab] OR (stage[tiab] AND threeb[tiab]) OR stage 4[tiab] OR stage iv[tiab] OR (stage[tiab] AND 1v[tiab]) OR stage four[tiab] OR stage 5[tiab] OR stage v[tiab] OR stage five[tiab]) AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	6436
9	Search ((stage3[tiab] OR stage3a[tiab] OR stage3b[tiab] OR stageiii[tiab] OR stageiiia[tiab] OR stageiiib[tiab] OR stage4[tiab] OR stageiv[tiab] OR stage1v[tiab] OR stage5[tiab] OR stagev[tiab]) AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	7
10	Search (early[tiab] AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	65025
11	Search (((kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]) AND injur*[tiab]))	58977
12	Search (CKF[tiab] OR CKD[tiab] OR CRF[tiab] OR CRD[tiab])	41304
13	Search (ESKD[tiab] OR ESRD[tiab] OR ESKF[tiab] OR ESRF[tiab])	16712
14	Search Renal Replacement Therapy [mh]	194294
15	Search "Dialysis" [mh:noexp]	12505
16	Search Hemodialysis Units, Hospital [mh:noexp]	1361
17	Search Kidneys, Artificial[mh:noexp]	4301
18	Search (dialys*[tiab] OR predialys*[tiab] OR dialyz*[tiab] OR predialyz*[tiab] OR dialytic*[tiab] OR predialytic*[tiab] OR dopps*[tiab])	116181
19	Search (hemodialy*[tiab] OR haemodialy*[tiab])	73664
20	Search (prehemodialy*[tiab] OR prehaemodialy*[tiab])	81
21	Search "Hemofiltration" [mh]	6491
22	Search "Ultrafiltration" [mh:noexp]	9770
23	Search (hemofiltra*[tiab] OR hemo-filtra*[tiab] OR hemodiafiltra*[tiab] OR hemodiafiltra*[tiab] OR haemofiltra*[tiab] OR haemo-filtra*[tiab] OR haemodiafiltra*[tiab] OR haemodiafiltra*[tiab])	6589
24	Search (ultrafiltra*[tiab] OR ultra-filtra*[tiab] OR biofiltra*[tiab] OR bio-filtra*[tiab])	17994
25	Search ((kidney*[tiab] OR renal*[tiab]) AND (transplant*[tiab] OR graft*[tiab] OR allograft*[tiab] OR replac*[tiab]))	137007
26	Search ((artificial*[tiab] OR extracorporeal[tiab] OR extra-corporeal[tiab]) AND (renal*[tiab] OR kidney*[tiab]))	10918
27	Search (CAPD[tiab] OR CCPD[tiab] OR APD[tiab])	11176
28	Search glomerular filtration rate[mh:noexp]	40772
29	Search ((low[tiab] OR reduc*[tiab]) AND (gfr[tiab] OR egfr[tiab] OR glomerular filtration rate*[tiab]))	28400
30	Search diabetic nephropathies[mh:noexp]	23654
31	Search (diabetic kidney disease*[tiab] OR diabetic renal disease*[tiab] OR diabetic nephropath*[tiab])	18871
32	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)	635744
33	Search "Anemia"[mh]	154482

#	Searches	Results
34	Search (anemi*[tiab] OR anaemi*[tiab])	145660
35	Search (#33 OR #34)	216144
36	Search (#32 AND #35)	21378
37	Search "Economics"[Mesh:NoExp]	26987
38	Search "Costs and Cost Analysis"[Mesh]	221299
39	Search economics, dental[mh:noexp]	1901
40	Search "economics, hospital"[mh]	23302
41	Search economics, medical[mh:noexp]	8989
42	Search economics, nursing[mh:noexp]	3986
43	Search economics, pharmaceutical[mh:noexp]	2835
44	Search (economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab])	718276
45	Search (expenditure*[tiab] NOT energy[tiab])	27046
46	Search value for money[tiab]	1408
47	Search budget*[tiab]	26888
48	Search (#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47)	851814
49	Search (energy cost[tiab] OR oxygen cost[tiab])	3823
50	Search metabolic cost[tiab]	1297
51	Search (energy expenditure[tiab] OR oxygen expenditure[tiab])	23310
52	Search (#49 OR #50 OR #51)	27464
53	Search (#48 NOT #52)	845662
54	Search (burden*[ti] OR resource*[ti])	63233
55	Search (burden*[tiab] AND (illness*[tiab] OR disease*[tiab] OR sickness*[tiab] OR treatment*[tiab] OR therap*[tiab]))	118082
56	Search (resource*[tiab] AND (use*[tiab] OR usage[tiab] OR utilit*[tiab] OR utilis*[tiab] OR utiliz*[tiab]))	66356
57	Search Office visits/sn[mh:noexp] OR Office visits/td[mh:noexp] OR Office visits/ut[mh:noexp]	2771
58	Search (visit[tiab] OR visits[tiab] OR visited[tiab])	181847
59	Search appointment*[tiab]	20590
60	Search "Hospitalisation"[mesh:noexp]	96508
61	Search (hospitalisation*[tiab] OR hospitalisation*[tiab] OR hospitalised[tiab] OR hospitalised[tiab])	216709
62	Search (admission*[tiab] OR readmission*[tiab] OR admitted[tiab] OR readmitted[tiab])	345633
63	Search "Length of Stay"[mesh:noexp] or los[tiab]	99934
64	Search hospital stay*[tiab]	73493
65	Search (bed[tiab] AND day*[tiab])	17335
66	Search ((days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND hospital*[tiab])	376775
67	Search ((days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND (stay[tiab] OR stays[tiab] OR stayed[tiab]))	127483

#	Searches	Results
68	Search ((days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND (discharge[tiab] OR discharged[tiab] OR home[tiab] OR homes[tiab]))	141991
69	Search (#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68)	1253132
70	Search Quality-adjusted Life Years [mh:noexp]	10664
71	Search (quality adjusted[tiab] OR adjusted life year*[tiab])	14326
72	Search (qaly*[tiab] OR qald*[tiab] OR qale*[tiab] OR qtime*[tiab])	9242
73	Search ((illness state*[tiab] OR health state*[tiab]))	5741
74	Search (hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab])	1333
75	Search (multiattribute*[tiab] OR multi attribute*[tiab])	807
76	Search (utility[tiab] AND (score*[tiab] OR valu*[tiab] OR health*[tiab] OR cost*[tiab] OR measur*[tiab] OR disease*[tiab] OR mean[tiab] OR gain[tiab] OR gains[tiab] OR index*[tiab]))	108914
77	Search utilities[tiab]	6314
78	Search (eq-5d[tiab] OR eq5d[tiab] OR eq-5[tiab] OR eq5[tiab] OR euro qual[tiab] OR euroqual[tiab] OR euro qual5d[tiab] OR euroqual5d[tiab] OR euro qol[tiab] OR euroqol[tiab] OR euro qol5d[tiab] OR euroqol5d[tiab] OR euro quol[tiab] OR euroquol[tiab] OR euro quol5d[tiab] OR euroquol5d[tiab] OR (eur[tiab] AND qol[tiab]) OR eurqol[tiab] OR (eur[tiab] AND qol5d[tiab]) OR (eur[tiab] AND qol5d[tiab]) OR euroqul[tiab] OR euroqul5d[tiab] OR (european[tiab] AND quality of life[tiab]) OR european qol[tiab])	15520
79	Search ((euro[tiab] OR european[tiab]) AND (5 d[tiab] OR 5d[tiab] OR 5 dimension*[tiab] OR 5dimension*[tiab] OR 5 domain*[tiab] OR 5domain*[tiab]))	1045
80	Search (sf36*[tiab] OR sf 36*[tiab] OR (sf[tiab] AND thirtysix[tiab]) OR (sf[tiab] AND thirty six[tiab]))	20206
81	Search (time trade off*[tiab] OR time tradeoff*[tiab] OR tto[tiab] OR timetradeoff*[tiab])	1721
82	Search "quality of life"[mesh:noexp] AND ((quality of life[tiab] OR qol[tiab]) AND (score*[tiab] OR measure*[tiab]))	65203
83	Search "quality of life"[mesh:noexp] AND "Economics"[sh:noexp]	9232
84	Search "quality of life"[mesh:noexp] AND (health[tiab] AND status[tiab])	15270
85	Search (quality of life[tiab] OR qol[tiab]) AND "Cost-Benefit Analysis"[mesh:noexp]	5501
86	Search ((qol[ti] OR hrqol[ti] OR quality of life[ti]) OR "quality of life"[majr:noexp]) AND ((qol[tiab] OR hrqol*[tiab] OR quality of life[tiab]) AND (increas*[tiab] OR decrease*[tiab] OR improv*[tiab] OR declin*[tiab] OR reduc*[tiab] OR high*[tiab] OR low*[tiab] OR effect[tiab] OR effects[tiab] OR worse[tiab] OR score[tiab] OR scores[tiab] OR change*[tiab] OR impact*[tiab] OR impacted[tiab] OR deteriorat*[tiab]))	67713
87	Search "Cost-Benefit Analysis"[mesh:noexp] AND (cost-effectiveness ratio*[tiab] AND (perspective*[tiab] OR life expectanc*[tiab]))	2959
88	Search "quality of life"[majr:noexp] AND (quality of life[ti] OR qol[ti])	48169
89	Search "quality of life"[mesh:noexp] AND ((quality of life[tiab] OR qol[tiab]) AND (improv*[tiab] OR chang*[tiab]))	58321
90	Search "quality of life"[mesh:noexp] AND health-related quality of life[tiab]	27567
91	Search "models,economic"[mesh:noexp]	9129

#	Searches	Results
92	Search (#70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91)	266874
93	Search (utility loss*[tiab] OR disutilit*[tiab] OR short form*[tiab] OR shortform*[tiab] OR SF-12[tiab] OR SF12[tiab])	31941
94	Search (15-D[tiab] OR 15D[tiab] OR SF-6[tiab] OR SF6[tiab] OR SF-6D[tiab] OR SF6D[tiab])	6963
95	Search discrete choice*[tiab]	1679
96	Search choice experiment*[tiab]	2372
97	Search (dce[tiab] or dces[tiab])	5118
98	Search standard gamble*[tiab]	813
99	Search sg[tiab]	8896
100	Search (#92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99)	301702
101	Search (#36 AND (#53 OR #69))	3741
102	Search (#36 AND #100)	562
103	Search (#101 OR #102)	4128
104	Search animals [mh] NOT humans [mh:noexp]	4539198
105	Search (news[pt] or editorial[pt] or case reports[pt]) or case report[ti]	2645168
106	Search (#103 NOT (#104 OR #105))	3338
107	Search medline[sb]	25524362
108	Search (#106 NOT #107)	460
109	Search (#106 NOT #107) Filters: Publication date from 2009/01/01 to 2019/12/31	421

H.1.2 Study selection

The eligibility criteria for the utility review is outlined in Table 130.

Table 130: Eligibility criteria applied in utility review

	Inclusion criteria	Exclusion criteria
Population	• Studies reporting data for adult (≥18 years of age) patients with CKD (stage 3-5) with anaemia were eligible for inclusion in this review	• Patients aged under 18 • Studies of mixed populations including anaemic and non-anaemic CKD patients in which data for the anaemic patients were not presented separately • Populations of patients who have already undergone a renal transplant
Interventions	• Any or none	• Any or none
Comparators	No restriction on comparator	-
Outcomes	• Studies reporting on one of these preference-based quality of life	• Studies reporting other relevant outcomes were not

	Inclusion criteria	Exclusion criteria
	measures, utilities and disutilities for the population of interest: ○ EuroQol five dimensions (EQ-5D) data (both EQ-5D 3L and EQ-5D 5L) ○ Short-Form (SF)-36, 6D and 15D ○ Health Utilities Index (HUI) ○ Discrete choice experiments, time trade off or standard gamble ○ Any other preference-based utility data • Studies reporting utilities mapped from other tools • Studies reporting on the mapping of quality of life/patient reported outcome measures to utility instruments	eligible
Study design	• The following types of study were eligible for inclusion: ○ Economic evaluations (cost effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses) ○ HTAs ○ Published models ○ Randomised controlled trials (RCTs) ○ Reports of utility elicitation exercises ○ Reports of utility validation exercises ○ Mapped values studies • Studies published as abstracts or conference presentations were eligible for inclusion if adequate information was provided. Studies reporting data used in economic evaluations were also followed-up and identified	• News items, editorials and case reports were excluded from the searches since they were unlikely to contain enough data to extract and use in the reviews
Language restrictions	No language restrictions	
Date of publication	• Full papers published in the last 10 years (2009 to date) • Conference abstracts published in the last 5 years (2014 to date).	
Countries/global reach	Studies undertaken in European countries, Turkey, South Africa, Israel and Russia	• Studies undertaken in other countries were not eligible

Abbreviations: CKD: chronic kidney disease; EQ-5D: EuroQol five dimensions; HTA: health technology assessment; HUI: health utilities index; RCT: randomised controlled trial; SF: short form.

H.2 Results

The PRISMA diagram below in Figure 33 and Figure 34 shows the number of articles screened at abstract and full text stage, and the number of included and excluded articles based on the PICOS criteria.

Figure 33: PRISMA diagram to show the number of articles included in the HRQoL evidence (original SLR)

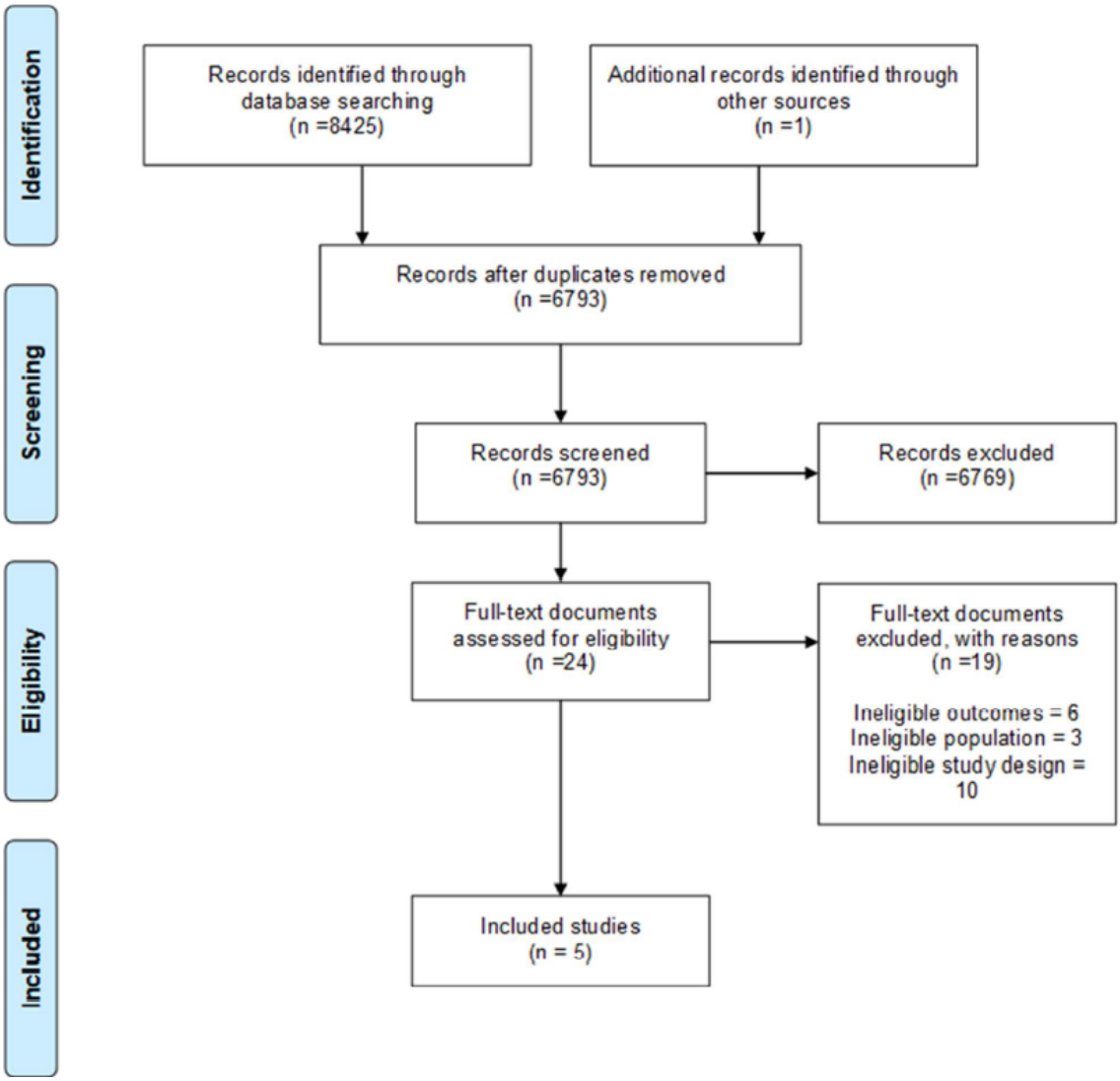
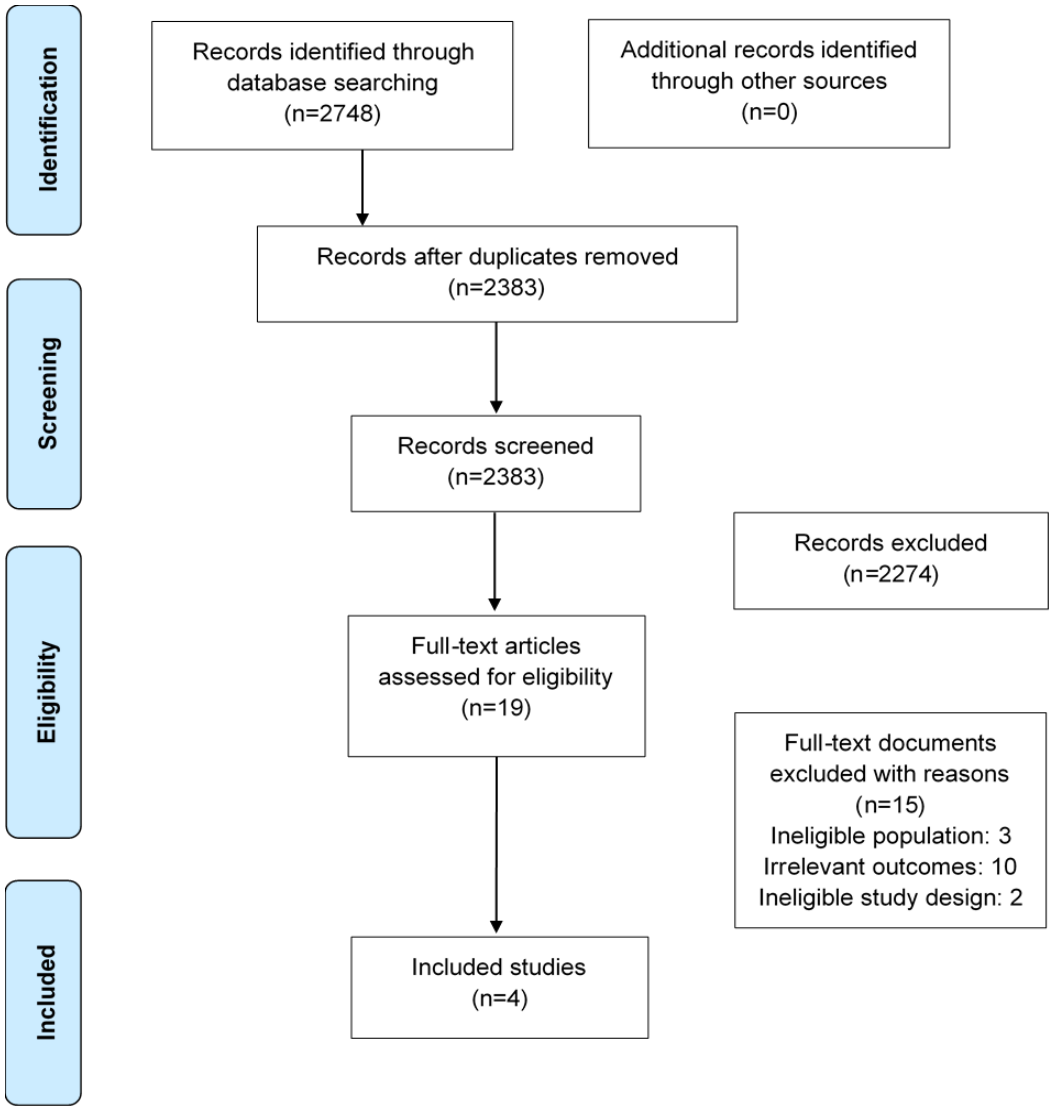


Figure 34: PRISMA diagram to show the number of articles included in the HRQoL evidence (SLR update)



The summary of included studies is presented in Table 131.

Table *131*: Summary of included studies

	Covic 2017 (159)	Eriksson 2016 (160)	Maoujoud 2016 (149)	van Haalen 2018 (161)	van Haalen 2018 (162)	Van Haalen 2020 (163)	Touzot 2020 (164)	Gernone 2020 (165)	Bondarchuk 2019 (166)
Population in which the health effects were measured	CKD stage 3 or 4 with anaemia	CKD stage 3, 4 and dialysis, with anaemia	Chronic haemodialysis patients with anaemia	Dialysis dependent CKD. Non-dialysis dependent CKD (not extracted)	CKD stage 3a, 3b, 4 or dialysis	CKD patients with and without anaemia	Adult haemodialysis patients	Stable haemodialysis patients with anaemia	Patients with EsRD undergoing haemodialysis
Information on recruitment	Those who had previously enrolled to take part in a survey of clinical practice	Survey of patients	Participants in a prospective observational study	Survey of patients	Survey of patients	Survey of patients	Participants in a pilot prospective observational study	Participants in a prospective observational case-control study	NR
Interventions and comparators	NA	NA	Intervention: continuous erythropoietin receptor activator once monthly Intervention: Epoetin Beta thrice weekly Comparator: red blood cell transfusion	NA	NA	NA	Oral iron and IV iron	Haemodialysis eXpanded, HDx and High-Flux filter	NA
Sample size	1,223	864	NR	4583	2233	2622	9	11	30
Response rates	531/1,223 (43.4%*) completed the EQ-5D	Total population: 46%* Anaemia: NR	NR	NR	NR	All Hb levels: 2319 (88.44%*) Hb <10 g/dL: 296 (98.34%*) Hb 10-12 g/dL: 1166 (95.89%*) Hb >12 g/dL: 857 (96.18%*)	NR	NR	NR

	Covic 2017 (159)	Eriksson 2016 (160)	Maoujoud 2016 (149)	van Haalen 2018 (161)	van Haalen 2018 (162)	Van Haalen 2020 (163)	Touzot 2020 (164)	Gernone 2020 (165)	Bondarchuk 2019 (166)
Description of health states	CKD stage 3 or 4 with anaemia	CKD stage 3 CKD stage 4 Dialysis patients	Dialysis patient receiving red blood cell transfusion Dialysis patient receiving erythropoiesis stimulating agent: Hb 9-10.5 g/dL Hb 10.5–12 g/dL Hb >12 g/dL	Dialysis dependent CKD: Hb <10 g/dL Hb 10-12 g/dL Hb >12 g/dL	CKD stage 3a: Hb <10 g/dL Hb 10-12 g/dL Hb >12 g/dL CKD stage 3b: Hb <10 g/dL Hb 10-12 g/dL Hb >12 g/dL CKD stage 4: Hb <10 g/dL Hb 10-12 g/dL Hb >12 g/dL CKD and dialysis: Hb <10 g/Dl Hb 10-12 g/dL Hb >12 g/dL	NDD and DD CKD patients Haemoglobin level: Hb <8 g/dL; Hb 8–10 g/dL; Hb 10–12 g/dL; Hb >12 g/dL	CKD Dialysis No Erythropoietin	Dialysis + red blood cell transfusion Dialysis + erythropoiesis stimulating agent	Dialysis + red blood cell transfusion Dialysis + erythropoiesis stimulating agent
Appropriateness of health states given the condition and treatment pathway	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Method of elicitation	EQ-5D-3L	EQ-5D-3L	NR	EQ-5D-3L	EQ-5D-3L	EQ-5D-3L; KDQOL-36; WPAI	SF-36	SF-36	FACT
Method of valuation – the scaling method of utility assessment adopted	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mapping	NR	None used	NR	NR	NR	NR	NR	NR	NR
Uncertainty around values	Standard deviation	Standard deviation	NR	NR	NR	Standard deviation	Standard deviation	Standard deviation	NR
Consistency with reference case	Consistent	Consistent	Consistent	Consistent	Consistent	Consistent	Consistent	Consistent	Consistent

Notes: * reviewer calculated data

Abbreviations: CKD: chronic kidney disease; g/dl: grams per decilitre; Hb: haemoglobin; NR: not reported

Nine studies were identified as eligible for the SLR (Table 132). Five studies were full publications and four studies were reported only as abstracts.

Five multinational studies reported health utility scores for patients with CKD and anaemia using the EQ-5D-3L questionnaire. These four studies each analysed data from the Adelphi CKD Disease-Specific Programme, a multinational cross-sectional survey of clinical practice (167, 168). The Adelphi Disease Specific Programmes are large observational studies for a range of common chronic conditions. Participating physicians provide information for a specific number of consecutive patients, and these patients are invited to fill out a self-completion form, which includes a quality of life assessment.

One study (149) was an economic evaluation undertaken in Morocco; this did not report the method of utility elicitation. The remaining three studies (164-166) were observational studies conducted in France (164), Italy (165) and Russian Federation (166). Two studies (164, 165) used SF-36 and one study (166) used FACT questionnaire for utility elicitation.

Table 132: Overview of utility data for CKD in anaemia

Reference	Health state	Mean utility values (SD)	Values used in the economic model
Covic 2017 (159)	No cardiovascular conditions	0.83 (0.22)	None
	With cardiovascular conditions	0.69 (0.30)	
Eriksson 2016 (169)	CKD stage 3	0.78 (0.29)	None
	CKD stage 4	0.71 (0.28)	
	Dialysis patients	0.70 (0.32)	
	Total	0.72 (0.31)	
Maoujoud 2016 (149)	Dialysis patient receiving red blood cell transfusion:	0.48	None
	Dialysis patient receiving erythropoiesis stimulating agent: Hb 9-10.5 g/dL	0.63	
	Dialysis patient receiving erythropoiesis stimulating agent: Hb 10.5–12 g/dL	0.64	
	Dialysis patient receiving erythropoiesis stimulating agent: Hb >12 g/dL	0.65	
van Haalen	Dialysis dependent CKD: Hb<10 g/dL	0.7	None

Reference	Health state	Mean utility values (SD)	Values used in the economic model
2018 (161)	Dialysis dependent CKD: Hb 10-12 g/dL	0.73	
	Dialysis dependent CKD: Hb >12 g/dL	0.77	
van Haalen 2018 (162)	NDD CKD stage 3a: Hb<10 g/dL	0.81	None
	NDD CKD stage 3a: Hb 10-12 g/dL	0.84	
	NDD CKD stage 3a: Hb >12 g/dL	0.9	
	NDD CKD stage 3b: Hb<10 g/dL	0.81	
	NDD CKD stage 3b: Hb 10-12 g/dL	0.81	
	NDD CKD stage 3b: Hb >12 g/dL	0.84	
	NDD CKD stage 4: Hb<10 g/dL	0.73	
	NDD CKD stage 4: Hb 10-12 g/dL	0.78	
	NDD CKD stage 4: Hb >12 g/dL	0.84	
	CKD and dialysis: Hb<10 g/dL	0.68	
	CKD and dialysis: Hb 10-12 g/dL	0.71	
	CKD and dialysis: Hb >12 g/dL	0.71	
Van Haalen 2020 (163)	NDD CKD stage 3a: Hb<10 g/dL (N=32)	0.81(0.28)	None
	NDD CKD stage 3a: Hb 10-12 g/dL (N=99)	0.83 (0.23)	
	NDD CKD stage 3a: Hb >12 g/dL (N=194)	0.89 (0.18)	
	NDD CKD stage 3a: All Hb levels (N=325)	0.87 (0.21)	
	NDD CKD stage 3b: Hb<10 g/dL (N= 34)	0.76 (0.30)	
	NDD CKD stage 3b: Hb 10-12 g/dL (N=190)	0.80 (0.27)	
	NDD CKD stage 3b: Hb >12 g/dL (N=232)	0.83 (0.24)	
	NDD CKD stage 3b: All Hb levels (N=456)	0.82 (0.26)	
	NDD CKD stage 4: Hb<10 g/dL (N=93)	0.66 (0.34)	
	NDD CKD stage 4: Hb 10-12 g/dL (N=366)	0.76 (0.24)	
	NDD CKD stage 4: Hb >12 g/dL (N=220)	0.81 (0.23)	
	NDD CKD stage 4: All Hb levels (N= 679)	0.76 (0.26)	
	NDD CKD stage 5: Hb<10 g/dL (N=4)	0.17 (0.45)	
	NDD CKD stage 5: Hb 10-12 g/dL (N=20)	0.83 (0.21)	
	NDD CKD stage 5: Hb >12 g/dL (N=6)	0.74 (0.54)	
	NDD CKD stage 5: All Hb levels (N=30)	0.72 (0.39)	
	NDD CKD All stages: Hb<10 g/dL (N= 163)	0.70 (0.34)	

Reference	Health state	Mean utility values (SD)	Values used in the economic model
	NDD CKD All stages: Hb 10-12 g/dL (N=675)	0.78 (0.25)	
	NDD CKD All stages: Hb >12 g/dL (N=652)	0.84 (0.22)	
	NDD CKD All stages: All Hb levels (N=1490)	0.80 (0.25)	
	DD CKD: All Hb levels (N=829)	0.70 (0.31)	
	DD CKD: Hb<10 g/dL (N=133)	0.71 (0.29)	
	DD CKD: Hb 10-12 g/dL (N=491)	0.69 (0.32)	
	DD CKD: Hb >12 g/dL (N=205)	0.73 (0.29)	
	NDD CKD stage 3a: Hb<10 g/dL (N=31)	43.2 (11.5)	
	NDD CKD stage 3a: Hb 10-12 g/dL (N=96)	43.6 (9.5)	
	NDD CKD stage 3a: Hb >12 g/dL (N=181)	46.9 (9.0)	
	NDD CKD stage 3a: All Hb levels (N=308)	45.5 (9.6)	
	NDD CKD stage 3b: Hb<10 g/dL (N= 31)	40.2 (9.7)	
	NDD CKD stage 3b: Hb 10-12 g/dL (N=181)	42.7 (9.7)	
	NDD CKD stage 3b: Hb >12 g/dL (N=216)	43.8 (9.5)	
	NDD CKD stage 3b: All Hb levels (N=428)	43.1 (9.6)	
	NDD CKD stage 4: Hb<10 g/dL (N=86)	34.9 (9.4)	
	NDD CKD stage 4: Hb 10-12 g/dL (N=353)	38.6 (9.7)	
	NDD CKD stage 4: Hb >12 g/dL (N=211)	41.5 (9.9)	
	NDD CKD stage 4: All Hb levels (N= 650)	39.0 (9.9)	
	NDD CKD stage 5: Hb<10 g/dL (N=3)	25.2 (3.0)	
	NDD CKD stage 5: Hb 10-12 g/dL (N=18)	45.8 (7.3)	
	NDD CKD stage 5: Hb >12 g/dL (N=5)	45.4 (12.5)	
	NDD CKD stage 5: All Hb levels (N=26)	43.3 (10.3)	
	NDD CKD All stages: Hb<10 g/dL (N= 151)	37.5 (10.5)	
	NDD CKD All stages: Hb 10-12 g/dL (N=648)	40.7 (9.9)	
	NDD CKD All stages: Hb >12 g/dL (N=613)	43.9 (9.8)	
	NDD CKD All stages: All Hb levels (N=1412)	41.8 (10.1)	

Reference	Health state	Mean utility values (SD)	Values used in the economic model
	DD CKD: All Hb levels (N=799)	37.0 (9.9)	
	DD CKD: Hb<10 g/dL (N=124)	34.5 (9.8)	
	DD CKD: Hb 10-12 g/dL (N=468)	37.1 (9.8)	
	DD CKD: Hb >12 g/dL (N=207)	38.2 (10.3)	
	NDD CKD stage 3a: Hb<10 g/dL (N=31)	47.2 (11.1)	
	NDD CKD stage 3a: Hb 10-12 g/dL (N=96)	45.9 (8.9)	
	NDD CKD stage 3a: Hb >12 g/dL (N=181)	49.0 (9.2)	
	NDD CKD stage 3a: All Hb levels (N=308)	47.9 (9.4)	
	NDD CKD stage 3b: Hb<10 g/dL (N= 31)	47.5 (10.4)	
	NDD CKD stage 3b: Hb 10-12 g/dL (N=181)	46.6 (9.6)	
	NDD CKD stage 3b: Hb >12 g/dL (N=216)	48.9 (9.0)	
	NDD CKD stage 3b: All Hb levels (N=428)	47.8 (9.4)	
	NDD CKD stage 4: Hb<10 g/dL (N=86)	43.6 (10.8)	
	NDD CKD stage 4: Hb 10-12 g/dL (N=353)	44.5 (9.5)	
	NDD CKD stage 4: Hb >12 g/dL (N=211)	46.7 (9.6)	
	NDD CKD stage 4: All Hb levels (N= 650)	45.1 (9.7)	
	NDD CKD stage 5: Hb<10 g/dL (N=3)	32.7 (6.5)	
	NDD CKD stage 5: Hb 10-12 g/dL (N=18)	46.2 (8.9)	
	NDD CKD stage 5: Hb >12 g/dL (N=5)	45.5 (9.8)	
	NDD CKD stage 5: All Hb levels (N=26)	44.6 (9.6)	
	NDD CKD All stages: Hb<10 g/dL (N= 151)	44.9 (10.9)	
	NDD CKD All stages: Hb 10-12 g/dL (N=648)	45.3 (9.4)	
	NDD CKD All stages: Hb >12 g/dL (N=613)	48.2 (9.3)	
	NDD CKD All stages: All Hb levels (N=1412)	46.5 (9.7)	
	DD CKD: All Hb levels (N=799)	44.0 (10.5)	
	DD CKD: Hb<10 g/dL (N=124)	42.6 (10.2)	
	DD CKD: Hb 10-12 g/dL (N=468)	43.4 (10.6)	
	DD CKD: Hb >12 g/dL (N=207)	46.3 (10.2)	
	Haemodialysis patient receiving oral iron (N=9),	Physical Functioning: 40 (31) Role functioning/physical:	None

Reference	Health state	Mean utility values (SD)	Values used in the economic model
Touzot 2020 (164)	Baseline	40 (35) Role functioning/emotional: 57(47) Energy/Fatigue: 29 (22) Emotional Well-being: 41 (25) Social functioning: 60 (19) Pain: 45 (31) General Health: 39 (26)	
	Haemodialysis patient receiving oral iron (N=9), Three-months	Physical Functioning: 42 (24), p=0.77 Role functioning/physical: 38 (35), p=0.73 Role functioning/emotional: 48 (36), p=0.63 Energy/Fatigue: 36 (21), p=0.30 Emotional Well-being: 55 (19), p=0.13 Social functioning: 53 (20), p=0.29 Pain: 50 (33), p=0.37 General Health: 38 (14), p=0.90	
Gernone 2020 (165)	Haemodialysis using High-Flux filter (N=11)	ISFa: 27.3 (10.1) ISMb: 43.8 (14.2)	None
	Haemodialysis using Haemodialysis eXpanded, HDx filter (N=11)	ISFa: 40.2 (8.4), p = 0.0001 ISMb: 51.1 (9.8), p = 0.001	
Bondarchuk 2019 (166)	Haemodialysis patients receiving erythropoiesis stimulating therapy	Physical well-being: r = -0.45, p < 0.05 Emotional well-being: r = -0.39, p < 0.05 Anaemia: r = -0.51, p < 0.05	None

Abbreviations: CKD: chronic kidney disease; Hb: haemoglobin; NDD: non-dialysis dependent; SD: standard deviation.

Appendix I. Cost and healthcare resource identification, measurement and valuation

I.1 Identification of studies

A systematic literature review was undertaken to identify and review published resource use data associated with the treatment of patients with anaemia in CKD. Literature searches were conducted by an information specialist between 22nd January 2019. The search was subsequently updated between 27th January 2021 and 2nd March 2021 using similar search strategies to capture any recently published evidence.

I.1.1 Search Strategy

The following electronic databases were searched via the given platforms for resource use data:

- MEDLINE, MEDLINE In-Process and MEDLINE(R) Daily Epub Ahead of Print (via OvidSP)
- Embase (via OvidSP)
- EconLit (via OvidSP)
- PsycInfo
- ScHARRHud
- PubMed, original SLR
- Cost-Effectiveness Analysis (CEA) Registry, original SLR
- Database of Abstracts of Reviews of Effects (DARE), original SLR
- Health Technology Assessment (HTA), original SLR
- NHS Economic Evaluation Database (NHS EED), original SLR

Additional studies were identified by searching the following sources:

- The organisational website of NICE

- The following conferences were identified as highly relevant (for 2016, 2017 and 2018):
- European Renal Association - European dialysis and Transplant Association (ERA EDTA) Congress
- American Society of Nephrology (ASN) Kidney Week
- International Society of Pharmacoeconomics and Outcomes Research (ISPOR) conference
- ASN Kidney Week 2016, 2017 and 2018, original SLR

I.1.1.1 Source: Ovid MEDLINE(R)

Table 133 Cost and resource use SLR search details (Ovid MEDLINE®)

	Original SLR	SLR Update
Interface / URL:	OvidSP	OvidSP
Database coverage dates:	1946 to January 28, 2019	2019 to January 27, 2021
Search date:	30/01/19	07/01/21
Retrieved records:	1382	408

Table 134 Cost and resource use SLR search strategy (Ovid MEDLINE®)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	exp Renal Insufficiency/	159109	176735
2	kidney diseases/ and (chronic or end-stage$ or endstage$ or final stage$).ti,ab,kf.	12991	13838
3	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	93865	108145
4	((kidney$ or renal$ or nephropath$) adj3 fail$).ti,ab,kf.	98257	104808
5	((kidney$ or renal$ or nephropath$) adj3 insufficien$).ti,ab,kf.	23621	25051
6	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).ti,ab,kf.	40274	46114
7	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	59	67
8	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5(kidney$ or renal$ or nephropath$)).ti,ab,kf.	2225	2778
9	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	2	4
10	(early adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kf.	14420	16030
11	((kidney$ or renal$ or nephropath$) adj3 injur$).ti,ab,kf.	37563	48080
12	(CKF or CKD or CRF or CRD).ti,ab,kf.	41526	50075

#	Searches	Hits (Original SLR)	Hits (SLR Update)
13	(ESKD or ESRD or ESKF or ESRF).ti,ab,kf.	16852	19540
14	exp Renal Replacement Therapy/	194449	213627
15	Dialysis/	12513	12642
16	Hemodialysis Units, Hospital/	1362	1427
17	Kidneys, Artificial/	4302	4347
18	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).ti,ab,kf.	116762	126127
19	(hemodialy$ or haemodialy$).ti,ab,kf.	74064	80664
20	(prehemodialy$ or prehaemodialy$).ti,ab,kf.	81	86
21	exp Hemofiltration/	6491	6847
22	Ultrafiltration/	9780	10185
23	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemo-filtra$ or haemodiafiltra$ or haemo-diafiltra$).ti,ab,kf.	6611	7098
24	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).ti,ab,kf.	18114	19654
25	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).ti,ab,kf.	104075	114405
26	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).ti,ab,kf.	2888	3021
27	(CAPD or CCPD or APD).ti,ab,kf.	11227	11899
28	glomerular filtration rate/	40810	45131
29	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).ti,ab,kf.	7268	8288
30	diabetic nephropathies/	23693	25814
31	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).ti,ab,kf.	19096	22120
32	or/1-31	534791	589645
33	exp Anemia/	154557	162737
34	(anemi$ or anaemi$).ti,ab,kf.	146500	158647
35	or/33-34	217009	232631
36	32 and 35	19228	20954
37	Economics/	26992	27278
38	exp "costs and cost analysis"/	221598	241333
39	Economics, Dental/	1901	1915
40	exp economics, hospital/	23325	24878
41	Economics, Medical/	8993	9116
42	Economics, Nursing/	3986	4002
43	Economics, Pharmaceutical/	2837	2963
44	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	707933	833445
45	(expenditure$ not energy).ti,ab.	27049	30983
46	value for money.ti,ab.	1527	1771
47	budget$.ti,ab.	26896	30300

#	Searches	Hits (Original SLR)	Hits (SLR Update)
48	or/37-47	853515	987618
49	((energy or oxygen) adj cost).ti,ab.	3830	4191
50	(metabolic adj cost).ti,ab.	1286	1466
51	((energy or oxygen) adj expenditure).ti,ab.	23265	25716
52	or/49-51	27448	30381
53	48 not 52	847224	980651
54	(burden or resource$1).ti.	62318	74910
55	(burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kf.	32554	41367
56	(resource$1 adj4 (use$1 or usage or utilit$ or utilis$ or utiliz$)).ti,ab,kf.	40600	48735
57	[Office Visits/sn, td, ut]	0	0
58	(visit or visits or visited).ti,ab,kf.	183971	218115
59	appointment$.ti,ab,kf.	20817	25080
60	Hospitalisation/	96654	111902
61	(hospitalisation$1 or hospitalisation$1 or hospitalised or hospitalised).ti,ab,kf.	219027	258835
62	(admission$1 or readmission$1 or admitted or readmitted).ti,ab,kf.	349003	405948
63	"length of stay"/ or los.ti,ab,kf.	107580	129193
64	hospital stay$1.ti,ab,kf.	74273	86708
65	(bed adj3 day$1).ti,ab,kf.	3260	3644
66	((days or time or length or duration$1) adj3 hospital$).ti,ab,kf.	80082	95013
67	((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kf.	88628	107030
68	((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kf.	20863	24954
69	or/54-68	959148	1124990
70	Quality-Adjusted Life Years/	10685	12737
71	(quality adjusted or adjusted life year$).ti,ab,kf.	14550	17915
72	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	9370	11373
73	(illness state$1 or health state$1).ti,ab,kf.	5850	6803
74	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1354	1595
75	(multiattribute$ or multi attribute$).ti,ab,kf.	816	958
76	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.	13453	16016
77	utilities.ti,ab,kf.	6394	7505
78	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf.	9600	12479
79	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.	3332	4419
80	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	20381	22895

#	Searches	Hits (Original SLR)	Hits (SLR Update)
81	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	1744	1962
82	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.	10482	12115
83	quality of life/ and ec.fs.	9245	10339
84	quality of life/ and (health adj3 status).ti,ab,kf.	8059	9331
85	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	11043	13223
86	((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	32293	40066
87	Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	2972	3713
88	*quality of life/ and (quality of life or qol).ti.	48368	55609
89	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf.	23719	28793
90	quality of life/ and health-related quality of life.ti,ab,kf.	27641	33527
91	models,economic/	9156	10372
92	or/70-91	146529	173641
93	(utility loss$ or disutilit$ or short form$ or shortform$ or SF-12 or SF12).ti,ab,kf.	32444	38665
94	(15-D or 15D or SF-6 or SF6 or SF-6D or SF6D).ti,ab,kf.	7397	8262
95	discrete choice$.ti,ab,kf. (1712)87 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf.	2972	2277
96	choice experiment$1.ti,ab,kf.	2438	3118
97	(dce or dces).ti,ab,kf.	5187	6282
98	standard gamble$.ti,ab,kf.	816	869
99	sg.ti,ab,kf.	8952	10751
100	92 or 93 or 94 or 95 or 96 or 97 or 98 or 99	184003	218321
101	36 and (53 or 69)	2963	3414
102	36 and 100	336	369
103	101 or 102	3176	3642
104	exp animals/ not humans/	4541167	4772383
105	(news or editorial or case reports).pt. or case report.ti.	2654121	2947045
106	103 not (104 or 105)	2551	2880
107	remove duplicates from 106	2535	2868
108	limit 107 to yr="2009-Current" / "2019-Current"	1382	408

I.1.1.2 Source: Embase

Table 135 Cost and resource use SLR search details (Embase)

	Original SLR	SLR Update
Interface / URL:	OvidSP	OvidSP
Database coverage dates:	1974 to 2019 January 29	2019 to 2021 January 27

Search date:	30/01/19	07/01/21
Retrieved records:	6389	1312

Table 136 Cost and resource use SLR search strategy (Embase)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	exp kidney failure/	318810	384053
2	kidney disease/ and (chronic or end-stage$ or endstage$ or final stage$).ti,ab,kw,dj.	22657	24821
3	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	135076	163825
4	((kidney$ or renal$ or nephropath$) adj3 fail$).ti,ab,kw,dj.	140452	155488
5	((kidney$ or renal$ or nephropath$) adj3 insufficien$).ti,ab,kw,dj.	31557	34406
6	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).ti,ab,kw,dj.	57268	69246
7	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	94	107
8	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	4218	5523
9	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	19	23
10	(early adj5 (kidney$ or renal$ or nephropath$)).ti,ab,kw,dj.	20825	24307
11	((kidney$ or renal$ or nephropath$) adj3 injur$).ti,ab,kw,dj.	55922	75953
12	(CKF or CKD or CRF or CRD).ti,ab,kw,dj.	64951	85133
13	(ESKD or ESRD or ESKF or ESRF).ti,ab,kw,dj.	26768	34371
14	exp renal replacement therapy/ or exp kidney transplantation/	296532	334660
15	dialysis/	45600	52107
16	dialyzer/	484	1091
17	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).ti,ab,kw,dj.	155796	178850
18	(hemodialy$ or haemodialy$).ti,ab,kw,dj.	101298	117299
19	(prehemodialy$ or prehaemodialy$).ti,ab,kw,dj.	96	103
20	ultrafiltration/	20078	22786
21	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemofiltra$ or haemodiafiltra$ or haemo-diafiltra$).ti,ab,kw,dj.	9672	10754
22	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).ti,ab,kw,dj.	24828	27540
23	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).ti,ab,kw,dj.	153296	176977
24	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).ti,ab,kw,dj.	1803	1992
25	(CAPD or CCPD or APD).ti,ab,kw,dj.	14765	16410
26	exp glomerulus filtration rate/ (86886)	86886	110826
27	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).ti,ab,kw,dj.	10890	13141
28	diabetic nephropathy/	37802	44021

#	Searches	Hits (Original SLR)	Hits (SLR Update)
29	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).ti,ab,kw,dj.	27161	32753
30	or/1-29	795812	924652
31	exp anemia/	325762	369235
32	(anemi$ or anaemi$).ti,ab,kw,dj.	191386	218566
33	or/31-32	363514	411099
34	30 and 33	46556	54563
35	Health Economics/	31687	33334
36	exp Economic Evaluation/	284834	314299
37	exp Health Care Cost/	272276	298683
38	pharmacoeconomics/	6988	7471
39	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	933299	1122330
40	(expenditure$ not energy).ti,ab.	35987	42196
41	(value adj2 money).ti,ab.	2205	2527
42	budget$.ti,ab.	34668	40189
43	or/35-42	1180769	1387752
44	(metabolic adj cost).ti,ab.	1364	1585
45	((energy or oxygen) adj cost).ti,ab.	3952	4488
46	((energy or oxygen) adj expenditure).ti,ab.	29152	32824
47	or/44-46	33434	37765
48	43 not 47	1173974	1379997
49	disease burden/	7595	21575
50	cost/	56200	59240
51	(burden or resource$1.ti	80947	101161
52	(burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$.ti,ab,kw,dj.	49372	64315
53	(resource$1 adj4 (use$1 or usage or utilit$ or utilis$ or utiliz$.ti,ab,kw,dj.	59735	73574
54	(visit or visits or visited).ti,ab,kw,dj.	292303	359841
55	appointment$.ti,ab,kw,dj.	34446	43656
56	hospitalisation/ or hospital admission/	472947	571189
57	(hospitalisation$1 or hospitalisation$1 or hospitalised or hospitalised).ti,ab,kw,dj.	345568	421199
58	(admission$1 or readmission$1 or admitted or readmitted).ti,ab,kw,dj.	576843	693888
59	"length of stay"/ or los.ti,ab,kw,dj.	186356	230808
60	hospital stay$1.ti,ab,kw,dj.	120635	144228
61	(bed adj3 day$1).ti,ab,kw,dj.	5180	6002
62	((days or time or length or duration$1) adj3 hospital$).ti,ab,kw,dj.	131473	160762
63	((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kw,dj.	153335	190987

#	Searches	Hits (Original SLR)	Hits (SLR Update)
64	((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kw,dj.	36637	45284
65	or/49-64	1625690	1957256
66	quality adjusted life year/	23089	28052
67	(quality adjusted or adjusted life year$).ti,ab,kw,dj.	21309	26497
68	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw,dj.	17654	21582
69	(illness state$1 or health state$1).ti,ab,kw,dj.	10008	11921
70	(hui or hui1 or hui2 or hui3).ti,ab,kw,dj.	2032	2438
71	(multiattribute$ or multi attribute$).ti,ab,kw,dj.	1045	1241
72	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw,dj.	21345	25713
73	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw,dj.	21345	25713
74	utilities.ti,ab,kw,dj.	10336	12383
75	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw,dj.	17652	22973
76	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw,dj.	5142	6760
77	short form 36/	24638	30711
78	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw,dj.	34477	39561
79	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw,dj.	2516	2917
80	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw,dj.	22218	26695
81	quality of life/ and ec.fs.	37656	44636
82	quality of life/ and (health adj3 status).ti,ab,kw,dj.	14258	16950
83	(quality of life or qol).ti,ab,kw,dj. and cost benefit analysis/	5037	5722
84	((qol or hrqol or quality of life).ti,kw,dj. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab.	49435	60488
85	cost benefit analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kw,dj.	725	877
86	*quality of life/ and (quality of life or qol).ti.	74274	89921
87	quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw,dj.	65781	79771
88	quality of life/ and health-related quality of life.ti,ab,kw,dj.	50075	61581
89	economic model/	1524	2295
90	or/66-89	275093	331934
91	(utility loss$ or disutilit$ or short form$ or shortform$ or SF-12 or SF12).ti,ab,kw,dj.	45269	54925
92	(15-D or 15D or SF-6 or SF6 or SF-6D or SF6D).ti,ab,kw,dj.	9329	10662

#	Searches	Hits (Original SLR)	Hits (SLR Update)
93	discrete choice$.ti,ab,kw,dj.	2470	3325
94	choice experiment$1.ti,ab,kw,dj.	3029	4001
95	(dce or dces).ti,ab,kw,dj.	7943	9693
96	standard gamble$.ti,ab,kw,dj.	1069	1150
97	sg.ti,ab,kw,dj.	13006	16239
98	90 or 91 or 92 or 93 or 94 or 95 or 96 or 97	323112	390612
99	34 and (48 or 65)	10343	12971
100	34 and 98	1587	1806
101	99 or 100	11340	14110
102	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	5655240	6185656
103	editorial.pt. or case report.ti.	860137	989670
104	101 not (102 or 103)	10710	13263
105	conference abstract.pt. and 104	3307	4575
106	104 not 105	7403	8688
107	limit 105 to yr="2014 -Current"	1930	3198
108	limit 106 to yr="2009/2019 -Current"	4550	1324
109	remove duplicates from 107	1924	3181
110	remove duplicates from 108	4465	1312
111	109 or 110	6389	-

I.1.1.3 Source: Health Technology Assessment Database (HTA)

Table 137 Cost and resource use SLR search details (HTA)

	Original SLR
Interface / URL:	CRD database
Database coverage dates:	Information not found. From 31 March 2018, the HTA database remains available, but CRD are no longer adding new records to it. INAHTA will be taking over production and the next phase of the database development. Updating and addition of new records will resume on their new platform, when it is ready
Search date:	30/01/19
Retrieved records:	19

Table 138 Cost and resource use SLR search strategy (HTA)

#	Searches	Hits (Original SLR)
1	((MeSH DESCRIPTOR Renal Insufficiency EXPLODE ALL TREES))	729
2	(((MeSH DESCRIPTOR kidney diseases) AND ((chronic or end-stage* or endstage* or final stage*))))	86
3	(((((chronic* or progressiv*) adj5 (kidney* or renal* or nephropath*)))))	571

#	Searches	Hits (Original SLR)
4	(((((kidney* or renal* or nephropath*) adj5 (chronic* or progressiv*)))))	588
5	(((((kidney* or renal* or nephropath*) adj3 fail*))))	859
6	((((fail* adj3 (kidney* or renal* or nephropath*)))))	171
7	(((((kidney* or renal* or nephropath*) adj3 insufficien*))))	326
8	((((insufficien* adj3 (kidney* or renal* or nephropath*)))))	18
9	(((((endstage* or end-stage*) adj5 (kidney* or renal or nephropath*)))))	357
10	(((((kidney* or renal or nephropath*) adj5 (endstage* or end-stage*)))))	43
11	((((final stage* adj5 (kidney* or renal* or nephropath*)))))	0
12	(((((kidney* or renal* or nephropath*) adj5 final stage*))))	0
13	(((((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney* or renal* or nephropath*)))))	12
14	(((((kidney* or renal* or nephropath*) adj5 (stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five)))))	11
15	(((((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney* or renal* or nephropath*)))))	0
16	(((((kidney* or renal* or nephropath*) adj5 (stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev)))))	0
17	((((early adj5 (kidney* or renal* or nephropath*)))))	49
18	((((kidney* or renal* or nephropath*) adj5 early))))	17
19	((((kidney* or renal* or nephropath*) adj3 injur*))))	192
20	((((injur* adj3 (kidney* or renal* or nephropath*)))))	15
21	((((CKF or CKD or CRF)) OR (CRD):TI))	114
22	((((ESKD or ESRD or ESKF or ESRF))))	158
23	((MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES))	881
24	((MeSH DESCRIPTOR Dialysis))	14
25	(MeSH DESCRIPTOR Hemodialysis Units, Hospital)	14
26	(MeSH DESCRIPTOR Kidneys, Artificial)	3
27	((((dialys* or predialys* or dialyz* or predialyz* or dialytic* or predialytic* or dopps*))))	920
28	((((hemodialy* or haemodialy*))))	456
29	((((prehemodialy* or prehaemodialy*))))	0
30	(MeSH DESCRIPTOR Hemofiltration EXPLODE ALL TREES)	50
31	(MeSH DESCRIPTOR Ultrafiltration)	15
32	((((hemofiltra* or hemo-filtra* or hemodiafiltra* or hemo-diafiltra* or haemofiltra* or haemo-filtra* or haemodiafiltra* or haemo-diafiltra*))))	73
33	((((ultrafiltra* or ultra-filtra* or biofiltra* or bio-filtra*))))	30
34	(((((kidney* or renal*) adj4 (transplant* or graft* or allograft* or replac*)))))	702
35	(((((transplant* or graft* or allograft* or replac*) adj4 (kidney* or renal*)))))	181

#	Searches	Hits (Original SLR)
36	(((((artificial* or extracorporeal or extra-corporeal) adj3 (renal* or kidney*)))))	11
37	(((((renal* or kidney*) adj3 (artificial* or extracorporeal or extra-corporeal)))))	6
38	((((CAPD or CCPD or APD))))	29
39	(MeSH DESCRIPTOR glomerular filtration rate)	92
40	(((((low or reduc*) adj4 (gfr or egfr or glomerular filtration rate*)))))	17
41	(((((gfr or egfr or glomerular filtration rate*) adj4 (low or reduc*)))))	4
42	((MeSH DESCRIPTOR diabetic nephropathies))	113
43	((((diabetic kidney disease* or diabetic renal disease* or diabetic nephropath*))))	150
44	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43))	2450
45	(MeSH DESCRIPTOR Anemia EXPLODE ALL TREES)	380
46	((((anemi* or anaemi*))))	731
47	(#45 OR #46)	791
48	(#44 AND #47)	138
49	(#48) IN DARE FROM 2009 TO 2019	43
50	(#48) IN NHSEED FROM 2009 TO 2019	12
51	(#48) IN HTA FROM 2009 TO 2019	19

I.1.1.4 Source: NHS Economic Evaluation Database (NHS EED)

Table 139 Cost and resource use SLR search details (NHS EED)

	Original SLR
Interface / URL:	CRD database
Database coverage dates:	Information not found. Bibliographic records were published on NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.
Search date:	30/01/19
Retrieved records:	12

Table 140 Cost and resource use SLR search strategy (NHS EED)

#	Searches	Hits (Original SLR)
1	((MeSH DESCRIPTOR Renal Insufficiency EXPLODE ALL TREES	729
2	(((MeSH DESCRIPTOR kidney diseases) AND ((chronic or end-stage* or endstage* or final stage*))))	86
3	(((((chronic* or progressiv*) adj5 (kidney* or renal* or nephropath*)))))	571
4	(((((kidney* or renal* or nephropath*) adj5 (chronic* or progressiv*)))))	588

#	Searches	Hits (Original SLR)
5	(((((kidney* or renal* or nephropath*) adj3 fail*))))	859
6	((((fail* adj3 (kidney* or renal* or nephropath*))))))	171
7	(((((kidney* or renal* or nephropath*) adj3 insufficien*))))	326
8	((((insufficien* adj3 (kidney* or renal* or nephropath*))))))	18
9	(((((endstage* or end-stage*) adj5 (kidney* or renal or nephropath*)))))	357
10	(((((kidney* or renal or nephropath*) adj5 (endstage* or end-stage*)))))	43
11	((((final stage* adj5 (kidney* or renal* or nephropath*))))))	0
12	(((((kidney* or renal* or nephropath*) adj5 final stage*))))	0
13	(((((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney* or renal* or nephropath*)))))	12
14	(((((kidney* or renal* or nephropath*) adj5 (stage 3 or stage iii or stage three or stage3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage ivor stage 1v or stage four or stage 5 or stage v or stage five)))))	11
15	(((((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney* or renal* or nephropath*)))))	0
16	(((((kidney* or renal* or nephropath*) adj5 (stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev)))))	0
17	((((early adj5 (kidney* or renal* or nephropath*))))))	49
18	(((((kidney* or renal* or nephropath*) adj5 early))))	17
19	(((((kidney* or renal* or nephropath*) adj3 injur*))))	192
20	((((injur* adj3 (kidney* or renal* or nephropath*))))))	15
21	((((CKF or CKD or CRF)) OR (CRD):TI))	114
22	((((ESKD or ESRD or ESKF or ESRF))))	158
23	((MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES))	881
24	((MeSH DESCRIPTOR Dialysis))	14
25	(MeSH DESCRIPTOR Hemodialysis Units, Hospital)	14
26	(MeSH DESCRIPTOR Kidneys, Artificial)	3
27	((((dialys* or predialys* or dialyz* or predialyz* or dialytic* or predialytic* or dopps*))))	920
28	((((hemodialy* or haemodialy*))))	456
29	((((prehemodialy* or prehaemodialy*))))	0
30	(MeSH DESCRIPTOR Hemofiltration EXPLODE ALL TREES)	50
31	(MeSH DESCRIPTOR Ultrafiltration)	15
32	((((hemofiltra* or hemo-filtra* or hemodiafiltra* or hemo-diafiltra* or haemofiltra* or haemo-filtra* or haemodiafiltra* or haemo-diafiltra*))))	73
33	((((ultrafiltra* or ultra-filtra* or biofiltra* or bio-filtra*))))	30
34	(((((kidney* or renal*) adj4 (transplant* or graft* or allograft* or replac*)))))	702
35	(((((transplant* or graft* or allograft* or replac*) adj4 (kidney* or renal*)))))	181
36	(((((artificial* or extracorporeal or extra-corporeal) adj3 (renal* or kidney*)))))	11

#	Searches	Hits (Original SLR)
37	(((((renal* or kidney*) adj3 (artificial* or extracorporeal or extra-corporeal)))))	6
38	((((CAPD or CCPD or APD))))	29
39	(MeSH DESCRIPTOR glomerular filtration rate)	92
40	(((((low or reduc*) adj4 (gfr or egfr or glomerular filtration rate*)))))	17
41	(((((gfr or egfr or glomerular filtration rate*) adj4 (low or reduc*)))))	4
42	((MeSH DESCRIPTOR diabetic nephropathies))	113
43	((((diabetic kidney disease* or diabetic renal disease* or diabetic nephropath*))))	150
44	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43))	2450
45	(MeSH DESCRIPTOR Anemia EXPLODE ALL TREES)	380
46	((((anemi* or anaemi*))))	731
47	(#45 OR #46)	791
48	(#44 AND #47)	138
49	(#48) IN DARE FROM 2009 TO 2019	43
50	(#48) IN NHSEED FROM 2009 TO 2019	12

I.1.1.5 Source: Database of Abstracts of Reviews of Effects (DARE)

Table 141 Cost and resource use SLR search details (DARE)

	Original SLR
Interface / URL:	CRD database
Database coverage dates:	Information not found. Bibliographic records were published on DARE until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.
Search date:	30/01/19
Retrieved records:	43

Table 142 Cost and resource use SLR search strategy (DARE)

#	Searches	Hits (Original SLR)
1	((MeSH DESCRIPTOR Renal Insufficiency EXPLODE ALL TREES))	729
2	(((MeSH DESCRIPTOR kidney diseases) AND ((chronic or end-stage* or endstage*or final stage*))))	86
3	(((((chronic* or progressiv*) adj5 (kidney* or renal* or nephropath*)))))	571
4	(((((kidney* or renal* or nephropath*) adj5 (chronic* or progressiv*)))))	588
5	(((((kidney* or renal* or nephropath*) adj3 fail*))))	859
6	((((fail* adj3 (kidney* or renal* or nephropath*)))))	171

#	Searches	Hits (Original SLR)
7	(((((kidney* or renal* or nephropath*) adj3 insufficien*))))	326
8	((((insufficien* adj3 (kidney* or renal* or nephropath*))))))	18
9	(((((endstage* or end-stage*) adj5 (kidney* or renal or nephropath*)))))	357
10	(((((kidney* or renal or nephropath*) adj5 (endstage* or end-stage*)))))	43
11	((((final stage* adj5 (kidney* or renal* or nephropath*))))))	0
12	(((((kidney* or renal* or nephropath*) adj5 final stage*))))	0
13	(((((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney* or renal* or nephropath*)))))	12
14	(((((kidney* or renal* or nephropath*) adj5 (stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five)))))	11
15	(((((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney* or renal* or nephropath*)))))	0
16	(((((kidney* or renal* or nephropath*) adj5 (stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev)))))	0
17	((((early adj5 (kidney* or renal* or nephropath*)))))	49
18	(((((kidney* or renal* or nephropath*) adj5 early))))	17
19	(((((kidney* or renal* or nephropath*) adj3 injur*))))	192
20	((((injur* adj3 (kidney* or renal* or nephropath*))))))	15
21	((((CKF or CKD or CRF)) OR (CRD):TI))	114
22	((((ESKD or ESRD or ESKF or ESRF))))	158
23	((MeSH DESCRIPTOR Renal Replacement Therapy EXPLODE ALL TREES))	881
24	((MeSH DESCRIPTOR Dialysis))	14
25	(MeSH DESCRIPTOR Hemodialysis Units, Hospital)	14
26	(MeSH DESCRIPTOR Kidneys, Artificial)	3
27	((((dialys* or predialys* or dialyz* or predialyz* or dialytic* or predialytic* or dopps*))))	920
28	((((hemodialy* or haemodialy*))))	456
29	((((prehemodialy* or prehaemodialy*))))	0
30	(MeSH DESCRIPTOR Hemofiltration EXPLODE ALL TREES)	50
31	(MeSH DESCRIPTOR Ultrafiltration)	15
32	((((hemofiltra* or hemo-filtra* or hemodiafiltra* or hemo-diafiltra* or haemofiltra* or haemo-filtra* or haemodiafiltra* or haemo-diafiltra*))))	73
33	((((ultrafiltra* or ultra-filtra* or biofiltra* or bio-filtra*))))	30
34	(((((kidney* or renal*) adj4 (transplant* or graft* or allograft* or replac*)))))	702
35	(((((transplant* or graft* or allograft* or replac*) adj4 (kidney* or renal*)))))	181
36	(((((artificial* or extracorporeal or extra-corporeal) adj3 (renal* or kidney*)))))	11
37	(((((renal* or kidney*) adj3 (artificial* or extracorporeal or extra-corporeal)))))	6
38	((((CAPD or CCPD or APD))))	29

#	Searches	Hits (Original SLR)
39	(MeSH DESCRIPTOR glomerular filtration rate)	92
40	(((((low or reduc*) adj4 (gfr or egfr or glomerular filtration rate*)))))	17
41	(((((gfr or egfr or glomerular filtration rate*) adj4 (low or reduc*)))))	4
42	((MeSH DESCRIPTOR diabetic nephropathies))	113
43	((((diabetic kidney disease* or diabetic renal disease* or diabetic nephropath*))))	150
44	((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43))	2450
45	(MeSH DESCRIPTOR Anemia EXPLODE ALL TREES)	380
46	((((anemi* or anaemi*))))	731
47	(#45 OR #46)	791
48	(#44 AND #47)	138
49	(#48) IN DARE FROM 2009 TO 2019	43

I.1.1.6 Source: Econlit

Table 143 Cost and resource use SLR search details (Econlit)

	Original SLR	SLR update
Interface / URL:	OvidSP	OvidSP
Database coverage dates:	Econlit 1886 to January 24, 2019	2019 to March 02, 2021
Search date:	30/01/19	22/03/21
Retrieved records:	7	0

Table 144 Cost and resource use SLR search strategy (Econlit)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).af.	21	21
2	((kidney$ or renal$ or nephropath$) adj3 fail$).af.	35	35
3	((kidney$ or renal$ or nephropath$) adj3 insufficien$).af.	3	3
4	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).af.	52	52
5	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).af.	0	0
6	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney$ or renal$ or nephropath$)).af.	0	0
7	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).af.	0	0
8	(early adj5 (kidney$ or renal$ or nephropath$)).af.	1	1
9	((kidney$ or renal$ or nephropath$) adj3 injur$).af.	3	3

#	Searches	Hits (Original SLR)	Hits (SLR Update)
10	(CKF or CKD or CRF or CRD).af.	66	66
11	(ESKD or ESRD or ESKF or ESRF).af.	33	33
12	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).af.	89	89
13	(hemodialy$ or haemodialy$).af.	31	31
14	(prehemodialy$ or prehaemodialy$).af.	0	0
15	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemofiltra$ or haemodiafiltra$ or haemo-diafiltra$).af.	1	1
16	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).af.	6	6
17	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).af.	101	101
18	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).af.	0	0
19	(CAPD or CCPD or APD).af.	14	14
20	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).af.	1	1
21	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).af.	3	3
22	or/1-21	321	321
23	(anemi$ or anaemi$).af.	195	195
24	22 and 23	10	10
25	limit 24 to yr="2009/2019 -Current"	7	0

I.1.1.7 Source: PsycINFO

Table 145 Cost and resource use SLR search details (PsycINFO)

	Original SLR	SLR update
Database coverage dates:	1806 to January Week 3 2019	April 2019 to March 02, 2021
Search date:	30/01/19	29/01/21
Retrieved records:	81	10

Table 146 Cost and resource use SLR search strategy (PsycINFO)

#	Searches	Hits (Original SLR)	Hits (SLR update)
1	Kidney Diseases/	2016	2016
2	((chronic$ or progressiv$) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	1412	1412
3	((kidney$ or renal$ or nephropath$) adj3 fail$).ti,ab,id.	1256	1256
4	((kidney$ or renal$ or nephropath$) adj3 insufficien$).ti,ab,id.	262	262
5	((endstage$ or end-stage$) adj5 (kidney$ or renal or nephropath$)).ti,ab,id.	1082	1082
6	(final stage$ adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	0	0
7	((stage 3 or stage iii or stage three or stage 3a or stage iiia or stage threea or stage 3b or stage iiib or stage threeb or	32	32

#	Searches	Hits (Original SLR)	Hits (SLR update)
	stage 4 or stage iv or stage 1v or stage four or stage 5 or stage v or stage five) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.		
8	((stage3 or stage3a or stage3b or stageiii or stageiiia or stageiiib or stage4 or stageiv or stage1v or stage5 or stagev) adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	0	0
9	(early adj5 (kidney$ or renal$ or nephropath$)).ti,ab,id.	76	76
10	((kidney$ or renal$ or nephropath$) adj3 injur$).ti,ab,id.	181	181
11	(CKF or CKD or CRF or CRD).ti,ab,id.	3317	3317
12	(ESKD or ESRD or ESKF or ESRF).ti,ab,id.	464	464
13	hemodialysis/ or dialysis/	1758	1758
14	[Organ Transplantation/ and (Kidneys/ or (kidney$ or renal$ or nephropath$)).ti,ab,id.]	0	0
15	(dialys$ or predialys$ or dialyz$ or predialyz$ or dialytic$ or predialytic$ or dopps$).ti,ab,id.	2511	2511
16	(hemodialy$ or haemodialy$).ti,ab,id.	1504	1504
17	(prehemodialy$ or prehaemodialy$).ti,ab,id.	2	2
18	(hemofiltra$ or hemo-filtra$ or hemodiafiltra$ or hemo-diafiltra$ or haemofiltra$ or haemofiltra$ or haemodiafiltra$ or haemo-diafiltra$).ti,ab,id.	14	14
19	(ultrafiltra$ or ultra-filtra$ or biofiltra$ or bio-filtra$).ti,ab,id.	48	48
20	((kidney$ or renal$) adj4 (transplant$ or graft$ or allograft$ or replac$)).ti,ab,id.	1004	1004
21	((artificial$ or extracorporeal or extra-corporeal) adj3 (renal$ or kidney$)).ti,ab,id.	19	19
22	(CAPD or CCPD or APD).ti,ab,id.	1014	1014
23	((low or reduc$) adj4 (gfr or egfr or glomerular filtration rate$)).ti,ab,id.	69	69
24	(diabetic kidney disease$ or diabetic renal disease$ or diabetic nephropath$).ti,ab,id.	79	79
25	or/1-24	10310	10310
26	anemia/	665	665
27	(anemi$ or anaemi$).ti,ab,id.	2052	2052
28	or/26-27	2103	2103
29	25 and 28	117	117
30	remove duplicates from 29	117	117
31	limit 30 to yr="2009/2019 -Current"	81	10

I.1.1.8 Source: PubMed

Table 147 Cost and resource use SLR search details (PubMed)

	Original SLR
Interface / URL:	https://www.ncbi.nlm.nih.gov/pubmed/
Search date:	23/01/19
Retrieved records:	421

Table 148 Cost and resource use SLR search strategy (PubMed)

#	Searches	Hits (Original SLR)
1	Search Renal Insufficiency[mh]	158910
2	Search kidney diseases [mh:noexp] AND (chronic[tiab] OR end-stage*[tiab] OR endstage*[tiab] OR final stage*[tiab])	12986
3	Search ((chronic*[tiab] OR progressiv*[tiab]) AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	143138
4	Search ((kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]) AND fail*[tiab])	137828
5	Search ((kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]) AND insufficien*[tiab])	30037
6	Search ((endstage*[tiab] OR end-stage*[tiab]) AND (kidney*[tiab] OR renal[tiab] OR nephropath*[tiab]))	41880
7	Search (final stage*[tiab] AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	192
8	Search ((stage 3[tiab] OR stage iii[tiab] OR stage three[tiab] OR stage 3a[tiab] OR stage iiia[tiab] OR (stage[tiab] AND threea[tiab]) OR stage 3b[tiab] OR stage iiib[tiab] OR (stage[tiab] AND threeb[tiab]) OR stage 4[tiab] OR stage iv[tiab] OR (stage[tiab] AND 1v[tiab]) OR stage four[tiab] OR stage 5[tiab] OR stage v[tiab] OR stage five[tiab]) AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	6436
9	Search ((stage3[tiab] OR stage3a[tiab] OR stage3b[tiab] OR stageiii[tiab] OR stageiiia[tiab] OR stageiiib[tiab] OR stage4[tiab] OR stageiv[tiab] OR stage1v[tiab] OR stage5[tiab] OR stagev[tiab]) AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	7
10	Search (early[tiab] AND (kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]))	65025
11	Search (((kidney*[tiab] OR renal*[tiab] OR nephropath*[tiab]) AND injur*[tiab]))	58977
12	Search (CKF[tiab] OR CKD[tiab] OR CRF[tiab] OR CRD[tiab])	41304
13	Search (ESKD[tiab] OR ESRD[tiab] OR ESKF[tiab] OR ESRF[tiab])	16712
14	Search Renal Replacement Therapy [mh]	194294
15	Search "Dialysis" [mh:noexp]	12505
16	Search Hemodialysis Units, Hospital [mh:noexp]	1361
17	Search Kidneys, Artificial[mh:noexp]	4301
18	Search (dialys*[tiab] OR predialys*[tiab] OR dialyz*[tiab] OR predialyz*[tiab] OR dialytic*[tiab] OR predialytic*[tiab] OR dopps*[tiab])	116181
19	Search (hemodialy*[tiab] OR haemodialy*[tiab])	73664
20	Search (prehemodialy*[tiab] OR prehaemodialy*[tiab])	81
21	Search "Hemofiltration" [mh]	6491
22	Search "Ultrafiltration" [mh:noexp]	9770
23	Search (hemofiltra*[tiab] OR hemo-filtra*[tiab] OR hemodiafiltra*[tiab] OR hemodiafiltra*[tiab] OR haemofiltra*[tiab] OR haemo-filtra*[tiab] OR haemodiafiltra*[tiab] OR haemodiafiltra*[tiab])	6589
24	Search (ultrafiltra*[tiab] OR ultra-filtra*[tiab] OR biofiltra*[tiab] OR bio-filtra*[tiab])	17994
25	Search ((kidney*[tiab] OR renal*[tiab]) AND (transplant*[tiab] OR graft*[tiab] OR allograft*[tiab] OR replac*[tiab]))	137007
26	Search ((artificial*[tiab] OR extracorporeal[tiab] OR extra-corporeal[tiab]) AND (renal*[tiab] OR kidney*[tiab]))	10918
27	Search (CAPD[tiab] OR CCPD[tiab] OR APD[tiab])	11176

#	Searches	Hits (Original SLR)
28	Search glomerular filtration rate[mh:noexp]	40772
29	Search ((low[tiab] OR reduc*[tiab]) AND (gfr[tiab] OR egfr[tiab] OR glomerular filtration rate*[tiab]))	28400
30	Search diabetic nephropathies[mh:noexp]	23654
31	Search (diabetic kidney disease*[tiab] OR diabetic renal disease*[tiab] OR diabetic nephropath*[tiab])	18871
32	Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)	635744
33	Search "Anemia"[mh]	154482
34	Search (anemi*[tiab] OR anaemi*[tiab])	145660
35	Search (#33 OR #34)	216144
36	Search (#32 AND #35)	21378
37	Search "Economics"[Mesh:NoExp]	26987
38	Search "Costs and Cost Analysis"[Mesh]	221299
39	Search economics, dental[mh:noexp]	1901
40	Search "economics, hospital"[mh]	23302
41	Search economics, medical[mh:noexp]	8989
42	Search economics, nursing[mh:noexp]	3986
43	Search economics, pharmaceutical[mh:noexp]	2835
44	Search (economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab])	718276
45	Search (expenditure*[tiab] NOT energy[tiab])	27046
46	Search value for money[tiab]	1408
47	Search budget*[tiab]	26888
48	Search (#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47)	851814
49	Search (energy cost[tiab] OR oxygen cost[tiab])	3823
50	Search metabolic cost[tiab]	1297
51	Search (energy expenditure[tiab] OR oxygen expenditure[tiab])	23310
52	Search (#49 OR #50 OR #51)	27464
53	Search (#48 NOT #52)	845662
54	Search (burden*[ti] OR resource*[ti])	63233
55	Search (burden*[tiab] AND (illness*[tiab] OR disease*[tiab] OR sickness*[tiab] OR treatment*[tiab] OR therap*[tiab]))	118082
56	Search (resource*[tiab] AND (use*[tiab] OR usage[tiab] OR utilit*[tiab] OR utilis*[tiab] OR utiliz*[tiab]))	66356
57	Search Office visits/sn[mh:noexp] OR Office visits/td[mh:noexp] OR Office visits/ut[mh:noexp]	2771
58	Search (visit[tiab] OR visits[tiab] OR visited[tiab])	181847
59	Search appointment*[tiab]	20590
60	Search "Hospitalisation"[mesh:noexp]	96508

#	Searches	Hits (Original SLR)
61	Search (hospitalisation*[tiab] OR hospitalisation*[tiab] OR hospitalised[tiab] OR hospitalised[tiab])	216709
62	Search (admission*[tiab] OR readmission*[tiab] OR admitted[tiab] OR readmitted[tiab])	345633
63	Search "Length of Stay"[mesh:noexp] or los[tiab]	99934
64	Search hospital stay*[tiab]	73493
65	Search (bed[tiab] AND day*[tiab])	17335
66	Search ((days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND hospital*[tiab])	376775
67	Search ((days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND (stay[tiab] OR stays[tiab] OR stayed[tiab]))	127483
68	Search ((days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND (discharge[tiab] OR discharged[tiab] OR home[tiab] OR homes[tiab]))	141991
69	Search (#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68)	1253132
70	Search Quality-adjusted Life Years [mh:noexp]	10664
71	Search (quality adjusted[tiab] OR adjusted life year*[tiab])	14326
72	Search (qaly*[tiab] OR qald*[tiab] OR qale*[tiab] OR qtime*[tiab])	9242
73	Search ((illness state*[tiab] OR health state*[tiab]))	5741
74	Search (hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab])	1333
75	Search (multiattribute*[tiab] OR multi attribute*[tiab])	807
76	Search (utility[tiab] AND (score*[tiab] OR valu*[tiab] OR health*[tiab] OR cost*[tiab] OR measur*[tiab] OR disease*[tiab] OR mean[tiab] OR gain[tiab] OR gains[tiab] OR index*[tiab]))	108914
77	Search utilities[tiab]	6314
78	Search (eq-5d[tiab] OR eq5d[tiab] OR eq-5[tiab] OR eq5[tiab] OR euro qual[tiab] OR euroqual[tiab] OR euro qual5d[tiab] OR euroqual5d[tiab] OR euro qol[tiab] OR euroqol[tiab] OR euro qol5d[tiab] OR euroqol5d[tiab] OR euro quol[tiab] OR euroquol[tiab] OR euro quol5d[tiab] OR euroquol5d[tiab] OR (eur[tiab] AND qol[tiab]) OR eurqol[tiab] OR (eur[tiab] AND qol5d[tiab]) OR (eur[tiab] AND qol5d[tiab]) OR euroqul[tiab] OR euroqul5d[tiab] OR (european[tiab] AND quality of life[tiab]) OR european qol[tiab])	15520
79	Search ((euro[tiab] OR european[tiab]) AND (5 d[tiab] OR 5d[tiab] OR 5 dimension*[tiab] OR 5dimension*[tiab] OR 5 domain*[tiab] OR 5domain*[tiab]))	1045
80	Search (sf36*[tiab] OR sf 36*[tiab] OR (sf[tiab] AND thirtysix[tiab]) OR (sf[tiab] AND thirty six[tiab]))	20206
81	Search (time trade off*[tiab] OR time tradeoff*[tiab] OR tto[tiab] OR timetradeoff*[tiab])	1721
82	Search "quality of life"[mesh:noexp] AND ((quality of life[tiab] OR qol[tiab]) AND (score*[tiab] OR measure*[tiab]))	65203
83	Search "quality of life"[mesh:noexp] AND "Economics"[sh:noexp]	9232
84	Search "quality of life"[mesh:noexp] AND (health[tiab] AND status[tiab])	15270
85	Search (quality of life[tiab] OR qol[tiab]) AND "Cost-Benefit Analysis"[mesh:noexp]	5501
86	Search ((qol[ti] OR hrqol[ti] OR quality of life[ti]) OR "quality of life"[majr:noexp]) AND ((qol[tiab] OR hrqol*[tiab] OR quality of life[tiab]) AND (increas*[tiab] OR decrease*[tiab] OR improv*[tiab] OR declin*[tiab] OR reduc*[tiab] OR high*[tiab] OR low*[tiab] OR effect[tiab] OR effects[tiab] OR	67713

#	Searches	Hits (Original SLR)
	worse[tiab] OR score[tiab] OR scores[tiab] OR change*[tiab] OR impact*[tiab] OR impacted[tiab] OR deteriorat*[tiab]))	
87	Search "Cost-Benefit Analysis"[mesh:noexp] AND (cost-effectiveness ratio*[tiab] AND (perspective*[tiab] OR life expectanc*[tiab]))	2959
88	Search "quality of life"[majr:noexp] AND (quality of life[ti] OR qol[ti])	48169
89	Search "quality of life"[mesh:noexp] AND ((quality of life[tiab] OR qol[tiab]) AND (improv*[tiab] OR chang*[tiab]))	58321
90	Search "quality of life"[mesh:noexp] AND health-related quality of life[tiab]	27567
91	Search "models,economic"[mesh:noexp]	9129
92	Search (#70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91)	266874
93	Search (utility loss*[tiab] OR disutilit*[tiab] OR short form*[tiab] OR shortform*[tiab] OR SF-12[tiab] OR SF12[tiab])	31941
94	Search (15-D[tiab] OR 15D[tiab] OR SF-6[tiab] OR SF6[tiab] OR SF-6D[tiab] OR SF6D[tiab])	6963
95	Search discrete choice*[tiab]	1679
96	Search choice experiment*[tiab]	2372
97	Search (dce[tiab] or dces[tiab])	5118
98	Search standard gamble*[tiab]	813
99	Search sg[tiab]	8896
100	Search (#92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99)	301702
101	Search (#36 AND (#53 OR #69))	3741
102	Search (#36 AND #100)	562
103	Search (#101 OR #102)	4128
104	Search animals [mh] NOT humans [mh:noexp]	4539198
105	Search (news[pt] or editorial[pt] or case reports[pt]) or case report[ti]	2645168
106	Search (#103 NOT (#104 OR #105))	3338
107	Search medline[sb]	25524362
108	Search (#106 NOT #107)	460
109	Search (#106 NOT #107) Filters: Publication date from 2009/01/01 to 2019/12/31	421

I.2 Study selection

The eligibility criteria for the utility review is outlined in Table 130.

Table 149: Eligibility criteria applied in utility review

	Inclusion criteria	Exclusion criteria
Population	• Adult patients (≥18 years of age) with CKD and anaemia.	• Patients aged under 18 • Studies of mixed populations including anaemic and non-anaemic CKD patients in which data for the anaemic

	Inclusion criteria	Exclusion criteria
		patients were not presented separately • Populations of patients who have already undergone a renal transplant
Interventions and comparators	• Any	
Outcomes	• Direct medical costs (overall and specific costs) • Indirect medical costs (overall and specific costs) • Resource utilisation data	
Study design	• HTAs • Costing studies • Budget impact models • Burden/cost of illness studies • Studies reporting resource utilization and costs • Observational studies • Economic evaluations	• Case reports • Case studies
Limits	• No language limits were applied • Limited to full papers published in the last 10 years (2009 to date) and conference abstracts published in the last 5 years (2014 to date).	• News • Comments • Editorials

Abbreviations: CKD: chronic kidney disease; HTA: health technology assessment.

I.3 Results

The PRISMA diagram below in Figure 35 and Figure 36 show the number of articles screened at abstract and full text stage, and the number of included and excluded articles based on the PICOS criteria.

Figure 35: PRISMA diagram (original SLR)

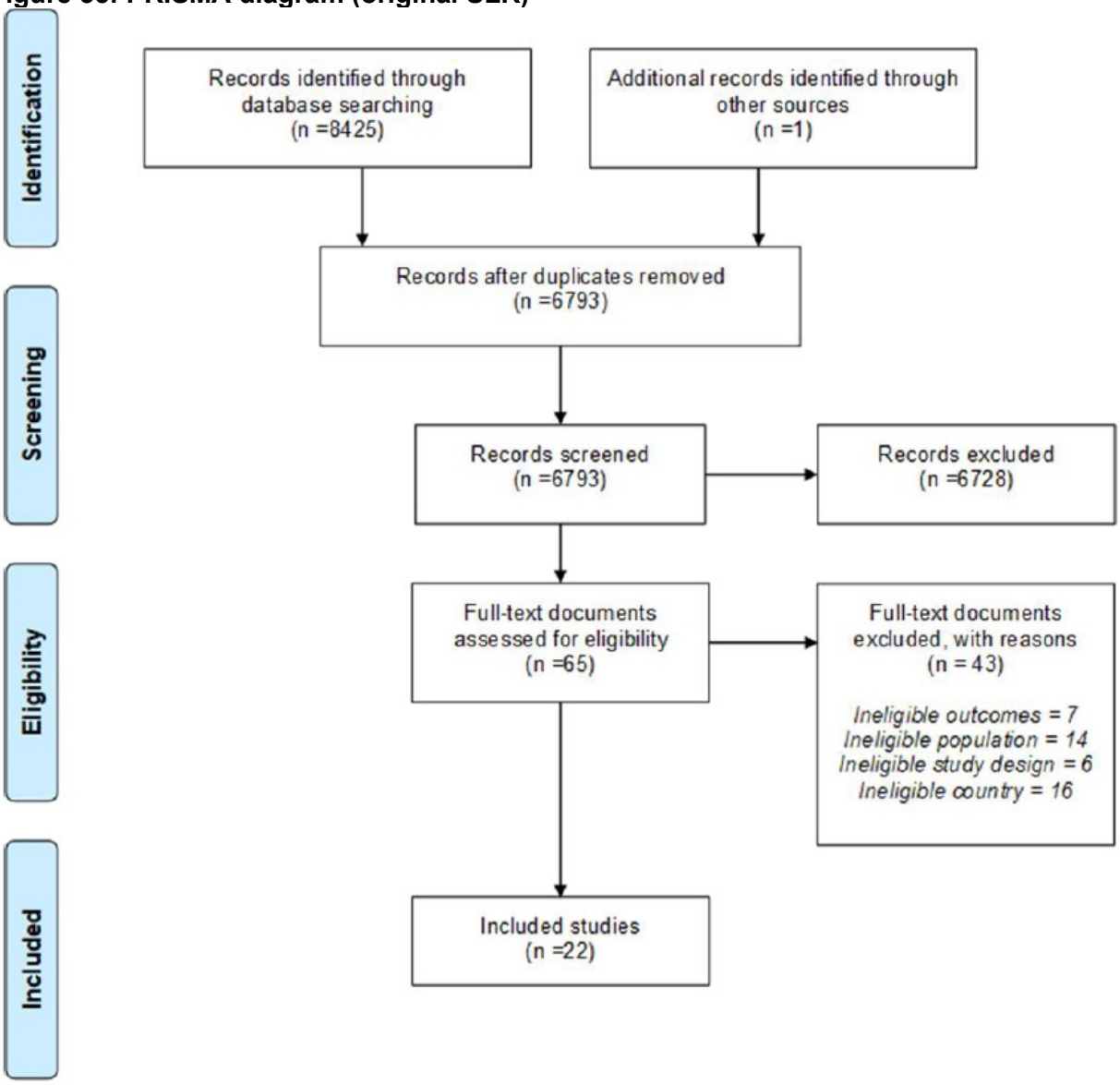
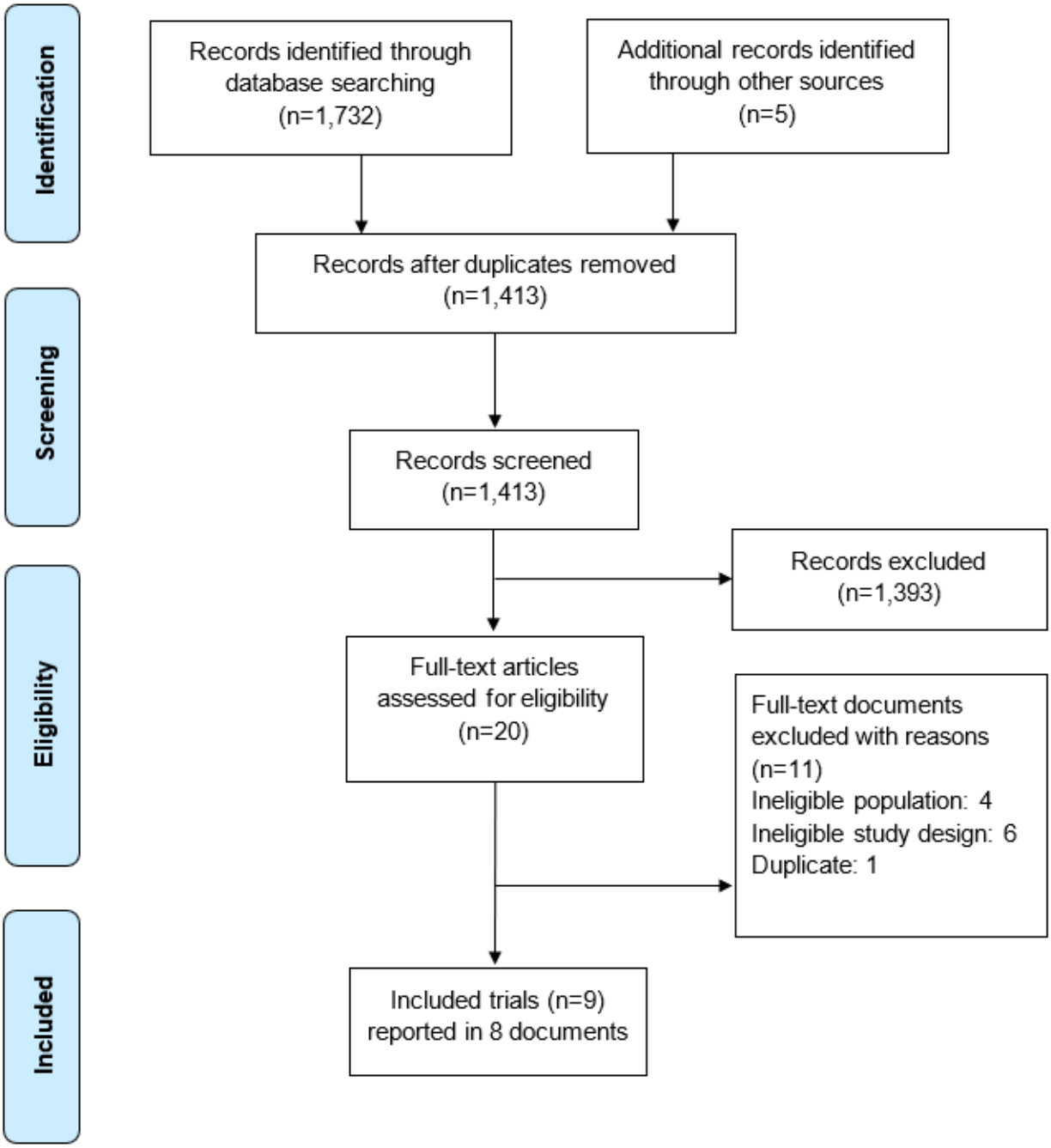


Figure 36: PRISMA diagram (SLR update)



Twenty-two studies (in 22 documents) were eligible for the SLR from the original SLR and 9 studies (in 8 documents) from the SLR update. In total, 31 studies were identified. Two main categories of direct medical costs were reported in the literature: treatment costs and hospital costs. Treatment costs included pharmacological treatments and

prescriptions. Hospital costs referred to inpatient stays and outpatient services. Other direct costs (such as diagnostic examinations and tests) were not reported.

Direct costs were reported in 20 studies. One study was multinational (170). The remaining studies were conducted in France (4 studies (171-174)), Germany (2 studies (175, 176)), Greece (1 study (147)), Italy (3 studies (177-179)), Portugal (1 study (180)), Russia (2 studies (148, 181)) and Spain (6 studies (182-187)), Fifteen of the studies were in dialysis dependent patients, two studies were in both dialysis dependent and non-dialysis dependent patients, and three studies were in non-dialysis patients.

Resource use data were reported in seven studies. One study was multinational (169); the remaining studies were conducted in France (3 studies (171, 173, 174)), Germany (1 study (176)) and Spain (2 studies (183, 185)). One study was in non-dialysis patients, one was in both dialysis dependent and non-dialysis dependent patients and five of the studies were in dialysis dependent patients. Data were reported for hospitalisations, consultations and tests and treatments.

In the SLR update, a total of nine studies (150, 188-194) were identified for inclusion in the current SLR update. Of these, two studies (189, 190) reported the resource use data, five studies reported direct healthcare costs (188, 191, 193), one study (192) reported direct and indirect healthcare costs and resource use data and one study (194) reported data on both direct healthcare costs and resource use.

Three studies (188, 192, 193) were conducted in Italy, two studies (150, 189) were conducted in UK and one study was conducted in Spain (195), France (191), Germany (194), and Denmark (190). Two studies (191, 193) were in DD patients, three studies (189, 192, 194) were in NDD patients, two studies (188, 190) were in both dialysis and non-dialysis depended patients, and two studies did not specify information on dialysis (150, 195).

The summary of included studies is presented in Table 150.

Table 150: Summary of included studies

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
Baumeister 2010 (176)	To determine whether baseline and incident CKD translate into excess health care costs after 10 years Secondary objectives: To examine whether the effect of CKD on costs is modified by comorbid conditions, including anaemia	Cohort study	General population of adults with stage 3 and 4 CKD with anaemia Total with CKD at baseline: n=134 Incident cases of CKD over 10 years: n=240 Mean age: 63.4 years (SD 10.1) in those with CKD at baseline	Inclusion criteria: Age 25-74 years, eligible for 10 year follow-up, CKD defined as eGFR between 15 and 59 ml/min per 1.73 m2, anaemia defined as haemoglobin level <13 g/dL in men and <12 g/dL in women and a normal mean corpuscular volume. Exclusion criteria: Stage 5 CKD (eGFR < 15 ml/min per 1.73 m2)	NA	Direct health care costs and risk of hospitalisations are markedly increased in participants with CKD and these costs are higher if CKD coexists with comorbidities, including anaemia	None
Horbrand 2014 (175)	To estimate treatment costs of originator or biosimilar ESA in people with renal anaemia and undergoing dialysis	Retrospective cross-sectional study	CKD stage 5 on haemodialysis and with renal anaemia N=16,895 Mean age: 67 years (SD 15) Subgroups of interest: Dialysis stable cohort (n=6177): treated with a specific erythropoiesis-stimulating agent for at least 6 quarters Mean age: NR, (at least 1.5 years)	Inclusion criteria: CKD stage 5 included in the medical claims database with international classification of diseases codes for CKD and dialysis or dependence on enabling machines or devices or with the German medical fee schedule items that relate to receiving chronic haemodialysis	Originator and biosimilar erythropoiesis stimulating agents Darbepoetin alfa Epoetin theta (Biopoin) Epoetin theta (Eporatio) Epoetin alfa (Erypo) Methoxy polyethylene glycol-epoetin beta Epoetin beta Epoetin alfa (Abseamed) Epoetin alfa (Binocrit) Epoetin alfa (Epoetin alfa Hexal) Epoetin zeta (Retacrit)	Using biosimilars in people with CKD and renal anaemia provides a noteworthy economic savings potential	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
					Epoetin zeta (Silapo)		
Darsonval 2017 (171)	To determine the cost impact of administering methoxy polyethylene glycol-epoetin beta every 4 weeks compared to administration of ESA one to three times a week in patients undergoing dialysis	Single centre retrospective before and after study with cost-minimisation analysis	Patients undergoing haemodialysis with anaemia who were treated with an erythropoiesis-stimulating agent N=27 Mean age: 70.3 years (SD 11.5)	Inclusion criteria: Age >= 18 years, undergoing haemodialysis, anaemia treated with an erythropoiesis-stimulating agent one to three times a week over a 6-month period, and then methoxy polyethylene glycol-epoetin beta once every 4 weeks over a subsequent 6-month period	Intervention: methoxy polyethylene glycol-epoetin beta once every 4 weeks Comparator: erythropoiesis-stimulating agent one to three times a week	Treating anaemia with methoxy polyethylene glycol-epoetin beta once every 4 weeks compared to treatment with an erythropoiesis-stimulating agent one to three times a week in patients undergoing haemodialysis may reduce costs related to the management of these patients in a hospital environment	None
Rottembourg 2015 (173)	To evaluate the direct cost of anaemia treatment in patients on haemodialysis and to determine factors that predict costs at one year Secondary objectives: To explore the impact of cyclic fluctuations in haemoglobin levels on the cost of anaemia treatment	Retrospective study of patient data from 5 centres in France	Haemodialysis patients with haemoglobin assays N= 636 Mean age 66.6 years (SD 14.9) Subgroups of interest: Haemoglobin categories (if <75 % of time in respective category) Ideal: 10 to 12 g/dL (n=119) High: >12 g/dL (n=61) Low: <10 g/dL (n=18) Fluctuating (n=438)	Inclusion criteria: Haemodialysis; had at least one haemoglobin assay per month and were monitored for at least 4 months; died or received kidney transplant during 2009 with at least one haemoglobin assay during study period	NA	Treatment of anaemia with ESA accounted for 90% of the direct costs although with great disparities. Factors predictive of direct costs at one year included centres, patients in the low haemoglobin category and dialysis duration of less than 2 years.	None
Rottemborg 2011 (172)	To compare the impact of the switch from originator iron	Observational before and after study, retrospective	Stable haemodialysis patients receiving intravenous iron	Inclusion criteria: Stable haemodialysis patients receiving	Intervention: Iron sucrose similar (5-mL ampoules with 100 mg iron)	The switch from originator iron sucrose to an iron sucrose similar	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
	sucrose to iron sucrose similar on haemoglobin levels and iron parameters in stable haemodialysis patients receiving twice weekly ESA Secondary objectives: To describe the usage of intravenous iron and ESA and estimate anaemia drug expenditure	and prospective data collection.	weekly and intravenous ESA twice weekly. N=75 Mean age: 63.4 years (SD 15.2)	intravenous iron weekly and intravenous ESA twice weekly. Patients undergoing chronic haemodialysis (three times a week) and at least 60 dialysis sessions during both periods; at least one prescription of intravenous iron during the study; erythropoiesis-stimulating agent (darbepoetin-a) once every 2 weeks	injected intravenously once a week over 27 week period Comparator: Iron sucrose (originator) (5-mL ampoules with 100 mg iron) injected intravenously once a week over 27 week period	preparation led to a significant decrease in haemoglobin levels and iron indices and a need to increase anaemia drug consumption in previously well-controlled haemodialysis patients. The economic rationale for switch to a less expensive iron preparation was negated by the increase in total drug costs.	
Therasse 2018 (174)	To assess the impact of a change in funding relating to ESA use during dialysis activity on the budget of 37 Public University Hospitals in Paris	Observational before and after study. Budget Impact analysis	Haemodialysis patients requiring ESA 27 hospitals Age not reported	Inclusion criteria: 20 University Public University Hospitals in Paris that deployed SAP (Engineered Resource Planner) software; the consumption of erythropoiesis-stimulating agent in the year 2013 in more than 50% of care units carrying out medicine, surgery or obstetrics activities (as other activities and home care facility are not funded in the same way) Exclusion criteria:	Comparators: Before switching funding sources (ESA funded on top of diagnostic related groups) After switching (ESA funded within diagnostic related groups)	There was no change in medical practices of dialysis after the delisting of ESA from the out-of-diagnostic related groups list. However, the budget impact of the change in funding is negative for the French hospitals, although it is positive to the French National Health Insurance. With the price decrease, the ESA are more costly for hospitals (not funded on top-of-diagnostic related groups), but less costly for society.	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
				Care units which do not carry out medicine, surgery or obstetrics activities			
Albero Molina 2012 (182)	To analysis effectiveness of monthly treatment with SC CERA vs weekly SC erythropoietin for maintaining Hb levels and the evaluate dose equivalence of the 2 treatments	Single centre, prospective before and after study with some analysis of costs	Patients of the haemodialysis unit of a single hospital previously treated with erythropoietin alpha or beta N=30 Mean age 71.7 years (SD 13.8)	Inclusion criteria: Age >18 years, on haemodialysis >6 months, Kt/V ≥1.2, previously treated with erythropoietin alpha or beta administrated subcutaneously 1 to 3 times per week with a stable dose for 3 months, baseline Hb levels (mean of monthly Hb in past 3 months) 10.5-13 g/dL, serum ferritin ≥100ng/ml, and transferrin saturation ≥20% Exclusion criteria: Transfusions, major surgery in past 3 months, vascular access procedures in the past 3 months, uncontrolled blood pressure (≥160/100mmHg), systemic haematological conditions, symptomatic inflammatory conditions, and uncontrolled infections. During the study patients who presented with	Monthly SC dose of CERA vs SC erythropoietin alpha or beta 1 to 3 times per week. All patients switched to CERA treatment at the beginning of the study. Patients received different doses based on their requirements and, in the case of CERA, previous dosing of erythropoietin. The dose of CERA was adjusted during the study to maintain Hb at appropriate levels.	Replacing erythropoietin with CERA did maintain Hb at baseline levels but resulted in an increase in dose and cost, although this may be variable (depeding on prices in each hospital)	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
				clinical processes that could intefere with Hb levels.			
Bucalo 2018 (196)	To evaluate the impact of the anaemia control model for anaemia in haemodialysis	Before and after study	Haemodialysis patients with anaemia Anaemia control model phase 1: n=213 Mean age 66.29 years (SD 14.82) Usual practice (used as control): n=219 Mean age 67.05 years (SD 14.54) Anaemia control model phase 2: n=218 Mean age 67.15 years (SD 14.7)	Inclusion criteria: Age >18 years, at least one haemodialysis session and one haemoglobin determination	Intervention: anaemia control model (software tool to help clinician decision making for prescription of erythropoiesis stimulating agents and iron for anaemia in haemodialysis patients) Comparator: usual practice	The anaemia control model helps to improve anaemia results in haemodialysis patients, minimises the risks of treatment with erythropoiesis stimulating agents and reduces costs	None
Darba 2018 (183)	To evaluate the economic impact of oral iron Fisiogen Ferro Forte for iron deficiency in CKD patients in Spain	Budget impact model	Peritoneal dialysis patients with iron deficiency N=NR Age NR	Inclusion criteria: Peritoneal dialysis patients with iron deficiency who were candidates for intravenous iron due to a lack of response to oral iron	Intervention: oral iron Fisiogen Ferro Forte Comparators: intravenous iron Ferinject, Venofer, and Feriv	An increase in use of Fisiogen Ferro Forte, with a decrease in use of intravenous iron, leads to overall budget savings of €775,464 for the Spanish National Health Service over 4 years for 2017-2020	None
Escudero-Vilaplana 2013 (184)	To conduct a cost-minimization analysis to determine the economic impact of the principal erythropoiesis stimulating agents used for anaemia in CKD in daily outpatient practice	Cost minimisation analysis	Patients treated with erythropoiesis stimulating agents for anaemia due to CKD (stage 2-5). N=409 Median age 77 to 78 across erythropoiesis stimulating agents. Subgroups of interest:	Inclusion criteria: Adult outpatients treated with erythropoiesis stimulating agents for anaemia due to CKD. Exclusion criteria: Change in erythropoiesis stimulating agent type during the 12	Not applicable	Lower doses of continuous erythropoietin receptor activator are used in clinical practice than recommended on label, directly influencing cost and treatment efficiency. Cost stratification based on iron deposits	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
	Secondary objectives: To determine patient-month cost based on the erythropoietin resistance index; to analyse the difference in cost between predialysis and peritoneal dialysis patients; and to analyse the association between iron deposits and erythropoiesis stimulating agent cost		Nondialysis Peritoneal dialysis	weeks prior to inclusion or change in dose in the last 4 weeks; variation in haemoglobin levels ± 1 g/dL in the last 4 weeks; haemodialysis or kidney transplant; multiple myeloma, myelodysplastic syndromes, active bleeding or chronic anaemia different from CKD		demonstrates that patients with low transferrin saturation index or ferritin require higher doses and therefore an associated higher cost. Guaranteeing adequate iron levels is essential in the rational use of erythropoiesis stimulating agents.	
Garcia 2014 (185)gar	To assess the economic impact of different erythropoiesis stimulating agents in a cost-minimisation analysis Secondary objectives: To assess the economic impact of different vitamin D analogues for secondary hyperparathyroidism	Retrospective cross-sectional study	CKD on haemodialysis and with anaemia (not defined but requiring erythropoiesis stimulating agents) N=473 Age not reported	Inclusion criteria: Adult haemodialysis patients treated with erythropoiesis stimulating agents and active vitamin D analogues	Epoetin Darbopoetin	Generally, epoetin and darbopoetin have similar costs.	None
Padulles-Zamora 2012 (186)	To evaluate the use and effectiveness of methoxy polyethylene glycol-epoetin beta in a group of pre-dialysis patients	Retrospective before and after study.	Patients with stage 3, 4, or 5 chronic kidney disease not currently receiving dialysis treatment and requiring anaemia treatment N=190	Inclusion criteria: Patients with stage 3, 4, or 5 chronic kidney disease not currently receiving dialysis who started treatment with methoxy	Intervention: methoxy polyethylene glycol-epoetin beta. Comparator: other ESA.	The change from other ESA to methoxy polyethylene glycol-epoetin beta caused no significant difference in the	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
	and perform a cost analysis comparing this to previous treatments with other ESA		Mean age 65 years (range 22-93)	polyethylene glycol-epoetin beta Exclusion criteria: Patients on dialysis		mean haemoglobin level reached but the percentage of those with haemoglobin >13g/dL was higher. The doses used in the switch to methoxy polyethylene glycol-epoetin beta were lower than the recommendations from the drug leaflet, with good control of haemoglobin within 12 months after making the switch and the mean cost was also lower than expected.	
Sanz-Granda 2009 (187)	To estimate the cost in Spain of treating anaemia secondary to chronic renal failure with darbepoetin alpha vs epoetin alpha Secondary objectives: Investigate the role of the route of administration as a driver of costs	Cost minimisation analysis from the perspective of a hospital pharmacy. The study included a literature review investigating the clinical efficacy of the 2 treatments (found to be equivalent, hence the choice of a cost-minimisation analysis) and associated resource use (i.e. dosing information). The time horzon for analyses was aligned with the included studies (usually 24 weeks).	Patients with anaemia secondary to chronic renal insufficiency N=NR Age NR Subgroups of interest: Patients in dialysis and pre-dialysis were considered separately. A sub analysis was also performed in patients receiving IV vs SC darbepoetin alpha and epoetin alpha.	Inclusion criteria: Studies included in the literature review: present direct comparison of darbepoetin alpha vs epoetin alpha, either in terms of costs or efficacy; report doses used in the study; use of doses recommended in Spain Exclusion criteria: Studies using doses that are not recommended/authorised in Spain	Darbepoetin alpha (IV or SC) vs epoetin alpha (IV or SC)	Treatment of anaemia secondary to chronic renal insufficiency with darbepoetin alpha generates cost savings when compared with epoetin alpha. Among patients on dialysis, estimated cost savings are higher when darbepoetin alpha is administered intravenously than subcutaneously.	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
Bolasco 2011 (179)	To undertake a long-term comparison of haemodialysed patients who had received IV administration of ESA for 1 year and subsequently switched to subcutaneous administration to examine effects on comorbidity and costs Secondary objectives: To determine effects of switching from IV to subcutaneous administration of ESA on efficacy and safety	Retrospective before and after study	Haemodialysis patients N=75 Mean age 59.4 years (SD 21.3)	Inclusion criteria: Haemodialysed patients who had received IV administration of ESA for 1 year and subsequently switched to subcutaneous administration, without any important or different comorbidity factors capable of inducing EPO-resistance during the 2 year retrospective observation period Exclusion criteria: Acute and chronic infections, immunosuppressant therapy, chemotherapy, malignancies, haemorrhages, haemoglobinopathies, active systemic diseases, uncompensated hepatopathies, malnutrition, poorly functioning arteriovenous fistulas, heart disease, poor glycaemic control, life expectancy < 12 months, other conditions potentially resulting in drop-out	Intervention: Subcutaneous administration of erythropoiesis stimulating agents for 12 months Comparator: IV administration of erythropoiesis stimulating agents for 12 months	The subcutaneous route of administration of erythropoiesis stimulating agents was considered the safest. With the exception of darbepoetin there were significant cost savings, and minimum discomfort for patients, with the switch from IV to subcutaneous administration.	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
Di Iorio 2018 (178)	To determine costs of erythropoiesis stimulating agents whilst using an additional ultrafilter (Estorclean PLUS) to produce ultrapure dialysis water	Post-hoc analysis of a randomised cross over study	Haemodialysis patients N=29 Mean age 71 years (SD 16)	Inclusion criteria: Patients treated with epoetin alfa and darbepoetin alfa Exclusion criteria: Patients treated with methoxy-polyethylene-glycol-epoetin beta; inflammatory diseases; therapy with anti-inflammatory drugs or steroids; signs of malnutrition such as abnormal serum levels of albumin, cholesterol or triglycerides change in dialysis prescription or ESA therapy within the last 3 months.	Intervention: dialysis with EstorClean PLUS ultrafilter Comparator: conventional dialysis	When using the EstorcleanPLUS filter there were savings of €11 per patient per month with epoetin alfa and €30 per patient per month with darbepoetin alfa to treat anaemia in dialysis patients.	None
Pessina 2015 (177)	To assess healthcare resource utilization and costs associated with anaemia in non-dialysis dependent CKD	Retrospective observational study	Non-dialysis CKD stage 3b-5 with anaemia N=1654 Age NR Subgroups of interest: CKD stage 3b treated CKD stage 3b non treated CKD stage 4 treated	Inclusion criteria: Non-dialysis CKD stage 3b-5 with anaemia (≥ 2 haemoglobin measurements 1 week–3 months apart < 13 g/dL for males, < 12 g/dL for females)	Intervention: treated for anaemia with erythropoiesis stimulating agents and/or oral iron Comparator: not treated for anaemia	Anaemia management may reduce anaemia-related outpatient services and complications costs of cardiovascular disease	None
Carrilho 2014 (180)	To assess the impact of a frequent fixed low dose of iron sucrose on erythropoiesis stimulating agent	Before and after study	Haemodialysis patients with anaemia N=51 Mean age 66 years (SD 14)	Inclusion criteria: Stable haemodialysis; receiving maintenance iron and erythropoiesis stimulating agents;	Intervention: erythropoiesis stimulating agent once weekly plus three times weekly fixed dose intravenous 10 mg	Target haemoglobin was achieved by administration of less but more frequent iron. There was also a	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
	responsiveness index in prevalent haemodialysis patients Secondary objectives: To describe intravenous iron and erythropoiesis stimulating agent consumption for anaemia and global anaemia drug expenditure		Subgroups of interest: Stable dialysis	major blood losses were not evident, disregard of ferritin levels if they were between 150 and 600ng/mL. Exclusion criteria: Haematological, active oncological disease or recent blood transfusion.	iron sucrose Comparator (baseline): erythropoiesis stimulating agent once weekly variable, intermittent dose of intravenous iron sucrose	reduction in erythropoiesis stimulating agent dose, suggesting an improvement in erythropoiesis. The possibility of having an intravenous route for three times weekly iron administration should be explored	
Kourlaba 2014 (147)	To assess cost-effectiveness of darbepoetin alfa compared to other erythropoiesis stimulating agents for anaemia due to chronic kidney disease in patients on haemodialysis or peritoneal dialysis	Economic evaluation	CKD on dialysis and with anaemia (two haemoglobin targets 10 (±1) g/dL and 11 (±1) g/dL) requiring erythropoiesis stimulating agents N = NR Age: NR	NR	Darbepoetin alfa Originator and biosimilar short-acting erythropoiesis stimulating agents Pegylated epoetin beta	Compared to other erythropoiesis stimulating agents, darbepoetin alfa may be the most cost saving treatment to manage anaemia in CKD patients on dialysis	None
Fakeeva 2015 (181)	To assess the cost effectiveness of darbepoetin alfa compared with other erythropoiesis stimulating agents for anaemia in patients on haemodialysis or peritoneal dialysis	Cost consequence analysis	Patients with haemodialysis or peritoneal dialysis and anaemia N=NR Age: NR	Inclusion criteria: Patients with haemodialysis or peritoneal dialysis and anaemia	Intervention: darbepoetin alfa Comparator: other erythropoiesis stimulating agents	Darbepoetin alfa for anaemia in patients on haemodialysis or peritoneal dialysis is more cost-effective than other alternative erythropoiesis stimulating agents	None
Krysanov 2018 (148)	To undertake an economic evaluation of biosimilar epoetin alpha, originator darbepoetin alpha and pegylated	Economic evaluation	CKD patients on haemodialysis and requiring erythropoiesis stimulating agents for anaemia N=NR	NR	Biosimilar epoetin alpha Originator darbepoetin alpha Pegylated epoetin beta	Biosimilar epoetin alfa is consistently cost saving over treatment with originator epoetin alfa and darbepoetin alfa in	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
	epoetin beta in CKD patients on haemodialysis		Age: NR			people with CKD requiring haemodialysis	
Burnier 2009 (170)	To determine whether cost savings would be possible with twice weekly dosing of ESA compared to other regimens in haemodialysis patients Secondary objectives: To help establish a benchmark for sharing best practice among European haemodialysis centres by describing the whole process of ESA delivery at each study centre	Observational study	21 hospitals across Belgium, France, Italy, the Netherlands, Spain, Sweden, Switzerland, the UK Haemodialysis patients receiving ESA N=2,984 Age NR	NR	Various erythropoiesis stimulating agent regimens (thrice-weekly, twice-weekly, once-weekly, once every 2 weeks and once-monthly) Darbepoetin alfa every 2 weeks	This was the first comprehensive study to assess the process of anaemia management in European haemodialysis centres. ESA administration has quantifiable labour and material costs which are affected by dosing frequency where costs savings were seen for administration twice weekly. There is high variation in the operational costs between centres due to differences in environmental and structural factors and because practice patterns vary considerably.	None
Eriksson 2015 (169)	To assess the impact of anaemia on burden of disease in patients with CKD stages 3–4 and in patients on dialysis	Cross-sectional study	France, Germany, Italy, Spain, UK CKD stage 3 or 4 or dialysis patients with anaemia N=1336 Mean age 63.7 years (SD 15.1) Anaemia: n=864 Subgroups of interest:	Inclusion criteria: CKD stage 3 (eGFR 30 to <60 mL/min/1.73 m2), stage 4 (eGFR 15 to < 30 mL/min/1.73 m2), or dialysis; anaemia defined as Kidney Disease Improving Global Outcomes Clinical Practice Guideline: serum	Not applicable	CKD patients with anaemia typically have a lower HRQoL than those without anaemia. The impairment attributed to anaemia was greater in patients with CKD stages 3 or 4 without dialysis than in those receiving dialysis. CKD and anaemia	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
			Non dialysis stage 3 Non dialysis stage 4 Dialysis	haemoglobin <12 g/dL in women and < 13 g/dL in men and/or current use of erythropoiesis stimulating agents		may have an impact on patient HRQoL similar to other chronic conditions such as diabetes, epilepsy or certain forms of cancer. Anaemia in patients with CKD may have a substantial impact on healthcare resource utilisation and work productivity; further research is needed to evaluate humanistic impact and direct economic burden.	
Ingrasciotta 2021	The study was aimed at investigating direct healthcare costs of CKD patients treated with ESA and the potential savings achievable by increasing the use of biosimilars and preventing inappropriate ESA use	Retrospective cohort, observational study, budget Impact analysis	Patients with new ESA users in Italy with CKD N=7810, Age (Mean (SD)): 75.6 (13.5) years Subgroup of interest : CKD stage I-III, N=1179 CKD Stage IV-V, N=776 Dialysis, N=966 Mean age not reported for subgroups	Inclusion Criteria: Patients (a) had at least two ESA pharmacy claims during the study period (first pharmacy claim: Index date, ID) separated by <365 days and no ESA pharmacy claims within 1 y prior to ID (ie, incident ESA users); (b) had at least 365 days pre- and post-index continuous enrolment in their database; c) had at least one medical claim with a diagnosis of CKD any time prior to the ID, including the ID. Finally, among incident	ESA treatment i. epoetin alfa (ATC: B03XA01; Eprex, Abseamed, Binocrit); ii. epoetin beta (B03XA01; Neorecormon); iii. darbepoetin alfa (B03XA02; Aranesp); iv. epoetin zeta (B03XA01; Retacrit); and v. methoxy polyethylene glycolepoetin beta (B03XA03; Mircera).	Higher use of lowest cost ESA, prevention of inappropriate ESA use as well as other strategies aimed at slowing down the progressive renal impairment are essential for minimizing clinical and economic burden of CKD	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
				ESA users with CKD, all patients with known CKD stage were identified			
Riccio 2020 (192)	The aim of this study was to perform a cost-minimisation analysis of oral Sucrosomial iron, compared with IV iron gluconate from an Italian societal perspective	Randomised, open-label controlled trial, cost-minimisation analysis	Patients with ND-CKD and iron-deficiency anaemia in Italy N=99, Age (Mean (SD)): 51.3 (15.3) years Randomised groups: Oral : N = 66; Age (Mean (SD): 53.1 (15) years IV: N = 33; Age (Mean (SD)): 47.6 (16) years	Inclusion criteria: Age >18 years, estimated glomerular filtration rate (eGFR, Modification of Diet in Renal Disease equation) ≤60 mL/min/1.73 m2, Hb levels ≤12 g/dL, plasma ferritin levels ≤100 ng/mL, transferrin saturation (TSAT) ≤25%, parathormone (PTH) serum levels between 30 and 300 pg/mL, according to the suggested values for kidney disease stage and calcium and phosphate plasma levels within their normal values (i.e. <10.5 and <4.5 mg/dL, respectively). Exclusion criteria: High-sensitivity C-reactive protein (hsCRP) levels ≥5 mg/L, presence of inflammatory, infectious disease or surgical interventions in the last 3 months, haematological disorders, bleeding	1. IV iron gluconate, divided into eight administrations of 125 mg diluted in 250 ml normal saline, infused weekly for 3 months (Group IV); 2. Oral capsule (one/day) containing 30 mg of pyrophosphate liposomal iron and 70 mg of ascorbic acid (Sideral® Forte, Pharmanutra Spa) for 3 months (Group OS)	Study showed that oral Sucrosomial® iron could offer specific advantages in terms of potential savings and allowed identifying some implications for future research. Such advantages still persist with the new single dose IV iron formulation available in the market, although to a lesser extent	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
				or blood transfusions in the last 6 months, malignancies, treatment with immunosuppressive drugs, severe malnutrition, concomitant severe liver or CV disease, chronic alcohol or drug abuse within the past 6 months, known hepatitis B or C infection, pregnant or lactating women.			
Rognoni 2019 (193)	To assess the clinical and economic implications of switching from IV ferric gluconate (FG) to ferric carboxymaltose (FCM) on achievement of adequate haemoglobin (Hb) values and iron balance	Retrospective cohort study, cost-minimisation analysis	HD patients with iron deficiency anaemia in Italy N = 38; Age (Mean (SD)): 67 (15) years (range 39–91)	Inclusion Criteria: HD patients with iron deficiency, despite IV iron supplementation, were gradually switched from FG to FCM. Lack of efficacy in reaching Hb target values (Hb\10.5 g/dL), inadequate iron status (ferritin\200 lg/l or TSAT\20%) or evidence of a progressive increase of the Erythropoietin Resistance Index [ERI = erythropoietin (international units/week per kg)/Hb(g/dL)] with consequently increasing ESA costs.	Induction phase: FG of 15 infusions of 62.5 mg each (1000 mg cumulative elemental iron). FCM 10 infusions of 100 mg each were applied (for FCM a single maximum daily dose of 200 mg iron should not be exceeded in HD patients) (1000 mg cumulative elemental iron). Maintenance Schedule: FCM and FG consisted of 100–200 mg and 125 mg of elemental iron, respectively, given every 2–4 weeks, with corrections based	IV ferric carboxymaltose in haemodialysis patients was shown to provide a favourable efficacy profile over IV ferric gluconate, with a lower cost per patient, mainly driven by a consistent reduction of ESA consumption	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
					on Hb values (>=10.5 g/dl).		
Darba 2020 (195)	To review the characteristics of CKD patients who attended primary and specialised care centres in Spain, and to analyse patients use of medical resources and direct medical costs of specialised care.	Retrospective multicentre observational study, cost analysis	Patients with CKD with different comorbidities, who attended primary and specialised healthcare centres in Spain N=24,389; Age (Mean (SD)): 60.79 (19.69) years	Inclusion Criteria: Patients with CKD who attended primary and specialised healthcare centres in Spain between 2011 and 2017. Any healthcare visit was considered an admission (inpatient and outpatient) in each dataset. Primary care admissions are inherently outpatient and specialised care inpatient and outpatient admissions are discernible by the length of stay parameter, including both inpatient and outpatient care.	NR	The costs of specialised care decreased with the length of hospital stay reduction. Cardiovascular risk factors were crucial in in-hospital mortality. The study provides population-based data to assist decision-makers at the national level and to contribute to worldwide evaluations and disease surveillance.	None
Borchert 2019 (194)	To compare ESA prescriptions, need for blood transfusions, hospitalisations, and healthcare costs of ND-CKD patients with diagnosed ID and/or anaemia treated with different types of iron treatment in Germany.	Retrospective cohort study, cost analysis	Patients with Non-dialysis Chronic Kidney Disease and iron deficiency/Anaemia in Germany N=1840, Age (Mean)=76.5 years Cohort are 1. Oral iron; N=37; Age (Mean)=77.1 years 2. IV low dose iron; N=37; Age (Mean)=76 years 3. IV high dose	Inclusion Criteria: Patients with an ICD-10-GM diagnosis code for ND-CKD stages 3 or 4, a diagnosis for ID/A, and incident iron treatment in 2014	Iron treatments 1. Oral 2. IV low dose (<1000mg/year) and 3. IV high dose (≥1000mg/year) based on ATC codes and Pharmacy Central Numbers.	The overall cost comparison between the matched cohorts showed that high dose IV iron treatment was associated with highest cost savings compared to oral and low dose IV iron in terms of total healthcare costs, costs for all-cause hospitalisations and blood	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
			iron; N=37; Age (Mean)=76.5 years			transfusions. High dose IV iron patients had the lowest share of blood transfusions and ESA treatment and the number of CV related hospitalisations was lower than in patients treated with oral iron	
Oliver 2020 (150)	The objective of this study was to develop a natural history model to characterise the consequences of anaemia in patients with CKD	Lifetime Markov model	CKD stage 3b with and without Anaemia, Age (Mean)=58 years Subgroup of Interest: CKD with Anaemia patients; N and age not reported	CKD stage 3b were modelled with and without anaemia (Hb 9-10 g/dL and Hb > 12 g/dL)	No Reported	Analysis supports that those without anaemia have increased LE and QALYs, and account for less costs to the healthcare system. Therefore, anaemia management, aligned with clinical guidelines, has the potential for better outcomes for both the patient and the healthcare system.	None
Karla 2020 (189)	To evaluate the impact of high-versus low-dose IV iron isomaltoside on the probability of retreatment with IV iron in iron-deficient ND-CKD patients.	Prospective observational study	Patients with ND-CKD in UK N=256; Age >=18 years	Inclusion Criteria: Patients diagnosed with iron deficiency anaemia as a consequence of CKD or IBD (on the basis of local definition or clinical judgement), treated on the doctor's discretion with Monofer® as standard treatment according to current practice Exclusion Criteria: Patients diagnosed	Iron isomaltoside 1000/ferric derisomaltose (IIM)	The >1000 mg iron isomaltoside regimen reduced the probability of retreatment, achieved a greater haemoglobin response irrespective of erythropoiesis-stimulating agent treatment, and reduced the total number of appointments required, compared to the ≤1000 mg regimen. Many of	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
				with both CKD and IBD		the patients who received ≤1000 mg of iron were eligible for >1000 mg, indicating that there was considerable underdosing in this study	
Toft 2020 (190)	To identify major clinical consequences of anaemia in DD and ND patients with severe CKD	Retrospective cohort study	Patients with severe CKD with anaemia in Denmark N=28,510; Age (Median (IQR)): 76 (13.9) years Subgroup of Interest 1. Anaemia grade 1 (10–12/13 g/dL Hgb in women/men); N=10,033; Age (Median (IQR)): 77 (13.7) years 2. Anaemia grade 2 (8–10 g/dL Hgb); N=9632; Age (Median (IQR)): 77 (13.8) years 3. Anaemia grade 3+ (< 8 g/dL Hgb); N=4740; Age (Median (IQR)): 74 (14.5) years in NDD and DD patients (Number of patients and Age not reported)	Inclusion Criteria: Patients with severe CKD with anaemia were defined as individuals with two plasma-creatinine tests at least 3 months (90 days) apart showing an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 in the period 2000–2016. During 2009–2016, CKD patients (who had either prevalent severe CKD on Jan 1, 2009 or incident severe CKD between 2009 and 2016) to different anaemia grade cohorts. Excluded Criteria: Patients with any of the following at any time prior to the index date: any cancer (except non-melanoma skin cancer), hereditary hematologic disease, chronic inflammatory disease,	NR	Among NDD or DD patients with severe CKD, presence and severity of anaemia were associated with increased risks of incident dialysis for NDD patients and with acute hospitalisations, death and MACE for all patients.	None

Reference	Objectives	Design	Population	Inclusion/exclusion criteria	Interventions	Conclusions	Values used in economic model
				gastrointestinal bleeding, or organ transplants.			
Pages 2020 (191)	To evaluate how cost and effectiveness were impacted when chronic haemodialysis patients were switched from an original iron sucrose product to an iron sucrose similar preparation.	Retrospective cohort, sequential observational study, cost-minimisation analysis	Patients with chronic haemodialysis remained stable during the entire study N=105, Age (Mean (SD)): 64.6 (15.1) years	Inclusion criteria: a) adult patients; b) undergoing chronic HD at the centre for at least 3 months before 1 September 2014; c) at least 2 administrations of IS in P1 and ISS in P2; and d) at least one iron status assessment during both periods. Exclusion Criteria: Patients had iron hypersensitivity and/or haemoglobinopathy.	ESA treatments administered during or at the end of the dialysis session. i) Epoetin alfa; 1-3 injections/week ii) Darbepoetin alfa; 1 injection/week or 15 days and iii) methoxy polyethylene glycol-epoetin beta (MPEG-epoetin beta) Monthly injection. Doses were adjusted in order to maintain a target Hb between 10.5 and 12 g/dL, serum ferritin ≤ 500 ng/ml and TSAT ≥ 30%	The cost minimisation analysis suggests that for chronic haemodialysis patients, iron sucrose and iron sucrose similar have the same efficacy and that using iron sucrose similar was more expensive in 66.7% of iterations	None

Abbreviations: CERA: continuous erythropoietin receptor activator; CI: confidence interval; CKD: chronic kidney disease; IU: international unit; IV: intravenous; NR: not reported; RR: relative risk; SC: subcutaneous; SD: standard deviation; UI: international unit; UK: United Kingdom.

Appendix J. Clinical outcomes and disaggregated results from the model

J.1 Clinical outcomes from the model

The clinical outcomes for pre-dialysis patients treated with roxadustat and ESA are presents in Table 151. No differences are observed among intervention and comparator in terms of survival or probability of being dialysis free. In terms of proportion of patients under the anaemia established Hb threshold of 11 g/dL, more patients are non-anaemic at 5,10, and 20 year when treated with ESA compared to roxadustat. The frequency of adverse events is higher for ESA in the case of stroke and MI, and higher for roxadustat in the case of VAT. All in all, both intervention and comparator result in similar QALYs with a positive benefit associated to roxadustat.

Table 151: Base-case clinical outcomes for pre-dialysis anaemic CKD patients treated with roxadustat or ESA

	Roxadustat	ESA
Survival		
5 year	[redacted]	[redacted]
10 years	[redacted]	[redacted]
20 years	[redacted]	[redacted]
Discounted life years per patient	7.923	7.923
Probability of being dialysis free (if alive)		
5 year	[redacted]	[redacted]
10 years	[redacted]	[redacted]
20 years	[redacted]	[redacted]
Proportion in state (if alive)		
5 years: <11 Hb	[redacted]	[redacted]
10 years: <11 Hb	[redacted]	[redacted]
20 years: <11 Hb	[redacted]	[redacted]
Lifetime event rates per patient		
Stroke	0.125	0.129
MI	0.201	0.258
VAT	0.157	0.043
Health related quality of life per patient		
Mean Discounted QALYs	4.137	4.126

Abbreviations: Hb, haemoglobin; QALY: quality-adjusted life year; MI: myocardial infarction; VAT: vascular Access thrombosis

J.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

The predicted QALY per patients by health state and due to adverse events per patient for the base case cost-effectiveness analysis are presented in Table 152. As seen before, roxadustat is associated with small incremental QALYs. When segmentizing this increment by Hb levels, ESA are associated with incremental

QALYs in the Hb ranges 8.00-8.99, 9.00-9.99, 10.00-10.99 and >13 g/dL. As well, ESA generate more QALYs when considering adverse events. Roxadustat is associated with incremental QALYs in all other segments.

Table 152: Summary of QALY per patient by health state

Health state	QALY roxadustat	QALY ESA	Increment	Absolute increment	% absolute increment
Hb <7	0.014	0.010	0.004	0.004	40.98%
Hb 7.00 - 7.99	0.068	0.038	0.030	0.030	80.35%
Hb 8.00 - 8.99	0.216	0.233	-0.017	-0.017	-7.14%
Hb 9.00 - 9.99	0.549	0.793	-0.244	-0.244	-30.78%
Hb 10.00-10.99	1.293	1.432	-0.139	-0.139	-9.70%
Hb 11.00-11.99	1.437	1.092	0.345	0.345	31.60%
Hb 12.00-12.99	0.496	0.440	0.056	0.056	12.75%
Hb >= 13	0.083	0.107	-0.024	-0.024	-22.18%
Adverse events decrement	-0.019	-0.018	-0.001	-0.001	2.94%
Total	**4.137**	**4.126**	**0.012**	**0.012**	**0.28%**

Abbreviations: Hb, haemoglobin; ESA, erythropoiesis-stimulating agents

The predicted costs use by health state for the base case cost-effectiveness analysis are presented in Table 153. Overall, costs per patient are higher in the case of roxadustat and given the distribution of patients in Hb levels along the modelled horizon, this is driven by the Hb ranges <7, 7.00-7.99, 11.00-11.99 and 12.00-12.99. Roxadustat is associated with lower costs than ESA in all other ranges.

Table 153: Summary of costs by health state

Health state	Cost roxadustat	Cost ESA	Increment	Absolute increment	% absolute increment
Hb <7	£741	£528	£213	£213	40.36%
Hb 7.00 - 7.99	£3,385	£1,086	£2,299	£2,299	211.65%
Hb 8.00 - 8.99	£9,366	£9,852	-£485	-£485	-4.93%
Hb 9.00 - 9.99	£20,688	£32,678	-£11,990	-£11,990	-36.69%
Hb 10.00-10.99	£48,611	£55,306	-£6,695	-£6,695	-12.11%
Hb 11.00-11.99	£47,610	£32,669	£14,940	£14,940	45.73%
Hb 12.00-12.99	£14,026	£11,650	£2,376	£2,376	20.39%
Hb >= 13	£2,584	£3,149	-£565	-£565	-17.95%
Total	£147,012	£146,919	£93	£93	0.06%

Abbreviations: Hb, haemoglobin; ESA, erythropoiesis-stimulating agents

The predicted resource use by category of cost for the base case cost-effectiveness analysis are presented in Table 154. Costs are equal for both intervention and comparator in the case of haemodialysis, peritoneal dialysis, and monitoring. Roxadustat is associated with higher costs than ESA in terms of drug of interest cost, vascular access thrombosis, and blood transfusions. On the other hand, ESA

are associated with higher costs than ESA in terms of treatment of interest administration, IV iron, IV iron administration, stroke, and MI.

Table 154: Summary of predicted resource use by category of cost

Item	Cost Roxadustat	Cost ESA	Increment	Absolute increment	% absolute increment
Haemodialysis	£92,739	£92,739	£0	£0	0%
Peritoneal Dialysis	£27,628	£27,628	£0	£0	0%
Treatment (drug)	£22,925	£22,334	£591	£591	3%
Treatment (administration)	£0	£749	-£749	-£749	-100%
Monitoring appointments	£1,488	£1,488	£0	£0	0%
IV iron (drug)	£5	£10	-£5	-£5	-48%
IV iron (administration)	£38	£69	-£31	-£31	-45%
Stroke	£850	£878	-£28	-£28	-3%
MI	£485	£621	-£137	-£137	-22%
Vascular Access Thrombosis	£447	£122	£324	£324	265%
Blood transfusion	£409	£281	£128	£128	46%
Total	£147,012	£146,919	£93	£93	0.06%

Abbreviations: ESA, erythropoiesis-stimulating agents; IV, intravenous; MI, myocardial infarction.

Appendix K. Checklist of confidential information

This appendix is provided separately

Appendix L. Clinical trials data of dialysis population (HIMALAYAS, PYRENEES, SIERRAS and ROCKIES)

In dialysis-dependent population, four active-controlled trials namely HIMALAYAS, PYRENEES, SIERRAS and ROCKIES were conducted. HIMALAYAS was a global phase III, randomised, open-label, active-controlled study to evaluate the efficacy and safety of roxadustat in the maintenance treatment of anaemia in incident-dialysis (ID) patients. PYRENEES and SIERRAS were phase III, randomised, open-label, active-controlled studies to evaluate the efficacy and safety of roxadustat in the maintenance treatment of anaemia in ESRD patients on stable dialysis (SD). ROCKIES was a phase III, multicentre, randomised, open-label, active-controlled study to evaluate the efficacy and safety of roxadustat for the treatment of anaemia in CKD patients on dialysis.

L.1 Summary of methodology

L.1.1 HIMALAYAS

HIMALAYAS (47) was a phase III, randomised, open-label, active-controlled study in incident dialysis patients. As depicted in Figure 37, the study consisted of three periods: screening period (up to 6 weeks), treatment period (minimum of 52 weeks, maximum up to approximately 4 years) and a post-treatment follow-up period (4 weeks) (47).

Eligible patients were randomised (1:1) to receive roxadustat or epoetin alfa (47):

- Roxadustat orally dosed TIW, or
- Epoetin alfa IV/SC, dosed according to epoetin alfa package insert or SmPC

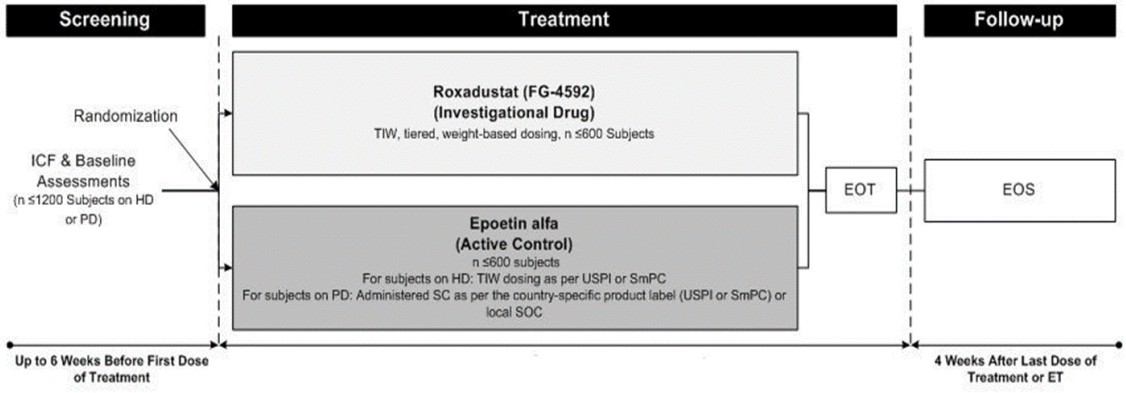
The initial roxadustat dose was based on a tiered, weight-based dosing scheme:

- Weight ≤70.0 kg: 70 mg
- Weight >70.0 kg to ≤160.0 kg: 100 mg

Roxadustat was dosed orally TIW throughout the treatment period, except if a patient required <20 mg TIW to maintain Hb levels in the maintenance phase, then the dosing frequency was reduced in a step-wise fashion to twice weekly, once weekly, then once every 2 weeks. Dose adjustments occurred according to two dosing

phases: during the Hb correction phase (with the goal to attain the targeted Hb range of 10-12 g/dL) and during the Hb maintenance phase (with the goal to maintain the Hb in the target range). From week 4 and every 4 weeks thereafter, dose adjustments were permitted (47).

Figure 37: Study design for HIMALAYAS trial



Abbreviations: EOS: end of study; EOT: end of treatment; ESA: erythopoesis-stimulating agent; ET:early termination; HD: Haemodialysis; ICF:informed consent form; n: number of patients; IV:intravenous; PD:peritoneal dialysis; SmPC: summary of product characteristics; SOC: standard of care; SC: subcutaneous; TIW: three times a week; USPI: US Package Insert.

L.1.2 PYRENEES

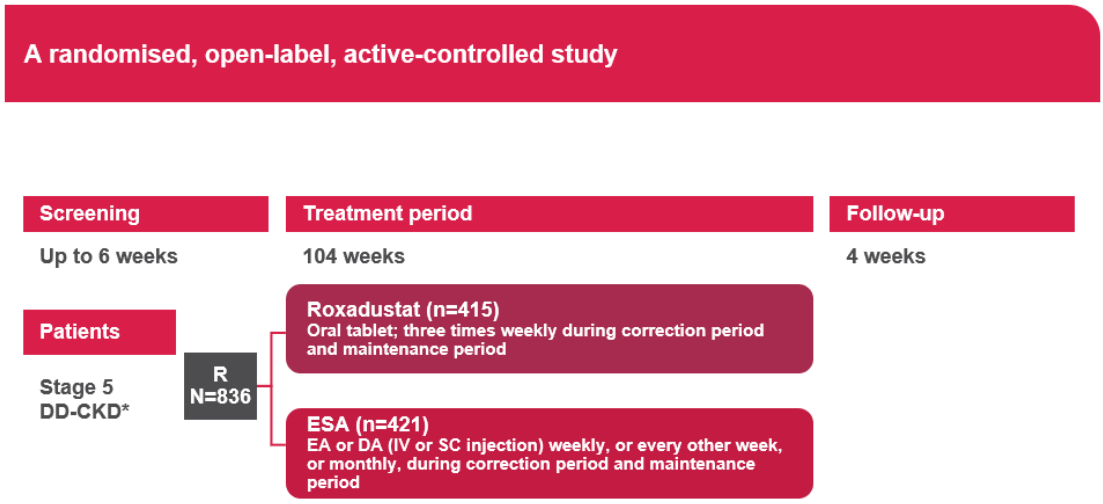
PYRENEES (44) was a phase III, multicentre, randomised, open-label, active-controlled study to assess the efficacy and safety of roxadustat treatment in adult patients with ESRD who were on stable haemodialysis or peritoneal dialysis and on stable treatment with epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa for anaemia. As depicted in Figure 38, the study consisted of three study periods: screening period (up to 6 weeks), treatment period (minimum of 52 weeks, maximum of 104 weeks) and a post-treatment follow-up period (4 weeks) (44).

Eligible patients were randomised to receive roxadustat or ESA (44):

- Treatment group 1: patients were switched from epoetin or darbepoetin alfa treatment to roxadustat
- Treatment group 2: patients continued with current ESA treatment (epoetin alfa if pre-treated with any epoetin [i.e. epoetin alfa, beta, theta, zeta, delta, or omega] and darbepoetin alfa if pre-treated with darbepoetin alfa). Patients were treated with approximately the same average weekly dose as prior to randomisation. Patients were not allowed to switch from epoetin alfa to darbepoetin alfa, or vice versa, during the treatment period

Dose adjustments were permitted at 4 weekly intervals from week 4 onwards. These adjustments were aimed at keeping patients' Hb levels between 10.0 to 12.0 g/dL and were based on current Hb levels and change in Hb over the preceding 4 weeks. Deviation from the 4-week period was allowed anytime during the study in case of Hb rate of rise >2 g/dL within 4 weeks or Hb ≥13.0 g/dL) (44).

Figure 38: Study design for PYRENEES trial



Abbreviations: DD-CKD: dialysis dependent chronic kidney disease; ESA: erythropoiesis stimulating agent; IV: intravenous; R: randomised; SC: subcutanous.

L.1.3 SIERRAS

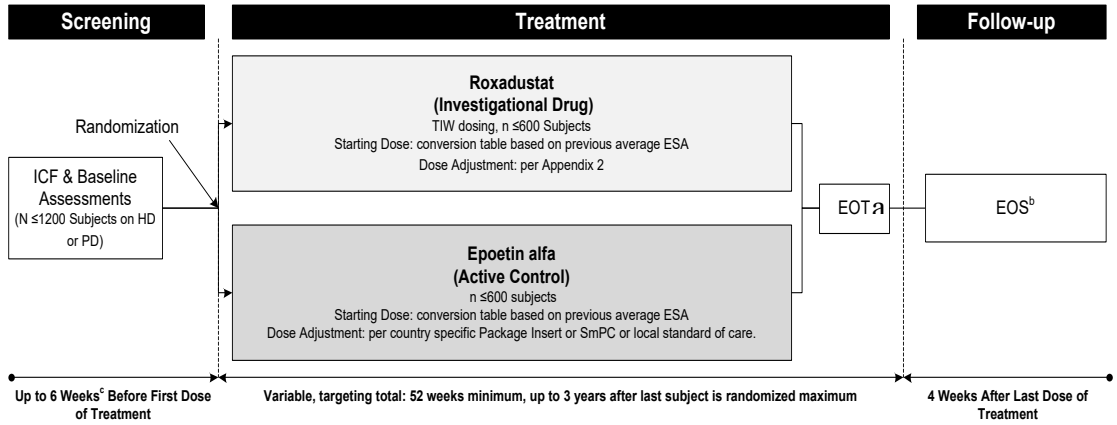
SIERRAS (48) was a phase III, randomised, open-label, active-controlled study to assess the efficacy and safety of roxadustat treatment in adult patients with ESRD who were on haemodialysis (HD) or peritoneal dialysis (PD) and were originally on ESA for treatment of anaemia. As depicted in Figure 39, the study consisted of three periods: screening period (up to 6 weeks or 8 weeks for subjects who were taking Mircera®), treatment period (maximum up to 3 years after the last patient was randomised) and a post-treatment follow-up period (4 weeks) (48).

Eligible patients were randomised (1:1) to receive roxadustat or epoetin alfa (48):

- Treatment group 1: patients were required to switch from epoetin or darbepoetin alfa treatment to roxadustat which was administered orally three TIW
- Treatment group 2: patients that were receiving non-epoetin alfa ESA treatment were switched to epoetin alfa treatment on Day 1. Selection of initial epoetin alfa doses was administered IV or subcutaneous TIW starting from Day 1

Dose adjustments were permitted at four weekly intervals from week 4 onwards. These adjustments were aimed at keeping patients' Hb levels of approximately 11 g/dL and were based on current Hb levels and change in Hb over the preceding 4 weeks. Deviation from the 4-week period was allowed anytime during the study in case of Hb rate of rise >2 g/dL within 4 weeks or Hb ≥13.0 g/dL) as this was considered excessive haematopoiesis (48).

Figure 39: Study design for SIERRAS trial



Notes: a: EOT/ET + 4 weeks ±7 days. c: For patients currently taking Mircera®, the screening period can be extended up to 8 weeks.

Abbreviations: ESA: erythopoesis-stimulating agent; EOS: end of study; EOT: end of treatment; ICF: Informed consent form; HD: haemodialysis; PD: peritoneal dialysis; TIW: thrice in week; SmPC: summary of product characteristics.

L.1.4 ROCKIES

ROCKIES (49) is a phase III, multicentre, randomised, open label, active-controlled study designed to provide key efficacy and safety data for roxadustat compared with epoetin alfa in the treatment of anaemia associated with DD CKD. As depicted in Figure 40, the three study periods for ROCKIES were as follows: screening period (up to 6 weeks), treatment period (treatment end date was defined based on when the target number of cardiovascular [CV] events was reached) and a post-treatment follow-up period (4 weeks).

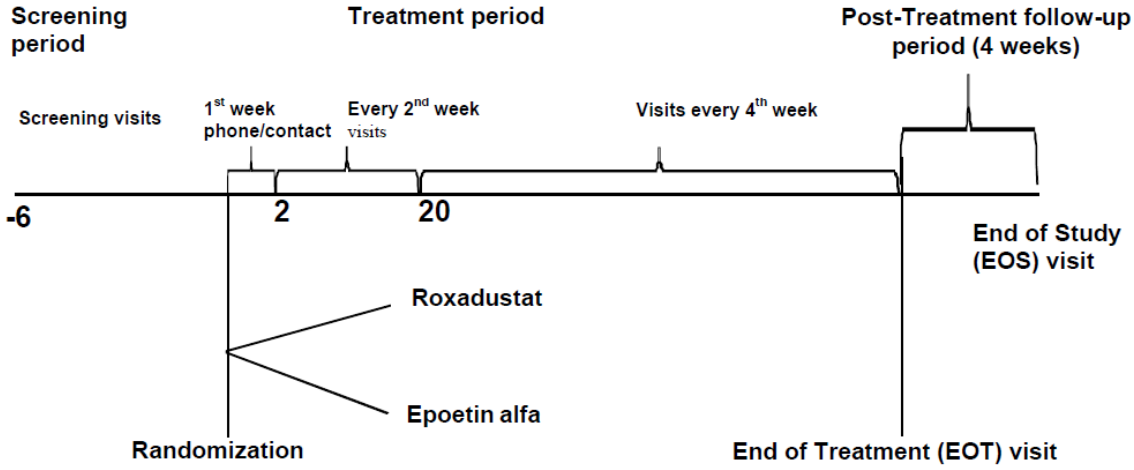
Eligible patients were randomised (1:1) to receive roxadustat or epoetin alfa (49):

- Treatment group 1: patients were administered roxadustat tablets orally TIW
- Treatment group 2: epoetin alfa was administered subcutaneous or IV and was dosed TIW

The starting dose of roxadustat for patients on ESA at the start of the study was 70, 100, 150, or 200 mg TIW depending on the baseline ESA dose. For subjects who did

not receive ESA treatment at study entry, the dose was 70 or 100 mg TIW depending on body weight. Dose adjustments were to be reviewed every 4 weeks, using a dose adjustment algorithm (49).

Figure 40: Study design for ROCKIES trial



Abbreviations: EOS: end of study; EOT: end of treatment.

Table 155: Summary of trial methodology (DD population)

Study	HIMALAYAS	PYRENEES	SIERRAS	ROCKIES
Location		This multinational, multicentre study was conducted at approximately 150 centres in 17 countries: Belgium, Bulgaria, Croatia, Czech Republic, France, Georgia, Germany, Hungary, Italy, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Spain, and United Kingdom.	Multicentre study conducted in the U.S. Up to 200 centres were planned worldwide; however, no ex-U.S. centres enrolled subjects in the study.	This study was performed at 197 centres in 18 countries worldwide: Australia, Bulgaria, Canada, Czech Republic, Hungary, India, Mexico, Peru, Philippines, Poland, Russia, Slovakia, Spain, Sweden, Thailand, Ukraine, United States and Vietnam
Trial Design	Phase III, randomised, open-label, active-controlled study in incident dialysis patients. The study consisted of three periods: screening period (up to 6 weeks), treatment period (minimum of 52 weeks, maximum up to approximately 4 years) and a post-treatment follow-up period (4 weeks)	Phase III, multicentre, randomised, open-label, active-controlled study to assess the efficacy and safety of roxadustat treatment in adult patients with ESRD who were on stable haemodialysis or peritoneal dialysis and on stable treatment with epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa for anaemia. The study consisted of three study periods: screening period (up to 6 weeks), treatment period (minimum of 52 weeks, maximum of 104 weeks) and a post-treatment follow-up period (4 weeks).	Phase III, randomised, open-label, active-controlled study to assess the efficacy and safety of roxadustat treatment in adult patients with ESRD who were on HD or PD and were originally on ESA for treatment of anaemia. The study consisted of three periods: screening period (up to 6 weeks or 8 weeks for subjects who were taking Mircera®), treatment period (maximum up to 3 years after the last patient was randomised) and a post-treatment follow-up period (4 weeks)	Phase III, multicentre, randomised, open label, active-controlled study designed to provide key efficacy and safety data for roxadustat compared with epoetin alfa in the treatment of anaemia associated with DD-CKD. The three study periods for ROCKIES were as follows: screening period (up to 6 weeks), treatment period (treatment end date was defined based on when the target number of CV events was reached) and a post-treatment follow-up period (4 weeks)
Eligibility criteria for participants	Inclusion criteria: At least 18 years of age Patient received HD or PD for ESRD for a minimum of 2 weeks and a maximum of 4 months, prior to randomisation	Inclusion criteria: At least 18 years of age Subject is receiving stable HD, HDF or PD treatment with the same mode of dialysis for ≥4 months prior to randomisation For subjects receiving HD or HDF, the vascular access must	Inclusion criteria: At least 18 years of age Receiving adequate dialysis using the same modality of dialysis for native kidney ESRD for ≥3 months prior to screening and during screening. Under Protocol Amendment 2, incident-dialysis	Inclusion criteria: At least 18 years of age Receiving or initiating haemodialysis or peritoneal dialysis for treatment of native kidney ESRD for a minimum of 2 weeks and a maximum of 4 months prior to randomisation

Study	HIMALAYAS	PYRENEES	SIERRAS	ROCKIES
	For patients receiving HD or HDF, the vascular access must be via native AV fistula or graft, or permanent, tunnelled catheter Mean of the patients two most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 2 days apart, must been ≤10.0 g/dL, with a difference of ≤1.3 g/dL between the highest and the lowest values. The last Hb value must have been drawn within 10 days prior to randomisation. Ferritin level ≥100 ng/mL (≥220 pmol/L) at screening TSAT level ≥20% at screening Exclusion criteria: Total duration of prior ESA use was ≤3 weeks within the 12 weeks before informed consent was obtained Patient has received an RBC transfusion within 4 weeks prior to randomisation Active, clinically significant infection that was manifested by WBC count	be via native AV fistula or graft, or permanent, tunnelled catheter Subject is on IV or SC epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or IV or SC darbepoetin alfa treatment for ≥8 weeks prior to randomisation with stable weekly doses (≤ 30% change from the maximum prescribed average weekly dose, i.e. ([max-min]/max≤ 0.3) during 4 weeks prior to randomisation Mean of the subject's three most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart, must be ≥9.5 g/dL and ≤12.0 g/dL with an absolute difference ≤1.3 g/dL between the highest and the lowest value. The last Hb value must be within 10 days prior to the randomisation visit Ferritin level ≥100 ng/mL (≥220 pmol/L) at screening TSAT level ≥20% at screening Exclusion criteria: Subject has received an RBC transfusion within 8 weeks prior to randomisation Known hereditary haematologic disease such as thalassemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD	subjects receiving dialysis for ESRD for ≥2 weeks but ≤4 months at the time of randomisation. For patients receiving HD, the vascular access must be via native AV fistula or graft, or permanent, tunnelled catheter Patient is on IV or SC epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or IV or SC darbepoetin alfa treatment for ≥8 weeks prior to randomisation with stable weekly doses (≤ 30% change from the maximum prescribed average weekly dose, i.e. ([max-min]/max≤ 0.3) during 4 weeks prior to randomisation Mean of the patients three most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart, must be ≥9.0 g/dL and ≤12.0 g/dL with an absolute difference ≤1.3 g/dL between the highest and the lowest value. The last Hb value must be within 10 days prior to the randomisation visit Ferritin level ≥100 ng/mL (≥220 pmol/L) at screening TSAT level ≥20% at screening Exclusion criteria: Patient has received an RBC transfusion within 8 weeks prior to randomisation Known hereditary haematologic disease such as thalassemia or	Two central laboratory Hb values during the screening period, obtained at least 7 days apart, were to be <12 g/dL in subjects treated with an erythropoietin analogue at the time of enrolment or <10 g/dL in subjects not treated with an erythropoietin analogue at the time of enrolment. Ferritin ≥100 ng/mL at randomisation Transferrin saturation (TSAT) ≥20% at randomisation Exclusion criteria: Patient has received RBC transfusion during the screening period. Uncontrolled hypertension at the time of randomisation Known chronic inflammatory disease that could impact erythropoiesis

Study	HIMALAYAS	PYRENEES	SIERRAS	ROCKIES
	>ULN, and/or fever with clinical signs or symptoms of infection at the time of randomisation	Known chronic inflammatory disease that could impact erythropoiesis	sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD Known chronic inflammatory disease that could impact erythropoiesis Patient had uncontrolled hypertension within 2 weeks prior to randomisation.	
Trial drugs	Group 1: roxadustat 70/100 mg* TIW (N=522) Group 2: epoetin alfa dosed according to epoetin alfa package insert or SmPC; TIW (N=521)	Group 1: roxadustat 100/150/200 mg# TIW (N=415) Group 2: ESA (epoetin alfa if pre-treated with any epoetin [i.e. epoetin alfa, beta, theta, zeta, delta or omega] and darbepoetin alfa if pre-treated with darbepoetin alfa; with approximately the same average weekly dose as prior to randomisation (N=421)	Group 1: roxadustat dosed based on previous average ESA TIW (N=370) Group 2: epoetin alfa dosed based on previous average ESA; TIW (N=371)	Group 1: roxadustat 70/100/150/200 mg (depending on the baseline ESA dose, for patients on ESA) or 70/100 mg* (for patients who did not receive ESA previously) TIW (N=1,068) Group 2: epoetin alfa dosed in accordance with accepted clinical practice guidelines and approved local prescribing information; TIW (N=1,065)
Permitted and disallowed concomitant medication	Permitted concomitant medications: • Phosphate Binders • Hydroxymethylglutaryl Coenzyme A Reductase Inhibitors (statins) • Supplemental Iron Use – oral or intravenous Prohibited concomitant medications: • Androgens and iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox	Permitted concomitant medications: • Supplemental Iron Use • Statins and Other Substrates for Organic Anion Transporting Polypeptide 1B1 • Phosphate Binders and Other Multivalent Cation-containing Drugs and Mineral Supplements • Anti-hypertensive and lipid-lowering medication Prohibited concomitant medications:	Permitted concomitant medications: • Phosphate Binders • Statins • Supplemental Iron Use – oral or intravenous Prohibited concomitant medications: • Any investigational drug from 4 weeks prior to screening until EOS • Androgens from screening until EOS • Iron-chelating agents (e.g., deferoxamine/desferrioxamine, deferiprone, or deferasirox therapy)	Permitted concomitant medications: • Statins • Phosphate binders • Herbal medicines Prohibited concomitant medications: • Any other investigational drug from randomisation until EOS • Any erythropoietin analogue during the treatment period, except for IP or rescue medication • Iron-chelating agents (e.g., deferoxamine/desferrioxamine, deferiprone, or deferaxirox therapy)

Study	HIMALAYAS	PYRENEES	SIERRAS	ROCKIES
	therapy) • Dapsone in any dose amount • For subjects receiving roxadustat: chronic use of acetaminophen or paracetamol >2.0 g/day during the Treatment Period and up to 1 week after EOT. • Use of herbal medicine was not prohibited, but strongly discouraged.	• Any investigational drug: Within 30 days or 5 half-lives or limit set by national law (whichever was longer), prior to the initiation of Screening until EOS. • Roxadustat or another HIF-PH: at any time prior to randomisation. After randomisation any HIF-PH other than roxadustat, as allocated by randomisation, until EOS. • Iron-chelating agents (e.g., deferoxamine, deferiprone, or deferasirox therapy): from 4 weeks prior to randomisation until EOS. • Androgens: From randomisation onwards until EOS. • Dapsone in any dose amount, or chronic doses of acetaminophen/paracetamol >2.0 g/day, from randomisation until EOS.	from 4 weeks prior to randomisation until EOS • Dapsone (at any dose) from screening until EOS • Chronic doses acetaminophen/paracetamol >2.0 g/day from randomisation until 1 week after EOT	from 4 weeks prior to screening until EOS • Androgens from randomisation onwards until EOS • Dapsone (at any dose) from randomisation onwards until EOS • Chronic doses of acetaminophen/paracetamol >2.0 g/day from randomisation until EOS.
Primary outcome	• Hb (g/dL) change from baseline to the average Hb in weeks 28 to 52, regardless of recue therapy • The proportion of patients who achieved an Hb response at 2 consecutive visits during the first 24 weeks of treatment, without rescue therapy	• Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period • Hb (g/dL) change from baseline to the average Hb in weeks 28 to 52, regardless of recue therapy	• Hb (g/dL) change from baseline to the average Hb in weeks 28 to 52 regardless of rescue therapy • Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period	• Hb (g/dL) change from baseline to the average Hb from weeks 28 to 52 • Hb (g/dl) change from baseline to the average level from week 28 to 36
Key secondary outcomes	• The proportion of patients who achieved an Hb response at during the first	• Proportion of Hb responders in the average of weeks 28 to 36 without having received rescue therapy	• Proportion of responders with Hb level ≥10.0 g/dL from weeks 28 to 52 regardless of rescue therapy	• Mean change from LDL cholesterol (mmol/L) from baseline to week 24 • Change in Hb from baseline to the average Hb from weeks 28-52 for

Study	HIMALAYAS	PYRENEES	SIERRAS	ROCKIES
	24 weeks of treatment, without rescue therapy • Mean Hb change from baseline to the average level from weeks 28-36 within 6 weeks prior to and during the evaluation period • The time to achieve the first Hb response at 2 consecutive visits during the first 24 weeks of treatment, without rescue therapy • Proportion of patients with Hb ≥10 g/dL during weeks 28–52 • Mean change from baseline in LDL cholesterol averaged over weeks 12–24 • Mean change from baseline in Hb levels between week 18 to 24 in patients whose baseline hs-CRP >ULN • Average monthly IV iron use per subject from weeks 28–52 • Time to first RBC transfusion during treatment • Mean change in mean MAP from weeks 8–12 • Time to first exacerbation of hypertension from weeks 28–52	• LDL cholesterol change (mmol/L) from BL to the average of weeks 12 to 28 • Monthly IV iron (mg) use per subject during weeks 1 to 36 • SF-36 PF subscore (points) change from BL to the average of weeks 12 to 28 • SF-36 VT sub score (points) change from BL to the average of weeks 12 to 28 • MAP (mmHg) change from BL to the average MAP of weeks 20 to 28 • Time (incidence per 100 patient years at risk) to an increase in blood pressure during weeks 1 to 36 • MAP (mmHg) change from BL to the average MAP of weeks 20 to 28 • Time (incidence per 100 patient years at risk) to an increase in blood pressure during weeks 1 to 36	• Proportion of responders within the target Hb range of 10.0 to 12.0 g/dL from weeks 28 to 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period. • LDL cholesterol change (mmol/L) from baseline to the average of Weeks 12 to 28 • Hb change from baseline to the average level during the Weeks 18 to 24 for patients with baseline hs-CRP > ULN • Average monthly IV iron use during the treatment period from weeks 28 to 52 • Time to first RBC transfusion during the treatment period. MAP (mmHg) change from BL to the average MAP of weeks 20 to 28 • Time to first exacerbation of hypertension during Weeks 28 to 52	patients with baseline hsCRP greater than the ULN • Proportion of total time of interpolated Hb values greater than or equal to 10 g/dL over Week 28-52 • Proportion of total time of interpolated Hb values within the interval 10 to 12 g/dL over Week 28-52 • Mean monthly IV iron use from Week 36 to EOS • Time to first administration of RBC transfusion

Study	HIMALAYAS	PYRENEES	SIERRAS	ROCKIES
Pre-planned subgroups	The primary efficacy endpoints were examined in the following subgroups: • Sex: Male or Female • Age: 18 – 64, 65 – 74, >=75 • Iron Repletion Status: ferritin>=100 ng/mL and TSAT>=20%, ferritin<100 ng/mL or TSAT<20% • CRP Category: <=ULN, >ULN • Hb Category: <=8, >8 • Cardiovascular History: Yes or No • Geographic Region: US, EX-US	Selected efficacy and safety endpoints were summarised for the following subgroups: • Age group: < 65 years, 65 to 74 years, ≥ 75 years • Sex: Female or Male • Previous ESA treatment: darbepoetin alfa, epoetin alfa • Region: Western Europe; Central and Eastern Europe • Baseline Hb: ≤ 11 g/dL, > 11 g/dL • Dialysis type: Haemodialysis, Peritoneal dialysis • History of cardiovascular, cerebrovascular or thromboembolic diseases: Yes or No • Baseline hs-CRP: ≤ ULN > ULN	The primary efficacy endpoints were examined in the following subgroups: • Sex: Male or Female • Age Group: 18 – 64, 65 – 74, >=75 • Dialysis Status: > 4 months, <= 4 months • Iron Repletion Status: ferritin>=100 ng/mL and TSAT>=20%, ferritin<100 ng/mL or TSAT<20% • CRP Category: <=ULN, >ULN • Hb Category: <=10.5, >10.5 • Cardiovascular History: Yes or No • Prescribed Weekly Epoetin Alfa Dose Categories: <= 150 IU/kg/week, > 150 IU/kg/week	Subgroup analyses were performed on the primary efficacy endpoints of Hb on the following subgroups: • Age: <65 and ≥65; <75, and ≥75 years • Gender: Male versus Female • Race: White, Black, or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska native, Other • Baseline weight: <70 kg versus ≥70 kg; and <100 kg versus ≥100 kg • Weight by gender-specific median (4 groups) • Body mass index: <30 versus ≥30 kg/m^2 • Geographical region: US versus Ex-US • Geographical region: North America, South America, Asia and Australia, Europe • Peritoneal dialysis versus haemodialysis • Cardiovascular/ cerebrovascular/thromboembolic history: Yes or No • Baseline Hb value: ≤10.5 g/dL versus >10.5 g/dL • Incident versus stable dialysis: dialysis duration ≤4 months versus >4 months from the randomisation date • Diabetes history: Yes versus No • Epoetin alfa dose prior to randomisation: ≤12500 IU/week and >12500 IU/week • Baseline C-reactive protein (≤ULN versus >ULN).

Notes: *The dose of roxadustat was adjusted based on patient's body weight; patients weighing ≥45.0 to ≤70.0 kg receiving 70 mg while those weighing >70.0 to ≤160.0 kg receiving 100 mg #The starting dosing of roxadustat in PYRENEES was based on the following conversions: a) If the patient was initially receiving < 8000 IU/week epoetin or < 40 µg/week darbepoetin alfa, then patient received 100 mg roxadustat dose TIW, b) If the patient was initially receiving 8000 to 16000 IU/week epoetin or 40 to 80 µg/week darbepoetin alfa, then patient received 150 mg roxadustat dose TIW. However, if the initial dose of 150 mg exceeded the maximum dose of 3.0 mg/kg, then 100 mg was to be used as the starting dose, c) If the patient was initially receiving > 16000 IU/week epoetin or > 80 µg/week darbepoetin alfa, then patient received 200 mg roxadustat dose TIW. Howver, if the initial dose of 200 mg exceeded the maximum dose of 3.0 mg/kg, then 150 mg was to be used as the starting dose.

Abbreviations: AV: arteriovenous; BL: baseline; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; CRP: C-reactive protein; DD: dialysis dependant; eGFR: estimated glomerular filtration rate; EOS: end of study visit; ESA: erythropoiesis-stimulating agent; ESRD: end-stage renal disease; g/dL: grams per decilitre; Hb: haemoglobin; HD: haemodialysis; HDF: haemodiafiltration; hs-CRP: high-sensitivity C-reactive protein; IV: intravenous; LDL: low density lipoprotein; MAP: mean arterial pressure; PF: physical functioning; PD: peritoneal dialysis; RBC: red blood cell; SC: subcutaneous; SmPC: summary of product characteristics; SF-36: 36-item short form survey; TIW: thrice in week; TSAT: transferrin saturation; ULN: upper limit of normal; VT: vitality

L.2 Baseline characteristics and demographics

A comparison of the baseline demographics and characteristics across different treatment arms in trials conducted in the DD population is given in Table 156.

L.2.1 HIMALAYAS

Overall, demographic and baseline characteristics between the roxadustat and the epoetin alfa treatment groups were similar (47). Most patients in both treatment groups were white 415 (79.5) and 400 (76.8) in the roxadustat and epoetin alfa groups, respectively. Patients had a mean age of 53.8 (± 14.74) years in the roxadustat group and 54.3 (± 14.55) years in the epoetin alfa group. In addition, baseline demographics were comparable in both treatment groups. Most of the patients in both treatment groups were on haemodialysis. Mean Hb levels were nearly identical between the roxadustat and epoetin alfa (8.43 g/dL and 8.46 g/dL respectively).

L.2.2 PYRENEES

Overall, there was no difference in demographics and baseline characteristics between the roxadustat and the ESA treatment groups (44). Most patients were white (97.4%) and were randomised in Central and Eastern Europe (79.2%). In addition, baseline demographics in the darbepoetin and epoetin treatment groups were comparable with the overall population (44). It should be noted that in the subgroup of patients previously treated with darbepoetin, a greater proportion of patients had previous peritoneal dialysis (11.5%) compared with the subgroup of patients previously treated with epoetin (2.5%), in the subgroup of patients previously treated with darbepoetin, median time since dialysis was shorter for patients receiving roxadustat (2.746 years) compared with darbepoetin (3.411 years), this was reversed in the subgroup of patients previously treated with roxadustat versus epoetin, respectively (3.139 years vs 2.598 years) (44).

L.2.3 SIERRAS

Overall, demographic and baseline characteristics between the roxadustat and the epoetin alfa treatment groups were similar (48). Most patients in both treatment groups were <65 years old. The mean Hb across groups was 10.3 g/dL, with a 65%

incidence rate in diabetes, approximately 97% of patients had ferritin ≥100 ng/mL and TSAT ≥20% at baseline (48).

L.2.4 ROCKIES

Overall, baseline characteristics of patients from the ITT of ROCKIES were comparable between the treatment groups (49). Demographic characteristics were representative of the target population. Most patients were white (56.7%) and male (59.4%) (49). Dialysis history at baseline was balanced between treatment groups (49).

Table 156: Baseline demographics and disease characteristics of patients included in DD population trials

		HIMALAYAS		PYRENEES		SIERRAS		ROCKIES	
Parameter	**Category/statistic**	**Roxadustat (N=522)**	**Epoetin alfa (N=521)**	**Roxadustat (N=414)**	**ESA (N=420)**	**Roxadustat (N=370)**	**Epoetin alfa (N=371)**	**Roxadustat (N=1051)**	**ESA (N=1055)**
Baseline demographics									
Sex	Male	309 (59.2%)	307 (58.9%)	245 (59.2%)	235 (56.0%)	187 (50.5%)	215 (58.0%)	625 (59.5%)	626 (59.3%)
	Female	213 (40.8%)	214 (41.1%)	169 (40.8%)	185 (44.0%)	183 (49.5%)	156 (42.0%)	426 (40.5%)	429 (40.7%)
Age (years)	Mean	53.8	54.3	61.0	61.8	57.6	58.4	53.5	54.5
	SD	14.74	14.55	13.8	13.4	13.6	13.3	15.3	15.0
Age (years)	<65	381 (73.0%)	391 (75.0%)	222 (53.6%)	229 (54.5%)	253 (68.4%)	246 (66.3%)	798 (75.9%)	783 (74.3%)
	65-74	100 (19.2%)	94 (18.0%)	114 (27.5%)	115 (27.4%)	80 (21.6%)	77 (20.8%)	174 (16.6%)	177 (16.8%)
	≥75	41 (7.9%)	36 (6.9%)	78 (18.8%)	76 (18.1%)	37 (10.0%)	48 (12.9%)	79 (7.5%)	95 (9.0%)
Race	White	415 (79.5%)	400 (76.8%)	405 (97.8%)	407 (96.9%)	165 (44.6%)	184 (49.6%)	597 (56.8%)	598 (56.7%)
	Black or African American	44 (8.4%)	50 (9.6%)	6 (1.4%)	6 (1.4%)	158 (42.7%)	156 (42.0%)	148 (14.1%)	158 (15.0%)
	Asian	43 (8.2%)	51 (9.8%)	1 (0.2%)	3 (0.7%)	21 (5.7%)	15 (4.0%)	208 (19.8%)	198 (18.8%)
	American Indian/Alaskan Native	1 (0.2%)	4 (0.8%)	-	-	10 (2.7%)	7 (1.9%)	-	-
	Native Hawaiian or Other Pacific Islander	-	-	-	-	1 (0.3%)	3 (0.8%)	-	-
	Other	19 (3.6%)	16 (3.1%)	2 (0.5%)	4 (1.0%)	2 (0.5%)	4 (1.0%)	98 (9.4%)	101 (9.6%)
BMI (kg/m²)	N	522	521	413	419	370	371	1050	1052
	Mean	26.7	27.01	26.87	26.95	30.2	30.5	27.01	26.93
	SD	5.84	6.03	4.86	5.59	7.4	7.5	6.75	6.36
Region	Western Europe	-	-	86 (20.8%)	90 (21.4%)	-	-	-	-
	Central and Eastern Europe	-	-	328 (79.2%)	330 (78.6%)	-	-	-	-
	Europe	-	-	-	-	-	-	345 (32.8%)	343 (32.5%)
	Rest of the World	-	-	-	-	-	-	706 (67.2%)	712 (67.5%)
Baseline disease characteristics									
Hb (g/dL)	Mean	8.43	8.46	10.75	10.78	10.30	10.31	9.99	10.02
	SD	1.04	0.96	0.62	0.62	0.66	0.66	1.20	1.24
	≤8.0	166 (31.8%)	157 (30.1%)	-	-	-	-	-	-
	>8.0	356 (68.2%)	364 (69.9%)	-	-	-	-	-	-
	<10.0	-	-	-	-	-	-	448 (42.6%)	435 (41.2%)
	≥10.0	-	-	-	-	-	-	603 (57.4%)	620 (58.8%)
	≤10.5	-	-	-	-	230 (62.2%)	235 (63.3%)	-	-
	>10.5	-	-	-	-	140 (37.8%)	136 (36.7%)	-	-
	≤11.0	-	-	266 (64.3%)	265 (63.1%)	-	-	-	-
	>11.0	-	-	148 (35.7%)	155 (36.9%)	-	-	-	-

		HIMALAYAS		PYRENEES		SIERRAS		ROCKIES	
Parameter	**Category/statistic**	**Roxadustat (N=522)**	**Epoetin alfa (N=521)**	**Roxadustat (N=414)**	**ESA (N=420)**	**Roxadustat (N=370)**	**Epoetin alfa (N=371)**	**Roxadustat (N=1051)**	**ESA (N=1055)**
Iron repletion at baseline	Ferritin <100 ng/mL and TSAT <20%	116 (22.2%)	115 (22.1%)	4 (1.0%)	2 (0.5%)	10 (2.7%)	8 (2.2%)	-	-
	Ferritin <100 ng/mL and TSAT ≥20%	-	-	11 (2.7%)	4 (1.0%)	-	-	-	-
	Ferritin ≥100 ng/mL and TSAT< 20%	-	-	43 (10.4%)	48 (11.4%)	-	-	-	-
	Ferritin ≥100 ng/mL and TSAT ≥20%	406 (77.8%)	406 (77.9%)	355 (86.0%)	366 (87.1%)	360 (97.3%)	363 (97.8%)	-	-
CRP (nmol/L)	>ULN	228 (43.7%)	226 (43.4%)	204 (49.3%)	194 (46.2%)	189 (51.1%)	177 (47.7%)	-	-
	≤ULN	289 (55.4%)	289 (55.5%)	210 (50.7%)	226 (53.8%)	178 (48.1%)	192 (51.8%)	-	-
	Missing	5 (1.0%)	6 (1.2%)					-	-
Baseline dialysis type	Haemodialysis	469 (89.8%)	462 (88.7%)	379 (91.5%)	405 (96.4%)	354 (95.7%)	354 (95.4%)	-	-
	Peritoneal Dialysis	53 (10.2%)	58 (11.1%)	35 (8.5%)	15 (3.6%)	16 (4.3%)	17 (4.6%)	-	-
Type 2 diabetes mellitus	Incidence rate	183 (35.1%)	179 (34.4%)	89 (21.5%)	127 (30.2%)	241 (65.1%)	244 (65.8%)	459 (43.7%)*	454 (43.0%)*
Haemodialysis	Current dialysis	-	-	-	-	-	-	938 (89.2%)	938 (88.9%)
	Past dialysis	-	-	-	-	-	-	33 (3.1%)	26 (2.5%)
	No dialysis	-	-	-	-	-	-	79 (7.5%)	91 (8.6%)
Peritoneal dialysis	Current dialysis	-	-	-	-	-	-	111 (10.6%)	117 (11.1%)
	Past dialysis	-	-	-	-	-	-	64 (6.1%)	51 (4.8%)
	No dialysis	-	-	-	-	-	-	874 (83.2%)	887 (84.1%)
Baseline SBP (mmHg)	Mean	-	-	-	-	-	-	140.77	140.60
	SD	-	-	-	-	-	-	16.86	17.15
Baseline DBP (mmHg)	Mean	-	-	-	-	-	-	78.21	77.92
	SD	-	-	-	-	-	-	10.11	10.30

Note: * In ROCKIES, Medical history events in the MedDRA version 20.0 used high level term "Diabetes mellitus" including subtypes (and not specified Type 2 diabetes mellitus)

Abbreviations: BMI: body mass index; CRP: C-reactive protein; DBP: diastolic blood pressure; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; SBP: systolic blood pressure; SD: standard deviation; TSAT: transferrin saturation; ULN: upper limit of normal

L.3 Statistical analysis

In the DD population, all four trials (PYRENEES, SIERRAS, HIMALAYAS, and ROCKIES) (44, 47-49) provided at least 99% power, with at least 600 patients, to demonstrate statistical non-inferiority of roxadustat versus ESA in the primary endpoint. This assumed a difference (roxadustat minus ESA) of -0.30 g/dL, a non-inferiority margin for this difference of 0.75 g/dL and a SD of 1.25 g/dL.

Statistical comparisons made for each endpoint in the trials conducted for DD population are defined in Table 157 to Table 160.

Table 157: Sequential testing of primary and key secondary efficacy endpoints in the HIMALAYAS trial (DD population)

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb response	The proportion of patients who achieved an Hb response at 2 consecutive visits during the first 24 weeks of treatment, without rescue therapy	PPS	Miettinen & Nurminen approach	**Non-inferiority** concluded if the lower bound of the 95% CI was greater than -15%
Secondary endpoints				
Hb response	The proportion of patients who achieved an Hb response at during the first 24 weeks of treatment, without rescue therapy	ITT	All secondary endpoints were tested using a fixed-sequence testing procedure, to preserve the overall 2-sided type I error of 0.05	**Non-inferiority** concluded if the lower bound of the 95% CI was greater than -15%
Hb maintenance	Mean Hb change from baseline to the average level from weeks 28-36 within 6 weeks prior to and during the evaluation period	PPS		**Non-inferiority** concluded if the lower bound of the 95% CI was above the non-inferiority margin of -0.75 g/dL
Hb response	The time to achieve the first Hb response at 2 consecutive visits during the first 24 weeks of treatment, without rescue therapy	FAS		**Non-inferiority** concluded if the lower bound of the 95% CI of the HR was was greater than 0.77
Hb maintenance	Proportion of patients with Hb ≥10 g/dL during weeks 28–52	FAS		**Non-inferiority** concluded if the lower bound of the 95% CI was greater than -15%
LDL Cholesterol	Mean change from baseline in LDL cholesterol averaged over weeks 12–24	FAS		**Superiority**
Hb maintenance	Mean change from baseline in Hb levels between week 18 to 24 in patients whose baseline hs-CRP >ULN	FAS		**Non-inferiority** concluded if the lower bound of the 95% CI was above the non-inferiority margin of -0.75 g/dL
Rescue medication	Average monthly IV iron use per subject from weeks 28–52	FAS		**Superiority**
Rescue medication	Time to first RBC transfusion during treatment	FAS		**Non-inferiority** concluded if the upper bound of the 95% CI of the HR was less than 1.8
CV profile	Mean change in mean MAP from weeks 8–12	FAS		**Superiority**
CV profile	Time to first exacerbation of hypertension from weeks 28–52	FAS		**Non-inferiority** margin for the difference between groups was 1.8

Abbreviations: BL: baseline; CI: confidence interval; CV: cardiovascular; Ex-US: Outside of the US; FAS: full analysis set; Hb: haemoglobin; hs-CRP: high-sensitivity C-reactive Protein; IV: intravenous; ITT: intention-to-treat; LDL: low density lipoprotein; MAP: mean arterial pressure; PPS: per-protocol set; RBC: red blood cell; US: United States; ULN: upper limit of normal

Table 158: Sequential testing of primary and key secondary efficacy endpoints in the PYRENEES trial (DD population)

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb maintenance	Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period	PPS	The primary efficacy endpoint was analysed using a Mixed Model of Repeated Measures (MMRM) method adjusting for stratification factors, comparing roxadustat to ESA. After fitting the data, a computation statement was added to the model to calculate the average Hb values estimate during the period under consideration. Difference of least square means (LSM) (roxadustat minus ESA) and its 2-sided 100*(1-α*2)% confidence interval were estimated for the change from baseline to the average of weeks 28 to 36. The significance level α was fixed by the parametric chain procedure	**Non-inferiority** margin for the difference between groups is 15%
Secondary endpoints				
Hb response	Proportion of Hb responders in the average of weeks 28 to 36 without having received rescue therapy	PPS	The key secondary endpoints were tested using a fixed sequence testing procedure in order to maintain the overall 1-sided type I error rate for the set of key secondary endpoints at 0.025. If the null hypothesis was rejected for a test, the claim of superiority (or noninferiority) was considered successful and the test progressed to the next comparison in sequence.	**Non-inferiority** margin for the difference between groups is 15%
LDL Cholesterol	LDL cholesterol change (mmol/L) from BL to the average of weeks 12 to 28	FAS		**Superiority**
Rescue medication	Monthly IV iron (mg) use per subject during weeks 1 to 36	FAS		**Superiority**
HRQoL	SF-36 PF subscore (points) change from BL to the average of weeks 12 to 28	PPS		**Non-inferiority** margin is fixed as a difference of 3 points
HRQoL	SF-36 VT subscore (points) change from BL to the average of weeks 12 to 28	PPS		**Non-inferiority** margin is fixed as a difference of 3 points
CV profile	MAP (mmHg) change from BL to the average MAP of weeks 20 to 28	PPS		**Non-inferiority** margin for the difference between groups is 1 mmHg

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
CV profile	Time (incidence per 100 patient years at risk) to an increase in blood pressure during weeks 1 to 36	PPS		**Non-inferiority** margin is fixed as a HR of 1.3
CV profile	MAP (mmHg) change from BL to the average MAP of weeks 20 to 28	FAS		**Superiority**
CV profile	Time (incidence per 100 patient years at risk) to an increase in blood pressure during weeks 1 to 36	FAS		**Superiority**

Abbreviations: BL: baseline; CV: cardiovascular; EU: Europe; FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; ITT: intention-to-treat; IV: intravenous; LDL: low density lipoprotein; MAP: mean arterial pressure; PF: physical functioning; PPS: per-protocol set; SF-36: short form 36 health survey questionnaire; US: United States; VT: vitality.

Table 159: Sequential testing of primary and key secondary efficacy endpoints in the SIERRAS trial (DD population)

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb maintenance	Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period	PPS	The primary endpoint was analysed using MMRM with baseline Hb value as covariate and treatment group, visit (up to Week 52), interaction of treatment group and visit, and stratification factors	**Non-inferiority** concluded if the lower bound of the 95% CI was above the non-inferiority margin of -0.75 g/dL.
Secondary endpoints				
Hb response	Proportion of responders within the target Hb range of 10.0 to 12.0 g/dL from weeks 28 to 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.	PPS	A 2-sided 95% confidence interval for the difference of 2 responder rates (roxadustat – ESA) based on the Miettinen & Nurminen approach adjusting for treatment group and stratification factors was calculated and non-inferiority was declared if the lower bound of the 95% CI was greater than -15%.	**Non-inferiority** concluded if the lower bound of 95% CI was above the non-inferiority margin of -15%
LDL Cholesterol	LDL cholesterol change (mmol/L) from baseline to the average of Weeks 12 to 28	FAS	The same strategy as that used in MMRM for Hb was used to choose variance covariance structure.	**Superiority**
Hb maintenance	Hb change from baseline to the average level during the Weeks 18 to 24 for patients with baseline hs-CRP > ULN	FAS	Multiple Imputation Analysis of Covariance (MI-ANCOVA) method was used for analysis	**Non-inferiority** margin was fixed as a difference of -0.75

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Rescue medication	Average monthly IV iron use during the treatment period from weeks 28 to 52	FAS	A rank ANCOVA method was used due to skewed IV iron dose data distribution. It included baseline iron repletion status, treatment group, and stratification factors as fixed effects	**Superiority**
Rescue medication	Time to first RBC transfusion during the treatment period.	FAS	Cox Proportional Hazards model adjusting for baseline Hb, treatment group, and stratification factors except the binary Hb (≤10.5 versus >10.5 g/dL) was used for analysis	**Superiority, non-inferiority** was declared if the upper bound of the 2-sided 95% CI of the HR was <1.8
CV profile	MAP (mmHg) change from BL to the average MAP of weeks 20 to 28	FAS	MMRM model with baseline MAP as a covariate, treatment group, visit (up to Week 52), the interaction of treatment and visit, baseline MAP, treatment group, and stratification factors except the binary Hb (≤10.5 versus >10.5 g/dL) as fixed effects.	**Superiority**
CV profile	Time to first exacerbation of hypertension during Weeks 28 to 52	FAS	Cox Proportional Hazards model adjusting for treatment group and stratification factors	**Superiority**

Abbreviations: BL: baseline; CI: confidence interval; CV: cardiovascular; Ex-US: Outside of US; FAS: full analysis set; Hb: haemoglobin; hs-CRP: high-sensitivity C-reactive Protein; IV: Intravenous; ITT: intention-to-treat; LDL: low density lipoprotein; MAP: mean arterial pressure; PPS: per-protocol set; RBC: red blood cell; ULN: upper limit of normal; US: United States.

Table 160: Sequential testing of primary and key secondary efficacy endpoints in the ROCKIES trial (DD population)

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb maintenance	Hb (g/dL) change from baseline to the average level from week 28 to 36	PPS	MMRM method	**Non-inferiority** was concluded if the lower bound of the 2-sided 95% CI exceeded -0.75 g/dL
Secondary endpoint(s)				
CV profile	Mean change from LDL cholesterol (mmol/L) from baseline to week 24	ITT	ANCOVA with baseline Hb and baseline LDL cholesterol as covariates, and treatment, CV history, geographic region, and dialysis duration as fixed effects.	**Superiority**
Hb maintenance	Change in Hb from baseline to the average Hb from weeks 28-52 for patients with baseline hsCRP greater than the ULN	ITT	Missing at random (MAR)-based MI ANCOVA method	**Superiority**

Hb response	Proportion of total time of interpolated Hb values greater than or equal to 10 g/dL over Week 28-52	ITT	ANCOVA with treatment, geographic region, CV history, and dialysis duration as fixed effects, and baseline Hb as a covariate	**Non inferiority** declared, if the lower bound of CI of the difference exceeded -0.15
Hb response	Proportion of total time of interpolated Hb values within the interval 10 to 12 g/dL over Week 28-52	ITT	ANCOVA with treatment, geographic region, CV history, and dialysis duration as fixed effects and baseline Hb as a covariate	**Non inferiority** declared, if the lower bound of CI of the difference exceeded -0.15
Rescue medication	Mean monthly IV iron use from Week 36 to EOS	ITT	Wilcoxon Rank Sum test	**Superiority**
Rescue medication	Time to first administration of RBC transfusion	OT+3	Cox proportional hazard model with Baseline Hb, geographic region, dialysis duration, and CV history included as covariates	**Non-inferiority** declared if the upper limit of the 2-sided 95% CI for the HR was <1.8.

Abbreviations: CI: Confidence interval; CV: cardiovascular; EU: European Union; EOS: end of study visit; FAS: full analysis set; FDA: Food and Drug Administration; hb: haemoglobin; hs-CRP: high-sensitivity C-reactive protein; IV: intravenous; ITT: intention-to-treat; LDL: low density lipoprotein; OT+3: On treatment 3 days (3 days after last study treatment); RBC: red blood cell; ULN: Upper Limit of Normal; RBC: red blood cell; US: United States; ULN: upper limit of normal.

L.4 Clinical effectiveness results

L.4.1 HIMALAYAS

L.4.1.1 Primary endpoint

HIMALAYAS trial met both primary efficacy endpoints. It demonstrated non-inferiority of roxadustat to epoetin alfa for the maintenance treatment of anaemia in incident-dialysis patients (47).

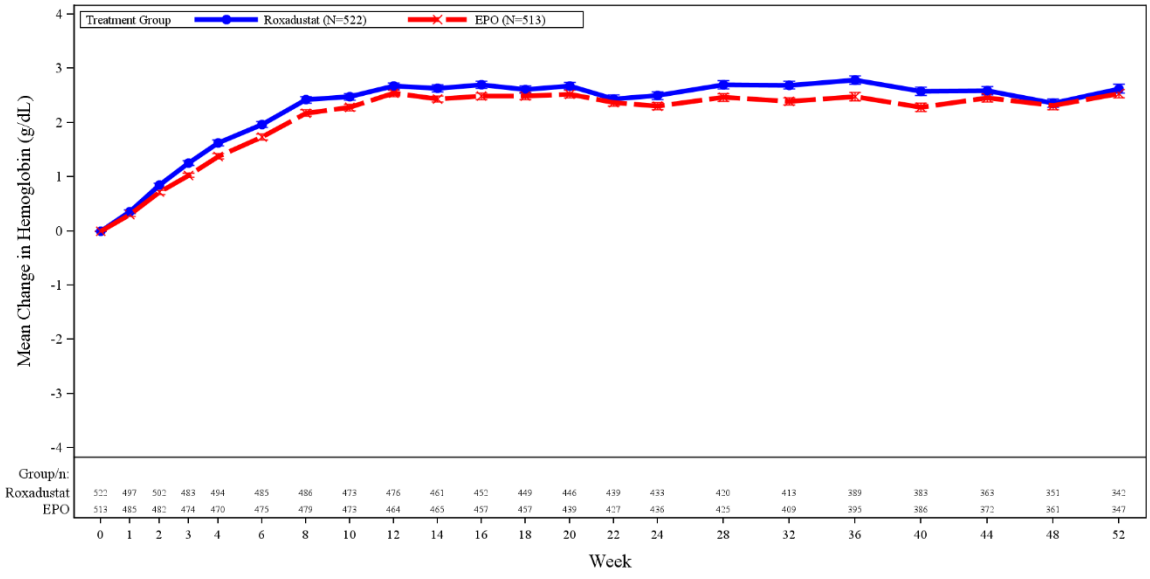
Having met its primary endpoint, HIMALAYAS trial demonstrated statistical non-inferiority of roxadustat to epoetin alfa treatment in terms of the responder rate difference of Hb from baseline to the average Hb during the first 24 weeks of treatment, without rescue therapy (3.5% [-0.7%, 7.7%]) (Table 161) (47). Change in Hb from baseline to week 36 is shown in Figure 41 (47).

Table 161. Hb responder analysis during the first 24 weeks without rescue therapy (PPS population)

Endpoint	Roxadustat (N=490)	Epoetin alfa (N=468)	Responder rate difference
Number of Responders (%)	432 (88.2%)	395 (84.4%)	3.5
95% CI	85.0, 90.9	80.8, 87.6	-0.7, 7.7

Abbreviations: CI: confidence interval; Hb: haemoglobin; LSM: least square mean; PPS: per-protocol set

Figure 41. Mean (±SD) Hb change from baseline to week 52 (FAS population)



Abbreviations: EPO: epoetin alfa; FAS: full analysis set, Hb: haemoglobin; SD: standard deviation.

L.4.1.2 Key secondary endpoints

Non-inferiority was demonstrated for Hb response rate, Hb change in inflamed patients, time to first RBC transfusion and time to first occurrence of hypertension;

superiority was demonstrated for LDL change from baseline and use of IV iron (Table 162) (47).

Table 162. Summary of key secondary endpoints (HIMALAYAS)

Classification	Endpoint (population)	Population assessed	Roxadustat vs. Epoetin alfa (95% CI)	Test type
Hb response	Hb change from baseline to the average over selected Weeks 28 to 52 censoring for rescue therapy	PPS	[redacted]	[redacted]
Hb maintenance	Mean Hb change from baseline to the average level from weeks 28-36 within 6 weeks prior to and during the evaluation period	PPS	[redacted]	[redacted]
Hb maintenance	The time to achieve the first Hb response at 2 consecutive visits during the first 24 weeks of treatment, without rescue therapy	FAS	[redacted]	[redacted]
Hb maintenance	Proportion of patient exposure time with Hb ≥10 g/dL during weeks 28–52	FAS	[redacted]	[redacted]
LDL Cholesterol	Mean change from baseline in LDL cholesterol averaged over weeks 12–24	FAS	[redacted]	[redacted]
Hb maintenance	Mean change from baseline in Hb levels between week 18 to 24 in patients whose baseline hs-CRP >ULN	FAS	[redacted]	[redacted]
Rescue medication	Average monthly IV iron use per subject from weeks 28–52	FAS	[redacted]	[redacted]
Rescue medication	Time to first RBC transfusion during treatment	FAS	[redacted]	[redacted]
CV profile	Mean change in mean MAP from weeks 8–12	FAS	[redacted]	[redacted]
CV profile	Time to first exacerbation of hypertension during Weeks 28 to 52	FAS	[redacted]	[redacted]

Abbreviations: CI: confidence interval; CV: cardiovascular; Ex-US: Outside of the US; FAS: full analysis set; Hb: haemoglobin; HR: hazard ratio; hs-CRP: high-sensitivity C-reactive Protein; IV: intravenous; ITT: intention-to-treat; LDL: low density lipoprotein; MAP: mean arterial pressure; RBC: red blood cell; US: United States; ULN: Upper limit of normal

L.4.2 PYRENEES

L.4.2.1 Primary endpoint

PYRENEES trial met both primary efficacy endpoints. It demonstrated non-inferiority of roxadustat to ESA treatment in terms of maintaining Hb levels in SD patients who had previously received ESA (44).

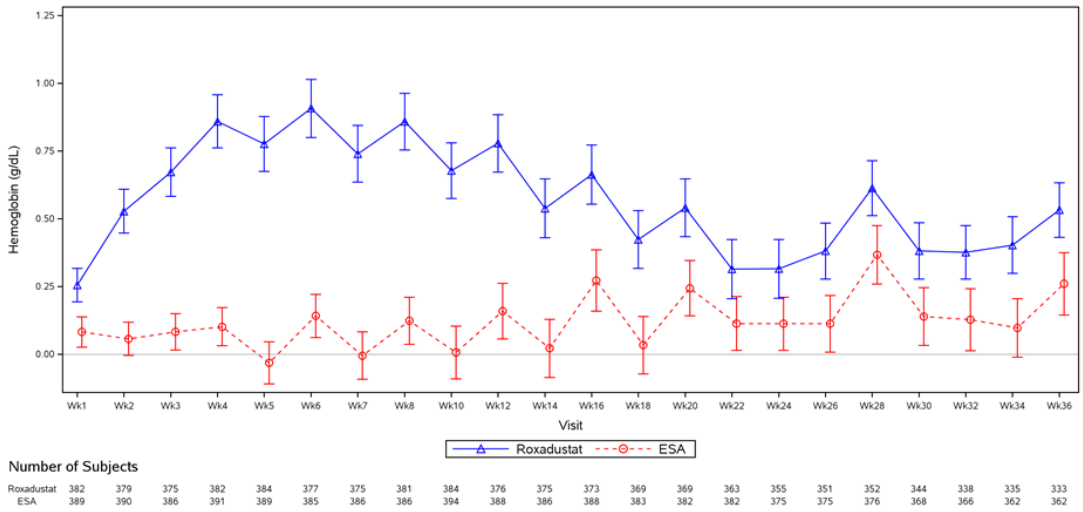
Having met its primary endpoint, PYRENEES trial demonstrated statistical non-inferiority of roxadustat versus ESA treatment in terms of the difference in least squares mean (LSM) change in Hb from baseline to the average Hb of weeks 28–36, regardless of rescue therapy (0.2 [95% CI: 0.1, 0.3; p<0.001]) (Table 163). Change in Hb from baseline to week 36 is shown in Figure 42. (44).

Table 163. Change from baseline to the average Hb in weeks 28-36 regardless of rescue therapy (PPS population)

Endpoint	Roxadustat (n=386)	ESA (n=397)	LSM difference
Hb change from baseline to the average Hb of weeks 28–36, difference in LSM	0.428	0.193	0.235
95% CI	0.350, 0.506	0.117, 0.268	0.132, 0.339 p<0.001

Abbreviations: CI: confidence interval; ESA: erythropoiesis stimulating agent; Hb: haemoglobin; LSM: least square mean; PPS: per-protocol set.

Figure 42. Mean (± 95% CI) Hb change from baseline to week 36 (PPS population)



Abbreviations: CI: confidence interval; ESA: erythropoiesis stimulating agent; Hb: haemoglobin; PPS: per-protocol set

L.4.2.2 Key secondary endpoints

Amongst the key secondary endpoints, superiority was demonstrated for LDL change from baseline and use of IV iron. Higher decrement in LDL cholesterol levels was seen in the roxadustat treatment group compared with the ESA group (~15% vs

<5% respectively). IV iron was required by 30% fewer patients in the roxadustat treatment group. Non-inferiority was demonstrated for Hb response rate, MAP, time to first occurrence of hypertension and changes from baseline in SF-36 physical functioning and SF-36 vitality sub-scores (Table 164) (44).

Table 164. Summary of key secondary endpoints (PYRENEES)

Classification	Endpoint (population)	Population assessed	Roxadustat vs. ESA (95% CI)	Test type
Hb response	Hb response during weeks 28-36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8 week evaluation period; difference of proportions (95% CI)	PPS	[redacted]	[redacted]
LDL Cholesterol	LDL cholesterol (mmol/L) change from baseline to average in weeks 12–28 regardless of fasting status; difference in LSM (95% CI)	FAS	[redacted]	[redacted]
Rescue medication	Mean monthly use of IV iron (mg) from day 1 to week 36; difference in LSM (95% CI)	FAS	[redacted]	[redacted]
HRQoL	Change from baseline in SF-36 PF subscore in weeks 12–28; difference in LSM (95% CI)	PPS	[redacted]	[redacted]
HRQoL	Change from baseline in SF-36 VT subscore in weeks 12–28; difference in LSM (95% CI)	PPS	[redacted]	[redacted]
CV profile	Change from BL in MAP (mmHg) in weeks 12–28; difference in LSM (95% CI)	PPS	[redacted]	[redacted]
CV profile	Time to first increase in blood pressure during weeks 1 to 36; incidence per 100 patient years at risk (95% CI)	PPS	[redacted]	[redacted]
CV profile	Change from BL in MAP (mmHg) in weeks 20–28; difference in LSM (95% CI)	FAS	[redacted]	[redacted]
CV profile	Time to first increase in blood pressure; incidence per 100 patient years at risk (95% CI)	FAS	[redacted]	[redacted]

Abbreviations: BL: baseline; CI: confidence interval; CV: cardiovascular; ESA: erythropoiesis stimulating agent; FAS: full analysis set; Hb: haemoglobin; IV: intravenous; HRQoL: health-related quality of life; LSM: least square mean; LDL: low density lipoprotein; MAP: mean arterial pressure; PF: physical functioning; PPS: per-protocol set; VT: vitality

L.4.3 SIERRAS

L.4.3.1 Primary endpoint

SIERRAS trial met both primary efficacy endpoints. It demonstrated non-inferiority of roxadustat to epoetin alfa for the maintenance treatment of anaemia in ESRD patients on SD (48).

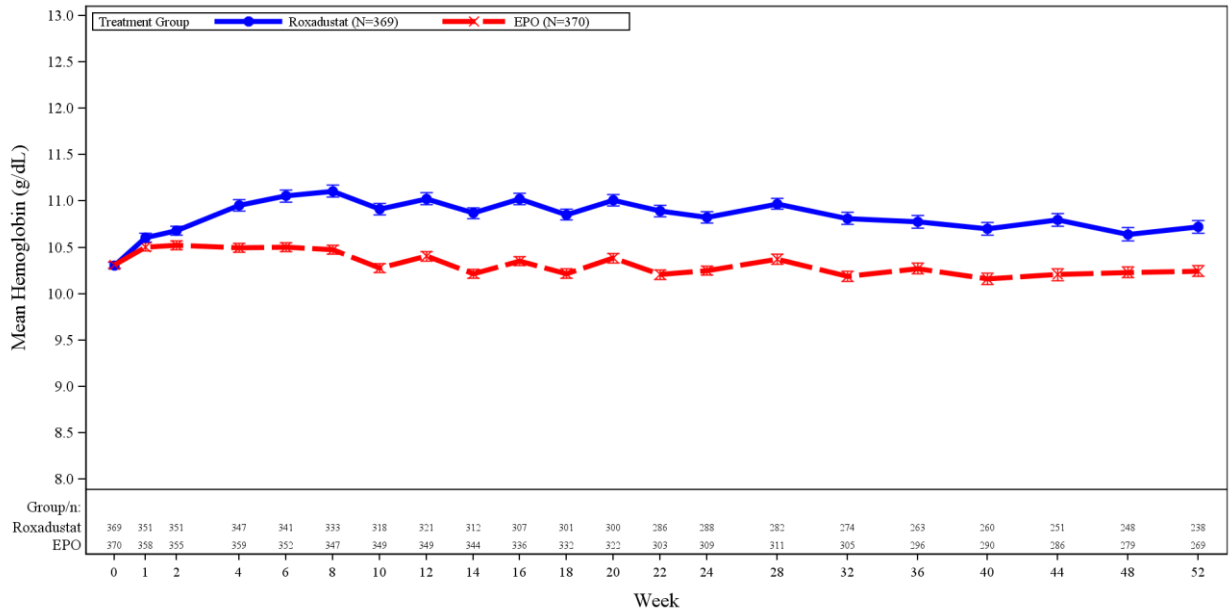
Having met its primary endpoint, SIERRAS trial demonstrated statistical non-inferiority of roxadustat to epoetin alfa treatment in terms of the difference in LSM change in Hb from baseline to the average Hb in weeks 28 to 36, without the use of rescue therapy (0.6 [95% CI: 0.4, 0.7]) (Table 165) (48). Change in Hb from baseline to week 36 is shown in Figure 43 (48).

Table 165. Hb change from baseline to the average Hb in weeks 28 without having received rescue therapy (PPS population)

Endpoint	Roxadustat (n=303)	Epoetin alfa (n=324)	LSM difference
Hb change from baseline to the average Hb of weeks 28–36, difference in LSM	0.63	0.09	0.55
95% CI	0.373, 0.896	-0.169, 0.347	0.404, 0.687 P<0.0001

Abbreviations: CI: confidence interval; Hb: haemoglobin; LSM: least square mean; PPS: per-protocol set

Figure 43. Mean (±SD) Hb change from baseline to week 52 (FAS population)



Abbreviations: EPO: epoetin alfa, FAS: full analysis set, Hb: haemoglobin; SD: standard deviation.

L.4.3.2 Key secondary endpoints

Amongst the key secondary endpoints, superiority was demonstrated for LDL change from baseline and use of IV iron. Non-inferiority was demonstrated for Hb response rate, Hb change in inflamed patients, time to first RBC transfusion and time to first occurrence of hypertension. Superiority was not met for MAP change from baseline (Table 166) (48).

Table 166. Summary of key secondary endpoints (SIERRAS)

Classification	Endpoint (population)	Population assessed	Roxadustat vs. Epoetin alfa (95% CI)	Test type
Hb response	Proportion of responders with Hb level ≥10.0 g/dL.from weeks 28 to 52 regardless of rescue therapy	FAS	[redacted]	[redacted]
Hb response	Proportion of responders within the target Hb range of 10.0 to 12.0 g/dL from weeks 28 to 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.	PPS	[redacted]	[redacted]
LDL Cholesterol	LDL cholesterol change (mmol/L) from BL to the average of weeks 12 to 28	FAS	[redacted]	[redacted]
Hb maintenance	Hb change from BL to the average level during the Weeks 18 to 24 for patient with baseline hs-CRP > ULN.	FAS	[redacted]	[redacted]
Rescue medication	Average monthly IV iron use during the treatment period from weeks 28 to 52	FAS	[redacted]	[redacted]
Rescue medication	Time to first RBC transfusion during the treatment period.	FAS	[redacted]	[redacted]
CV profile	MAP (mmHg) change from BL to the average MAP of weeks 20 to 28	FAS	[redacted]	[redacted]
CV profile	Time to first exacerbation of hypertension during Weeks 28 to 52	FAS	[redacted]	[redacted]

Abbreviations: BL: baseline; CI: confidence interval: FAS: full analysis set; hs-CRP: high-sensitivity C-reactive protein; Hb: haemoglobin; HRQoL: health-related quality of life; HR: hazard ratio; IV: intravenous; LSM: least square mean; LDL: low density lipoprotein; MAP: mean arterial pressure; PPS: per-protocol set; RBC: red blood cell; US: United States.

L.4.4 ROCKIES

L.4.4.1 Primary endpoint

ROCKIES trial met its primary endpoint. It demonstrated non-inferiority of roxadustat to epoetin alfa in terms of response to treatment from week 28 to 36. The adjusted LSM change in Hb from baseline was 0.9 g/dL in the roxadustat group compared with 0.7 g/dL for the epoetin alfa group. The LS mean difference between the groups was 0.1 g/dL (95% CI: 0.0, 0.3; p=0.012) (Table 167) (49).

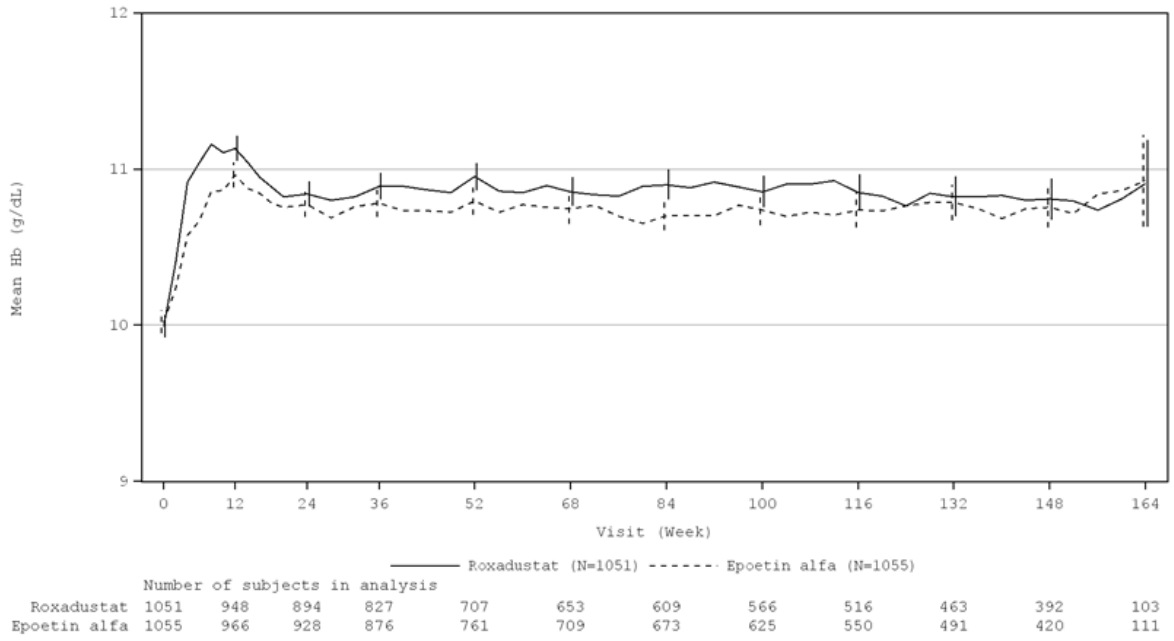
Table 167. Change in Hb (g/dL) from baseline to mean during weeks 28 to 36

	Roxadustat (N=842)	Epoetin alfa (N=869)	LSM Difference
Adjusted LSM change	0.88	0.74	0.14

95% CI	N/A	N/A	0.03, 0.25; p<0.001

Abbreviations: LSM: least squares mean; CI: confidence interval; Hb: haemoglobin; g/dL: grams per decilitre.

Figure 44. Mean Hb (g/dL) over time (ITT Analysis Set)



Abbreviations: CI: confidence interval; Hb: haemoglobin; ITT: intention-to-treat.

L.4.4.2 Key secondary endpoints

Amongst key secondary endpoints, non-inferiority of roxadustat to epoetin alfa was demonstrated for time taken to reach Hb levels of ≥10 g/dL, time taken to reach Hb levels of 10-12 g/dL and time to first administration of RBC transfusion. Superiority was demonstrated for change in LDL cholesterol from baseline and mean monthly IV iron use and change in Hb from baseline in inflamed patients (Table 168) (49).

Table 168. Summary of key secondary endpoints (ROCKIES)

Classification	Endpoint	Population assessed	Roxadstat vs. epoetin alfa P value	Conclusion
LDL Cholesterol	Mean change from LDL cholesterol (mmol/L) from baseline to week 24	ITT	[redacted]	[redacted]
Hb maintenance	Change in Hb from baseline to the average Hb from weeks 28-52 for patients with baseline hsCRP greater than the ULN	ITT	[redacted]	[redacted]
Hb response	Proportion of total time of interpolated Hb values greater than or equal to 10 g/dL over Week 28-52	ITT	[redacted]	[redacted]

Classification	Endpoint	Population assessed	Roxadstat vs. epoetin alfa P value	Conclusion
Hb response	Proportion of total time of interpolated Hb values within the interval 10 to 12 g/dL over Week 28-52	ITT	[redacted]	[redacted]
Rescue medication	Mean monthly IV iron use from Week 36 to EOS	ITT	[redacted]	[redacted]
Rescue medication	Time to first administration of RBC transfusion	OT+3	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EOS: end of study visit; ; Hb: haemoglobin; HR: Hazard ratio; hs-CRP: high-sensitivity C-reactive protein; IV: intravenous; ITT: intention-to-treat; FAS: full analysis set; NI: non-inferior; OT+3: On treatment 3 days (3 days after last study treatment); RBC: red blood cell; ULN: upper limit of normal.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

July 2021

File name	Version	Contains confidential information	Date
ID1483 roxadustat clarification questions to company [ACIC]	3.1	Yes	18/03/2022

Tables and figures

Table 1. CS Table 76 corrected- Clinical SLR search details (MedlineALL) 7
Table 2. CS Table 79 corrected- Clinical SLR search strategy (Embase) 9
Table 3. CS Table 81 corrected- Clinical SLR search strategy (DARE) 10
Table 4 CS Table 83 corrected- Clinical SLR search strategy (HTA database) 11
Table 5 Clinical SLR search strategy (NHS EED) 11
Table 6 CS Table 86 corrected- Clinical SLR search details (CDSR and CENTRAL) 12
Table 7 CS Table 87 corrected- Clinical SLR search strategy (CDSR and CENTRAL) 12
Table 8 Clinical SLR search strategy (Econlit) 13
Table 9. CS Table 1 new scope- The decision problem 18
Table 10. Patient baseline characteristics used in the statistical analyses 21
Table 11. CS Table 6 corrected- Demographic and baseline characteristics of patients included in trials conducted on NDD population 25
Table 12 Cumulative Incidence of Patients Starting Chronic Dialysis or Renal Transplant During the Safety Emergent Period (Kaplan-Meier Method) (Full Analysis Set) 28
Table 13. Summary of hospitalisations during efficacy emergent period (Full Analysis Set) in ALPS 29
Table 14. Summary of hospitalisations during treatment up to week 52 (Full analysis set) in ANDES 31
Table 15. Summary of hospitalisations (OT+28 analysis set) in OLYMPUS 31
Table 16. Summary of hospitalisations during efficacy emergent period (Full Analysis Set) in DOLOMITES 32
Table 17 UK participants in ALPS 38
Table 18 UK participants in DOLOMITES 38
Table 19. Type of dialysis in DOLOMITES 43
Table 20 Dose adjustment rules 48
Table 21. CV safety and mortality in ESA controlled pool 50
Table 22 Early Treatment Discontinuation (All randomised patients) 51
Table 23 Early Treatment Discontinuation (All randomised patients) 51
Table 24 Early Treatment Discontinuation (All randomised patients) 51
Table 25 Early Treatment Discontinuation (All randomised patients) 53
Table 26 Overview of TEAEs and death (SAF population) 54
Table 27 Overview of TEAEs and death (Safety Population) 54
Table 28 Adverse events in the OLYMPUS trial (OT+28) 54
Table 29 Overview of TEAEs and death (SAF population) 56
Table 30. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population) 57
Table 31. Summary of most common TEAEs occurring in ≥5% of patients in both treatment arms (OT+28) 57
Table 32 Summary of most common AEs occurring in ≥5% of patients in both treatment arms (OT+28) 59
Table 33. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population) 59
Table 34 Lifetime event rates per patient (stroke, myocardial infarction and vascular access thrombosis) 63
Table 35 Mean weights from the clinical trials 67
Table 36 Predicted health state occupancy within the cost-effectiveness model (all data) 73
Table 37 Scenario analysis supporting C5 74
Table 38 Proportional hazard assumption check 76
Table 39 Long-term extrapolation estimates of survival 76
Table 40 Proportional hazard assumption check. 78
Table 41 Long-term extrapolation estimates of proportion of patients not on dialysis. 79
Table 42 Long-term extrapolation estimates of survival. 82

Table 43 Long-term extrapolation estimates of proportion of patients not on dialysis. 82
Table 44 Predicted health state occupancy within the cost-effectiveness model (all data) . 83
Table 45 Predicted health state occupancy within the cost-effectiveness model (DOLOMITES data only) 84
Table 46 Scenario analysis supporting C7 b) 85
Table 47: Additional scenario analysis supporting C7b 86
Table 48 Proportion in state coefficients derived from the DOLOMITES study only. 86
Table 49 Scenario analysis supporting C7c 87
Table 50 Predicted health state occupancy within the cost-effectiveness model (all data) . 88
Table 51 Predicted health state occupancy within the cost-effectiveness model (DOLOMITES data only) 88
Table 52 Baseline population characteristics. 89
Table 53 Health state occupancy at baseline. 89
Table 54 Long-term survival extrapolations. 91
Table 55 Long-term time-to-dialysis extrapolations (conditional on being alive) 92
Table 56. Cost-effectiveness results (Response to C9) 94
Table 57 Test for multicollinearity. 97
Table 58. Cost-effectiveness results using utility from Sullivan 102
Table 59 Coefficients for EQ-5D-3L regression analysis 103
Table 60 Test for multicollinearity. 108
Table 61 Test for multicollinearity. 112
Table 62 Number of patients and observations stratified by Hb level and treatment arm... 114
Table 63 Scenario analysis supporting C14 d) 116
Table 64 Test for multicollinearity. 118
Table 65 Scenario analysis supporting C14 e). 119
Table 66 Test for multicollinearity. 122
Table 67 Scenario analysis supporting C14 e).2 123
Table 68. Weekly dose (mcg per kg) for ESAs in NDD patients 124
Table 69. Conversion ratios to adjust the clinical trial derived ESA dose 125
Table 70. Proportion of patients receiving each type of ESA in scenario (C15e) 128
Table 71 Cost-effectiveness results C15d 128
Table 72. Probabilistic sensitivity analysis results 131
Table 73. DSA results for discount rate parameters 133
Table 74. Incremental results of roxadustat vs. ESAs at different time horizons. 134
Table 75. CS Table 62 corrected- Probability of receiving a blood transfusion 140
Table 76. CS Table 64 corrected- Regression coefficients for proportion of patients receiving IV iron 141
Table 77. CS Table 66 corrected- Dose of IV iron per administration 142
Table 78. CS Table 68 corrected-TRAE costs 143
Table 79 HCRU SLR search details (ScHARRHud) 150
Table 80 HCRU SLR search details (CEA Registry) 150
Table 81 HCRU SLR search details (NICE) 151
Table 82 Phase II Trials 157
Table 83: Phase II/III 158
Table 84: Phase III trials 158
Table 85: Phase Ib trial 161
Table 86: Phase III trials 161
Table 87: Pooled data from phase III trials 162

Figure 1 Probability of being on dialysis (if alive) 63
Figure 2: Roxadustat and ESA MoA 65
Figure 3 Multinomial logistic regression (solid lines) fitted to the observed data (dots) 70
Figure 4 Graphical proportional hazard assumption checks. 79
Figure 5 Kaplan-Meier plot and number at risk table for all-cause mortality (On-treatment + 28 days analysis set) 81

Figure 6 Kaplan-Meier plot and number at risk table for time-to-dialysis (On-treatment + 28 days analysis set) 81
Figure 7 Kaplan-Meier plot and number at risk table for all-cause mortality (DOLOMITES study only; On-treatment + 28 days analysis set) 90
Figure 8 Kaplan-Meier plot and number at risk table for time-to-dialysis (DOLOMITES study only; On-treatment + 28 days analysis set) 91
Figure 9 Model residuals versus fitted values 96
Figure 10 Histogram of model residuals. 97
Figure 11 Model predictions (blue triangle) compared to observed data (red circle). 98
Figure 12 Model predictions (blue triangle) compared to observed data (red circle). 99
Figure 13 Model residuals versus fitted values. 107
Figure 14 Histogram of model residuals. 108
Figure 15 Model predictions (blue triangle) compared to observed data (red circle). 109
Figure 16 Model diagnostic plots. 112
Figure 17 Histogram of model residuals. 112
Figure 18 Model predictions (blue triangle) compared to observed data (red circle). 113
Figure 19 Mean roxadustat weekly dose (observed data). 114
Figure 20 Mean ESA weekly dose (observed data). 115
Figure 21 Model residuals versus fitted values. 118
Figure 22 Model predictions (blue triangle) compared to observed data (red circle). 119
Figure 23 Model residuals versus fitted values. 122
Figure 24 Model predictions (blue triangle) compared to observed data (red circle). 123
Figure 25. Cost-effectiveness (CE) plane 132
Figure 26. Cost-effectiveness acceptability curve (CEAC) 132
Figure 27. PRISMA flow diagram of study selection during clinical original SLR 156
Figure 28. PRISMA flow diagram of study selection during clinical SLR update 160

Abbreviation list

Abbreviation	Term
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
ASN	American Society of Nephrology
BIC	Bayesian information criterion
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Credibility interval
CKD	Chronic kidney disease
CRD	Centre for Reviews and Dissemination
CRP	C-Reactive protein
CS	Company submission
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
DARE	Database of Abstracts of Reviews of Effects
DD	Dialysis dependent
DM	Diabetes mellitus
DSA	Deterministic sensitivity analysis
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EPO	Erythropoietin
ERA EDTA	European Renal Association- European dialysis and Transplant Association
ERG	Evidence review group
ESA	Erythropoiesis stimulating agents
ESRD	End-stage renal disease
FAS	Full analysis set
GB	Great Britain
GLM	Generalised linear model
GLMM	Generalised linear mixed model
GVIF	Generalised variance inflation factor
Hb	Haemoglobin
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment

Abbreviation	Term
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ID	Identification
IPD	Individual patient data
ISN	International Society of Nephrology
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
IV	Intravenous
Kg	Kilogram
KOL	Key opinion leader
LY	Life year
MACE	Major adverse cardiovascular events
Max	Maximum
Mcg	Microgram
MI	Myocardial infarction
Min	Minimum
NA	Not available
ND	Non-dialysis
NDD	Non-dialysis dependent
NHS	National Health Service
NHS EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
OR	Odds ratio
PEY	Patient exposure years
PICOS	Patient, intervention, comparator, outcomes and study design
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SLR	Systematic literature review
TA	Technology assessments
TRAE	Treatment-related adverse events
UK	United Kingdom
VAT	Vascular access thrombosis

Section A: Information retrieval

Clinical Effectiveness – Identification and selection of relevant studies

A1. Section B2.1 states that a systematic literature review (SLR) was conducted in July 2019 and updated in March 2021. Section D.1, however, states that the SLR was conducted in two stages: an initial SLR in January 2019 and an update in January 2021.

Please confirm which search dates are correct.

The original clinical effectiveness SLR was conducted in 2019. The searches for the updated SLR were conducted between 21st January 2021 and 19th March 2021.

A2. Table 76 (MEDLINE search) has two columns for 'Original SLR', stating that one search was conducted on 29/04/2019, covering 1946-April 15, 2019, and that another search was conducted on 27/01/2017, covering 2019-January 27 2021.

Please confirm the date searched and column names for the SLR update search.

This corresponds to a typo in the Company Submission (CS) Table 76 headers and content. Please see below the corrected table (Table 1).

Table 1. CS Table 76 corrected- Clinical SLR search details (MedlineALL)

	Original SLR	Updated SLR
Interface / URL:	Ovid Medline	Ovid Medline
Database coverage dates:	1946 to April 15, 2019	2019 to January 27, 2021
Search date:	29/04/2019	27/01/2021
Retrieved records:	50	87

Abbreviations: SLR, systematic literature review.

A3. Table 78 (Embase search) states that the SLR update was conducted on 27/01/2017, covering 2019-January 27, 2021.

Please confirm the date searched.

This corresponds to a typo in the table content. The correct search date is 27th January 2021.

A4. The numbers provided in Table 78 do not match those listed in Table 79. Table 78 states that 24 records were found by the original Embase SLR search. Table 79 states that 120 were found by this search.

Please confirm the numbers of records found. If needed, please provide a list of any missing references as well as PDFs for these references.

This corresponds to a typo in the CS Table 78. The number of records identified and retrieved in the original SLR is 120. All references for studies included in the SLR were provided in the reference pack.

A5. Please confirm that the strategy provided in Table 79 is the correct strategy used for Embase via Ovid, as some of the field names are not used in Embase, and the indexing terms are MeSH and not EMTREE.

This search would not work if run in Ovid Embase. If necessary, please provide the correct search strategy and database host.

This corresponds to a typo in the table content. Please see below the correct EMBASE search strategy via Ovid SP (Table 2).

Table 2. CS Table 79 corrected- Clinical SLR search strategy (Embase)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat$.ti,ab,kw,dj,rn,tn,dy.	113	305
2	asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kw,dj,rn,tn,dy.	105	176
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kw,dj,rn,tn,dy	99	260
4	1 or 2 or 3	146	341
5	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	5715131	6179050
6	4 not 5	120	285
7	limit 6 to yr="2019-current"	NA	169

A6. Table 80 (DARE (Database of Abstracts of Reviews of Effects) search) states that the SLR update was conducted on 27/01/2017, covering 2019-January 27, 2021.

Please confirm the date searched.

This corresponds to a typo in the CS Table 80 content. The correct search date is 27th January 2021.

A7. The numbers provided in Table 80 do not match those listed in Table 81. Table 80 states that 169 records were found by the DARE SLR update search. Table 81 states that 0 records were found by both the original and update searches. Please confirm the numbers of records found.

If necessary, please provide a list of any missing references as well as PDFs for these references.

This corresponds to a typo in the table content. No records were identified on DARE in the SLR update.

A8. Please confirm that the strategy provided in Table 81 is the correct strategy used for DARE via Ovid, as some of the field names are not used in DARE. This search would not work if run in Ovid DARE.

If necessary, please provide the correct search strategy and database host.

This corresponds to a typo in the table content. The search was conducted in the Centre for Reviews and Dissemination (CRD) platform on 21st January 2021. Please see below the correct DARE search strategy via CRD (Table 3).

Table 3. CS Table 81 corrected- Clinical SLR search strategy (DARE)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	(roxadustat*)	0	0
2	(808118-40-3 or "808118403" or x3o30d9ymx)	0	0
3	(asp1517* or asp-1517* or "asp 1517" or fg4592* or fg-4592* or sp1517* or sp-1517* or azd9941* or azd-9941*)	0	0
4	#1 OR #2 OR #3	0	0

A9. Table 82 (HTA (health technology assessment) search) states that the SLR update was conducted on 27/01/2017.

Please confirm the date searched.

This corresponds to a typo in the CS Table 82 content. The correct search date is 27th January 2021.

A10. Please confirm that the strategy provided in Table 83 is the correct strategy used for the HTA database.

This search would not work if run in Ovid HTA Database. If necessary, please provide the correct search strategy and database host.

This corresponds to a typo in the table content. The search was conducted in the CRD platform on 21st January 2021. Please see below the correct HTA search strategy via CRD (Table 4).

Table 4 CS Table 83 corrected- Clinical SLR search strategy (HTA database)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	(roxadustat*)	0	0
2	(808118-40-3 or "808118403" or x3o30d9ymx)	0	0
3	(asp1517* or asp-1517* or "asp 1517" or fg4592* or fg-4592* or sp1517* or sp-1517* or azd9941* or azd-9941*)	0	0
4	#1 OR #2 OR #3	0	0

A11. Table 84 (NHS EED (National Health Service Economic Evaluations Database) search) states that the SLR update was conducted on 27/01/2017.

Please confirm the date searched.

This corresponds to a typo in the CS Table 84 content. The correct search date is 27th January 2021.

A12. Table 84 states that the search was conducted via the CRD website, however the strategy provided in Table 85 is an Ovid strategy (which would not run correctly in Ovid NHS EED).

Please correct either Table 84 or Table 85.

This corresponds to a typo in the CS Table 85 content. The search was conducted in the CRD platform. Please see below the correct NHS EED search strategy via CRD.

Table 5 Clinical SLR search strategy (NHS EED)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	(roxadustat*)	0	0
2	(808118-40-3 or "808118403" or x3o30d9ymx)	0	0
3	(asp1517* or asp-1517* or "asp 1517" or fg4592* or fg-4592* or sp1517* or sp-1517* or azd9941* or azd-9941*)	0	0
4	#1 OR #2 OR #3	0	0

A13. Please confirm that the search provided in Table 87 is for the Cochrane Central Register of Controlled Trials (not "CRD CENTRAL").

This is not listed in the resources detailed in D.1.1.

This corresponds to a typo in the CS Table 87 content. The search was conducted together for the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library / Wiley interface. Please see below the correct CDSR and CENTRAL SLR search details (Table 6) and search strategy (Table 7).

Table 6 CS Table 86 corrected- Clinical SLR search details (CDSR and CENTRAL)

	Original SLR	SLR Update
Interface / URL:	Cochrane Library / Wiley interface	Cochrane Library / Wiley interface
Database coverage dates:	Issue 5 of 12, May 2019	26th April 2019 – 19th March 2021
Search date:	29/04/2019	19/03/2021
Retrieved records:	63	52

Table 7 CS Table 87 corrected- Clinical SLR search strategy (CDSR and CENTRAL)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	(roxadustat*)	30	81
2	(808118-40-3 or "808118403" or x3o30d9ymx)	49	59
3	(asp1517* or asp-1517* or "asp 1517" or fg4592* or fg-4592* or sp1517* or sp-1517* or azd9941* or azd-9941*)	5	6
4	#1 OR #2 OR #3	63	-
5	#1 OR #2 OR #3 with Publication Year from 2019 to 2021, in Trials	-	52

A14. Table 86 states that the search was conducted via the Cochrane Library, however the strategy provided in Table 87 is an Ovid strategy (although would not run correctly in Ovid CENTRAL).

Please correct either Table 86 or Table 87.

See response to question A13.

A15. Please confirm that the strategy provided in Table 88 is the correct strategy used for EconLit via Ovid, as some of the field names are not used in EconLit.

This search would not work if run in Ovid EconLit. If necessary, please provide the correct search strategy and database host.

This corresponds to a typo in the CS Table 89 content. Please see below the correct Econlit search strategy via Ovid SP.

Table 8 Clinical SLR search strategy (Econlit)

#	Searches	Hits (Original SLR)	Hits (SLR Update)
1	roxadustat*.ti,ab,kw,hw.	0	0
2	(asp1517$2 or asp-1517$2 or asp 1517$2 or fg4592$2 or fg-4592$2 or sp1517$2 or sp-1517$2 or azd9941$2 or azd-9941$2).ti,ab,kw,hw.	0	0
3	(808118-40-3 or "808118403" or x3o30d9ymx).ti,ab,kw,hw.	0	0
4	1 or 2 or 3	0	0

A16. Please confirm if an update search was conducted on Pubmed (B.5.1.1.7). Currently only the April 2019 (original SLR) search is provided (Table 91). If an update search was conducted, please provide the strategy used.

A search on Pubmed was not included in the updated SLR given the resources contained in this repository are already indexed in Medline.

A17. Please provide the strategies used for following resources, as listed in section D.1.1:

- **PsycInfo**
- **ScHARRHud**
- **Cost-Effectiveness Analysis (CEA) Registry**
- **The organisational website of the National Institute for Health and Care Excellence (NICE)**
- **International Society of Pharmacoeconomics and Outcomes Research (ISPOR) conference**

Regarding PsycInfo, ScHARRHud, and Cost-Effectiveness Analysis (CEA) Registry, this corresponds with a typo in CS Section D.1.1. These resources were not included in the clinical effectiveness SLR.

The following electronic databases were searched via the given platforms for resource use data:

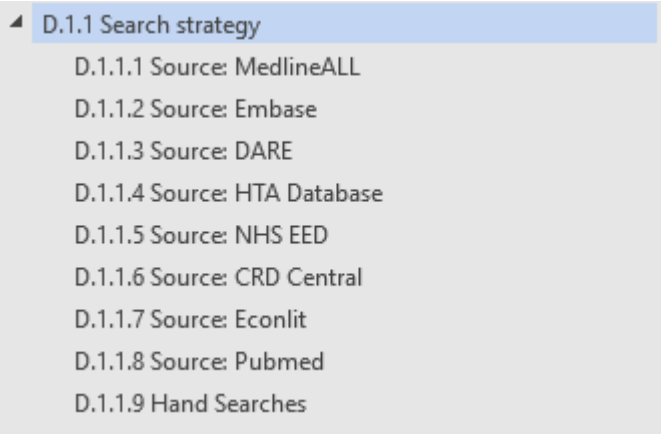
- MEDLINE ALL
- Pubmed (Original SLR)
- Embase
- EconLit
- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment Database
- NHS Economic Evaluation Database (NHS EED)
- Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)
- American Society of Nephrology (ASN)
- European Renal Association- European dialysis and Transplant Association (ERA EDTA)
- International Society of Nephrology (ISN)
- Clinicaltrials.gov
- International Clinical Trials Registry Platform (ICTRP)

A18. There are strategies provided for additional resources in section B.5.1.1.8, but they are not listed in section D.1.1 (International Society of Nephrology, ClinicalTrials.gov, ICTRP).

Please update section D.1.1.

See answer to question A17.

A19. The section heading numbering is incorrect in D.1.1. Please amend.



Health-related quality of life – Identification and selection of relevant studies

A20. Please provide the strategies used for following resources, as listed in section H.1.1:

- **CEA Registry**
- **ScHARRHud**
- **NICE website**
- **European Renal Association - European dialysis and Transplant Association (ERA EDTA) Congress [2016, 2017, 2018, 2019, 2020]**
- **American Society of Nephrology (ASN) Kidney Week [2016, 2017, 2018, 2019, 2020]**
- **ISPOR conference [2016, 2017, 2018, 2019, 2020]**

See appendix A for a detailed response on the search strategies used.

A21. Please confirm if a Pubmed update search was conducted. Currently only the January 2019 (original SLR search) is provided (Table 129). If an update search was conducted, please provide the strategy used.

No update search was conducted on Pubmed given the resources contained in this repository are already indexed in Medline.

A22. Please explain the rationale for applying a 2009 publication date limit to the health-related quality of life study searches.

A 2009 publication date limit was applied to the health-related quality of life study searches as the company considered sufficient the evidence captured in the last 10 years at the time of conducting the SLR.

Cost and healthcare resource use – Identification and selection of relevant studies

A23. Please provide the strategies used for following resources, as listed in section I.1.1:

- **ScHARRHud**
- **CEA Registry**
- **The organisational website of NICE**
- **ERA EDTA Congress**
- **ASN Kidney Week**
- **ISPOR conference**
- **ASN Kidney Week 2016, 2017 and 2018, original SLR**

See appendix B for a detailed response on the strategies used.

A24. Please confirm if a Pubmed update search was conducted. Currently only the January 2019 (original SLR search) is provided (Table 148). If an update search was conducted, please provide the strategy used.

No update search was conducted on Pubmed given the resources contained in this repository already indexed in Medline.

A25. Please explain the rationale for applying a 2009 publication date limit to the cost and healthcare resource identification, measurement, and valuation searches.

A 2009 publication date limit was applied to the cost and healthcare resource use searches as the company considered sufficient the evidence captured in the last 10 years at the time of conducting the SLR.

A26. Please confirm that the searches conducted in Appendix H (Health related quality of life studies) were identical to those in conducted in Appendix I (Cost and healthcare resource identification, measurement, and valuation studies).

The same searches were conducted for both appendices, while applying different criteria for each SLR.

Section B: Clarification on effectiveness data

Decision problem / final scope

B1. Priority question. The NICE scope states that the population of interest is adults with anaemia associated with chronic kidney disease (CKD). The company analysed data for a subgroup of this population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation.

Please revise Table 1 (decision problem) to explicitly state a narrower population was included in the company submission (CS).

CS Table 1 has been updated to address the comments received in questions B1 and B3.

Table 9. CS Table 1 new scope- The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with anaemia associated with Chronic Kidney Disease (CKD)	Adult patients with symptomatic anaemia associated with CKD 3-5 who are non-dialysis dependent (NDD) at the time of treatment initiation.	The population of interest in the submission is narrower than the one detailed in the final NICE scope. See question B1 and section B.1.3.6 of CS.
Intervention	Roxadustat	Per scope	NA
Comparator(s)	Erythropoiesis stimulating agents (ESA)	Per scope	NA
Outcomes	• Haemoglobin response • Maintenance of haemoglobin levels • Use of additional therapy (including blood transfusion and intravenous iron) • Hospitalisation • Adverse effects of treatment including major adverse cardiovascular events • Health-related quality of life	Per scope with the exclusion of hospitalisation.	Hospitalisation was not explicitly modelled in the economic model. Hospitalisation rates from the clinical trials were similar for roxadustat, placebo and ESA. Hospitalisation costs were

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			indirectly captured through adverse event management, drug administration and monitoring.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Per scope	NA
Subgroups to be considered	NA	Per scope	NA
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers	Per reference case	NA
Perspective for costs	Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective.	Per reference case	NA
Time horizon	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Per reference case	NA
Synthesis of evidence on health effects	Based on systematic review	Per reference case	NA
Measuring and valuing health effects	Health effects should be expressed in quality adjusted life years (QALY). The EQ-5D is the preferred measure of health-related quality of life in adults.	Per reference case	NA
Source of data for measurement of health-	Reported directly by patients and/or carers	Per reference case	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
related quality of life			
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the United Kingdom (UK) population	Per reference case	NA
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Per reference case	NA
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Per reference case	NA
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Per reference case	NA

Abbreviations: CKD: chronic kidney disease; CV: cardiovascular; EPO: erythropoietin; ESA: erythropoiesis-stimulating agents; NA: not applicable; NDD: non-dialysis dependent; NHS: National Health Service; NICE: National Institute for Health and Care Excellence;PSS: Personal Social Services; UK: United Kingdom.

B2. Priority question. The NICE scope states that the comparators of interest are other erythropoiesis stimulating agents (ESAs), whereas the company included trials in their analysis which compared roxadustat with placebo. Please revise the decision problem (Table 1) to explicitly state that they focused on different comparators.

Roxadustat is a first-in-class oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). The comparators of interest for the submission are erythropoiesis stimulating agents (ESAs). The trials supporting the clinical and economic case presented in the submission included one ESA controlled study and three trials comparing roxadustat with placebo [1-3]. However, data from the placebo trials was not directly used and placebo and ESA outcomes were not pooled. Instead the roxadustat data was pooled across studies.

As a result of pooling the data at the individual patient level, it was possible to leverage the additional roxadustat data from the other trials. In essence, an individual patient-level data (IPD) analysis has been performed in order to borrow

strength across the pooled studies to generate relative efficacy estimates for roxadustat compared to ESAs.

In order to account for any limitations with this approach, all statistical models accounted for any potential differences between clinical trials by using a hierarchical model structure and used each unique study identification (ID) to control for any impacts of “nesting” (i.e. patients from the same study are more likely to behave in a similar manner compared with patients from another study) where possible.

Furthermore, imbalances in baseline patient characteristics were also controlled for within the statistical models. Apart from a potential increase in the proportion of patients with a history of cardiovascular disease (CVD) at baseline in the DOLOMITES[4], all patient characteristics used within the cost-effectiveness modelling were balanced between studies as shown in Table 10.

All statistical models were checked using diagnostic plots and the variance inflation factor (VIF) was calculated to measure multicollinearity (whether there is a linear relationship between two or more variables).

Table 10. Patient baseline characteristics used in the statistical analyses

Study ID	N	Treatment	Age years	Weight Kg	Male	CVD history	Diabetic	eGFR* ml/min/1.73m2
OLYMPUS	1,357	Placebo	62.40 (14.12)	70.53 (18.90)	44%	31%	58%	20.0 (11.8)
	1,371	Roxadustat	60.86 (14.67)	69.89 (18.46)	41%	30%	57%	19.7 (11.7)
ANDES	305	Placebo	64.84 (13.20)	71.23 (18.37)	43%	33%	65%	22.4 (11.4)
	608	Roxadustat	64.98 (12.59)	71.33 (19.46)	39%	34%	65%	21.9 (11.5)
ALPS	203	Placebo	61.71 (13.76)	76.50 (16.51)	49%	44%	44%	17.2 (11.7)
	389	Roxadustat	60.54 (13.55)	73.85 (16.50)	43%	36%	37%	16.5 (10.2)
DOLOMITES	292	ESA	65.75 (14.42)	78.45 (17.68)	44%	48%	47%	20.4 (10.7)
	322	Roxadustat	66.87 (13.57)	76.93 (16.35)	45%	47%	46%	20.3 (11.5)

* Baseline eGFR was only used as a predictor for time-to-dialysis in the ND population

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ND, non-dialysis; sd, standard deviation.

B3. Priority question. The ALPINE studies (that include the DOLOMITES trial) recruited only patients with CKD stages 3-5:

a) **Please clarify and amend the population in Table 1 of document B to state explicitly that the population is restricted to CKD stages 3-5. Otherwise, please provide evidence that the cost-effectiveness analysis is generalisable beyond this population, i.e. to CKD stages 1 and 2.**

See answer to B1.

b) **Please specify which reference covers the following: "*In a United Kingdom (UK) observational study with a nationally representative sample (N=1,099,292), 8.6% of patients with CKD stage 3–5 had anaemia.*"**

The reference informing this statement is:

Dmitrieva, O., de Lusignan, S., Macdougall, I.C. et al. Association of anaemia in primary care patients with chronic kidney disease: cross sectional study of quality improvement in chronic kidney disease (QICKD) trial data. BMC Nephrol 14, 24 (2013). https://doi.org/10.1186/1471-2369-14-24 [5]

Specifically, this information was taken from Dmitrieva et al. [5] Table 1. A screenshot is provided below.

Table 1 Prevalence of anaemia in patients with CKD

Class CKD		Hb < 13 g/dl(M)* Hb < 12 g/dl(F)		Hb > 11 g/dl		Hb ≤ 11 g/dl**		Hb ≤ 10 g/dl***		Hb ≤ 9 g/dl	
		N	%	N	%	N	%	N	%	N	%
eGFR > 90	F	11545	18.5%	61287	92.8%	4732	7.2%	1523	2.3%	536	0.8%
	M	3552	6.3%	54902	98.6%	790	1.4%	340	0.6%	142	0.3%
eGFR 60-89	F	16032	11.1%	132285	96.0%	5455	4.0%	1747	1.3%	612	0.4%
	M	7228	6.0%	106310	98.8%	1281	1.2%	541	0.5%	235	0.2%
Stage 3A	F	4542	14.3%	28205	94.5%	1654	5.5%	508	1.7%	173	0.6%
	M	2997	20.4%	12760	95.1%	657	4.9%	254	1.9%	101	0.8%
Stage 3B	F	2340	36.4%	5065	82.6%	1065	17.4%	329	5.4%	96	1.6%
	M	1616	48.7%	2654	83.5%	523	16.5%	207	6.5%	86	2.7%
Stage 4	F	663	59.8%	680	63.6%	389	36.4%	167	15.6%	35	3.3%
	M	553	71.3%	516	69.2%	230	30.8%	102	13.7%	38	5.1%
Stage 5	F	128	61.2%	108	55.1%	88	44.9%	43	21.9%	16	8.2%
	M	176	81.5%	123	59.4%	84	40.6%	38	18.4%	18	8.7%
CKD stage 3-5	F	7673	19.4%	34058	91.4%	3196	8.6%	1047	2.8%	320	0.9%
	M	5342	28.1%	16053	91.5%	1494	8.5%	601	3.4%	243	1.4%
Total CKD 3-5		13015	22.2%	50111	91.4%	4690	8.6%	1648	3.0%	563	1.0%

*WHO anaemia definition. **NICE – UK guidelines ***FDA recommended level for anaemia correction.

Source: [5]

c) Please comment, and provide supporting reference explaining whether patients with CKD stages 1 and 2 are likely to develop anaemia and what proportion of patients in the UK are likely to be affected.

The prevalence of anaemia in patients with CKD increases as kidney function declines. A cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES) in the US reported that anaemia was twice as prevalent in people with CKD (15.4 %) as in the general population (7.6 %) Furthermore, the study found that the prevalence of anaemia in patients with stage 1 CKD was 8.4 % and stage 2 was 12.2%. The NHANES study used the KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease for the definition of anaemia (< 12 g/dL in women and < 13 g/dL in men). Data for UK patients with anaemia and stages 1 or 2 CKD are limited. A UK study looking at the prevalence of anaemia in diabetic patients specifically, reported that prevalence of anaemia in patients with eGFR > 60m/min/1.73m2 was 9%.

B4. Table 6 in Document B of the CS does not provide details of the numbers of patients with each stage of CKD and appears to be missing some details such as region, estimated glomerular filtration rate (eGFR), c-reactive protein (CRP) and Type 2 diabetes mellitus (DM) for all trials.

Please provide these details for all relevant trials.

The information requested available from the NDD clinical trials [1-4] can be found in Table 11.

Table 11. CS Table 6 corrected- Demographic and baseline characteristics of patients included in trials conducted on NDD population

		ALPS			ANDES		OLYMPUS			DOLOMITES		
Parameter	**Category/statistic**	**Roxadustat (N=391)**	**Placebo (N=203)**	**Total (N=594)**	**Roxadustat (N=616)**	**Placebo (N=306)**	**Roxadustat (N=1384)**	**Placebo (N=1377)**	**Total (N=2761)**	**Roxadustat (N=323)**	**Darbepoetin alfa (N=293)**	**Total (N=616)**
Baseline demographics												
Sex	Male	169 (43.2%)	99 (48.8%)	268 (45.1%)	241 (39.1%)	130 (42.5%)	564 (40.8%)	603 (43.8%)	1167 (42.3%)	145 (44.9%)	129 (44.0%)	274 (44.5%)
	Female	222 (56.8%)	104 (51.2%)	326 (54.9%)	375 (60.9%)	176 (57.5%)	820 (59.2%)	774 (56.2%)	1594 (57.7%)	178 (55.1%)	164 (56.0%)	342 (55.5%)
Age (years)	Mean	60.6	61.7	61.0	64.9	64.8	60.9	62.4	61.7	66.8	65.7	66.3
	SD	13.5	13.8	13.6	12.6	13.2	14.67	14.14	14.43	13.6	14.4	14.0
	Median	62.0	63.0	63.0	66.0	66.0	62.0	63.0	63.0	69.0	69.0	69.0
	(Min, Max)	20, 89	26, 90	20, 90	22, 94	22, 91	19, 100	18, 93	18, 100	19, 91	22, 91	19, 91
Age range (years)	<65	225 (57.5%)	110 (54.2%)	335 (56.4%)	271 (44.0%)	146 (47.7%)	796 (57.5%)	730 (53.0%)	1526 (55.2%)	127 (39.3%)	110 (37.5%)	237 (38.5%)
	65-74	108 (27.6%)	55 (27.1%)	163 (27.4%)	192 (31.2%)	79 (25.8%)	321 (23.2%)	350 (25.4%)	671 (24.3%)	83 (25.7%)	85 (29.0%)	168 (27.3%)
	≥75	58 (14.8%)	38 (18.7%)	96 (16.2%)	153 (24.8%)	81 (26.5%)	267 (19.3%)	297 (21.6%)	564 (20.4%)	113 (35.0%)	98 (33.4%)	211 (34.3%)
Race	White	335 (85.7%)	182 (89.7%)	517 (87.0%)	176 (28.6%)	99 (32.4%)	623 (45.0%)	611 (44.4%)	1234 (44.7%)	306 (94.7%)	281 (95.9%)	587 (95.3%)
	Black or African American	10 (2.6%)	3 (1.5%)	13 (2.2%)	76 (12.3%)	28 (9.2%)	112 (8.1%)	115 (8.4%)	227 (8.2%)	8 (2.5%)	2 (0.7%)	10 (1.6%)
	Asian	9 (2.3%)	0	9 (1.5%)	310 (50.3%)	151 (49.3%)	544 (39.3%)	538 (39.1%)	1082 (39.2%)	9 (2.8%)	10 (3.4%)	19 (3.1%)
	Other	37 (9.5%)	18 (8.9%)	55 (9.3%)	52 (8.8%)	28 (9.1%)	105 (7.6%)	113 (8.2%)	218 (7.9%)	0	0	0
BMI (kg/m²)	N	391	203	594	614	306	1380	1374	2754	322	293	615
	Mean	27.06	27.63	27.26	27.4	27.3	26.68	26.85	26.76	27.95	28.74	28.33
	SD	5.53	5.51	5.52	6.3	6.0	6.009	6.121	6.064	5.76	6.06	5.92
Region	Western Europe and Israel	-	-	-	-	-	-	-	-	99 (30.7%)	85 (29.0%)	184 (29.9%)
	Central and Eastern Europe	-	-	-	-	-	-	-	-	224 (69.3%)	208 (71.0%)	432 (70.1%)
	US	-	-	-	209 (33.9)	101 (33.0)	343 (24.8%)	340 (24.7%)	683 (24.7%)	-	-	-
	Ex-US	-	-	-	407 (66.1)	205 (67.0)	1041 (75.2%)	1037 (75.3%)	2078 (75.3%)	-	-	-

		ALPS			ANDES		OLYMPUS			DOLOMITES		
Parameter	**Category/statistic**	**Roxadustat (N=391)**	**Placebo (N=203)**	**Total (N=594)**	**Roxadustat (N=616)**	**Placebo (N=306)**	**Roxadustat (N=1384)**	**Placebo (N=1377)**	**Total (N=2761)**	**Roxadustat (N=323)**	**Darbepoetin alfa (N=293)**	**Total (N=616)**
	Western Europe	28 (7.2%)	16 (7.9%)	44 (7.4%)	-	-	-	-	-	-	-	-
	Rest of the World	363 (92.8%)	187 (92.1%)	550 (92.6%)	-	-	-	-	-	-	-	-
Baseline disease characteristics												
CKD stage	Stage 3	83 (21.2%)	52 (25.6%)	135 (22.7%)	129 (20.9%)	65 (21.2%)	256 (18.5%)	255 (18.5%)	511 (18.5%)	72 (22.3%)	62 (21.2%)	134 (21.8%)
	Stage 4	161 (41.2%)	80 (39.4%)	241 (40.6%)	292 (47.4%)	146 (47.7%)	534 (38.6)	520 (37.8%)	1054 (38.2%)	155 (48.0%)	143 (48.8%)	298 (48.4%)
	Stage 5	147 (37.6%)	71 (35.0%)	218 (36.7%)	195 (31.7%)	95 (31.0%)	591 (42.1%)	598 (42.9%)	1189 (43.1)	96 (29.7%)	88 (30.0%)	184 (29.9%)
Hb (g/dL)	Mean	9.08	9.10	9.08	9.10	9.09	9.11	9.10	9.10	9.55	9.55	9.55
	SD	0.76	0.72	0.75	0.75	0.69	0.733	0.742	0.738	0.75	0.69	0.72
	≤8.0	32 (8.2%)	20 (9.9%)	52 (8.8%)	52 (8.4%)	23 (7.5%)	129 (9.3%)	131 (9.5%)	260 (9.4%)	11 (3.4%)	10 (3.4%)	21 (3.4%)
	>8.0	359 (91.8%)	183 (90.1%)	542 (91.2%)	-	-	-	-	-	312 (96.6%)	283 (96.6%)	595 (96.6%)
	>8 - ≤9	-	-	-	173 (28.1%)	97 (31.7%)	386 (27.9%)	402 (29.2%)	788 (28.5%)	-	-	-
	>9	-	-	-	391 (63.5%)	186 (60.8%)	869 (62.8%)	844 (61.3%)	1713 (62.0%)	-	-	-
Iron repletion at baseline	Ferritin <100 ng/mL and TSAT <20%	-	-	-	241 (39.1%)	134 (43.8%)	-	-	-	51 (15.8%)	64 (21.8%)	115 (18.7%)
	Ferritin <100 ng/mL and TSAT ≥20%	-	-	-			-	-	-	27 (8.4%)	23 (7.8%)	50 (8.1%)
	Ferritin ≥100 ng/mL and TSAT <20%	-	-	-	241 (39.1%)	134 (43.8%)	-	-	-	63 (19.5%)	54 (18.4%)	117 (19.0%)
	Ferritin ≥100 ng/mL and TSAT ≥20%	-	-	-	-	-	-	-	-	182 (56.3%)	152 (51.9%)	334 (54.2%)
	Ferritin <30 ng/mL or TSAT <5%	17 (4.3%)	5 (2.5%)	22 (3.7%)	-	-	-	-	-	-	-	-
	30 ≤Ferritin <100 ng/mL and 5% ≤TSAT <20%	53 (13.6%)	28 (13.8%)	81 (13.6%)	-	-	-	-	-	-	-	-
	30 ≤Ferritin <100 ng/mL and TSAT	45 (11.5%)	25 (12.3%)	70 (11.8%)	-	-	-	-	-	-	-	-

		ALPS			ANDES		OLYMPUS			DOLOMITES		
Parameter	**Category/statistic**	**Roxadustat (N=391)**	**Placebo (N=203)**	**Total (N=594)**	**Roxadustat (N=616)**	**Placebo (N=306)**	**Roxadustat (N=1384)**	**Placebo (N=1377)**	**Total (N=2761)**	**Roxadustat (N=323)**	**Darbepoetin alfa (N=293)**	**Total (N=616)**
	>20%											
	Ferritin >100 ng/mL and 5% ≤TSAT <20%	72 (18.4%)	36 (17.7%)	108 (18.2%)	-	-	-	-	-	-	-	-
	Ferritin >100 ng/mL and TSAT >20%	204 (52.2%)	109 (53.7%)	313 (52.7%)	373 (60.6%)	170 (55.6%)	809 (58.5%)	799 (58.0%)	1608 (58.2%)	-	-	-
	Missing				2 (0.3%)	2 (0.7%)	-	-	-	-	-	-
eGFR (mL/min/1.73 m^2)	Mean	16.5	17.2	16.7	21.9	22.4	19.69	19.95	19.82	20.31	20.34	20.32
	SD	10.2	11.7	10.7	11.5	11.4	11.74	11.75	11.74	11.49	10.73	11.12
CRP	≤ULN	245 (62.6%)	135 (66.5%)	380 (63.9%)	457 (74.2%)	223 (72.9%)	520 (37.6%)	497 (36.1%)	1017 (36.8%)	209 (64.7%)	177 (60.4%)	386 (62.7%)
	>ULN	143 (36.6%)	67 (33.0%)	210 (35.4%)	156 (25.3%)	81 (26.5%)	227 (16.4%)	209 (15.2%)	436 (15.8%)	111 (34.4%)	116 (39.6%)	227 (36.8%)
	Missing	3 (0.8%)	1 (0.5%)	4 (0.7%)	3 (0.5%)	2 (0.7%)	637 (46%)	671 (48.7%)	1308 (47.4%)	3 (0.9%)	0	3 (0.5%)
Type 2 diabetes mellitus	Number (%) of patients	131 (33.5%)	76 (37.4%)	207 (34.8%)	248 (40.6)	117 (38.4)	737 (53.3%)	771 (56.0%)	1508 (54.6%)	141 (43.7%)	124 (42.3%)	265 (43.0%)

B5. According to section B.2.2, it appears that different patients have different rates of becoming dialysis dependent.

Please provide data about the chances of patients who took roxadustat becoming dialysis dependent compared with patients who took ESAs.

There was no difference observed in eGFR rate of change between roxadustat and ESA. Patients progressing on to dialysis or renal transplant were comparable between the two groups.

Table 12 Cumulative Incidence of Patients Starting Chronic Dialysis or Renal Transplant During the Safety Emergent Period (Kaplan-Meier Method) (Full Analysis Set)

Time at risk (years)	Roxadustat (n=322)	Darbepoetin alfa (n=292)
0.5	[redacted]	[redacted]
1	[redacted]	[redacted]
1.5	[redacted]	[redacted]
2	[redacted]	[redacted]

B6. The CS (Document A, page 10) states: *"Hospitalisation was not explicitly modelled in the economic model. Hospitalisation rates from the clinical trials were similar for Roxadustat, placebo and ESA. Hospitalisation costs were indirectly captured through adverse event management, drug administration and monitoring."*

a) Please provide a rationale for capturing hospital costs indirectly

The cost effectiveness model is based on health states tracking anaemia severity levels (hereafter: haemoglobin [Hb] levels). To model hospitalisation costs directly, a link between Hb level and hospitalisation rate (i.e. multinomial regression model) would be required to directly relate hospitalisations to the main anaemia progression factor (Hb level) captured in the cost-effectiveness model. Evidence from the roxadustat clinical programme (see response to B6b) shows that hospitalisation rates in DOLOMITES [4] were similar for roxadustat and darbepoetin. In addition, the low number of total hospitalisations limited the feasibility of a multinomial regression model linking Hb level to hospitalisations. Since a direct treatment effect of

roxadustat in hospitalisations was not expected and the available evidence from the clinical studies was not enough to fit a robust statistical model, hospitalisations were not captured directly in relation to Hb level (i.e. anaemia progression).

The main driver of hospitalisation costs in the cost-effectiveness model are adverse events. This is in line with the evidence from the clinical trials where for example, in ALPS [1] and DOLOMITES [4] around half of all hospitalisations were due to adverse events.

b) Please provide a supporting reference for the similar hospitalisation rates for roxadustat, placebo and ESA.

Hospitalisation-related outcomes from the roxadustat NDD trials [1-4] can be found below:

ALPS

In ALPS [1], as shown in Table 13, during the efficacy emergent period the mean number of hospitalisations per patient, the mean number of days total duration of hospitalisation, and the mean number of days of hospitalisation patient exposure years (PEY) were comparable between treatment groups. As well, there was no significant difference in the time to first hospitalisation between the treatment groups, with a comparable incidence rate of [redacted] events per 100 years at risk in the roxadustat group compared with [redacted] in the placebo group. The most common reason given for hospitalisation in both treatment groups was adverse events.

Table 13. Summary of hospitalisations during efficacy emergent period (Full Analysis Set) in ALPS

Parameter	Category/statistic	Roxadustat (N=389)	Placebo (N=203)
Hospitalisation	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Number of	Mean (SD)	[redacted]	[redacted]

Parameter	Category/statistic	Roxadustat (N=389)	Placebo (N=203)
hospitalisations	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Total duration of hospitalisation (days)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Average duration of each hospitalisation (days)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Number of days of hospitalisation per PEY [1]	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Time to first hospitalisation	Number of Patients with Event [2] (Percentage)	[redacted]	[redacted]
	Cumulative Time at Risk (years)	[redacted]	[redacted]
	Incidence Rate (per 100 Patient Years at Risk)	[redacted]	[redacted]
	Hazard Ratio[3]	[redacted]	
	95% CI	[redacted]	
	P value	[redacted]	
Reason for hospitalisation[2]	Anaemia	[redacted]	[redacted]
	Adverse Event	[redacted]	[redacted]
	Other	[redacted]	[redacted]

Notes: The efficacy emergent period is defined as the evaluation period from the analysis date of first dose intake up to 7 days after the analysis date of last dose or EOT visit, whichever occurs first.

[1] The number of days of hospitalisation per patient-exposure-year is calculated as the sum of the durations of all hospitalisations in days [Minimum (Date of discharge, End of Efficacy Emergent Period) - Date of admission + 1] / [Duration of Efficacy Emergent Period in days / 365.25]

[2] A patient can have more than 1 hospitalisation.

[3] Hazard Ratio is calculated using stratified Cox Proportional Hazards regression stratifying on CV history and Region and adjusting on Hb and eGFR at baseline as continuous covariates. Superiority is declared if the upper bound of the 95% CI is below 1

Abbreviations: EOT, End of Treatment; max, maximum; min, minimum; PEY, patient exposure year.

ANDES

In ANDES [2] (Table 14) by the end of week 52, [redacted] roxadustat-treated patients were hospitalised ([redacted], incidence rate per 100 PEY: [redacted]) compared to [redacted] placebo-treated patients ([redacted] incidence rate per 100 PEY: [redacted]). The hazard ratio was [redacted] and there was no significant difference between the two treatment arms up to week 52. The mean number hospitalisation-free days was [redacted] in the roxadustat group compared with the placebo group.

Table 14. Summary of hospitalisations during treatment up to week 52 (Full analysis set) in ANDES

Parameter	Category/statistic	Roxadustat (N=608)	Placebo (N=305)
Hospitalisation	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Time to first hospitalisation	Total patient exposure year (PEY)	[redacted]	[redacted]
	Incidence Rate (per 100 Patient Years)	[redacted]	[redacted]
	Hazard Ratio [1]	[redacted]	
	95% CI	[redacted]	
	P value	[redacted]	
Number of days of Hospitalisation-free	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

Notes: [1] Hazard Ratio is calculated using stratified Cox Proportional Hazards regression stratifying on CV history and Region and adjusting on Hb and eGFR at baseline as continuous covariates. Superiority is declared if the upper bound of the 95% CI is below 1.0

Abbreviations: CI, credibility interval; SD, standard deviation; max, maximum; min, minimum; PEY, patient exposure year.

OLYMPUS

As shown in Table 15, in OLYMPUS [3] the number of patients who were hospitalised at least once during the study was [redacted] in the roxadustat group compared with the placebo group. However, the PEY corrected number of patients who were hospitalised at least once during the study was similar between treatment groups. The total number of hospitalisations for roxadustat and placebo ([redacted] and [redacted] respectively), and the total number of days of hospitalisation per PEY ([redacted] days and [redacted] days per PEY respectively) were [redacted] in the roxadustat group compared with the placebo group.

Table 15. Summary of hospitalisations (OT+28 analysis set) in OLYMPUS

Category/statistic	Roxadustat (N=1384)	Placebo (N=1376)
Subjects who were hospitalized at least once [1, 2]	[redacted]	[redacted]
Total patient exposure year (PEY)	[redacted]	[redacted]
Subjects who were hospitalised at least once, per PEY [2]	[redacted]	[redacted]
Total number of hospitalisations [2,3]	[redacted]	[redacted]
Number of days of hospitalisation per PEY [2]	[redacted]	[redacted]
Total number of days spent in hospital [2]	[redacted]	[redacted]

Notes: [1] Percentages are based on the number of subjects in the OT+28 set in that treatment group. [2] Hospitalisation includes

elective and AE related hospitalisations and Emergency Room visits with an outcome of hospitalization.[3] Overlapping hospitalisations are counted once

DOLOMITES

In DOLOMITES [4] (Table 16), a [redacted] proportion of patients in the roxadustat group compared with the darbepoetin group were hospitalised during the efficacy emergent period. However, the mean number of hospitalisations per patient and average duration of hospitalisations were comparable between treatment groups. Regarding time to first hospitalisation, there was no significant difference in the time to first hospitalisation between the treatment groups, with a comparable incidence rate of [redacted] events per 100 patient years at risk in the roxadustat group compared with [redacted] in the darbepoetin group.

The most common reason given for hospitalisation in both treatment groups was adverse events (AEs).

Table 16. Summary of hospitalisations during efficacy emergent period (Full Analysis Set) in DOLOMITES

Parameter	Category/statistic	Roxadustat (N=323)	Darbepoetin alfa (N=292)
Hospitalisation	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Number of hospitalisations	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Total duration of hospitalisation (days) [1]	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Average duration of each hospitalisation (days)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Number of days of hospitalisation per PEY [2]	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Reason for hospitalisation [3]	Anaemia	[redacted]	[redacted]
	Adverse event	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Time to first hospitalisation	Number of Patients with Event [4] (Percentage)	[redacted]	[redacted]
	Cumulative Time at Risk (years)	[redacted]	[redacted]

Parameter	Category/statistic	Roxadustat (N=323)	Darbepoetin alfa (N=292)
	Incidence Rate (per 100 Patient Years at Risk)	[redacted]	[redacted]
	Hazard Ratio [5]	[redacted]	
	95% CI	[redacted]	
	P value	[redacted]	

Notes: The FAS consisted of all randomised patients who received at least 1 dose of study drug and had at least 1 post dose Hb assessment. The Efficacy Emergent Period is defined as the evaluation period from the analysis date of first dose intake up to EOT visit or last nonmissing Hb assessment (for patients who died during the treatment period). [1] The number of days of hospitalisation is calculated as the sum of the durations of all hospitalisations in days using (Minimum (Date of discharge, End of Efficacy Emergent Period) – Date of Admission + 1). [2] The number of days of hospitalisation per PEY is calculated as the sum of the durations of all hospitalisations in days (Minimum ([Date of discharge, End of Efficacy Emergent Period] – ([Date of admission + 1]) / ([Duration of Efficacy Emergent Period in days / 365.25]). [3]A patient can have more than 1 hospitalisation. [4] For patients who had experienced more than 1 hospitalisation, only their first event was used. [5]Hazard Ratio is calculated using stratified Cox Proportional hazards regression stratifying on cardiovascular history and region and adjusting on Hb and estimated glomerular filtration rate at baseline as continuous covariates. Superiority is declared if the upper bound of the 95% CI is below 1.0.

Abbreviations: EOT, End of Treatment; max, maximum; min, minimum; PEY, patient exposure year.

Systematic review

B7. Table 92 in appendix D of document B provides eligibility criteria for the SLR. Please clarify:

a) Whether the eligibility criteria of the SLR informing the CS match those in the NICE scope i.e. (1) use of additional therapy (including blood transfusion and intravenous iron), (2) mortality. If the SLR did not include the outcomes, please justify and discuss potential implications.

We consider the NICE scope to be well matched by the eligibility criteria of the SLR. While the specific use of additional therapy and mortality were not stated as such in the SLR inclusion criteria, these were not excluded from the searches. Furthermore, blood transfusions and intravenous (IV) iron usage were addressed by the inclusion of best supportive care in the eligibility criteria, allowing results of such studies to be included where available. Similarly, mortality outcomes were implicitly addressed in the SLR by the inclusion of life-years gained and discontinuation due to any cause (including death).

b) Why the studies conducted in wholly Chinese or Japanese populations were excluded and discuss potential implications.

Patient baseline characteristics in Japan and China have been shown to differ from those in European populations, with it being highly possible that such differences affect the progression and treatment of CKD [Imori, 2013]. Differences in clinical practice between these countries and the UK include the use of best supportive care such as IV iron and blood cell transfusions, dialysis practices, as well as different therapeutic targets of haemoglobin levels [Bieber, 2013]. As worsening CKD is associated with increased prevalence of CKD anaemia, further differences in clinical practice between these countries and the UK would weaken the applicability of data collected wholly from China or Japan on a decision problem based on UK CKD anaemia patients, thus supporting the exclusion of wholly Chinese and Japanese studies from the SLR. Such an approach of excluding Chinese or Japanese clinical studies was also undertaken for the roxadustat regulatory submission which considered the same non-dialysis trials as those included within the present evidence dossier.

c) **If any observational studies were considered for inclusion in the SLR. If not, please provide the rationale for excluding observational studies and discuss potential implications**.

The SLR did not exclude observational studies from consideration. However, in the absence of a marketing authorisation, no such studies were identified at the time of undertaking and updating the SLR.

B8. Appendix D of Document B does not include information regarding the process of screening studies at the title/abstract or full-text stage or information about the tool used and the process of risk of bias assessment.

a) **Please provide additional details about the screening process.**

Additional details about the screening process are detailed below:

<u>Original SLR</u>

The original SLR screening process underwent several phases. First, a single reviewer removed obviously irrelevant records, such as animal studies, commentaries and news items, and records on issues unrelated to the topic of interest.

Then, two reviewers independently undertook the record selection screening title and abstracts within Covidence® systematic review software. Irrelevant records were excluded and relevant records or records about which we were uncertain went on to full text assessment.

Two reviewers independently assessed the eligibility of full texts. They assessed the eligibility criteria for each study. Disagreements were resolved by consulting a third independent reviewer.

Regarding the data extraction, one reviewer extracted data from the included studies and a second reviewer checked the data extraction. Any discrepancies were resolved through discussion or by consulting a third reviewer. A data extraction sheet was developed as an Excel spreadsheet and piloted on a number of studies before progressing to full data extraction.

SLR update

In the SLR update, as a first step all records identified through the searches were exported to EndNote®, bibliographic management software. After excluding duplicates, Microsoft Software Excel© spreadsheet was used for screening and exporting citations.

At the abstracts review stage, all records were reviewed by two reviewers independently based on their abstracts and titles against the set of pre-defined inclusion and exclusion criteria. In all publications where uncertainty or any disagreement were present, there was either “reconciliation” (discussion between the two reviewers) or “arbitration” by a third independent reviewer

For the full text review publications selected as potentially relevant from abstract review were retained. Full text publications were independently assessed by two reviewers and discrepancies resolved by consulting a third reviewer and on reaching

consensus. All full-text papers excluded for lack of relevance were entered into an excluded studies table, which noted the reason for exclusion for each study reference. The inclusion and exclusion of studies are summarised in a PRISMA flow diagram.

Regarding the data extraction, one reviewer extracted data from the included studies and a second reviewer checked the data extraction. Any discrepancies were resolved through discussion or by consulting a third reviewer. A data extraction sheet was developed as an Excel spreadsheet and piloted on a number of studies before progressing to full data extraction.

b) Please state if the risk of bias assessment was done, what tool was used, and the process for assessing the risk of bias.

A formal risk of bias assessment was not performed in the identification of relevant studies. We are therefore unable to offer commentary on the quality of studies identified in the literature review within the current timeframe. It is worth noting, that the purpose of the literature review was to identify relevant studies to the decision problem. Irrespective of the quality of studies identified, none of the findings or parameters were in turn used to inform any key modelling parameters, as the CEM centred more on primary evidence generated from the four NDD clinical trials in the population of interest. All trials were conducted in accordance to the International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

c) Please comment on the quality of included studies and provide all relevant information.

See answer to B8b.

B9. Figures 16 and 17 of Appendix D (in Document B) provide information regarding the original and updated SLR. The original SLR included 13 studies (reported in 18 documents), the update included 9 trials (reported in 12 documents). However, Appendix D reports on 13 trials for roxadustat in patients with anaemia and CKD whereas Tables 93 to 95 include 35 references.

Please clarify the numbers of trials identified through the original and updated SLR and how they correspond to the trials of roxadustat for the population of interest.

The results of the original and update clinical SLR have been corrected and are reported in Appendix C.

B10 Priority question. Please explain whether the patients in the included trials discontinued roxadustat if they went on to have a transplant, whether this would be expected in clinical practice, and how many patients in each trial went on to have a transplant.

In alignment with the discontinuation criteria in the included trials, it may be expected in clinical practice that a patient would discontinue a newly approved therapy such as roxadustat at the time of a transplant.

The requested information for each of the included trials is provided below.

- DOLOMITES – In the safety emergent period, [redacted] ([redacted]) patient in the roxadustat arm and [redacted] ([redacted]) in the darbepoetin arm had a renal transplant.
- ALPS – in the FAS, no patients in either arm had a kidney transplant
- ANDES – in the ITT population, [redacted]([redacted]) patients in the roxadustat arm and [redacted] ([redacted]) in the placebo arm had a kidney transplant.
- OLYMPUS – in the ITT population, [redacted] ([redacted]) patients in the roxadustat arm and [redacted] ([redacted]) in the placebo arm had a kidney transplant.

B11. Priority question. Please summarise the time to treatment discontinuation for both roxadustat and ESA using the DOLOMITES trial. Please justify that this is consistent with the UK clinical practice.

In the DOLOMITES trial the incidence of treatment discontinuation over time was greater overall in the roxadustat arm compared with the darbepoetin arm. Discontinuations over time in both treatment groups were driven by withdrawal by

patient and death in the safety analysis set (SAF) and full analysis set (FAS). Due to the open-label nature of the trial it was expected that there would be a higher discontinuation rate with the trial drug. Of all randomised patients, 108 patients on roxadustat (33.4%) and 84 patients on darbepoetin alpha (28.7%) discontinued treatment in the DOLOMITES trial. The discontinuation rate with darbepoetin was consistent with what was seen with ESAs in clinical practice in the UK. Over a two-year treatment period, the discontinuation rates seen with ESAs in the UK clinical practice were [redacted], similar to that observed in DOLOMITES. The primary reasons given for discontinuation were [redacted] (TUNE).

B12. Priority question. Table 6 provides some information about demographic and baseline characteristics of patients included in the trials.

a. Please provide the number of UK patients who took part in each of the trial.

The ANDES [2] and OLYMPUS [3] studies did not recruit any patients in the UK.

The number of United Kingdom (UK) patients recruited in ALPS [1] and DOLOMITES [4] studies are provided in Table 17 and Table 18 respectively.

Table 17 UK participants in ALPS

	Roxadustat (n=391)	Placebo (n=203)	Total (n=594)
United Kingdom	[redacted]	[redacted]	[redacted]

Table 18 UK participants in DOLOMITES

	Roxadustat (n=323)	Placebo (n=293)	Total (n=616)
United Kingdom	[redacted]	[redacted]	[redacted]

b. Please provide clinical effectiveness data for UK population only.

As mentioned in the response B12a, the ANDES [2] and OLYMPUS [3] studies did not enrol any patients in UK centres. Given the small number of patients in the ALPS [1] and DOLOMITES [4] studies, no robust statistical analysis could be performed to provide the same clinical effectiveness endpoints as reported in section B.2 of the

CS for the UK population. Performing statistical analyses in samples with low-statistical power has different problems associated such as reduced chance of detecting a true effect, low likelihood that a statistically significant result reflects a true effect, overestimated effect sizes, and low reproducibility.

B13. Priority question. Regarding the generalisability of the DOLOMITES trial to the UK population:

a) **Please comment on the comparability of the DOLOMITES trial (including inclusion and exclusion criteria, dosing regimens for the comparator) to clinical practice in the UK (include a supporting references).**

Hb levels should not routinely fall below 11 g/dL in patients, prior to initiation of ESA therapy (NICE guidelines). Therefore, the requirement for patients Hb threshold for inclusion within the trial to be ≤ 10.5 g/dL is not in line with current UK clinical practice. NICE guidelines stipulate that Hb <11g/dL should trigger investigation and possible treatment.

The requirement for patients in the DOLOMITES clinical trial to be iron replete (ferritin level ≥ 100 mcg/L and transferrin saturation (TSAT) level ≥ 20%) at treatment initiation was removed from the inclusion criteria in a protocol amendment. Renal association guidelines define iron repletion as ferritin and TSAT >100 microgram/L and >20% respectively. Furthermore, for patients receiving an ESA, supplementary iron therapy is recommended for all patients with serum ferritin values below 100 mcg/L or whose transferrin saturation is below 20%. (darbepoetin SmPC, NICE guidelines). Therefore, the decision to include these patients and initiate an ESA is not in line with current UK clinical practice.

As part of the exclusion criteria for the DOLOMITES study patients must not have received IV iron therapy within 12 weeks prior to randomisation. In the UK IV iron therapy is routinely used in NDD patients to maintain iron repletion when a patient is being treated with an ESA. Data from a non-interventional retrospective study found that for patients receiving an ESA for anaemia associated with CKD, in the UK, [redacted]% received IV iron vs [redacted]% receiving oral iron (TUNE study). This is not in line with the use of iron within the DOLOMITES study. However, the use of blood transfusions as

rescue therapy in the DOLOMITES trial is thought to be in line with clinical practice and NICE guidelines who recommend use only after an adequate response has not been observed with iron or ESA therapy.

b) **Please highlight any differences between the conditions in the DOLOMITES trial and the conditions in clinical practice in the UK and comment on their impact on the generalisability of the results to the UK population.**

The majority of patients in the DOLOMITES study had CKD stage 4, (45%) vs stages 3 and 5 (22.3% and 29.7%). In the placebo-controlled trials (pooled), the majority of patients had CKD stage 5 (42) vs 4 or 3 (40, 17). This is likely due to the difference in the inclusion criteria for patients average Hb levels of the Hb from (<10g/dL for placebo and <10.5g/dL for roxadustat for the placebo and DOLOMITES trials respectively). In light of the Dmitrieva study discussed in the answer to B3, the inclusion of the placebo-controlled studies improves the generalisability to the UK population in terms of representing the prevalence of anaemia in various CKD stages, particularly in more advanced disease.

B14. Table 4 of the CS includes "Reported outcomes specified in the decision problem", however, mortality is not included as an outcome, but it is specified in the NICE scope.

Please comment on the reason why this outcome is not considered in Table 4 and provide details if it was covered by the eligible trials for the population and comparator of interest.

The omission of mortality from Table 4 is a typo, as this outcome was included in the CS (section B.2.10.1). A meta-analysis of adjudicated MACE and MACE+ events was conducted to synthesise the information from the roxadustat phase 3 program. MACE, MACE+, and all-cause mortality outcomes were analysed using the pooled hazard ratio (HR) and its 95% confidence interval (CI). The results from these analyses showed no statistically significant differences in all-cause mortality between roxadustat and ESA. Furthermore, data from the pooled NDD trials of roxadustat was implemented in the model to estimate the survival curve of the patient cohort

(CS section B.3.3.2).

B15. Table 9 of the CS provides the summary of trial methodology. For example, exclusion criteria for the DOLOMITES trial include "*Treatment with IV* [intravenous] *iron within six weeks prior to randomisation"* or "*Patient had received an RBC* [red blood cells] *transfusion within eight-weeks prior to randomisation*". Moreover, the NICE guideline NG8 states that patients who are iron deficient and receiving ESA are being offered an iron therapy (i.e., "*for adults and young people, offer intravenous iron therapy"*).

a) **Please comment if the exclusion criteria are consistent with the current clinical practice within the UK and provide a supporting information.**

The exclusion criteria for DOLOMITES was not considered to be consistent with current UK clinical practice in line with NICE guidelines requiring iron to be offered to patients receiving ESA therapy with respect to IV iron. However, with reference to blood transfusions the exclusion criteria was not considered inconsistent.
Please see response to question B13 for further details.

b) **Please provide more information how iron status was monitored in the DOLOMITES trial. Please comment if IV supplementation was the only iron therapy offered to patients in the DOLOMITES trial.**

For DOLOMITES iron status was monitored by measuring patients' serum iron, ferritin, total iron binding capacity and transferrin saturation levels. These measurements were taken at the following timepoints throughout the study:

- Screening period
- Day 1 (prior to first study drug administration)
- Weeks 4, 8, 12, 20 28, 36, 44, 52, 60, 68, 76, 84, 92, 100
- End of treatment (week 104)
- 4 weeks after the end of treatment visit.

For subjects receiving roxadustat, oral iron was recommended for supplementation to support erythropoiesis and as the first-line treatment for iron deficiency, unless the

subject was intolerant to this treatment. The recommended daily dose was 200 mg of elemental iron. For subjects receiving darbepoetin, oral or IV iron supplementation was required to maintain iron repletion. IV iron was only to be administered if ferritin was < 100 ng/mL or TSAT is < 20%. IV iron was to be administered per local practice.

B16. Across the trials there is a considerable difference between the number of patients consenting to participate and those randomised.

Please explain whether any patients left the trials prior to the treatment phase, and, if necessary, update the flow charts with these details.

The trial protocols specified a screening phase, during which time patients who consented, but may either not have met the inclusion criteria, or had met the exclusion criteria were not included into the randomisation. Such patients were therefore considered as screen failures. It was not considered necessary to update the flow charts. Please see the trial CSRs for further details.

B17. In Figure 20 of Appendix D, the OLYMPUS trial is missing numbers of discontinuations due to death. Please supply these.

In the OLYMPUS trial, discontinuation due to death was not categorised in the same way as the other NDD trials. Instead these events were reported as known vital status. The number of patients in the trial died during the study was 266 (19.2%) on roxadustat and 215 (15.6%) taking placebo. In addition to this, 18 (1.3%) patients in the roxadustat group and 30 (2.2%) patients in the placebo group who had withdrawn their consent were confirmed by public records to have died.

B18. The economic model uses type of dialysis received based on DOLOMITES.

a) **What proportion in DOLOMITES went on to receive haemodialysis and what proportion peritoneal dialysis?**

The proportion of people on haemodialysis and peritoneal dialysis in DOLOMITES [4] is presented below (Table 19). In the CS, this information can be found in Table

31 and Table 60. This data is not reported in the DOLOMITES CSR [4], and it has been extracted from the IPD analysis performed in order to inform the cost-effectiveness model.

The information detailed in Table 19 accounts for those patients who move onto dialysis over time. After accounting for censoring events (patient drop out and death) Kaplan-Meier plots show that approximately [redacted] of the NDD population would be receiving dialysis treatment by week 227 (the final recorded patient follow-up event from the clinical trial program).

Table 19. Type of dialysis in DOLOMITES

Dialysis type	DOLOMITES trial
Haemodialysis	78.3%
Peritoneal dialysis	21.7%

b) Were any differences in results observed between these two groups for any analyses?

A subgroup analysis was not performed based on the modality of dialysis the patients in the trial went on to receive therefore we do not have the data available to answer this question.

c) Did patients who went on to receive dialysis typically continue with roxadustat?

The proportion of people on haemodialysis and peritoneal dialysis in DOLOMITES [4] is presented in Table 19. In the CS, this information can be found in Table 31 and Table 60. This data is not reported in the DOLOMITES CSR [4], and has been extracted from the IPD statistical analysis performed in order to inform the cost-effectiveness model. The information detailed in Table 19 accounts for those patients who moved onto dialysis over time. After accounting for censoring events (patient drop out and death) Kaplan-Meier plots showed that approximately [redacted]% of the NDD population was receiving dialysis treatment by week 227 (the final recorded patient follow-up event from the clinical trial program). There were no protocol mandated discontinuation criteria for roxadustat or ESA on the initiation of dialysis, and typically, patients who went on to receive dialysis, continued treatment. The number of patients who discontinued treatment due to the TEAE of ESRD in DOLOMITES

was [redacted] ([redacted]%) for roxadustat and [redacted] ([redacted]%) for darbepoetin.

B19. The CS states on page 16 that *"conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason"*.

Please clarify what proportion of patients do the company anticipate will convert to roxadustat.

We do not expect dialysis patients who are stable on ESA treatment to convert to roxadustat.

Analyses

B20. Priority question. Please clarify whether the analyses in section B.2.10 were conducted by pooling all participants of all studies or whether meta-analysis was used. If the former, please redo the pooled analyses in section B.2.10 as fixed effect-effect or random-effects meta-analyses, treating all studies as separate.

All analyses conducted in section B.2.10 were conducted by pooling all participants of all studies together to create a "master dataset". However, it should be noted that the placebo and darbepoetin outcome data are not pooled together. Instead the roxadustat outcome data is pooled across studies. While this approach may have its limitations, as a result of pooling the data at the individual patient level, it was possible to leverage the additional roxadustat data from the other trials when comparing roxadustat to darbepoetin. In essence, an individual patient-level data (IPD)-meta analysis was performed in order to borrow strength across the pooled studies to generate relative efficacy estimates for roxadustat compared to other treatments of interest (particularly darbepoetin). It should be noted that the cost-effectiveness model does not compare placebo with darbepoetin at any point (as these were never compared directly with any of the clinical trials).

In order to account for any limitations with this approach, all statistical models accounted for any potential differences between clinical trials by using a hierarchical

model structure and used each unique study ID to control for any impacts of "nesting" (i.e. patients from the same study are more likely to behave in a similar manner compared with patients from another study) where possible. Where it was not possible to conduct hierarchical models due to limitations in the available software (multinomial logistic regressions for proportion in state), study IDs were included as fixed effect variables. Although this is not an ideal approach to account for nesting effects, it was deemed appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all.

Furthermore, imbalances in baseline patient characteristics were also controlled for within the statistical models, something that cannot be done using fixed/random effect meta-analyses. Meta-analyses do not adjust for any heterogeneity in study populations that may influence treatment outcomes. Apart from a potential increase in the proportion of patients with a history of CVD at baseline in DOLOMITES, all patient characteristics used within the cost-effectiveness modelling are broadly balanced between studies as shown in Table 10.

All statistical models were checked using diagnostic plots, graphical checks of raw data versus predicted outcomes and the generalised variance inflation factor (GVIF) was calculated to measure multicollinearity (whether there is a linear relationship between two or more variables). This approach of pooling trials together is common in health technology assessments [6-8]

Finally, the structure of the economic model has been designed to incorporate regression coefficients. Changing the analysis to meta-analysis techniques would require an overhaul of the economic model to take into account the outcomes of this analysis. This is not feasible in the clarification question response period.

Therefore, we deem the analysis that has been conducted is appropriate and there is no need to reconduct analysis of the data using fixed/random effect meta-analysis techniques.

B21. Priority question. Please provide annotated analysis code for all analyses.

All analysis code has been supplied with annotations. All code has been supplied as commercial in confidence. The following files have been made available:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

B22. Priority question. Section B.2.4.2 provides information regarding analysis timepoints for each trial included in the CS.

Please explain why different analysis sets were used for different analyses, and why the per protocol set was used in preference to the intention to treat set.

Due to significant dropout of placebo patients in the placebo-controlled NDD studies there was an imbalance in risk favouring the placebo arms. The lower the eGFR at baseline, the greater the probability of treatment discontinuation happening earlier; this was most evident in the placebo arm (patients with baseline eGFR <10 mL/min/1.73 m2). As a result, a substantially greater proportion of patients in the placebo arm discontinued treatment compared to the roxadustat arm, especially those with lower baseline eGFRs who were most susceptible to experiencing cardiovascular events. Conversely, a larger proportion of susceptible patients in the roxadustat arm were available (as they remained on study) to contribute to cardiovascular events. Therefore, the intent to treat methodology was used to address the differential drop out and informative censoring. While there is no single method that can reliably address the issues resulting from the bias from informative censoring, this approach was accepted by regulators.

B23. Priority question. Table 2 of document B of the CS provides information about marketing authorisation i.e., *"CHMP opinion is expected in June 2021 with the submission to the MHRA in June 2021 also"*.

a) **Please provide an update on the status of the Committee for Medicinal Products for Human Use (CHMP) opinion and comment on the submission status to the Medicines and Healthcare products Regulatory Agency (MHRA).**

Roxadustat received positive CHMP opinion on 24 June 2021. The Great Britain (GB) Marketing Authorisation Application was submitted to MHRA on [redacted]. The application was submitted via the European Commission (EC) Decision Reliance Procedure so MHRA approval is anticipated soon after the expected EC approval of the European Union (EU) application in [redacted].

b) **Please provide the full wording of the expected marketing authorisation.**

The full wording of the expected marketing authorisation for roxadustat is as follows:

Evrenzo is indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

c) **Please clarify if the target haemoglobin (Hb) range of 10.0 g/dl and 12.0 g/dl and the DOLOMITES dosing recommendations are consistent with the intended use of roxadustat.**

The target Hb range in all four NDD trials was 10g/dL to 12g/dL and is therefore consistent with how roxadustat will be used in UK clinical practice and in accordance with existing guidelines.

For initiation of roxadustat in the DOLOMITES study, patients who were ≤70kg were to take 70mg three times weekly (TIW) and patients > 70kg were to take 100mg TIW. As per the roxadustat draft Summary of Product Characteristics (SmPC) it is expected in clinical practice the recommended initial dose of roxadustat will be [redacted]mg in patients [redacted]kg and [redacted]mg in patients [redacted]kg.

Maintenance dosing in the DOLOMITES trial was consistent with how it is expected to be used in clinical practice with regard to the step wise dosing (20mg, 40mg,

50mg, 70mg, 100mg, 150mg, 200mg, 250mg, 300mg, 400mg) and the recommendation to increase or decrease in response to the Hb measured in the patient. Dose adjustment rules can be found in Table 20.

Table 20 Dose adjustment rules

Change in Hb over the previous 4 weeks[1]	Current Hb level (g/dL):			
	Lower than 10.5	10.5 to 11.9	12.0 to 12.9	13.0 or higher
Change in value of more than +1.0 g/dL	No change	Reduce dose by one step	Reduce dose by one step	Withhold dosing, monitor Hb level and resume dosing when Hb is less than 12.0 g/dL, at a dose that is reduced by two steps
Change in value between -1.0 and +1.0 g/dL	Increase dose by one step	No change	Reduce dose by one step	
Change in value of less than -1.0 g/dL	Increase dose by one step	Increase dose by one step	No change	

In the DOLOMITES trial the exclusion criteria stated that patients could not have received an ESA for 12 weeks prior to the trial. In clinical practice this will not be the case. In accordance with the roxadustat SmPC, for patients who are on an ESA the first roxadustat dose should replace the next scheduled dose of the current ESA. Please see the dose conversion table for each ESA in the roxadustat SmPC.

B24. A full network meta-analysis (NMA) comparing roxadustat, ESA and placebo, was not considered or performed.

a) Please provide a rationale for why a full NMA, comparing roxadustat, ESA and placebo, was not considered or performed, given 3 of the 4 NDD Alpine studies had placebo as the comparator.

While the evidence submission for roxadustat includes data from all four trials conducted in the NDD population, it is important to note that placebo data is not pooled with ESA data from the head-to-head trial. Instead, the roxadustat outcome data is pooled across studies in order to leverage the additional roxadustat data from the other trials when comparing roxadustat to ESA. It should be noted that the cost-effectiveness model does not compare placebo with ESA at any point (as these were never compared directly with any of the clinical trials).

Importantly, placebo is not used in UK clinical practice for the treatment of anaemia associated with CKD and is therefore out of scope as a relevant comparator against roxadustat, as evidenced by the NICE scope (see response to question B2). The comparator of interest (ESA) however, exist as a range of individual agents that share the same mechanism of action [9] and are considered equivalent in terms of efficacy and safety profile [10-12]. Furthermore, as the submission benefited from the only head-to-head trial of roxadustat against ESA (as described above), an NMA comparing roxadustat to individual ESAs as separate nodes would have not added value to the evidence package for roxadustat.

b) If you consider there are no suitable studies comparing ESA with placebo, please provide evidence to support this.

As described in the responses to B24a and B2, placebo is not a relevant comparator for roxadustat. As the submission benefitted from head-to-head data against the relevant comparator, it was not appropriate to perform an NMA of evidence of ESA against placebo trials for the current decision problem.

B25. Table 26 of Document B in the CS provides *"CV safety and mortality in ESA controlled pool"*, however, the last column labelled as *"ACM"* is missing the number of participants in both treatment arms.

Please provide those numbers.

This corresponds to a typo in the table content. This comment has been addressed in Table 21, where the number of patients in MACE and MACE+ has been corrected as well.

Table 21. CV safety and mortality in ESA controlled pool

	MACE		MACE+		ACM	
	Roxadustat n= 1,083	ESA n = 1,059	Roxadustat n= 1,083	ESA n = 1,059	Roxadustat n= 1,083	ESA n = 1,059
On treatment						
Number of events (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FAIR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	

Abbreviations: ACM: all-cause mortality; ACM is a component of MACE/MACE+. CI: confidence interval; FAIR: follow-up adjusted incidence rate (number of patients with event/100 patient years); HR: hazard ratio; ITT: intent-to-treat; MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

B26. Appendix F of document B summarises information of the adverse reactions for the ALPS, ANDES, OLYMPUS, and DOLOMITES trials. However, the Tables provided the data for different populations in the trials (e.g. all randomised patients, safety analysis set (SAF) population, OT+28 etc.) or events that are not covered by all trials (i.e. treatment-emergent serious adverse events (TESAEs) provided only for the ANDES trial).

Please comment on the comparability of the results and provide the tables to allow the comparison of additional safety results between trials. More specifically:

a. **Early Treatment Discontinuation for (1) all randomised patients and (2) the population used in the analysis making sure that parameters are consistent between tables.**

An overview of early treatment discontinuation has been provided below for ALPS, ANDES, OLYMPUS and DOLOMITES trials for all randomised patients. Where values have not been provided, they were not recorded in the CSR. All parameters have been consistently reported.

<u>ALPS</u>

Table 22 Early Treatment Discontinuation (All randomised patients)

Parameter	Category	Roxadustat (n=391)	Placebo (n=203)	Total (n=594)
Early treatment discontinuation up to two years	Yes	146 (37.3%)	114 (56.2%)	260 (43.8%)
	No	245 (62.7%)	89 (43.8%)	334 (56.2%)
Primary reason for discontinuation†	Adverse event	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Lack of efficacy	3 (0.8%)	26 (12.8%)	29 (4.9%)
	Lost to follow-up	[redacted]	[redacted]	[redacted]
	Progressive disease	[redacted]	[redacted]	[redacted]
	Protocol deviation	[redacted]	[redacted]	[redacted]
	Withdrawal by patient	[redacted]	[redacted]	[redacted]
	Study terminated by sponsor	[redacted]	[redacted]	[redacted]
	Physician decision	[redacted]	[redacted]	[redacted]
	Noncompliance with study drug	[redacted]	[redacted]	[redacted]
	Pregnancy	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]

ANDES

Table 23 Early Treatment Discontinuation (All randomised patients)

Parameter	Category	Roxadustat (n=616)	Placebo (n=306)	Total (n=922)
Treatment discontinuation	Yes	267 (43.3%)	208 (68.0%)	475 (51.5%)
	No	349 (56.7%)	98 (32.0%)	447 (48.5%)
Primary reason for discontinuation	Adverse event	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]
	Lack of efficacy	2 (0.3%)	43 (14.1%)	45 (4.9%)
	Lost to follow-up	28 (4.5%)	7 (2.3%)	35 (3.8%)
	Progressive disease			
	Protocol deviation	6 (1%)	5 (1.6%)	3 (0.5%)
	Withdrawal by patient	83 (13.5%)	89 (29.1%)	172 (18.7%)
	Study terminated by sponsor	4 (0.6%)	1 (0.3%)	5 (0.5%)
	Physician decision	16 (2.6%)	17 (5.6%)	33 (3.6%)
	Noncompliance with study drug			
	Pregnancy	[redacted]	[redacted]	[redacted]
	Other	43 (7%)	16 (5.2%)	59 (6.4.3%)

OLYMPUS

Table 24 Early Treatment Discontinuation (All randomised patients)

Parameter	Category	Roxadustat (n=1,393)	Placebo (n=1,388)	Total (n=2,781)
Treatment discontinuation	Yes	499 (36.1%)	801 (58.2%)	1300 (46.7%)
	No	894 (63.9.%)	587 (41.8%)	1481 (53.3%)
Primary reason for discontinuation	Adverse event	79 (5.7%)	52 (3.8%)	131 (4.7%)
	Death	[redacted]	[redacted]	[redacted]
	Lack of efficacy			
	Lost to follow-up	[redacted]	[redacted]	[redacted]
	Progressive disease			
	Protocol deviation	12 (0.9%)	13 (0.9%)	25 (0.9%)
	Withdrawal by patient	250 (18.1%)	390 (28.3%)	640 (23.0%)
	Study terminated by sponsor			
	Physician decision			
	Noncompliance with study drug			
	Pregnancy	[redacted]	[redacted]	[redacted]
	Other	82 (5.9%)	93 (6.8%)	175 (6.3%)

DOLOMITES

Table 25 Early Treatment Discontinuation (All randomised patients)

Parameter	Category	Roxadustat (n=323)	Darbepoetin (n=293)	Total (n=616)
Treatment discontinuation	Yes	108 (33.4%)	84 (28.7%)	192 (31.2%)
	No	215 (66.6%)	209 (71.3%)	424 (68.6%)
Primary reason for discontinuation	Adverse event	21 (6.5%)	8 (2.7%)	29 (4.7%)
	Death	27 (8.4%)	30 (10.2%)	57 (9.3%)
	Lack of efficacy	[redacted]	[redacted]	[redacted]
	Lost to follow-up	[redacted]	[redacted]	[redacted]
	Progressive disease	8 (0.3%)	15 (5.1%)	23 (3.7%)
	Protocol deviation	[redacted]	[redacted]	[redacted]
	Withdrawal by patient	32 (9.9%)	20 (6.8%)	52 (8.4%)
	Study terminated by sponsor	[redacted]	[redacted]	[redacted]
	Physician decision	[redacted]	[redacted]	[redacted]
	Noncompliance with study drug	[redacted]	[redacted]	[redacted]
	Pregnancy	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]

b. Overview of treatment emergent adverse events (TEAEs) and death for (1) all randomised patients and (2) the population used in the analysis making sure that parameters are consistent between tables.

An overview of treatment emergent adverse events (TEAEs) and death has been provided below for ALPS, ANDES, OLYMPUS and DOLOMITES trials. Not all patients who were randomised went on to receive a dose of treatment drug therefore the data that has been provided is as follows:

- ALPS – Overview of TEAEs and death in SAF (all patients randomised who received at least one dose of drug)
- ANDES – Overview of TEAEs and death in Safety population (all patients randomised who received at least one dose of drug)
- OLYMPUS – Overview of TEAEs and death in OT+28 (all patients randomised who received at least one dose of drug to 28 days after last dose
- DOLOMITES – Overview of TEAEs and death in SAF (all patients randomised who received at least one dose of drug)

The safety emergent period in the trials was used to identify the minimum or maximum values collected on-treatment, defined as values collected from day 2 up to the end of the safety emergent period. The OT+28 analysis was the same as safety emergent period where death date from adjudication database was used. If death date was before the first dose date, then death date was imputed as the last dose date. Where values have not been provided, they were not recorded in the CSR.

ALPS

Table 26 Overview of TEAEs and death (SAF population)

	Roxadustat (N=391)	Placebo (N=203)
TEAE	343 (87.7%)	176 (86.7%)
Drug-related TEAE	[redacted]	[redacted]
Serious TEAE	241 (61.6%)	115 (56.7%)
Drug-related serious TEAE	[redacted]	[redacted]
TEAE leading to death	40 (10.2%)	19 (9.4%)
Drug-related TEAE leading to death	[redacted]	[redacted]
TEAE leading to withdrawal of treatment	23 (5.9%)	8 (3.9%)
Drug-related TEAE leading to withdrawal of treatment	[redacted]	[redacted]
TEAE NCI CTC grades ≥3	185 (47.3%)	88 (43.3%)
Death during the safety emergent period	37 (9.5%)	16 (7.9%)
Death (overall)	[redacted]	[redacted]

ANDES

Table 27 Overview of TEAEs and death (Safety Population)

	Roxadustat (N=611)	Placebo (N=305)
TEAE	564 (92.3%)	273 (89.5%)
Drug-related TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
Drug-related serious TEAE	[redacted]	[redacted]
TEAE leading to death	[redacted]	[redacted]
Drug-related TEAE leading to death	[redacted]	[redacted]
TEAE leading to withdrawal of treatment	[redacted]	[redacted]
Drug-related TEAE leading to withdrawal of treatment	[redacted]	[redacted]
TEAE NCI CTC grades ≥3	[redacted]	[redacted]
Death during the safety emergent period	[redacted]	[redacted]
Death (overall)		

OLYMPUS

Table 28 Adverse events in the OLYMPUS trial (OT+28)

	Roxadustat (N=1,384)	Placebo (N=1,376)
TEAE	[redacted]	[redacted]
Drug-related TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
Drug-related serious TEAE	[redacted]	[redacted]
TEAE leading to death	[redacted]	[redacted]
Drug-related TEAE leading to death		
TEAE leading to withdrawal of treatment	[redacted]	[redacted]
Drug-related TEAE leading to withdrawal of treatment		
TEAE NCI CTC grades ≥3	[redacted]	[redacted]
Death during the safety emergent period		

DOLOMITES

Treatment-emergent AEs (TEAEs) were defined as AEs which started during the treatment period and were not present prior to the first dose of study drug, or the AE was present prior to the first dose of study drug but increased in severity during the treatment period. An AE that occurs after the end day of the safety emergent period will not be counted as a TEAE

Table 29 Overview of TEAEs and death (SAF population)

	Roxadustat (n=323)	Darbepoetin alfa (n=293)
TEAE	296 (91.6%)	271 (92.5%)
Drug-related TEAE	[redacted]	[redacted]
Serious TEAE	209 (64.7%)	181 (61.8%)
Drug-related serious TEAE	[redacted]	[redacted]
TEAE leading to death	34 (10.5%)	34 (11.6%)
Drug-related TEAE leading to death	[redacted]	[redacted]
TEAE leading to withdrawal of treatment	25 (7.7%)	11 (3.8%)
Drug-related TEAE leading to withdrawal of treatment	[redacted]	[redacted]
TEAE NCI-CTCAE Grades ≥3	181 (56.0%)	164 (56.0%)
Death during the Safety Emergent Period	30 (9.3%)	31 (10.6%)
Death (Overall)	[redacted]	[redacted]

c. Summary of most common TEAEs occurring in ≥5% of patients in either treatment arm for (1) all randomised patients and (2) the population used in the analysis making sure that parameters are consistent between

A summary of most common TEAEs that occurred in ≥5% of patients in either treatment arm has been provided below for ALPS, ANDES, OLYMPUS and DOLOMITES trials. As stated previously not all patients who were randomised went on to receive a dose of treatment drug therefore the data that has been provided is as follows:

- ALPS – Overview of TEAEs and death in SAF (all patients randomised who received at least one dose of drug)
- ANDES – Overview of TEAEs and death in OT+28 (all patients randomised who received at least one dose of drug to 28 days after last dose)
- OLYMPUS – Overview of TEAEs and death in OT+28 (all patients randomised who received at least one dose of drug to 28 days after last dose)
- DOLOMITES – Overview of TEAEs and death in SAF (all patients randomised who received at least one dose of drug)

Parameters below have been consistently reported as occurred in each trial.

ALPS

Table 30. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population)

	Roxadustat (N=391)		Placebo (N=203)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Overall	373 (87.7%)	476.7	176 (86.7%)	514.7
End-stage renal disease	135 (34.5%)	27.2	62 (30.5%)	30.0
Hypertension	87 (22.3%)	28.6	28 (13.8%)	21.9
Oedema peripheral	45 (11.5%)	10.9	21 (10.3%)	10.5
Glomerular filtration rate decreased	43 (11.0%)	9.7	23 (11.3%)	13.3
Hyperkalaemia	39 (10.0%)	10.5	15 (7.4%)	10.0
Viral upper respiratory tract infection	38 (9.7%)	10.1	9 (4.4%)	7.1
Nausea	37 (9.5%)	9.5	6 (3.0%)	2.9
Diarrhoea	33 (8.4%)	8.3	7 (3.4%)	4.8
Pneumonia	28 (7.2%)	7.0	14 (6.9%)	8.1
Iron deficiency	26 (6.6%)	5.2	8 (3.9%)	4.8
Anaemia	24 (6.1%)	5.4	37 (18.2%)	25.7
Headache	21 (5.4%)	4.4	11 (5.4%)	5.7
Arteriovenous fistula thrombosis	20 (5.1%)	5.4	2 (1.0%)	1.4
Pruritus	20 (5.1%)	4.4	2 (1.0%)	1.0
Asthenia	19 (4.9%)	4.6	12 (5.9%)	7.1
Hyperuricaemia	9 (2.3%)	1.8	11 (5.4%)	5.2

ANDES

Table 31. Summary of most common TEAEs occurring in ≥5% of patients in both treatment arms (OT+28)

	Roxadustat (N=611)		Placebo (N=305)	
	n (%)	Events (Event rate per 100 PEY)	n (%)	Event rate per 100 PEY
Overall	490 (80.2)	2801 (246.8)	224 (73.4)	1001 (265.3)
Anaemia	17 (2.8)	19 (1.7)	44 (14.4)	58 (15.4)
Constipation	105 (17.2)	139 (12.2)	34 (11.1)	39 (10.3)
Nausea	85 (13.9)	110 (9.7)	29 (9.5)	35 (9.3)
Diarrhoea	78 (12.8)	106 (9.3)	31 (10.2)	39 (10.3)
Vomiting	54 (8.8)	65 (5.7)	20 (6.6)	22 (5.8)
Dyspepsia	39 (6.4)	45 (4.0)	12 (3.9)	12 (3.2)
Abdominal pain	35 (5.7)	44 (3.9)	13 (4.3)	14 (3.7)
Oedema peripheral	89 (14.6)	128 (11.3)	28 (9.2)	38 (10.1)
Oedema	48 (7.9)	62 (5.5)	9 (3.0)	12 (3.2)
Pyrexia	39 (6.4)	61 (5.4)	9 (3.0)	12 (3.2)
Asthenia	31 (5.1)	35 (3.1)	11 (3.6)	11 (2.9)

	Roxadustat (N=611)		Placebo (N=305)	
	n (%)	Events (Event rate per 100 PEY)	n (%)	Event rate per 100 PEY
Viral upper respiratory tract infection	98 (16.0)	192 (16.9)	40 (13.1)	58 (15.4)
Upper respiratory tract infection	79 (12.9)	145 (12.8)	48 (15.7)	68 (18.0)
Urinary tract infection	68 (11.1)	103 (9.1)	29 (9.5)	56 (14.8)
Pneumonia	44 (7.2)	52 (4.6)	18 (5.9)	21 (5.6)
Bronchitis	34 (5.6)	44 (3.9)	13 (4.3)	16 (4.2)
Cellulitis	32 (5.2)	37 (3.3)	7 (2.3)	22 (5.8)
Hyperkalaemia	111 (18.2)	154 (13.6)	41 (13.4)	47 (12.5)
Hypoglycaemia	53 (8.7)	69 (6.1)	15 (49)	17 (4.5)
Decreased appetite	41 (6.7)	51 (4.5)	8 (2.6)	8 (2.1)
Hyperphosphataemia	40 (6.5)	46 (4.1)	10 (3.3)	10 (2.7)
Gout	32 (5.2)	46 (4.1)	20 (6.6)	33 (8.7)
Metabolic acidosis	29 (4.7)	31 (2.7)	18 (5.9)	20 (5.3)
Back pain	55 (9.0)	66 (5.8)	18 (5.9)	20 (5.3)
Arthralgia	45 (7.4)	50 (4.4)	24 (7.9)	27 (7.2)
Muscle spasms	41 (6.7)	53 (4.7)	9 (3.0)	10 (2.7)
Pain in extremity	39 (6.4)	42 (3.7)	14 (4.6)	14 (3.7)
Headache	66 (10.8)	99 (8.7)	26 (8.5)	31 (8.2)
Dizziness	58 (9.5)	85 (7.5)	32 (10.5)	35 (9.3)
Insomnia	63 (10.3)	75 (6.6)	9 (3.0)	10 (2.7)
End-stage renal disease	67 (11.0)	74 (6.5)	18 (5.9)	18 (4.8)
Chronic kidney disease	54 (8.8)	61 (5.4)	21 (6.9)	22 (5.8)
Acute kidney injury	49 (8.0)	55 (4.8)	11 (3.6)	13 (3.4)
Cough	57 (9.3)	71 (6.3)	28 (9.2)	33 (8.7)
Dyspnoea	34 (5.6)	49 (4.3)	23 (7.5)	28 (7.4)
Pruritus	54 (8.8)	72 (6.3)	19 (6.2)	24 (6.4)
Hypertension	95 (15.5)	128 (11.3)	27 (8.9)	38 (10.1)
Hypotension	31 (5.1)	37 (3.3)	10 (3.3)	10 (2.7)

OLYMPUS

Table 32 Summary of most common AEs occurring in ≥5% of patients in both treatment arms (OT+28)

	Roxadustat (N=1,384)		Placebo (N=1,376)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Overall	[redacted]	[redacted]	[redacted]	[redacted]
End-stage renal disease	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Azotaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]

DOLOMITES

Table 33. Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population)

	Roxadustat (n=323)		Darbepoetin alfa (n=293)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Overall	296 (91.6)	[redacted]	271 (92.5)	[redacted]
End-stage renal disease	108 (33.4)	[redacted]	106 (36.2)	[redacted]
Hypertension	96 (29.7)	[redacted]	99 (33.8)	[redacted]
Glomerular filtration rate decreased	55 (17.0)	[redacted]	49 (16.7)	[redacted]
Oedema peripheral	49 (15.2)	[redacted]	36 (12.3)	[redacted]
Hyperkalaemia	38 (11.8)	[redacted]	42 (14.3)	[redacted]
Nausea	35 (10.8)	[redacted]	25 (8.5)	[redacted]
Viral upper respiratory tract infection	29 (9.0)	[redacted]	25 (8.5)	[redacted]
Diarrhoea	28 (8.7)	[redacted]	30 (10.2)	[redacted]
Hyperphosphataemia	28 (8.7)	[redacted]	15 (5.1)	[redacted]

	Roxadustat (n=323)		Darbepoetin alfa (n=293)	
	n (%)	Event rate per 100 PEY	n (%)	Event rate per 100 PEY
Muscle spasms	25 (7.7)	[redacted]	15 (5.1)	[redacted]
Pneumonia	25 (7.7)	[redacted]	22 (7.5)	[redacted]
Dyspnoea	24 (7.4)	[redacted]	12 (4.1)	[redacted]
Bronchitis	22 (6.8)	[redacted]	18 (6.1)	[redacted]
Constipation	21 (6.5)	[redacted]	15 (5.1)	[redacted]
Headache	21 (6.5)	[redacted]	12 (4.1)	[redacted]
Iron deficiency	21 (6.5)	[redacted]	25 (8.5)	[redacted]
Urinary tract infection	21 (6.5)	[redacted]	27 (9.2)	[redacted]
Vomiting	21 (6.5)	[redacted]	19 (6.5)	[redacted]
Back pain	20 (6.2)	[redacted]	17 (5.8)	[redacted]
Pruritus	20 (6.2)	[redacted]	13 (4.4)	[redacted]
Insomnia	19 (5.9)	[redacted]	8 (2.7)	[redacted]
Arthralgia	18 (5.6)	[redacted]	14 (4.8)	[redacted]
Atrial fibrillation	18 (5.6)	[redacted]	12 (4.1)	[redacted]
Cardiac failure	18 (5.6)	[redacted]	18 (6.1)	[redacted]
Arteriovenous fistula thrombosis	16 (5.0)	[redacted]	10 (3.4)	[redacted]
Dizziness	16 (5.0)	[redacted]	15 (5.1)	[redacted]
Anaemia	14 (4.3)	[redacted]	19 (6.5)	[redacted]

Section C: Clarification on cost-effectiveness data

Model structure

C1. Priority question. In the economic model patients could move between eight health states defined to reflect the anaemia status based on different ranges of Hb levels and death. The impact of dialysis status and treatment related adverse events (stroke, myocardial infarction (MI) and vascular access thrombosis (VAT)) were captured implicitly within the economic model.

a) **Please justify the use of eight health states with ranges of Hb levels and death to model this condition (NB: Hb was not statistically significantly different in DOLOMITES). Please justify the ranges and cut-off points used for the Hb levels as opposed to for instance fewer health states with larger Hb ranges. Moreover, provide arguments why these health states would differ in terms of health related quality of life (HRQoL), costs and survival.**

The use of eight health states was based on a previously published cost-effectiveness model of anaemia treatment for people with CKD [13]. The Hb categories used for the relative risks for blood transfusion in the model match the eight health states used in the company model. Yarnoff et al. also state the utility loss per 1 g/dL in Hb. This was based on Finklestein et al. (values mapped). Finklestein et al. [14] demonstrated that as Hb levels increased in increments of 1 g/dL in Hb there were significant improvements in a variety of quality-of-life domains. Other studies have shown that utility values differ per 1 g/dL change in Hb levels [15]. No significant impact of Hb on survival was shown in the economic analysis but the change in HRQoL in the literature justifies the use of the eight health states.

Using a smaller number of health states would lead to granularity in time trends being lost between treatment arms. Using a model with eight health states shows the nuances which could be important to demonstrate in the economic analysis. The use of eight health states was also approved by clinical experts.

b) **A disadvantage of not explicitly modelling a relationship is that the relation might become implausible/flawed during extrapolation. Please**

justify why dialysis and cardiovascular events (including the impact on mortality), were not explicitly modelled.

The IPD was used to model mortality, cardiovascular events and dialysis. These were modelled explicitly. The impact of the cardiovascular events and dialysis were modelled implicitly.

Implicitly captured outcomes in the model were not analysed directly using statistical analyses. Instead, the relationship between model inputs and implicitly captured outcomes was based on cohort averages (observed in the clinical trials). For example, because survival was an explicitly modelled outcome in the model, the impact of dialysis status on mortality was not modelled directly, but implicitly captured. By not directly modelling the relationship between all model inputs and outcomes, we avoid the possibility of double counting the outcome in the cost effectiveness model (CEM) where multiple inputs may have an impact on the outcome.

c) **Please provide a Figure similar to Figure 11 CS for the proportion of patients on dialysis and experiencing stroke, MI or VAT, over the time horizon of the model, for roxadustat and ESA separately.**

The probability of being on dialysis over time is shown in Figure 1. There was no treatment effect on time to dialysis and so this is the same for both roxadustat and ESA. For the adverse events (Stroke, MI or VAT), it is not possible to present the proportion of patients with each event as patients can experience multiple events. However, the lifetime event rates per patient for each event are presented in Table 34.

Figure 1 Probability of being on dialysis (if alive)

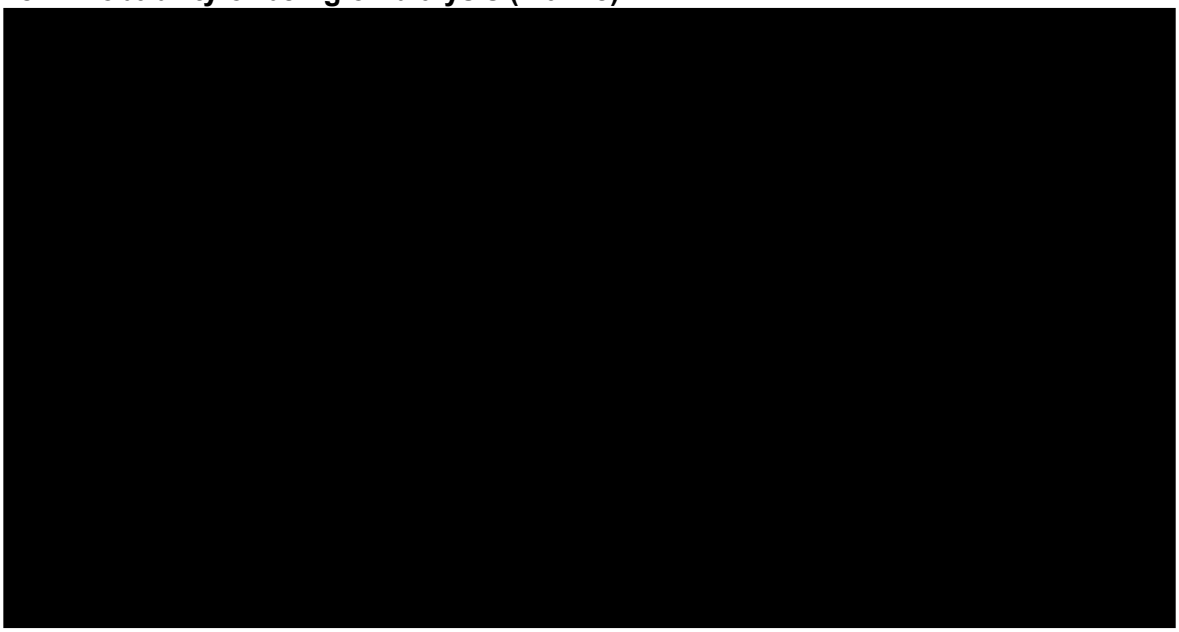


Table 34 Lifetime event rates per patient (stroke, myocardial infarction and vascular access thrombosis)

Event	Roxadustat	ESA	Difference
Stroke	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Vascular access thrombosis	[redacted]	[redacted]	[redacted]

d) Please justify why kidney transplant and CKD stages are not included in the model and elaborate on the implications.

The economic model analyses the cost-effectiveness of a treatment for anaemia in CKD patients. Roxadustat and ESA are not treatments for CKD and are used only to correct anaemia. CKD will progress regardless of the effect the anaemia treatments have on Hb level and so it would not be necessary to model progression of CKD. Baseline estimated glomerular filtration rate (eGFR) levels (which are used to signify kidney function) are taken into account for the time-to-dialysis and all-cause mortality analysis. It was found to have a significant impact on all-cause mortality and time to dialysis. Kidney transplant was not captured in the clinical trials and was part of the criterion for discontinuation and so was not modelled.

C2. The NICE reference case asks for a cost-utility analysis. In the DSU report "The use of cost minimisation analysis for the appraisal of health technologies" (http://nicedsu.org.uk/cost-minimisation/) it is stated that the use of cost-

minimisation analysis needs a strong rationale for clinical equivalence. The DOLOMITES trial showed non-inferiority on the primary outcome (difference in proportion with Hb response in first 24 weeks) for roxadustat versus darbepoetin alfa (while Hb is the main driver of difference in treatment effectiveness in the economic model).

Please justify that for roxadustat the criterion of a strong rational for clinical equivalence is not met, and hence a cost-minimisation analysis is not appropriate.

The non-inferiority trials design and margins for non-inferiority were agreed with the European Medicines Agency, in line with the regulator's expectations given the nature of anaemia associated with CKD and its treatment in clinical practice. Differentiating on the primary regulatory endpoint was understood to not be possible as the dose of treatment is adjusted in clinical practice to achieve a pre-specified target Hb level. Such an approach has also been seen in trial designs for the current standard of care in anaemia associated with CKD including darbepoetin and methoxy polyethylene glycol-epoetin.

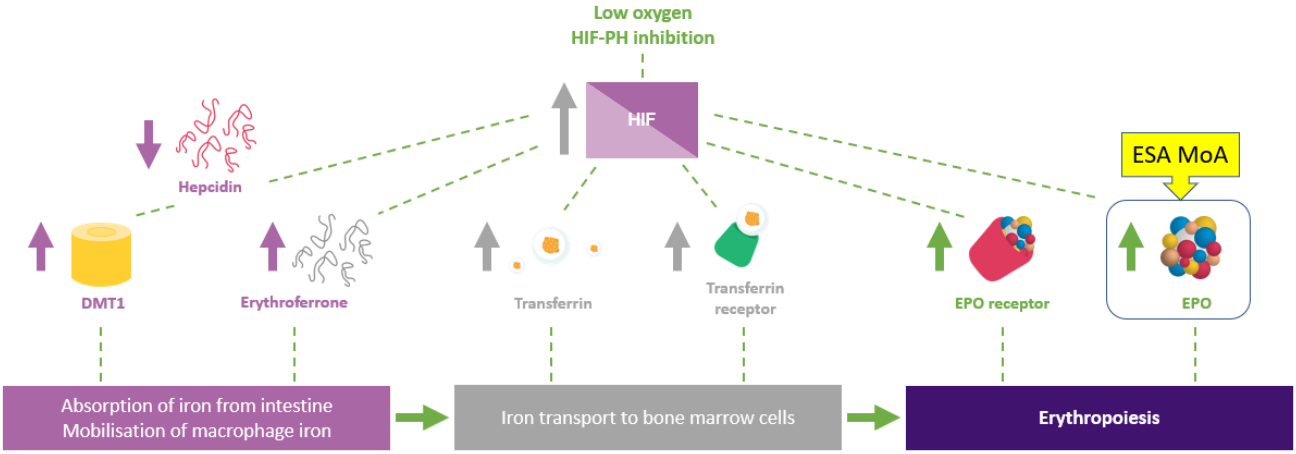
As stated in the DSU report "The use of cost minimisation analysis for the appraisal of health technologies", a cost-minimisation analysis (CMA) is not a form of full economic evaluation as it neglects any consideration of outcomes and is therefore inappropriate in most situations. Only in the case where outcomes are considered equivalent does the CMA become relevant. In establishing non-equivalence, it is useful to consider Hb response and the use of additional therapy including IV iron as these were key outcomes of interest in the NICE scope for roxadustat against ESA.

While the equivalence of efficacy between ESAs is well accepted, within the clinical trial programme for roxadustat, a higher proportion of patients achieved a Hb response within the first 24 weeks without the use of rescue therapy while on roxadustat when compared with darbepoetin. Within the DOLOMITES trial, this response was seen in 89.5% of patients in the roxadustat group vs 78.0% of patients in the ESA group, giving a difference of 11.51% [95% CI: 5.66%, 17.36%]). This was substantially larger than the pre-specified margin for non-inferiority (-15%) (Barratt et al, 2021).

Furthermore, a lower proportion of patients on roxadustat required IV iron during the efficacy emergent period compared to those on darbepoetin in the DOLOMITES trial (18.9% vs 25.0% respectively). The incidence rate per 100 patient years at risk for patients receiving IV iron was lower in the roxadustat group compared with the darbepoetin group (12.6 vs 17.5 respectively); HR: 0.7 (95% CI: 0.5, 1.0; p=0.052) in favour of roxadustat.

The causality of anaemia associated with CKD has been shown to be multifactorial, resulting from reduced oxygen-sensing in the kidney, reduced erythropoietin (EPO) production, increased hepcidin, and functional or absolute iron deficiency due to chronic inflammation. The Company notes that the DSU also states: “In the case of pharmaceuticals, there should be consideration of the biological plausibility of the claim and the extent to which the mechanisms of action of the new and reference drug differ”. In contrast to ESAs targeting a single part of the pathophysiology of anaemia associated with CKD, the roxadustat mechanism of action stimulates a coordinated erythropoietic response through the inhibition of HIF-PHI, and resultant increase of plasma EPO levels, regulation of iron transporter proteins, and reduction of hepcidin. This results in improved iron bioavailability, increased haemoglobin production and increased red cell mass. We therefore consider the difference in clinical outcomes against ESAs, as highlighted above, to be supported by biologically plausibility given the difference in mechanism of action as summarised in Figure 2 below:

Figure 2: Roxadustat and ESA MoA



- DMT1, divalent metal transporter 1; EPO, erythropoietin; HIF, hypoxia-inducible factor; HIF-PH, hypoxia-inducible factor-prolyl hydroxylase
- 1. Adapted from Locatelli F *et al. Am J Nephrol* 2017; 45:187–199.

Given the differences highlighted above, we believe it is inappropriate to consider clinical equivalence between roxadustat and ESAs, and therefore a CMA is unsuitable for the present decision problem. Furthermore, the Company considers roxadustat offers additional attributes of value both for patients and the healthcare system, including not having to be delivered or stored in cold-chain, as well as the convenience of an oral preparation (and avoidance of parenteral administration). While these factors were not incorporated into the base case analysis in line with NICE's reference case, the value of these attributes has been explored in scenario analyses 4, 6.1 and 6.2 in CS section B.3.7.3. As conducting a CMA would not allow for such attributes to be considered, we consider the cost-utility analysis presented to be the most appropriate option.

Systematic review

C3. Please specific the eligibility criteria for the review focussing on cost-effectiveness (CEA) studies (as specified for the utility review in CS Table 130 Appendix H and the cost and resource use review in CS Table 149 Appendix I). Additionally, provide PRISMA diagram(s) for the CEA review as done in CS Figures 33-36 for the utility review and cost and resource use review.

No eligibility criteria and PRISMA diagram are available as a systematic review of cost-effectiveness studies was not conducted. Instead, studies included in the cost and healthcare resource use SLR and health-related quality of life SLR detailed in cost and healthcare resource identification, measurement and valuation, and health-related quality of life studies were screened to identify cost-effectiveness models relevant for this submission. Additionally, a published SLR of cost-effectiveness evidence in anaemia associated with CKD was targeted and the evidence evaluated, a total of seven studies [15-20], were retrieved.

Intervention and comparator

C4. Priority question. Table 2 of the CS states that "for patients initiating anaemia treatment not previously treated with ESA the recommended starting dose of roxadustat is 70 mg three times per week in patients weighing less than

100 kg and 100 mg three times per week in patients weighing 100 kg and over." Table 53 of the CS stats that doses of roxadustat are based on Hb alone.

Please justify, for roxadustat and ESA separately, why body weight is not considered in the calculation of the dose in the economic model.

The patients in the clinical trials started with the recommended roxadustat dose according to their weight. The average weights of those in the trials (Table 35) are similar to the published average weight of patients with CKD in England (78kg +/- 17.1 SD) [21].

The clinical trial data are used to estimate the dose of roxadustat and ESA. The present model is a cohort model using the average weight across all four clinical trials. The economic analysis results are based on the average weights for each arm. Study ID was included as a random effect in the regression analyses which would take into account any differences between baseline weight between studies. Therefore, the model estimates represent predictions for the average weight of individuals in the trials, but the model does not allow the user to adjust these estimates using an input to change this weight in the model.

Table 35 Mean weights from the clinical trials

Treatment	Mean weight (kg)
Roxadustat	71.63 kg (18.33 SD)
ESA	78.45 (17.68 SD)

Effectiveness

C5. Priority question. The difference in treatment effectiveness (i.e. quality-adjusted life year (QALY) gains for roxadustat) is mainly driven by the multinomial logistic regression distributing the alive patients between the different Hb health states.

a. **According to CS Tables 22 and 23, roxadustat is non-inferior compared with ESA in terms of Hb response and maintenance. Please justify, given the above, that the difference in treatment effects (i.e. QALY gains) is mainly driven by the multinomial logistic regression model.**

Table 22 in the CS shows that roxadustat significantly improves Hb response during the first 24 weeks compared to darbepoetin (OR [redacted]; 95% confidence interval 1.53 to 4.04). This is reflected in the multinomial logistic regression coefficients displayed in CS Table 35. This table shows that the coefficients for darbepoetin and roxadustat differ in magnitude when compared to placebo. Furthermore, the relationship between time and treatment type also differs in magnitude for both darbepoetin and roxadustat compared to placebo. As previous studies have shown a utility loss per 1 g/dl decrease in Hb levels [13], these changes in proportion in state between darbepoetin and roxadustat drive the main QALY differences between the two arms (when the mortality rate is assumed to be the same in both treatment arms).

b. Please describe in detail the procedure used to estimate the multinomial logistic regression, including an overview of the data included, how missing data were handled, regression equation for the analysis included in CS Table 35, how diagnostics of the regression model were assessed, how the (candidate) covariates as well as interaction terms were selected (with rationale) and how the regression model accounted for nesting effects.

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of treatment type on Hb level. Patients were restricted to those being part of the Full Analysis Set (FAS).

The data was then stratified into a pre-12 week and post-12 week dataset. The reasoning for this is that for the first 12 weeks, patients undergo dose refinement and experience regular changes in their Hb level. As a result, it was not possible to fit a linear model that could accurately estimate this pre-12 week phase. As the economic model uses a 3-month cycle (~12 weeks), the baseline proportion in state were used for the first 12 weeks, with 12 weeks and beyond being estimated by the multinomial logistic regression.

Missing data was assumed to be missing completely at random. Baseline information for treatment type, cardiovascular disease (CVD) history and diabetic status at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The association between Hb level and treatment type was assessed using a multinomial logistic regression. The model contained the main effects of time (continuous), treatment type (categorical variable), history of CVD (binary variable) and diabetic status (binary variable). Study ID was included as a fixed effect to control for nesting. Although this is not an ideal approach to account for nesting effects, it was not possible to include study ID as a random effect due to computation software limitations. Therefore, it was deemed appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. A second order interaction between treatment type and time was included.

The rationale for including time within the statistical model was to be able to estimate the proportion in state for the patient cohort at any given time point. Treatment type was included to adjust for any impact treatment had on proportion in state. A history of CVD and diabetes were included as these have been shown to influence other outcomes such as treatment dose and were therefore also included within the proportion in state calculations to adjust for any potential impact they may exert. The second order interaction between time and treatment type was included to be able to analyse whether the relationship between time and Hb level differed by treatment type. All variables were selected prior to any statistical analyses were conducted in a statistical analysis plan (SAP) and were validated by medical experts as being the most relevant predictors.

Unlike standard logistic regression models, where a variety of statistical methods are available for assessing the diagnostics of the regression model, it is not straightforward to conduct diagnostics on multinomial logistic regressions. One could stratify the multinomial model into separate binary categories and conduct individual logistic regression models and conduct diagnostic tests on each one individually as a proxy to generate model diagnostics. This would involve running eight logistic regressions (one for each Hb level). However, assessing the diagnostics of individual logistic regressions as a proxy for a multinomial logistic regression is associated with its own limitations such as not accounting for the inter-relatedness of the results in each arm. Therefore, the suitability of the multinomial logistic regression was

assessed graphically by comparing the statistical model predictions to the observed data.

Figure 3 below shows the statistical model predictions (solid lines) versus the raw observed data (dots). The figure shows the model predictions fall nicely through the middle of the observed data.

Figure 3 Multinomial logistic regression (solid lines) fitted to the observed data (dots)

c. Please describe what data were used to create CS Figure 10, and please state to which patients the regression lines in CS Figure 10 apply: all patients in all NDD-CKD studies, ALPS patients alone, a subgroup of either with baseline values of all covariables, or some other patient population. If CS Figure 10 is only focused on a subset of patients, please provide additional graphs showing the fit of the regression models to cover all patients used in the regression model to assess how well the regression model fits all patients. Please also explicitly state whether the regression model started at week 14 rather than baseline.

CS Figure 10 shows the multinomial logistic regression predictions (solid line) versus the observed data (dots). A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of treatment type on Hb level. Patients were restricted to those being part of the FAS. The figure shows the model predictions fall nicely through the middle of the observed data. As stated in response to question C5b, the multinomial logistic regression use data from week 12 onwards.

d. It should be noted that including a covariate for each trial is considered suboptimal to account for the nested nature of the data, rather nesting effects should be incorporated using multilevel models (i.e. using one-stage meta-analysis, allowing for each of the studies to have an error term, rather than using regression with study identifiers as a covariable). Please provide a multinomial logistic regression model that appropriately incorporates nesting effects and provide an updated economic model and scenario analyses incorporating these revised analyses.

Study ID was included as a fixed effect to control for nesting. Although this is not an ideal approach to account for nesting effects, it was not possible to include study ID as a random effect due to computation software limitations. Therefore, it was deemed appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. As a result, no new analyses as requested by the ERG have been feasible.

e. Please justify the addition of log(time+1) as well as interaction terms for log(time+1) and treatment to the multinomial logistic regression model.

Initial model exploration of model structures showed that models using the natural log of time resulted in more clinically plausible extrapolations compared with models using time on a linear scale. The issue with using time on a linear scale resulted in rapid and sustained changes in Hb levels when extrapolated too far. Therefore, by using the log scale for time, it ensures changes in the proportion in state tend towards a plateau rather than assuming a constant increase/decrease. As time includes baseline (time 0), it is not mathematically possible to include it in any model

predictions using a natural log. As a result, by adding 1 to all time values in the statistical model we are able to use time 0 in any statistical model predictions.

The rationale for including time within the statistical model was to be able to estimate the proportion in state for the patient cohort at any given time point. Treatment type was included to adjust for any impact treatment had on proportion in state. The second order interaction between time and treatment type was included to be able to analyses whether the relationship between time and Hb level differed by treatment type.

f. Please justify for the proportions, estimated using the multinomial logistic regression model, the plausibility of the extrapolations beyond the observed data period in general (i.e. proportions in the different alive health states) as well as the differences between the treatments (i.e. extrapolation of the treatment benefit).

Table 36 below provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using all available data in the economic model. The average roxadustat patient spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). The average patient in the ESA arm spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). These outcomes were validated by clinical experts who agreed that the state occupancy results were in line with their expectations given the renal registry guidelines. The 22nd UK renal registry report estimated that approximately 60% of patients on in-centre haemodialysis in England have a Hb level between 10.00 and 12.00 g/dL [23] whereas the TUNE study estimated [redacted]% of patients maintained Hb target levels at 12 months [32].

Table 36 Predicted health state occupancy within the cost-effectiveness model (all data)

Hb level	Roxadustat	ESA
<7	[redacted]	[redacted]
7 – 7.99	[redacted]	[redacted]
8 – 8.99	[redacted]	[redacted]
9 – 9.99	[redacted]	[redacted]
10 – 10.99	[redacted]	[redacted]
11 – 11.99	[redacted]	[redacted]
12 – 12.99	[redacted]	[redacted]
≥ 13	[redacted]	[redacted]
Total years alive	[redacted]	[redacted]

g. Please examine and elaborate on the impact of the selected covariates on the extrapolations beyond the observed data period in general (i.e. proportions in the different alive health states) as well as the differences between the treatments (i.e. extrapolation of the treatment benefit).

The following covariables in CS Table 35 have no impact on the relation between time and Hb level: ESA, roxadustat, CVD history, diabetic status, Study IDs. These covariables adjust the intercept and simply adjust predicted curves up and down based on their values. This adjustment is fixed regardless of the time point assessed.

The time coefficients represent the multinomial logit estimate for a patient treated with placebo given the other variables in the model are held constant. A negative time coefficient indicates that the multinomial log-odds of being in a particular Hb level compared to Hb level 10-11 (reference level) would decrease while holding all other variables in the model constant. A positive time coefficient indicates that the multinomial log-odds of being in a particular Hb level compared to Hb level 10-11 (reference level) would increase while holding all other variables in the model constant. Therefore, the results of the model indicate that patients will tend to move into the higher Hb levels over time.

The interaction coefficients in CS Table 35 show the changes in Hb level over time that is unique to each treatment arm (i.e. what is the impact of time on Hb level that goes above and beyond that identified in the placebo arm). Coefficients indicate for both ESA and roxadustat that overtime patients are more likely to be in lower Hb

levels compared to Hb level 10-11 and less likely to be in the higher Hb levels compared to Hb level 10-11. However, it should be noted that interaction terms are tricky to interpret in isolation and must be considered in conjunction with the sum of their parts. Although the ESA and roxadustat coefficients do not alter the relationship between time and Hb level, they do significantly alter the starting point of each arm (i.e. patients are more likely to start in the higher health states and thus over time are likely to move to lower ones as they can't move to higher ones).

h. Please provide an updated economic model and scenario analyses with alternative assumptions regarding the extrapolation of the treatment benefit.

The model was built with the functionality to maintain the proportion in state at any given time point. This functionality allows the model to test the sensitivity of the results to changes in proportion in state over time. This functionality can be accessed via a switch on the model set-up page, meaning the ERG and other model users are able to run scenario analyses to test the sensitivity of the model to changes in proportion in state over time when required. We have conducted three scenarios to maintain proportion in state after 5, 10 and 15 years. Results show that by fixing the proportion in state over time (i.e. ignore impact of time), roxadustat remains cost-effective.

Table 37 Scenario analysis supporting C5

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C5.1: Proportion in state fixed after 5 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C5.2: Proportion in state fixed after 10 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C5.3: Proportion in state fixed after 15 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

C6. Details regarding the (appropriateness of the) procedure to estimate time to death (CS section B3.3.2) as well as time to dialysis (CS section B3.3.4) are unclear.

a. **Please describe in detail the procedure used to estimate the time to event models, including an overview of the data included, how missing data were handled, how diagnostics of the regression model were assessed, how the (candidate) covariates as well as interaction terms were selected and how the regression model accounted for nesting effects.**

Time to death

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of treatment type on all-cause mortality. Patients were restricted to those being part of the On-treatment +28 days analysis set.

Missing data was assumed to be missing completely at random. Baseline information for cardiovascular disease (CVD) history, diabetic status and estimated Glomerular Filtration Rate (eGFR) at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The effect of treatment type on all-cause mortality was assessed by parametric time-to-event analysis. Treatment type, history of CVD, diabetes status at baseline and eGFR were included as independent variables as these variables were suspected to predict all-cause mortality outcomes. As eGFR is an indicator of chronic kidney disease (CKD) stage, it is an extremely strong predictor of all-cause mortality [24]. Study ID was included as a fixed effect to control for nesting due to software limitations. Although this is not an ideal approach to account for nesting effects, it was deemed appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. A second order interaction between treatment type and eGFR was included to account for any differences in the relationship of eGFR and treatment type on all-cause mortality outcomes. Six functions (Exponential, Weibull, Gompertz, Log-normal, Log-logistic and Generalised Gamma) were fitted to the observable data. Akaike information

criterion (AIC) and Bayesian information criterion (BIC) were used to determine which distribution was used in the final economic model (CS Table 32).

A variety of error distributions were assessed during the statistical analyses. AIC and BIC values were generated for error distribution to assess the goodness of fit for each model. Models with lower AIC and BIC values were preferred to other models. A combination of factors was then used to assess each model diagnostics:

- Test of proportional hazards.
- Graphical visual inspection of the predicted values generated by the statistical model compared to the raw data (shown in CS Figure 9).
- Clinical plausibility of long-term results.

Table 38 shows that the proportional hazard assumption holds for all the covariables included within the analysis ($p > 0.05$ for all covariables).

Table 38 Proportional hazard assumption check

Coefficient	Chi-sq.	Degrees of freedom	p value
Treatment type	[redacted]	[redacted]	[redacted]
History of CVD at baseline	[redacted]	[redacted]	[redacted]
History of diabetes at baseline	[redacted]	[redacted]	[redacted]
Unique Study ID	[redacted]	[redacted]	[redacted]
Baseline Glomerular filtration rate	[redacted]	[redacted]	[redacted]
Treatment type * Baseline Glomerular filtration rate interaction	[redacted]	[redacted]	[redacted]
Global statistical model	[redacted]	[redacted]	[redacted]

The long-term extrapolations of predicted survival as estimated in the cost-effectiveness model are displayed in Table 39. These estimates are for a cohort with an average starting age of ~63 years old. The estimates are in line with the 22nd UK renal registry report that estimates that unadjusted survival in incident adults on renal replacement therapy age <65 years is ~73.2% and 56.4% at years 5 and 10 respectively [25]. Furthermore, the long-term extrapolations have been presented and validated with clinical experts.

Table 39 Long-term extrapolation estimates of survival

Time	Roxadustat	ESA

1 year		
5 years		
10 years		
20 years		
Median		

Time to dialysis

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of patient baseline characteristics on time-to-dialysis. Patients were restricted to those being part of the On-treatment +28 days analysis set.

Missing data was assumed to be missing completely at random. Baseline information for cardiovascular disease (CVD) history, diabetic status and estimated Glomerular Filtration Rate (eGFR) at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The effect of patient baseline characteristics on time-to-dialysis was assessed by parametric time-to-event analysis. History of CVD, diabetes status at baseline and eGFR were included as independent variables as these variables are suspected to predict time-to-dialysis outcomes. As eGFR is an indicator of chronic kidney disease (CKD) stage, it is an extremely strong predictor of time-to-dialysis. Study ID was included as a fixed effect to control for nesting due to software limitations. Although this is not an ideal approach to account for nesting effects, it was deemed appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. No second order interactions were considered. Six functions (Exponential, Weibull, Gompertz, Log-normal, Log-logistic and Generalised Gamma) were fitted to the observable data. AIC and BIC were used to determine which distribution was used in the final economic model (CS Table 37).

A variety of error distributions were assessed during the statistical analyses. AIC and BIC values were generated for error distribution to assess the goodness of fit for each model. Models with lower AIC and BIC values were preferred to other models. A combination of factors was then used to assess each model diagnostics:

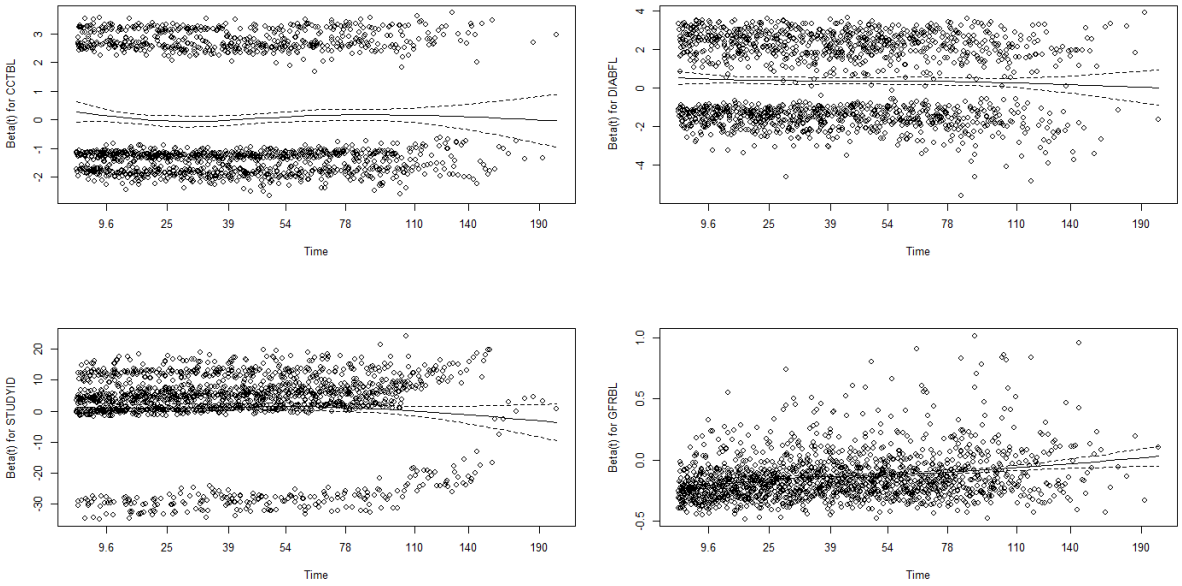
- Test of proportional hazards.
- Graphical visual inspection of the predicted values generated by the statistical model compared to the raw data (shown in CS Figure 12).
- Clinical plausibility of long-term results.

Table 40 shows that the proportional hazard assumption holds for all the covariables included within the analysis except baseline eGFR ($p > 0.05$ for all covariables). The relationship between baseline eGFR and time-to-dialysis was expected as it is an indicator of kidney function. Therefore, the lower the eGFR the sooner an individual is likely to begin dialysis treatment. The impact of baseline eGFR was investigated further by assessing it graphically using Schoenfeld residuals against time (Figure 4). The figure shows that the Beta (t) is predominately a flat line over the trial period. Whilst there is a minor relationship between eGFR and time to dialysis (with the slope rising from -0.2 to 0), this is not enough to challenge the PH assumption. Therefore, the flat line for all covariables indicates that they follow the proportional hazards assumption.

Table 40 Proportional hazard assumption check.

Coefficient	Chi-sq.	Degrees of freedom	p value
History of CVD at baseline	1.63	1	0.202
History of diabetes at baseline	3.19	1	0.074
Unique Study ID	4.13	3	0.248
Baseline Glomerular filtration rate	105.73	1	0.000
Global statistical model	108.86	6	0.000

Figure 4 Graphical proportional hazard assumption checks.



Legend: These plots show the relationship between the Schoenfeld residuals and time. To meet the proportional hazard assumption, there should be no relationship between the residuals and time (i.e. a plot that shows a non-random pattern against time is evidence that the variable violates the proportional hazard assumption). CCTBL; history of CVD at baseline, DIABFL; diabetic at baseline, STUDYID; unique clinical trial ID code, GFRBL; baseline glomerular filtration rate.

The long-term extrapolations of predicted time-to-dialysis as estimated in the cost-effectiveness model are displayed in Table 41. These estimates are for a cohort with an average starting age of ~63 years old. These long-term extrapolations were presented to clinical experts who deemed the long-term extrapolation values to be reasonable for a cohort with an average starting age of ~65 years old.

Table 41 Long-term extrapolation estimates of proportion of patients not on dialysis.

Time	All treatments
1 year	[redacted]
5 years	[redacted]
10 years	[redacted]
20 years	[redacted]
Median	[redacted]

b. It should be noted that including a covariate for each trial to account for the nested nature of the data is considered suboptimal, rather nesting

effects should be incorporated using multilevel models. Please provide for both, time to death and time to dialysis, analyses that appropriately incorporate nesting effects and provide an updated economic model and scenario analyses incorporating these revised time to event analyses.

Study ID was included as a fixed effect to control for nesting due to software limitations. Although this is not an ideal approach to account for nesting effects, it was not possible to include study ID as a random effect due to computation software limitations. Therefore, it was deemed appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. As a result, no new analyses as requested by the ERG has been feasible.

c. **Please provide for both, time to death and time to dialysis, an overview of patients at risks at different time points.**

Figure 5 Kaplan-Meier plot and number at risk table for all-cause mortality (On-treatment + 28 days analysis set)

Figure 6 Kaplan-Meier plot and number at risk table for time-to-dialysis (On-treatment + 28 days analysis set)

d. **Please justify for both time to death and time to dialysis the plausibility of the extrapolations beyond the observed data period.**

The long-term extrapolations of predicted survival as estimated in the cost-effectiveness model are displayed in Table 42. These estimates are for a cohort with an average starting age of ~63 years old. The estimates are in line with the 22nd UK renal registry report that estimates that unadjusted survival in incident adults on renal replacement therapy age <65 years is ~73.2% and 56.4% at years 5 and 10 respectively [25]. Furthermore, the long-term extrapolations have been presented and validated with clinical experts.

Table 42 Long-term extrapolation estimates of survival.

Time	Roxadustat	ESA
1 year	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
20 years	[redacted]	[redacted]
Median	[redacted]	[redacted]

The long-term extrapolations of predicted time-to-dialysis as estimated in the cost-effectiveness model are displayed in Table 43. These estimates are for a cohort with an average starting age of ~63 years old. These long-term extrapolations were presented to clinical experts who deemed the long-term extrapolation values to be reasonable for a cohort with an average starting age of ~65 years old.

Table 43 Long-term extrapolation estimates of proportion of patients not on dialysis.

Time	All treatments
1 year	[redacted]
5 years	[redacted]
10 years	[redacted]
20 years	[redacted]
Median	[redacted]

e. Please explain that the regression coefficients (CS Table 36) are plausible/have face validity, including the negative coefficients for "History of CVD – Yes" and "Diabetic – Yes".

As the log-normal distribution is an accelerated failure time (AFT) model, taking the exponential of the statistical coefficient results in an AFT factor of less than 1. An AFT factor less than 1 represents an increase in the speed on an event occurring.

Therefore, the negative coefficients for CVD history and diabetic status indicate that those patients with either condition are likely to start dialysis sooner compared to those without the conditions. However, it should be noted that the coefficient for CVD history was not significant.

Furthermore, the positive coefficient for eGFR represents a slowing down in the time to events (i.e. the higher a person's eGFR, the longer it takes them to start dialysis). This is perfectly aligned with the clinical expectations as eGFR represents kidney function (higher eGFR values represent stronger kidney function). All coefficients in CS Table 36 have face validity.

C7. Priority question. ESA is the comparator according to the scope. Therefore, DOLOMITES is the most relevant trial.

a) **Please provide an updated economic model and scenario analyses only including data from the DOLOMITES trial to estimate the multinomial logistic regression model to distribute alive patients between the Hb health states. Please provide this separately while**

A new model has been submitted using only the DOLOMITES study data to inform the main parameters as requested. This can be found in the model presented in file (ID1483_Astellas_Roxadustat_CEM_C7_CIC).

Table 44 below provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using all available data. The average roxadustat patient spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). The average patient in the ESA arm spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). These outcomes were validated by clinical experts who agreed that the state occupancy results were in line with their expectations given the renal registry guidelines. The 22nd UK renal registry report estimated that approximately 60% of patients on in-centre haemodialysis in England have a Hb level between 10.00 and 12.00 g/dL [25] whereas the TUNE study estimated [redacted]% of patients maintained Hb target levels at 12 months [32].

Table 44 Predicted health state occupancy within the cost-effectiveness model (all data)

Hb level	Roxadustat	ESA
<7	[redacted]	[redacted]
7 – 7.99	[redacted]	[redacted]
8 – 8.99	[redacted]	[redacted]
9 – 9.99	[redacted]	[redacted]
10 – 10.99	[redacted]	[redacted]
11 – 11.99	[redacted]	[redacted]
12 – 12.99	[redacted]	[redacted]
≥ 13	[redacted]	[redacted]
Total years alive	[redacted]	[redacted]

Table 45 below provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES only trial. The average roxadustat patient spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). The average patient in the ESA arm spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). These proportions are not substantially different to base case analysis.

Table 45 Predicted health state occupancy within the cost-effectiveness model (DOLOMITES data only)

Hb level	Roxadustat	ESA
<7	[redacted]	[redacted]
7 – 7.99	[redacted]	[redacted]
8 – 8.99	[redacted]	[redacted]
9 – 9.99	[redacted]	[redacted]
10 – 10.99	[redacted]	[redacted]
11 – 11.99	[redacted]	[redacted]
12 – 12.99	[redacted]	[redacted]
≥ 13	[redacted]	[redacted]
Total years alive	[redacted]	[redacted]

b) including time as a covariate and interaction term (as in the CS) and;

The cost-effectiveness results obtained when using only the DOLOMITES data to inform the statistical analyses as contained in the model presented in file (ID1483_Astellas_Roxadustat_CEM_C7_CIC) are shown in Table 46. When compared against the base case results where the statistical analyses are informed by a pooled sample of all relevant NDD trials, the incremental costs of the invention versus ESA increase marginally, while the incremental QALY gain for roxadustat

versus ESA decreases marginally also. Despite only marginal changes to the absolute figures for costs and QALYs in the base case vs the DOLOMITES only scenario, this results in an ICER of [redacted] per QALY in the DOLOMITES only scenario. Similarly, the difference in NMB over the lifetime horizon when expressed in annual terms is also of marginal magnitude.

Table 46 Scenario analysis supporting C7 b)

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C7b: DOLOMITES data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

It should be noted that the approach adopted in the base case model to inform this submission, where all statistical analyses were informed by pooling participants of all relevant NDD studies together, was preferred by the Company, as well as external experts, over a DOLOMITES only scenario given the representativeness to UK practice, improved statistical strength, and the optimised use of all available data obtained on roxadustat in accordance with NICE guidance. While using this larger dataset may have its limitations, as a result of pooling the data at the individual patient level, we were able to leverage the additional roxadustat data from the other trials when comparing roxadustat to ESA. In essence, an individual patient-level data (IPD)-meta analysis was performed in order to borrow strength across the pooled studies to generate relative efficacy estimates for roxadustat compared to other treatments of interest (particularly ESA). It should be noted that the cost-effectiveness model does not compare placebo with ESA at any point (as these were never compared directly with any of the clinical trials).

Additional information about the approach to the pooled analysis can be found in the response to question B20.

Finally, given the sensitivity of the ICER to marginal changes in costs as highlighted above, it is worth noting that even a small difference in costs results in roxadustat also being cost-effective in the DOLOMITES only scenario. The ERG will be aware that the Company has applied for a confidential, simple price discount of [redacted]

through PASLU. Taking this into account, as presented as an additional scenario in Table 47, this results in an [redacted] with a [redacted] for roxadustat.

Table 47: Additional scenario analysis supporting C7b

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C7b: DOLOMITES data with [redacted] PAS for roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

c) excluding time as a covariate and interaction term.

Both time [log(time + 1)] and the interaction between time and treatment type were found to be statistically significant (Table 48). Therefore, it is our opinion that it is not justifiable to remove time or the interaction between time and treatment type from the statistical model as this will reduce the predictive ability of the regression model. As a result, no new analyses has been conducted. However, the additional supporting model in file (ID1483_Astellas_Roxadustat_CEM_C7_CIC) incorporates a functionality to maintain the proportion in state at any given time point. This functionality allows the model to test the sensitivity of the results to changes in proportion in state over time. This functionality can be accessed via switch on the model set-up page, meaning the ERG and other model users are able to run scenario analyses to test the sensitivity of the model to changes in proportion in state over time when required. We have conducted three scenarios to maintain proportion in state after 5, 10 and 15 years. Results show that by fixing the proportion in state over time (i.e. ignoring the impact of time), roxadustat is a more cost-effective alternative of care compared to ESA in shorter time horizons, where it is associated to more incremental QALYs and less incremental costs than in the model presented to inform this submission. Within the three scenarios conducted, relatively small magnitudes of absolute differences in costs and QALYs can be seen as in Table 49 below.

Table 48 Proportion in state coefficients derived from the DOLOMITES study only.

	Intercept	Time[#]	Roxadustat	Time: Roxadustat[#]	CVD history at baseline (Yes)	Diabetic at baseline (Yes)
Hb level 0-7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hb level 13-20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [#] Time has been log transformed to be log(Time+1). * p ≤ 0.050, ** p ≤ 0.010, *** p ≤ 0.001.

Table 49 Scenario analysis supporting C7c

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C7b: DOLOMITES data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C7c1.: DOLOMITES data, proportion in state fixed after 5 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C7c2.: DOLOMITES data, proportion in state fixed after 10 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C7c3.: DOLOMITES data, proportion in state fixed after 15 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

d) Please justify for the proportions estimated using the multinomial logistic regression model the plausibility of the extrapolations beyond the observed data period.

Table 50 below provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using all available data. The average roxadustat patient spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). The average patient in the ESA arm spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). These outcomes were validated by clinical experts who agreed that the state occupancy results were in line with their expectations given the renal registry guidelines. The 22nd UK renal registry report estimated that approximately 60% of patients on in-centre haemodialysis in England have a Hb level between 10.00 and 12.00 g/dL[25] whereas the TUNE study

estimated [redacted]% of patients maintained Hb target levels at 12 months [32]. Therefore, the extrapolated proportion in state estimates derived from the multinomial logistic regressions are broadly aligned to what is expected for a UK population.

Table 50 Predicted health state occupancy within the cost-effectiveness model (all data)

Hb level	Roxadustat	ESA
<7	[redacted]	[redacted]
7 – 7.99	[redacted]	[redacted]
8 – 8.99	[redacted]	[redacted]
9 – 9.99	[redacted]	[redacted]
10 – 10.99	[redacted]	[redacted]
11 – 11.99	[redacted]	[redacted]
12 – 12.99	[redacted]	[redacted]
≥ 13	[redacted]	[redacted]
Total years alive	[redacted]	[redacted]

Table 51 below provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES only trial. The average roxadustat patient spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). The average patient in the ESA arm spends [redacted]% of their time in the clinically relevant Hb level (10 to 11.99). These proportions are not substantially different to base case analysis.

Table 51 Predicted health state occupancy within the cost-effectiveness model (DOLOMITES data only)

Hb level	Roxadustat	ESA
<7	[redacted]	[redacted]
7 – 7.99	[redacted]	[redacted]
8 – 8.99	[redacted]	[redacted]
9 – 9.99	[redacted]	[redacted]
10 – 10.99	[redacted]	[redacted]
11 – 11.99	[redacted]	[redacted]
12 – 12.99	[redacted]	[redacted]
≥ 13	[redacted]	[redacted]
Total years alive	[redacted]	[redacted]

e) CS Table 29 provides the population characteristics (at baseline). Please provide an updated economic model and scenario analyses only

including data from the DOLOMITES trial only to estimate these population characteristics.

The baseline characteristics used in the model for the DOLOMITES only population are displayed in Table 52 below.

Table 52 Baseline population characteristics.

Population characteristics at baseline	Non-dialysis: All trials	Non-dialysis: 0610 only
Starting age of population (years)	62.8	66.3
Proportion of patients male	43%	45%
Proportion of patients female	58%	56%
Proportion of patients with CVD history	38%	48%
Proportion of patients with diabetes	56%	46%
Median baseline eGFR	17.1	18.1

Results of a scenario analysis using the DOLOMITES only data can be found in response to question C7b.

f) CS Table 30 provides the health state occupancy at baseline. Please provide an updated economic model and scenario analyses only including data from the DOLOMITES trial only to estimate health state occupancy at baseline.

The baseline state occupancy used in the model for the DOLOMITES only population is displayed in Table 53 below.

Table 53 Health state occupancy at baseline.

Health state occupancy at baseline	Non-dialysis: All trials	Non-dialysis: 0610 only
Hb <7	[redacted]	[redacted]
Hb 7.00 - 7.99	[redacted]	[redacted]
Hb 8.00 - 8.99	[redacted]	[redacted]
Hb 9.00 - 9.99	[redacted]	[redacted]
Hb 10.00-10.99	[redacted]	[redacted]
Hb 11.00-11.99	[redacted]	[redacted]
Hb 12.00-12.99	[redacted]	[redacted]
Hb >= 13	[redacted]	[redacted]

Results of a scenario analysis using the DOLOMITES only data can be found in response to question C7b.

g) **Please provide an updated economic model and scenario analyses only including data from the DOLOMITES trial to estimate time to death and time to dialysis.**

Results of a scenario analysis using the DOLOMITES only data can be found in response to question C7b.

h) **Please provide for both, time to death and time to dialysis, an overview of patients at risks at different time points based on the DOLOMITES trial only.**

Figure 7 Kaplan-Meier plot and number at risk table for all-cause mortality (DOLOMITES study only; On-treatment + 28 days analysis set)

Figure 8 Kaplan-Meier plot and number at risk table for time-to-dialysis (DOLOMITES study only; On-treatment + 28 days analysis set)

i) Please justify for both time to death and time to dialysis, based on the DOLOMITES trial only, the plausibility of the extrapolations beyond the observed data period.

Table 54 shows the median survival, 5-year survival probability, 10-year survival probability and 20-year survival probability when using the DOLOMITES trial data only. Note the cohort starting age is ~65 years old. This is in line with the 22nd UK renal registry report that estimates that unadjusted survival in incident adults on renal replacement therapy age <65 years is ~73.2% and 56.4% at years 5 and 10 respectively [25].

Table 54 Long-term survival extrapolations.

Survival	Both treatment arms
Median survival (years)	[redacted]
5-year survival (%)	[redacted]
10-year survival (%)	[redacted]
20-year survival (%)	[redacted]

Table 55 shows the median time-to-dialysis, 5-year probability of being on dialysis, 10-year probability of being on dialysis and 20-year probability of being on dialysis when using the DOLOMITES trial data only. These long-term extrapolations were

presented to clinical experts who deemed the long-term extrapolation values to be reasonable for a cohort with an average starting age of ~65 years old.

Table 55 Long-term time-to-dialysis extrapolations (conditional on being alive)

Survival	Both treatment arms
Median time-to-dialysis (years)	[redacted]
5-year probability of being on dialysis (%)	[redacted]
10-year probability of being on dialysis (%)	[redacted]
20-year probability of being on dialysis (%)	[redacted]

Adverse events

C8. In section B.3.4.4 the company states that stroke, MI and VAT are included as adverse events because of special importance in terms of differences between drugs. It is stated that further adverse events are therefore not included because these would not lead to a substantial impact.

Please provide a scenario analysis including all adverse events (as per Appendix F) of grade ≥3 which occurred in ≥5% of patients in either treatment arm (per protocol population).

Patients with chronic kidney disease (CKD) and end stage renal disease (ESRD) are at high risk of major adverse cardiovascular events (MACEs). MACEs are important in any cardiovascular model, as these either result in death or worsening disease, and significantly reduce HRQoL. MACEs are commonly used as composite endpoints in cardiac research. However, in the current model these events are modelled separately in order to apply appropriate costs and utility decrements to each event as they are economically distinct. For the patient population in the model, MACEs are especially important for those treated with ESAs.

Three adverse events were included in the economic model – stroke, myocardial infarction (MI) and vascular access thrombosis (VAT) (and all-cause mortality, which was captured though separate time-to-event analysis). Stroke, MI and all-cause mortality were chosen as adverse events due to the pre-existing literature noting their prevalence in CKD and ESRD populations [4]. VAT was included following read out of the clinical trials, as it was noted that VAT occurred in a minority of patients, specifically in the dialysis dependent population. Furthermore, more of these events

occur in the roxadustat arm compared with ESAs in the dialysis dependent population. The model was reviewed by three KOLs who agreed this choice of AEs was appropriate.

Congestive heart failure was another adverse event which was considered to be included in the economic model. However, it was decided not to be included for the following reasons:

- The pooled event rates for congestive heart failure are extremely small and despite some populations having ~15% relative difference in event rates, they were statistically similar on the absolute scale (Table 2 to 5).
- When pooled, there were no significant differences between roxadustat and ESAs in the rate of congestive heart failure hospitalisation in any of the patient populations (see Table 2 to Table 5). Therefore, it was decided that inclusion of CHF hospitalisation into the cost-effectiveness model would not significantly impact the incremental costs and benefits.

Other TRAEs had either a low incidence rate or showed no significant difference between the roxadustat and ESA arms, therefore a negligible impact is expected in the model outcomes.

C9. The differences in the incidence of treatment related adverse events (TRAEs) were not statistically significant.

Please provide an updated economic model and scenario analyses assuming equal incidence and report the results.

Cost-effectiveness results assuming equal incidence of TRAE among roxadustat and ESA treatment arms have been generated. In this scenario, the likelihood of stroke, MI, and VAT events (defined in the model cells TRAE!G17:G18, TRAE!G22:G23, and TRAE!G27:G28 respectively) was set to 0 for both treatment arms to show the impact of the AEs in the cost-effectiveness results.

The results of this scenario are shown in Table 56.

If no differences are assumed in the rate of adverse events, roxadustat becomes as a dominant treatment option generating more QALYs and less costs than ESAs. The

incremental QALYs per patient remain the same as in the base-case ([redacted]), and therefore we can conclude the effect seen in the incremental cost-effectiveness ratio reported for this scenario is mainly driven by the costs associated with the modelled AEs.

In the base case presented in the submission, roxadustat is associated with less likelihood of stroke and MI, and more likelihood of VAT than ESAs. As shown in Figure 15 of the CS, the weighted cost associated to VAT is one of the main drivers of the model, thus assuming equal incidence of AEs results in a favourable scenario for roxadustat (in comparison with the base case)

Table 56. Cost-effectiveness results (Response to C9)

	Roxadustat	ESA
Total costs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental QALYs	[redacted]	
ICER	[redacted]	
NMB (£20,000 per QALY)	[redacted]	

Abbreviations: ESA, erythropoiesis-stimulating agents, QALY: quality adjusted life year, LY: life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit.

Quality of life

C10. Priority question. CS Table 40 reports the coefficients for the EQ-5D regression analysis. The estimated disutilities based on this model are subsequently subtracted from the general population norm values accounting for patients having kidney complications and potentially being on dialysis.

a. Please describe in detail the procedure used to estimate the coefficients for the EQ-5D regression analysis. Including an overview of the data included, how missing data were handled, how diagnostics of the regression model were assessed, how the (candidate) covariates as well as interaction terms were selected (with rationale) and how the regression model accounted for nesting effects.

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of Hb level

on health-related quality of life (HRQoL). Patients were restricted to those being part of the FAS. Originally study participants completed the EQ-5D-5L questionnaire. The EQ-5D-5L responses were mapped to EQ-5D-3L utility values using the crosswalk algorithm developed by van Hout *et al.* (2012) [26].

Missing data was assumed to be missing completely at random. Last observation carried forward was used to impute missing dosing and Hb level information. Baseline information for cardiovascular disease (CVD) history and diabetic status at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The association between HRQoL and Hb level was assessed using a generalised linear mixed model (GLMM) with a gaussian distribution and an identity link function. The fixed model contained the main effects of Hb level (categorical variable), history of CVD (binary variable) and diabetic status (binary variable). No second order interactions were considered during the analysis. The random model controlled for nesting effects through the incorporation of a unique ID for each clinical trial. The random model also included a unique ID for each subject to account for repeated measured.

The rationale for including Hb level as a covariate within the statistical model is that the effect of Hb level on HRQoL in anaemia is well established [13]. A history of CVD and diabetes status are known population comorbidities and therefore need to be controlled for in any estimation of HRQoL. All variables were selected prior to any statistical analyses were conducted in a statistical analysis plan (SAP) and were validated by medical experts as being the most relevant predictors.

A variety of error distributions and link functions were assessed during the statistical analyses. Akaike Information Criterion (AIC) values were generated for each combination of error distribution and link functions to assess the goodness of fit for each model. Models with lower AIC values were preferred to other models. A combination of factors was then used to assess each model diagnostics:

- Plotting the model residuals versus the fitted values to ensure there was no structured pattern.
- The distribution of model residuals was assessed using a histogram.

- Generalised variance inflation factor (GVIF) was used to assess multicollinearity between model covariables.
- Graphical visual inspection of the predicted values generated by the statistical model compared to the raw data.

Statistical models with a low AIC value and judged to have good model diagnostics were selected as the final model to be used in the economic model. Figure 9 shows the residual versus the fitted values plot. In this plot you would typically expect to see no pattern between the residuals and the fitted values. Furthermore, a sign of heteroskedasticity are all the points converging to a single point in a “wedge” shape. The figure for the final model shows signs of some heteroskedasticity. However, the distribution of the data is bounded between 0 and 1, therefore it is to be expected that some of the residuals will also follow a bounded relationship (i.e. fitted values would tend towards 1). Despite this diagnostic plot, the remaining checks were passed, and the final statistical model deemed appropriate.

Figure 9 Model residuals versus fitted values

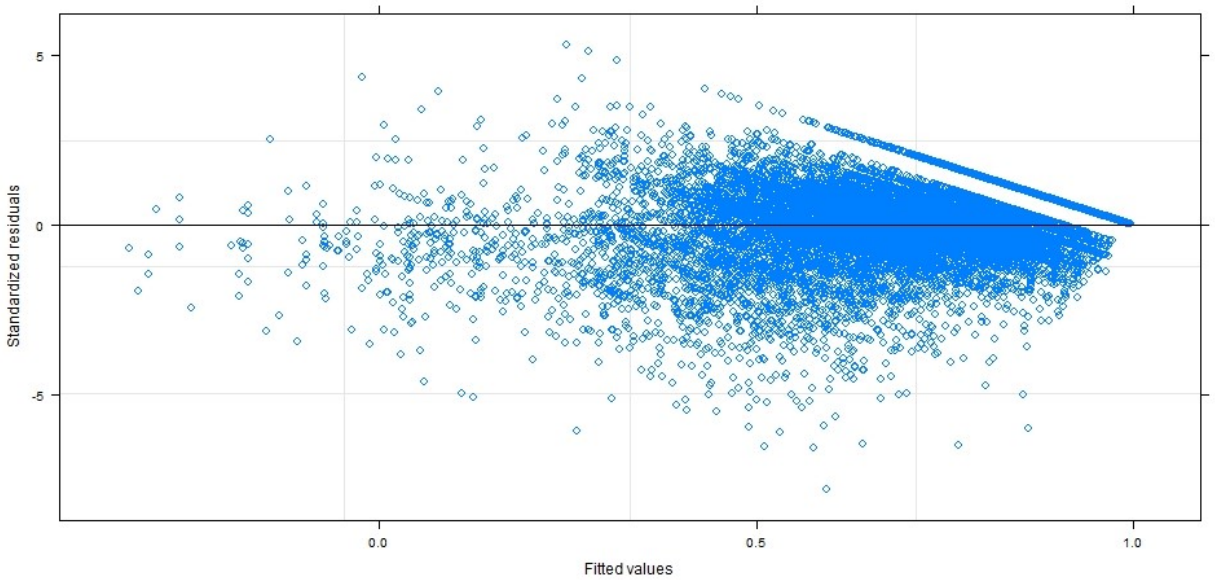


Figure 10 shows the histogram of the model residuals. In this plot you would typically expect a normal distribution (bell-shaped) curve. The figure shows that the residuals are evenly distributed around 0 and follow a normal distribution.

Figure 10 Histogram of model residuals.

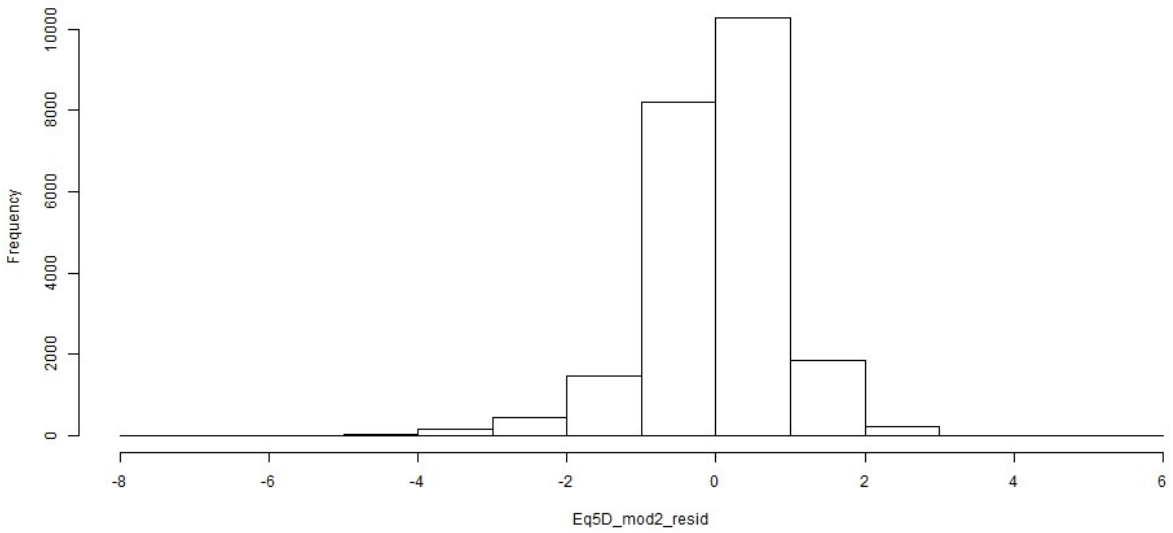


Table 57 shows the GVIF values for each of covariables included in the model. A value of three or lower indicates no multicollinearity.

Table 57 Test for multicollinearity.

Coefficient	GVIF
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Figure 11 below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle). The figure shows that although the statistical model does not predict the raw data exactly, it provides a reasonable estimate for the average utility value stratified by Hb level.

Figure 11 Model predictions (blue triangle) compared to observed data (red circle).

b. Please compare the estimated utilities using the abovementioned procedure with the average utilities for the different Hb categories, estimated directly on the trial data and elaborate on the (plausibility of the) differences.

Figure 12 below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle). The figure shows that although the statistical model does not predict the raw data exactly, it provides a reasonable estimate for the average utility value stratified by Hb level. All the model predictions fall within the 95% confidence intervals of the observed data. There are no differences between the predicted values and the observed data to elaborate on.

Figure 12 Model predictions (blue triangle) compared to observed data (red circle).

c. Please provide an updated economic model and scenario analyses applying the coefficients for the EQ-5D regression analysis (reported in CS Table 40) directly while only capping the estimated health state utility values to not exceed the actual population norm values (as reported in "'Population A - Roxa'!CR12:CR203" and "'Population A - ESA'!CR12:CR203" of the economic model).

We do not believe it is necessary to provide this. In the model we have subtracted the utility decrement from the actual population norm values. This method is commonly used and well-accepted and takes into account age-adjusted CKD and dialysis decrements [27].The IPD analysis produces coefficients for a single average age (the starting age in the model) and applying decrements to population norms allows for them to be adjusted by age. If the statistical model estimates were used directly rather than being used to calculate anaemia utility decrements, as people age eventually population norm utilities would be lower than those estimated by the statistical model. This would be an issue as the different Hb levels would be impacted at different times (i.e. there would be a period of time when Hb level >13 is capped by utility norms but Hb level <7 is not. As population norms do not include

decrements for CKD status or dialysis treatment, some Hb levels in the model would have a utility value including a CKD decrement whilst others would not. The literature suggests that there is a utility decrement based on Hb level [13]. Therefore, we believe applying utility decrements to population norms is the best approach and ensures all health states are treated equally in terms of methodology.

C11. In section B.3.4.1 the calculation of the baseline utility is explained. A utility decrement of 0.033 is applied for CKD. According to Sullivan et al. (https://doi.org/10.1177/0272989X11401031), the estimated utility for chronic kidney disease (category: "161 Other Diseases Of Kidney And Ureters") with a mean age of 60.3 is 0.59 while in the current assessment this is substantially higher (up to 0.77 for the Hb 12.00-12.99 health state). As a further example of a reference which uses considerably lower values, NICE TA 358 for Tolvaptan for treating dominant polycystic kidney disease uses utilities ranging from 0.688 to 0.9 for different CKD stages.

a. **Please justify the utility values used in the economic model and elaborate on the plausibility of the difference between the abovementioned values.**

The cost effectiveness model estimates patients' utility over the modelled time horizon in a progressive way, starting from a population norm utility reflective of patients with kidney complains, not on dialysis, and without anaemia. The model then incorporates the disutility associated with different Hb levels to reflect the impact of anaemia, and the impact of dialysis status, which is dependent of the percentage of patients transitioning to dialysis over the modelled time horizon, thus reflecting CKD progression.

The highlighted utility value of 0.77 represents the baseline utility of a patient not on dialysis with Hb level over the threshold considered for anaemia in the UK. In order to estimate this value, it was assumed that utility of a NDD patient with CKD 3-5 would be accurately represented by using the utility value for people with kidney complains, as reported in Ara et al. [28] The mean utility value for patients with kidney complaints reported in this publication is 0.845, with the mean age of the patients in this study being 44.8. To estimate a utility decrement, the mean utility

reported in Ara was subtracted to the mean utility for the age and gender matched general population (0.878 – 0.845 =0.033).

In the next step, utility decrements were applied specific to whether a person was on haemodialysis or peritoneal dialysis (0.35 and 0.26, respectively). These were sourced from a NICE technology appraisal (NICE TA358, Table B35) [29].

The general population norms, minus the CKD and dialysis decrements, results in the modelled population utility value norm. This is 0.76 at year 0, 0.51 in year 5, and 0.45 at year 20. These values account for patients having kidney complications and reflects CKD progression by incorporating a disutility associated with dialysis status.

These values are in line with the ones reported by Sullivan et al., which refer to patients having “Other Diseases Of Kidney And Ureters” (0.59) and are lower than the CKD ranges reported in NICE TA 358 for Tolvaptan (0.688-0.9).

As shown in section b), variations in the estimation of the modelled population utility norm affect equally both the modelled intervention of interest and comparator, and do not have an impact the cost-effectiveness results.

b. Please provide an updated economic model and scenario analyses incorporating the utility values reported by Sullivan et al. and report the results.

To incorporate the utilities reported by Sullivan et al., a similar approach to the base case was implemented. The utility reported by Sullivan was used as a proxy to inform the utility for patients with CKD 3-5 who are NDD and have an Hb level over the anaemia threshold in the UK. As in the base case, the decrement was estimated by subtracting the mean utility reported in Sullivan to the mean utility for the age and gender matched general population (0.767– 0.59 =0.207). Following the same approach as described above, the dialysis related utility decrements were subtracted to account for CKD progression resulting in adjusted population norms (accounting for the proportion of patients on dialysis) of 0.34 by year 5 and 0.27 by year 10.

The results from the scenario are presented in Table 58. Since this affects equally the intervention (roxadustat) and comparator (ESA), it does not have an impact on the incremental outcomes and, consequently the cost-effectiveness results.

Table 58. Cost-effectiveness results using utility from Sullivan

	Roxadustat	ESA
Total costs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental QALYs	[redacted]	
ICER	[redacted]	
NMB (£20,000 per QALY)	[redacted]	

Abbreviations: ESA, erythropoiesis-stimulating agents, QALY: quality adjusted life year, LY: life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit.

c. CKD is a progressive disease. Please reflect on the appropriateness of the CKD utility decrement given progression is not explicitly considered.

See response to question C11a.

d. Please provide an updated economic model and scenario analyses explicitly incorporating the impact of the progressive nature of CKD on the utility values. An example for utilities used over different stages of CKD can also be found in NICE TA358 for Tolvaptan.

Clinical trial data analysis demonstrated that there was no difference in the eGFR rate of change between patients treated with roxadustat and those treated with placebo or ESA in the NDD trials (discussed in response to B5). As highlighted in response to question C20.b), roxadustat and its comparator are used for the treatment of anaemia in CKD, and not CKD of itself. Similar to responses given above, given that incorporating the progressive nature of CKD on the utility values would equally affect both the modelled intervention of interest and comparator, doing so would have no impact on incremental outcomes, and consequently the cost-effectiveness results. Furthermore, as discussed with the ERG, the model has been robustly built with a heavy data analysis component. Therefore, producing a new model explicitly incorporating the impact of CKD progression would constitute a

significant change to the model structure, and a volume of work unfeasible within the timeframe allowed.

C12. The regression coefficients reported in CS Table 40 are not all consistently de/ascending. This seems counter-intuitive. These inconsistencies may imply that there are no meaningful differences in utility values between the Hb categories (with the ranges and cut-off as defined in the model structure).

a) Please justify the inconsistencies of the coefficients.

Previous studies have confirmed a positive correlation between Hb concentrations and patient quality of life [30]. CS Table 40 shows the coefficients for the EQ-5D-3L regression analysis for each health state in the model and has been reproduced below:

Table 59 Coefficients for EQ-5D-3L regression analysis

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: CVD: cardiovascular disease.

A coefficient smaller than 0 indicates an associated decrease in the utility of a patient whereas a coefficient larger than 0 indicates an associated increase in the utility of a patient as compared to the reference health state of Hb level 10-11. We can see that the lowest Hb level of <7 is associated with the smallest (most negative) coefficient, indicating the lowest utility for patients compared to the reference level. We can also see that health states with progressively less severe anaemia are associated with less negative coefficients, until the reference level Hb is exceeded, in which case the coefficient becomes a positive figure signifying an increase in the utility of a patient compared to the reference level at Hb levels above 10. This is in line with what we would expect clinically as the symptoms of anaemia become less severe and patient quality of life increases as a result.

The inconsistency in ascending coefficients noted by the ERG at Hb level >13 may be attributed to several factors:

- Extreme Hb levels have fewer patients and observations associated with them and therefore are subject to greater uncertainty and variance (see answer for C14b).

- Treatment guidelines do not recommend correction to 'normal' Hb levels [NG8]. Achieving Hb levels above the recommended target of 10-12g/dL may be associated with a higher incidence of adverse events in patients with anaemia associated with CKD. [31]

This was confirmed with clinical expert opinion which stated extreme Hb levels (too high or too low) were associated with an increased risk of adverse events.

b) Please estimate a regression model with fewer health states (wider Hb levels) and report the results to see whether the coefficients are more plausible (compared with the results reported in CS Table 40).

Please see response to question C1 regarding the justification of the 8 health state model. Furthermore, as discussed with the ERG, the model has been robustly built with a heavy data analysis component. Therefore, reproducing a model with large structural changes would constitute a volume of work unfeasible within the timeframe allowed.

c) Please provide an updated economic model incorporating the revised regression coefficients.

Please see response to C12b.

C13. All disutilities in the company submissions are assumed to be additive. Please justify this modelling choice.

There are broadly three ways to apply utility decrements in an economic model: additive, multiplicative or min/max values. To the best of our knowledge there is no consensus within the health economics community as to which one is more preferential, with NICE not stating a preference for one of the three approaches over

the other two in their methods guide or TSD 12 document. As such, the choice of which to use is often based on modeller preference. As previous studies in this disease area have shown that utility decrements are associated with 1 g/dL changes in Hb level (Yarnoff 2016 and Glenngard 2008), it was decided that the most appropriate way to capture Hb related utility decrements within the economic model was to use an additive approach.

Costs and resource use

C14. Priority question. CS Tables 50 and 51 presents regression coefficients to estimate weekly doses by Hb level that are not all consistently de/ascending. For instance, the coefficient for the HB level >13 is positive (or larger than the HB level 12 to 13). This seems counter-intuitive. These inconsistencies may imply that there are no meaningful differences in costs between the Hb categories (with the ranges and cut-off as defined in the model structure).

a) **Please describe in detail the procedure used to estimate the reported coefficients. Include an overview of the data included, how missing data were handled, how diagnostics of the regression model were assessed, how the (candidate) covariates as well as interaction terms were selected (with rationale) and how the regression model accounted for nesting effects.**

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of Hb level on roxadustat dose. Patients were restricted to those being part of the FAS who received roxadustat as their active treatment.

The data was then stratified into a pre-12 week and post-12 week dataset. The reasoning for this is that for the first 12 weeks, patients undergo dose refinement and experience regular dose adjustments. As a result it was not possible to fit a linear model that could accurately estimate this pre-12 week dosing phase. Therefore, a simple average dose was calculated for the first 12 weeks of the study and then a

linear model was used to estimate the average treatment dose for the remaining study period.

Missing data was assumed to be missing completely at random. Last observation carried forward was used to impute missing dosing and Hb level information. Baseline information for cardiovascular disease (CVD) history and diabetic status at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The association between treatment dose and Hb level was assessed using a GLMM with a Gamma distribution and an identity link function. The fixed model contained the main effects of Hb level (categorical variable), history of CVD (binary variable) and diabetic status (binary variable). No second order interactions were considered during the analysis. The random model controlled for nesting effects through the incorporation of a unique ID for each clinical trial. Initially, the random model also included a unique ID for each subject to account for repeated measured. However, inclusion of a subject ID within the model cause model convergence errors and therefore was removed.

The rationale for including Hb level as a covariate within the statistical model is that the effect of Hb level of treatment dose in anaemia is well established and one of the key drivers within the economic model. All variables were selected prior to any statistical analyses were conducted in a SAP and were validated by medical experts as being the most relevant predictors of treatment dose.

A variety of error distributions and link functions were assessed during the statistical analyses. AIC values were generated for each combination of error distribution and link functions to assess the goodness of fit for each model. Models with lower AIC values were preferred to other models. A combination of factors was then used to assess each model diagnostics:

- Plotting the model residuals versus the fitted values to ensure there was no structured pattern.
- The distribution of model residuals was assessed using a histogram.

- GVIF was used to assess multicollinearity between model covariables.
- Graphical visual inspection of the predicted values generated by the statistical model compared to the raw data.

Statistical models with a low AIC value and judged to have good model diagnostics were selected as the final model to be used in the economic model. Figure 13 shows the residual versus the fitted values plot. In this plot you would typically expect to see no pattern between the residuals and the fitted values. Furthermore, a sign of heteroskedasticity are all the points converging to a single point in a “wedge” shape. The figure for the final model shows no heteroskedasticity but does show a curved relationship along the top of the plot. This relationship is not unexpected as a Gamma error distribution was used. The distribution is one that is bounded at 0 and therefore it is to be expected that some of the residuals will also follow a bounded relationship. The key point of this plot is that the residuals do not converge to a single point in a wedge shape.

Figure 13 Model residuals versus fitted values.

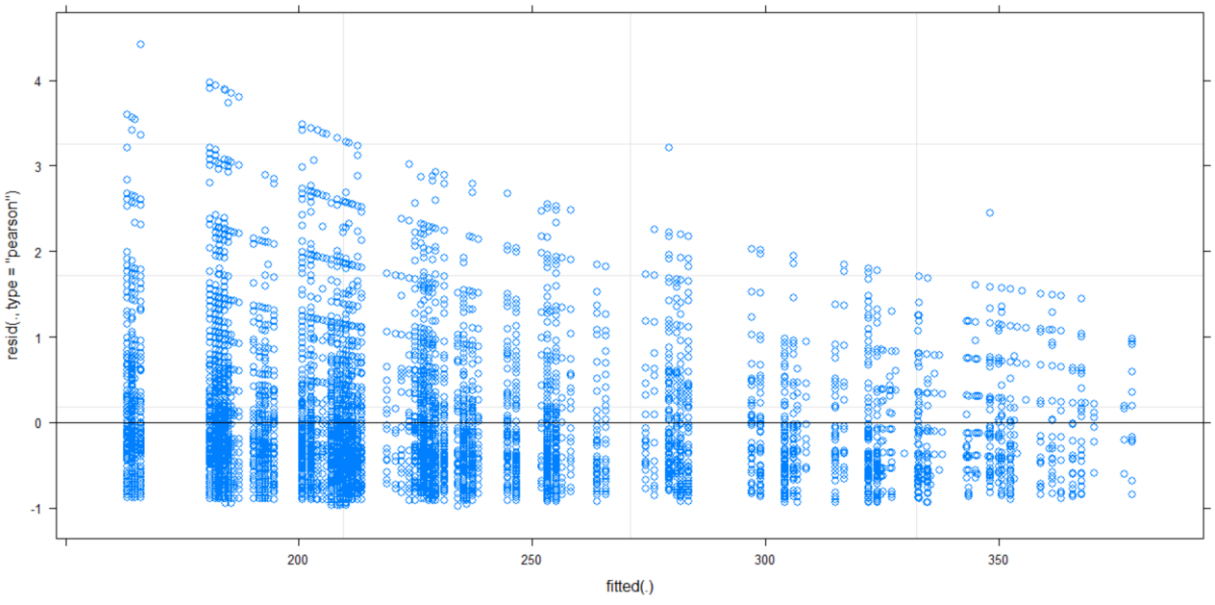


Figure 14 shows the histogram of the model residuals. In this plot you would typically expect a normal distribution (bell-shaped) curve, but as a Gamma distribution was used it is not unexpected to see the Gamma distribution reflected in the residuals.

Figure 14 Histogram of model residuals.

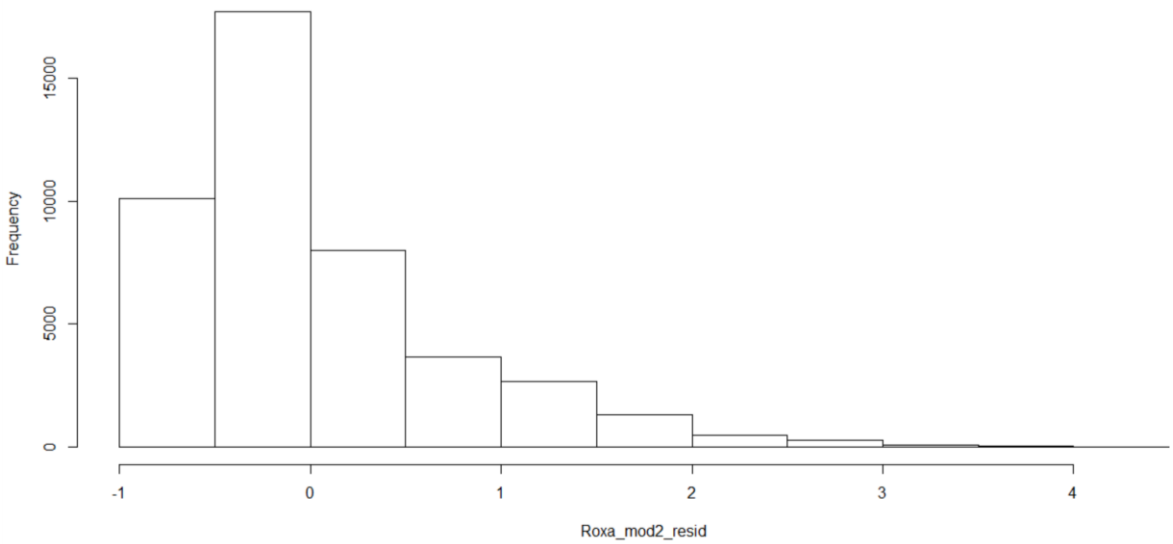


Table 60 shows the GVIF values for each of covariables included in the model. A value of three or lower indicates no multicollinearity.

Table 60 Test for multicollinearity.

Coefficient	GVIF
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Figure 15 below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle). The figure shows that although the statistical model does not predict the raw data exactly, it provides a reasonable estimate for the average roxadustat dose per week stratified by Hb level.

Figure 15 Model predictions (blue triangle) compared to observed data (red circle).

Table 51. Coefficients for ESA treatment dose regression analysis

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of Hb level on ESA dose. Patients were restricted to those being part of the FAS who received ESA as their active treatment. This narrowed the patient population down to a single clinical trial (DOLOMITES).

The data was then stratified into a pre-12 week and post-12 week dataset. The reasoning for this is that for the first 12 weeks, patients undergo dose refinement and experience regular dose adjustments. As a result it was not possible to fit a linear model that could accurately estimate this pre-12 week dosing phase. Therefore, a simple average dose was calculated for the first 12 weeks of the study and then a linear model was used to estimate the average treatment dose for the remaining study period.

Missing data was assumed to be missing completely at random. Last observation carried forward was used to impute missing dosing and Hb level information.

Baseline information for cardiovascular disease (CVD) history and diabetic status at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The association between treatment dose and Hb level was assessed using a generalised linear model (GLM) with a Gamma distribution and an identity link function. The fixed model contained the main effects of Hb level (categorical variable), history of CVD (binary variable) and diabetic status (binary variable). No second order interactions were considered during the analysis. As the population of interest was derived from a single study, there was no need to control for nesting effects. Initially, a random model was created which included a unique ID for each subject to account for repeated measured. However, inclusion of a subject ID within the model cause model convergence errors and therefore was removed.

The rationale for including Hb level as a covariate within the statistical model is that the effect of Hb level of treatment dose in anaemia is well established and one of the key drivers within the economic model. All variables were selected prior to any statistical analyses were conducted in a statistical analysis plan (SAP) and were validated by medical experts as being the most relevant predictors of treatment dose.

A variety of error distributions and link functions were assessed during the statistical analyses. Akaike Information Criterion (AIC) values were generated for each combination of error distribution and link functions to assess the goodness of fit for each model. Models with lower AIC values were preferred to other models. A combination of factors was then used to assess each model diagnostics:

- Plotting the model residuals versus the actual data to ensure there was no structured pattern.

- Plotting a Q-Q plot.
- Plotting a scale location plot.
- Plotting the module residuals versus the leverage.

- The distribution of model residuals was assessed using a histogram.
- Generalised variance inflation factor (GVIF) was used to assess multicollinearity between model covariables.
- Graphical visual inspection of the predicted values generated by the statistical model compared to the raw data.

Statistical models with a low AIC value and judged to have good model diagnostics were selected as the final model to be used in the economic model. Figure 16 shows four diagnostic plots. The top left plot shows the residual versus the fitted values plot. In this plot you would typically expect to see no pattern between the residuals and the fitted values and a horizontal red line. Furthermore, a sign of heteroskedasticity are all the points converging to a single point in a “wedge” shape. The figure for the final model shows no heteroskedasticity and a horizonal red line. The Q-Q plot is shown in the top right plot. The Q-Q plot should show a straight line of dots around the horizontal dashed line. As shown in the plot for the final model, the dots are predominately clustered around the line but do deviate at the extremes. The bottom left plot shows the scale-location plot. In this plot you would expect no pattern in the dots and a horizontal red line, as shown in the plot using the final model. Finally, the module residuals versus the leverage are shown in the bottom right. In this plot you would expect no pattern in the dots as well as a horizontal red solid line. Dots that fall outside the red dashed line (Cook’s distance) would indicate potential outlier values. The plot for the final model indicated no issues with the residuals versus leverage plot.

Figure 16 Model diagnostic plots.

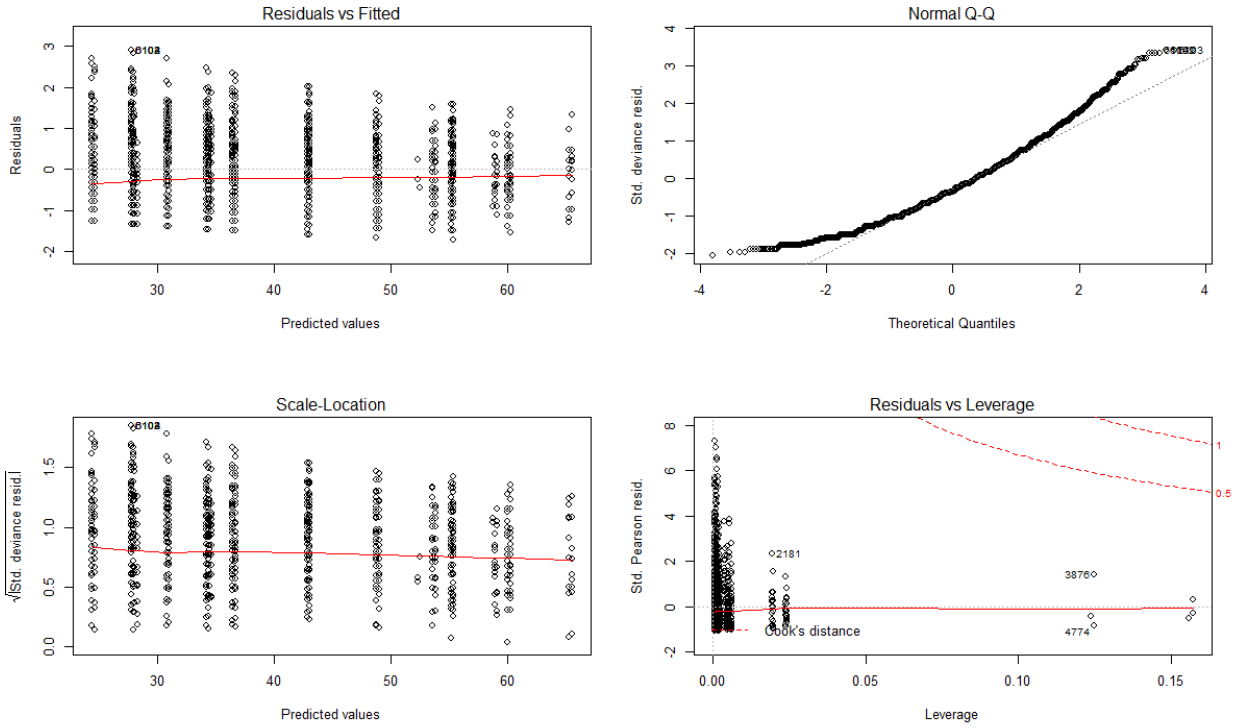


Figure 17 shows the histogram of the model residuals. In this plot you would typically expect a normal distribution (bell-shaped) curve, but as a Gamma distribution was used it is not unexpected to see the Gamma distribution reflected in the residuals.

Figure 17 Histogram of model residuals.

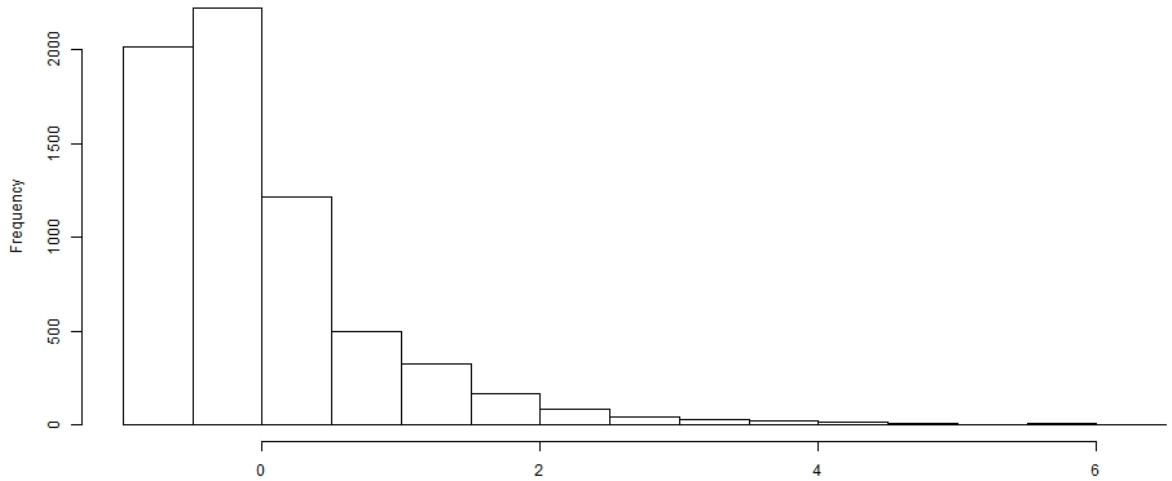


Table 61 shows the GVIF values for each of covariables included in the model. A value of three or lower indicates no multicollinearity.

Table 61 Test for multicollinearity.

Coefficient	GVIF
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Figure 18 below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle). The figure shows that the statistical model provides a reasonable estimate for the average ESA dose per week stratified by Hb level.

Figure 18 Model predictions (blue triangle) compared to observed data (red circle).

b) Please justify the inconsistencies of the estimated coefficients.

The inconsistencies noted by the ERG related to the fact that the extreme Hb levels have fewer patients and observations associated with them and therefore are subject to greater uncertainty and variance (Table 62). These inconsistencies are not a result of the statistical model as these patterns exist in the observable study data.

Table 62 Number of patients and observations stratified by Hb level and treatment arm.

Hb level	Roxadustat		Darbepoetin	
	N patients	N observations	N patients	N observations
< 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]

Figure 19 Mean roxadustat weekly dose (observed data).

[redacted]

Figure 20 Mean ESA weekly dose (observed data).

c) Please estimate a regression model with fewer health states (wider Hb levels) and report the results to see whether the coefficients are more plausible (compared with the results reported in CS Tables 50 and 51).

As the use of eight Hb levels in the economic model has previously been shown to be clinically reasonable (see response C1a), no new statistical analyses were conducted using fewer Hb levels. In the model presented in file (ID1483_Astellas_Roxadustat_CEM_C14_17_CIC) there is the option to apply a cap to the dose at each Hb level (e.g. the mean dose for somebody with a Hb level of less than seven is equal or higher than the mean dose for somebody with a Hb level eight). The cap is anchored to Hb level 10 to 11 as it is subject to less variance within the statistical analyses due to containing more patients over the course of the clinical trial programmes. Treatment dose in Hb levels <7 to 10 was set to always increase as Hb level declined. Whereas, treatment dose in Hb levels 11 to >13 was set to always decease as Hb level increased. By using a central Hb level as the anchor for the cap, it increases the likelihood that only the extreme Hb levels that are subject to high levels of variance are capped. The cap option can be selected via a drop-down box on the model set-up page and may be used by the ERG to run scenario analyses.

d) Please provide an updated economic model incorporating the revised regression coefficients.

The results shown in Table 63 report the cost-effectiveness results of the scenario described in section c), where a cap to the dose at each Hb level has been applied. Compared to the base-case model presented to inform this submission, there are no significant differences in terms of results and roxadustat remains a cost-effective alternative of care versus ESA.

Table 63 Scenario analysis supporting C14 d)

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C14d: Treatment dose cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

e) Please provide responses to the sub-questions listed above for the regression coefficients reported in Tables 61 and 64.

Table 61. Regression coefficients for blood transfusion rates

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving NDD patients were used to determine the effects of treatment type on the probability of requiring blood transfusion. Patients were restricted to those being part of the FAS who received roxadustat as their active treatment.

Missing data was assumed to be missing completely at random. Last observation carried forward was used to impute missing Hb level information. Baseline information for cardiovascular disease (CVD) history and diabetic status at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The association between probability of requiring a blood transfusion and Hb level was assessed using a GLMM with a binomial distribution and a logit link function. The fixed model contained the main effects of Hb level (categorical variable), Treatment type

(categorical), history of CVD (binary variable) and diabetic status (binary variable). No second order interactions were considered during the analysis. The random model controlled for nesting effects through the incorporation of a unique ID for each clinical trial. Initially, the random model also included a unique ID for each subject to account for repeated measured. However, inclusion of a subject ID within the model cause model convergence errors and therefore was removed.

The rationale for including Hb level as a covariate within the statistical model is that the effect of Hb level on the probability of requiring a blood transfusion is well established and one of the key drivers within the economic model. Treatment type was included to control for their impact of effectiveness outcomes. The inclusion of CVD history and diabetic status were for consistency with other statistical models that had shown outcomes to be affected by these baseline characteristics. All covariables were predefined in a SAP and were validated by medical experts as being the most relevant predictors.

A variety of error distributions and link functions were assessed during the statistical analyses. AIC values were generated for each combination of error distribution and link functions to assess the goodness of fit for each model. Models with lower AIC values were preferred to other models. A combination of factors was then used to assess each model diagnostics:

- Plotting the model residuals versus the fitted values to ensure there was no structured pattern.
- Generalised variance inflation factor (GVIF) was used to assess multicollinearity between model covariables.
- Calculating Theta.
- Graphical visual inspection of the predicted values generated by the statistical model compared to the raw data.

Statistical models with a low AIC value and judged to have good model diagnostics were selected as the final model to be used in the economic model. Figure 21 shows the residual versus the fitted values plot. In this plot you would typically expect to see

no pattern between the residuals and the fitted values. Furthermore, a sign of heteroskedasticity are all the points converging to a single point in a “wedge” shape. The figure for the final model shows no heteroskedasticity but does show two distinct curves. The key point of this plot is that the residuals do not converge to a single point in a wedge shape.

Figure 21 Model residuals versus fitted values.

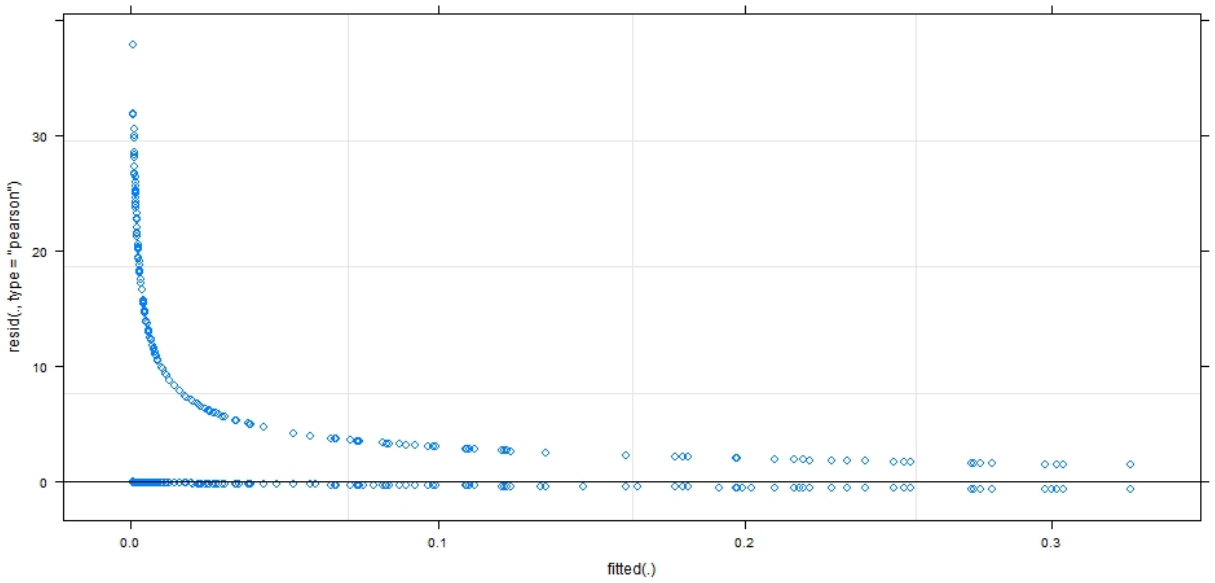


Table 64 shows the GVIF values for each of covariables included in the model. A value of three or lower indicates no multicollinearity.

Table 64 Test for multicollinearity.

Coefficient	GVIF
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

A Theta value of 0.10 was calculated which is an indication of model under-dispersion and a sign of model misspecification. Removing covariables from the model did not solve the under-dispersion and therefore no further action was taken.

Figure 22 below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle). The figure shows that although the statistical model does

not predict the raw data exactly, it provides a reasonable estimate for the probability of requiring a blood transfusion by Hb level.

Figure 22 Model predictions (blue triangle) compared to observed data (red circle).

In the model presented in file (ID1483_Astellas_Roxadustat_CEM_C14_17_CIC), there is the option to apply a cap to the probabilities at each Hb level (e.g. the probability of requiring a blood transfusion for somebody with a Hb level of less than seven is equal or higher than the probability of requiring a blood transfusion for somebody with a Hb level eight). The cap option can be selected via a drop-down box on the model set-up page and may be used by the ERG to run scenario analyses.

The results shown in Table 65 report the cost-effectiveness results of the scenario described above, where a cap to the probability of requiring a blood transfusion at each Hb level has been applied. Compared to the base-case model presented to inform this submission, there are no differences in terms of results and roxadustat remains a cost-effective alternative of care versus ESA.

Table 65 Scenario analysis supporting C14 e).

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C14e: Blood transfusion cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Table 64. Regression coefficients for the proportion of patients receiving IV iron

A total of four randomised controlled clinical trials (OLYMPUS, ANDES, ALPES and DOLOMITES) involving non-dialysis dependent patients were used to determine the effects of treatment type on probability of requiring IV iron. Patients were restricted to those being part of the FAS who received roxadustat as their active treatment.

Missing data was assumed to be missing completely at random. Last observation carried forward was used to impute missing Hb level information. Baseline information for CVD history and diabetic status at baseline were recorded for all patients.

All statistical analyses were performed in R v3.6.1 [22]. The association between probability of requiring IV iron and Hb level was assessed using a GLM with a binomial distribution and a logit link function. The fixed model contained the main effects of Hb level (categorical variable), Treatment type (categorical), history of CVD (binary variable) and diabetic status (binary variable). A second order interaction between Treatment type and Hb level was included in the model. Initially, the random model included a unique ID for each subject and each study to account for repeated measured and nesting respectively. However, inclusion of these random effects within the model cause model convergence errors and therefore was removed.

The rationale for including Hb level as a covariate within the statistical model is that the effect of Hb level on the probability of requiring IV iron is well established and one of the key drivers within the economic model. Treatment type was included to control for their impact of effectiveness outcomes. The inclusion of CVD history and diabetic status were for consistency with other statistical models that had shown outcomes to be affected by these baseline characteristics. Study ID was included as a fixed effect to control for nesting. Although this is not an ideal approach to account for nesting effects, it was deemed appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. A second order interaction between treatment type and Hb level was included as the model predictions were more accurate when it was

included in the model. All covariables were predefined in a SAP and were validated by medical experts as being the most relevant predictors.

A variety of error distributions and link functions were assessed during the statistical analyses. AIC values were generated for each combination of error distribution and link functions to assess the goodness of fit for each model. Models with lower AIC values were preferred to other models. A combination of factors was then used to assess each model diagnostics:

- Plotting the model residuals versus the fitted values to ensure there was no structured pattern.
- GVIF was used to assess multicollinearity between model covariables.
- Calculating Theta.
- Graphical visual inspection of the predicted values generated by the statistical model compared to the raw data.

Statistical models with a low AIC value and judged to have good model diagnostics were selected as the final model to be used in the economic model. Figure 23 shows the residual versus the fitted values plot. In this plot you would typically expect to see no pattern between the residuals and the fitted values. Furthermore, a sign of heteroskedasticity are all the points converging to a single point in a “wedge” shape. The figure for the final model shows no heteroskedasticity but does show two distinct curves. The key point of this plot is that the residuals do not converge to a single point in a wedge shape.

Figure 23 Model residuals versus fitted values.

Table 66 shows the GVIF values for each of covariables included in the model. A value of three or lower indicates no multicollinearity. Hb level and the interaction term show a high level of multicollinearity. However, this is expected as the two terms include Hb level and therefore are correlated.

Table 66 Test for multicollinearity.

Coefficient	GVIF
Hb level	12.4
Treatment type	2.95
History of CVD	1.03
Diabetic status	1.03
Study ID	1.18
Hb level * Treatment type	3.71

A Theta value of 0.06 was calculated which is an indication of model under-dispersion and a sign of model misspecification. Removing covariables from the model did not solve the under-dispersion and therefore no further action was taken.

Figure 24 below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle). The figure shows that although the statistical model does not predict the raw data exactly, it provides a reasonable estimate for the probability of requiring IV iron by Hb level.

Figure 24 Model predictions (blue triangle) compared to observed data (red circle).

In the model presented in file (ID1483_Astellas_Roxadustat_CEM_C14_17_CIC) there is the option to apply a cap to the probabilities at each Hb level (e.g. the probability of requiring IV iron for somebody with a Hb level of less than seven is equal or higher than the probability of requiring IV iron for somebody with a Hb level eight). The cap option can be selected via a drop-down box on the model set-up page and may be used by the ERG to run scenario analyses.

The results shown in Table 67 report the cost-effectiveness results of the scenario described above, where a cap to the probability of requiring IV iron at each Hb level has been applied. Compared to the base-case model presented to inform this submission, there are no significant differences in terms of results and roxadustat remains a cost-effective alternative of care versus ESA.

Table 67 Scenario analysis supporting C14 e).2

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario C14e: IV transfusion cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

C15. Priority question. CS Table 55 reports the ESA conversion ratios used to calculate the ESA dose. As highlighted in the CS "conversion of one ESA dose to the equivalent dose of an alternative ESA is not straightforward due to differing half-lives and route of administration of the different drugs" and "all

assumptions related to ESA conversion factors increased the ICER for Roxadustat".

a) Please describe in detail the procedure used to estimate the conversion ratios (including step by step calculations) as well as appropriate justification and references for each step.

As mentioned in section B.3.6.1 of the CS, treatment dosing was estimated from patient level data (DOLOMITES study [31]) to capture the link between the treatment effect and the treatment dose associated with it. However, all patients enrolled in the DOLOMITES study [4] received darbepoetin alfa, whereas different ESA with different costs are available in the market. Estimating equivaled doses between different ESA is challenging as different drugs have different half-lives and route of administration, with both factors impacting on the dose required to achieve the same effect. The procedure implemented assumes that all ESAs have the same effect at recommended weekly doses from the British National Formulary (as shown in Table 68).

Table 68. Weekly dose (mcg per kg) for ESAs in NDD patients

Treatment	Times per week		
Epoetin alfa	3		
Darbepoetin alfa	1		
Epoetin beta	3		
Epoetin zeta	3		
Methoxy polyethylene glycol-epoetin beta	0.2308 (once every 3 months)	1.2000	0.2769

Abbreviations: Kg, killogram.

The first step to estimate dose conversion ratios was to estimate the weekly recommended dose per kg as shown in Table 68. The second step was to estimate the ratio between the weekly recommended doses between each drug and the reference ESA (i.e., darbepoetin alfa): for instance, epoetin alfa estimated dose per week divided by darbepoetin alfa estimated dose per week (*0.63/0.45)* returns a ratio of 1.4. Therefore, for every 1mcg given of darbepoetin, the equivalent dose for epoetin alfa is 1.4 mcg.

Finally, to estimate the equivalent dose of each ESA, the actual dose derived from the multinomial regression model was multiplied by the correspondent dose conversion factor (Table 69).

Table 69. Conversion ratios to adjust the clinical trial derived ESA dose

ESA	Dose conversion factor
Epoetin alfa	[redacted]
Darbepoetin alfa (Reference)	[redacted]
Epoetin beta	[redacted]
Epoetin zeta	[redacted]
Methoxy polyethylene glycol-epoetin beta	[redacted]

Abbreviations: ESA, erythropoietin stimulating agents; Hb, haemoglobin.

b) Please compare the estimated ESA dosages with (external) observed data.

Estimated dose of epoetin alfa in NDD patients is 0.63mcg/kg. The CHOIR trial investigating epoetin alfa in NDD patients with eGFR 15-50ml/min/1.73m2 found that in patients targeting Hb levels of 11.3g/dL the average weekly dose was 50.4mcg. Assuming an average adult weight of 80kg dosing for this study is similar to estimation doses for conversion ratio. Additionally, the TUNE study reported that mean weekly dose in the UK to be [redacted]mcg for epoetin alfa; [redacted]mcg for darbepoetin alfa and [redacted]mcg for methoxy polyethylene glycol-epoetin beta.

c) CS Table 57 reports the proportion of patients receiving each ESA agent. Please justify that this retrospective study (using UK specific data) is representative for current UK clinical practice for the population of interest.

The TUNE study was a descriptive, non-interventional, retrospective cohort study of medical records in Germany, Spain, and the UK with UK specific data used to inform the NICE submission for roxadustat and CS Table 57 specifically. The study involved Real World data extraction from medical records of adult patients diagnosed with CKD stages 3b to 5, who were not receiving dialysis, and who initiated ESA treatment for anaemia between 1st January 2015 and 31st December 2015 inclusive.

A convenience sampling method was used to identify healthcare professionals (HCPs) who were willing and able to abstract data from medical records of patients meeting the inclusion criteria. Regional quotas were applied by geographical area in the UK to approximate a representative sample of patients. Furthermore, HCPs employed a qasi-random selection of patient records whereby HCPs were asked to identify a list of medical records that met the eligibility criteria. Then, from those records, the HCP was asked to select a medical record for a patient whose last

name began with a randomly generated letter between A and Z. If the HCP did not have an eligible patient whose last name began with the selected letter, the HCP was asked to select a patient whose last name began with the next letter in alphabetical order. Once the HCP had completed data extraction for a patient record, the HCP was requested to repeat the random selection process for the next patient, with the system randomly generating a new letter.

Overall, the TUNE study included data from [redacted] UK patients from [redacted] HCPs from across the UK, including the Midlands and East of England, North England, South-West of England, South-East of England and Wales.

d) Please clarify whether the ESA conversion ratios reported in CS Table 55 as well as the proportions reported in CS Table 57 have face validity (e.g. based on clinical expert opinion).

While the representativeness of the pooled trial population to UK patients was confirmed with clinical experts, ESA conversion ratios themselves were not explicitly validated clinically. However, given the use of data from reputable sources to arrive at the conversion factors, as well as the data available to do so, the approach taken

was considered the most pragmatic by the Company and was confirmed with health economic experts.

Clinical expert opinion confirmed there was no reliable or clear source of data to inform the proportion of patients receiving each ESA in UK clinical practice. However, the clinical expert confirmed the estimates from the TUNE study were in line with their expectation given there is a tendency to use long-acting ESAs in the non-dialysis space.

e) Please provide an updated economic model estimating the proportions of patients receiving each ESA agent based on an alternative evidence source.

The TUNE study [32] was a retrospective study specifically designed to generate real-world evidence documenting treatment patterns, health care resource utilisation, and costs associated with the management of anaemia among patients with non-dialysis-dependent CKD stages 3b to 5 who have initiated ESA therapy in three European countries: Germany, Spain, and the UK [32]. UK specific data was used to inform the proportions of ESA use in the model base case. These data was deemed to be the most representative data of the actual ESA usage for anaemia associated with CKD in the UK. Scenarios exploring alternative proportions of patients receiving each type of ESA have been presented in CS Section 3.7.3. In Scenarios 7.1 to 7.5 (CS Table 75), where it was assumed all patients received a single ESA. Costs per patient in the ESA arm varied from [redacted] with 100% darbepoetin alfa (CS Table 75). The differences were due to the estimated dose conversion factors and its effect on the drug acquisition costs (see response to question C15a), since all ESA were assumed to have equivalent efficacy (i.e. estimated from the DOLOMITES trial – darbepoetin alfa). It should be noted that all assumptions related to ESA conversion factors increased the ICER for roxadustat, as the scenario representing ESA use in the DOLOMITES (i.e., 100% darbepoetin alfa) where no conversion factors were used, was the most favourable for roxadustat.

Cost-effectiveness results incorporating the proportions of patients receiving each ESA agent based on an alternative evidence source have been generated.

- ESA proportion (tab “Population” E62: E66) was changed to reflect the values in Table 70.

The proportions of patients receiving each ESA in this scenario were based on data sourced from the IQVIA sales database representing total volume of ESA sales in various centres. It should be noted that these data represented total ESA sales, not differentiated by indication, and relied on many assumptions. Since ESA are also indicated for chemotherapy induced anaemia, we considered this data to be less robust and reliable in reflecting the actual ESA usage in patients with anaemia associated with CKD. As the TUNE study [32] collected this data directly from the medical records of the relevant patient population, it was therefore considered the appropriate data source to inform this input in the base case, as confirmed with expert feedback.

Table 70. Proportion of patients receiving each type of ESA in scenario (C15e)

ESA	Proportion of patients (%)
Epoetin alfa	[redacted]%
Darbepoetin alfa (Reference)	[redacted]%
Epoetin beta	[redacted]%
Epoetin zeta	[redacted]%
Methoxy polyethylene glycol-epoetin beta	[redacted]%

Abbreviations: ESA, erythropoietin stimulating agents

The cost effectiveness-results applying the percentages shown in Table 70 are displayed in Table 71.The estimated total QALYs and life years per patient in both treatment arms stay the same while the total costs per patient associated with ESA [redacted] per QALY.

Table 71 Cost-effectiveness results C15d

	Roxadustat	ESA
Total costs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Incremental costs	[redacted]	
Incremental QALYs	[redacted]	
ICER	[redacted]	
NMB (£20,000 per QALY)	[redacted]	

Abbreviations: ESA, erythropoiesis-stimulating agents, QALY: quality adjusted life year, LY: life year, ICER: incremental cost-effectiveness ratio, NMB: net monetary benefit.

C16. CS Table 57 presents the results of the deterministic sensitivity analyses. Oral iron use is included in this table but there is no information given on its implementation in section B.3.5. Please explain how it was implemented in the model.

The inclusion of oral iron in the results of the deterministic sensitivity analysis reported CS Table 74 is a typo as this parameter was not included in the model

A previous version of the model included an option to add oral iron as a supplementary therapy. However, based clinical expert feedback (see response to question C21a), it was assumed that roxadustat and ESA would be considered at a stage of the treatment pathway in which the vast majority of patients are managed with IV iron. In accordance, this feature was not included in the submitted economic model.

Results

C17. According to CS Tables 49 and 69, several variables for which it would seem plausible to assign distributions to reflect parameter uncertainty in the uncertainty analyses, are not assigned any distributions. Among these variables are the following: health state utility decrements, baseline patient characteristics, outpatient administration resource use, inpatient administration resource use, ESA proportions, proportion of patients requiring home district nurse. This is especially problematic as, according to the deterministic sensitivity analyses the proportion of patients with diabetes is the most influential factor in the model.

a. **Please reflect on the plausibility of not including the uncertainty related to these parameters in the probabilistic analyses.**

Among the variables mentioned above, we highlight that the health state utility decrements, although indirectly, were included in the probabilistic analyses. As detailed in section B.3.4.2 of the CS, a generalised linear mixed model (GLMM) with a Gaussian distribution and an identity link was used to predict mean utility score for each Hb level. The health state (i.e. Hb level) specific utility decrements were

estimated from the mean utility score predicted by the GLMM, assuming the Hb ≥ 13 level as the reference health state. We note that the covariates of the GLMM were included in the probabilistic sensitivity analyses using a multivariate normal distribution (variance covariance matrix and Cholesky decomposition are provided in the model tab 'HRQoL IPD' J38:AF47). In each run of the probabilistic sensitivity analysis, a new set of sampled parameters for the GLMM define the mean utility values and the Hb level specific decrements are re-estimated.

In regard to patient baseline characteristics, the following characteristics were excluded from the probabilistic analyses: Starting age, proportion of male/female patients, proportion with CVD history, proportion of patients with diabetes and median baseline eGFR. The patient baseline characteristics provided in the economic model are averages from all patients included in the pooled dataset that inform the analyses (deemed representative of the UK population by a UK clinical expert), thus representing the population for which the treatment effect captured in those models applies. It should be noted that starting age, proportion of male/female patients and median baseline eGFR were not included as covariates in the regression models used to estimate the treatment effect, hence including these variables in the probabilistic analyses may lead to implausible scenarios in some of the simulations, as there is no way to guarantee that the same treatment effect would apply to all sampled "cohorts".

In regard to CVD and diabetes history, it should be noted that the baseline values were not included in the sensitivity analyses for the same reasons mentioned above. However, the effect of the patient characteristics in the model outcomes was derived from the roxadustat clinical data and the "size" of this effect was included in the probabilistic analyses as CVD and diabetes history were included as covariates in the multinomial regression models to estimate Hb level, mortality, time to dialysis, treatment dose, IV iron use and HRQoL. All covariates in these multinomial regression models were included in the probabilistic analyses with multivariate normal distributions.

Inpatient and outpatient administration resource use and ESA proportions and proportion of patients requiring home district nurse have been included in the probabilistic analyses in the updated model prepared in the response to question b).

The results show that including these parameters had very little impact on the probabilistic analyses results in comparison with the results obtained in the model originally submitted.

b. Please provide an updated economic model including these parameters in the probabilistic analyses.

A model incorporating inpatient and outpatient administration resource use, ESA distribution and proportion of patients requiring home district nurse is provided in file (ID1483_Astellas_Roxadustat_CEM_C14_17_CIC):

- Probabilistic values for ESA proportion estimated with normal distributions
- Probabilistic values for proportion of patient requiring inpatient and outpatient administration and home district nurse estimated using beta distributions

It should be noted that the proportion of patients requiring home district nurse is set to 0 in the model base case, hence including this parameter in the probabilistic analyses had no effect on the results.

The average results of the updated model probabilistic sensitivity analyses are shown in Table 72. Updated cost-effectiveness planes and acceptability curves are provided in Figure 25 and

Figure ***26***, respectively.

The impact of the additional variables was very limited and the results and conclusions from the probabilistic analyses remain the same:

Table 72. Probabilistic sensitivity analysis results

	Roxadustat	ESA
Total costs (95% CI)	[redacted]	[redacted]
Total QALYs (95% CI)	[redacted]	[redacted]
Incremental costs (95% CI)	[redacted]	
Incremental QALYs (95% CI)	[redacted]	
ICER (95% CI)	[redacted]	
NMB £20,000 per QALY (95% CI)	[redacted]	

Abbreviations: CI: confidence interval, ESA: erythropoiesis-stimulating agents, QALY: quality adjusted life year, ICER: incremental cost effectiveness ratio, NMB: net monetary benefit.

Figure 25. Cost-effectiveness (CE) plane

Figure 26. Cost-effectiveness acceptability curve (CEAC)

C18. CS Table 74 presents the results of the deterministic sensitivity analyses.

a. The results for both analyses about the discount rates are blank. Please report the results of these analyses.

Please see below (Table 73) the discrete sensitivity analysis (DSA) results for the discount rate parameters.

Table 73. DSA results for discount rate parameters

Parameter	Inputs			ICER		NMB	
	Base case	Low	High	Low	High	Low	High
Discount rate - costs	3.5%	1.5%	6.0%	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate - QALYs	3.5%	1.5%	6.0%	[redacted]	[redacted]	[redacted]	[redacted]

b. Oral iron use seems to be included in the analyses, but all the reported inputs (for base case, low and high) are reported as the same. Please explain what was done in this sensitivity analysis.

See response to C16

C19. The results of the scenario analyses regarding different time horizons seem inconsistent with what would usually be expected. While shorter time horizons usually result in a larger Incremental cost-effectiveness ratio (ICER) as drugs accumulate a lower treatment effect, the ICER for shorter time horizons is lower (CS Table 75). Furthermore, the net monetary benefit (NMB) is decreasing with a decreasing ICER over the three scenario analyses. It would be expected that with a decreasing ICER the NMB would increase, however in the case of these three scenario analyses considering time horizons the decreasing ICER coincide with a decreasing NMB.

a. Please explain both inconsistencies.

In regard to the first inconsistency we note that individually, both incremental costs and incremental QALYS behave as expected (i.e. both increase with the time horizon). This reflects the expected behaviour as for larger time horizons a larger treatment benefit (at a higher incremental cost) is accrued in these scenarios. However, since the ICER is a ratio of these two quantities, the relative increase of one versus the other also affects the outcome. In the cost effectiveness model, the increase in the cost difference between the drugs is higher than the increase in the QALYs gained, resulting in slightly lower ICERs for shorter time horizons.

The disaggregated incremental costs and QALYs for time horizons of 5, 10, 15, 25 (Base case) and 35 years are provided in Table 74.

Table 74. Incremental results of roxadustat vs. ESAs at different time horizons.

Variable/Time horizon	5	10	15	Base case	35
ICER					
NMB					
QALY difference					
Health state values					
Stroke					
MI					
VAT					
Cost difference					
Treatment (drug)					
Treatment (administration)					
IV iron (drug)					
IV iron (administration)					

Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Access Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood transfusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

An explanation of the impact of the main variables in the model driving the changes described above is provided below.

- **Treatment administration costs (ESAs):** ESAs are associated with administration costs for those patients who are not on dialysis, whereas the same treatment effect is assumed when patients transition to dialysis. In turn, the model tracks the percentage of patients on dialysis, which increases over time. As a result, the cost per each QALY accrued in the ESA arm is higher during the 1st years of the model time horizon (since a higher proportion of patients is NDD) relative to later years. This drives a lower ICER for roxadustat in the short term.

- **VAT cost and disutility:** Roxadustat increases the number of VAT AEs and associated costs and reduces QoL compared to ESAs. For shorter time horizons this effect is lower as a constant rate of VAT is assumed throughout the model time horizon. This drives a lower ICER for roxadustat in the short term.

- **Blood transfusion cost:** Roxadustat increases the cost of blood transfusions compared to ESAs. For shorter time horizons this effect is lower as a constant rate of VAT is assumed throughout the model time horizon. This drives a lower ICER for roxadustat in the short term.

- **Hb level progression:** Roxadustat improves patients' Hb level and this is reflected in increased QALYs associated to health state occupancy. For shorter time horizons this effect is lower as the treatment effect is accrued over time. This drives a higher ICER for roxadustat in the short term.

- **Stroke cost and disutility:** Roxadustat reduces the number of stroke AEs and its associated costs and increases QoL compared to ESAs. For shorter time horizons this effect is lower as a constant rate of stroke is assumed

throughout the model time horizon. This drives a higher ICER for roxadustat in the short term.

- **MI cost and disutility:** Roxadustat reduces the number of MI AEs and its associated costs and increases QoL compared to ESAs. For shorter time horizons this effect is lower as a constant rate of MI is assumed throughout the model time horizon. This drives a higher ICER for roxadustat in the short term.

Overall, the impact of the variables driving a lower ICER for roxadustat (ESA administration, VAT and blood transfusions) offsets the impact of variables driving a higher ICER for roxadustat (Stroke, MI, and ESA treatment administration costs).

In regard to the second inconsistency highlighted, it should be noted that NMB has a linear relationship with costs while the ICER is a ratio, and therefore sensitive to the rates of accrual of incremental costs and QALYs. The rationale for the lower ICERs in shorter time horizons is provided above. The same effect is not observed in the NMB as the ICER never falls below willingness to pay threshold (i.e. £20,000/QALY) regardless of the time horizon chosen, therefore the net benefit increases over time (i.e. NMB increases)

b. If there are any errors found, please correct them and report the outcomes of the corrected scenario analyses.

No errors have been identified. See response to C19a.

Validation and transparency

C20. Priority question. CS section B.3.9.2 states that the model matches clinical guidelines for anaemia associated with CKD and that the modelled baseline characteristics are aligned with the UK patient population. Further external validation of modelled effects would be desirable.

a. Please report on the face validity assessment (by clinical and health economic experts as mentioned in CS B.3.9.2) of the model structure, model assumptions, model inputs, intermediate outcomes as well as

final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).

The cost-effectiveness model has been validated by clinical and health economic experts at different phases of the model development process:

- The first validation occurred in September 2020 and covered aspects such as overall modelling concept, statistical analyses and key model parameters
- The second validation occurred in March 2021 focused on validating baseline patient characteristics and generalisability to the UK population as well as gathering clinical feedback to inform key model inputs and generalisability of the UK population

Detailed minutes from these discussions have been provided in the reference pack [33].

During the first validation, an early version of the model and roxadustat main evidence were presented to three experts ([redacted]– HEOR expert, [redacted] and [redacted] – Clinical experts). During this session, the following modelling assumptions were discussed and validated:

- Minimal differences in efficacy are expected for the different ESA. Frequency of administration has an impact but provided these are administered at equivalent doses, the same outcome is expected
- ESA or roxadustat treatment would not start until patients had failed to achieve target Hb levels using iron alone. Clinical experts considered that given the point in the patient pathway ESA/roxadustat is given (i.e. once iron has failed to achieve target Hb levels) it is expected that all patients would be receiving IV iron.
- Method implemented to ensure long term survival from the clinical trial estimates does not exceed the expected survival of the target population was considered appropriate.

- Curve choices to extrapolate survival were validated by visual inspection and clinical plausibility of the mean, median and landmark survival estimates. external experts agreed that no clinical effect should be applied in mortality.

- Curve choices to extrapolate time to dialysis were validated by visual inspection and clinical validity of the mean, median and landmark estimates

During the second validation, two external experts ([redacted] – HEOR expert and [redacted] – Clinical Expert) commented on the applicability of the model to the UK population and validated key assumptions and inputs:

- The modelled pooled population was considered as reflective of the heterogeneous UK inhabitants in terms of race and diabetic status

- A pooled sample of all NDD trials was preferred than an only DOLOMITES [4] scenario to inform the main inputs of this model despite of the limitations related to the placebo observations contained in ALPS [1], ANDES [2] and OLYMPUS [3]. The main reason was the limited number of patients available from DOLOMITES [4].

- The clinical validity of the mean, median and landmark survival estimates in this model was confirmed

- The use of clinical trial data to inform adverse events rates was suggested as the preferred option

- It was suggested that around 20% of patients on ESA are not able to self-administer, requiring assistance from either a carer or an health care professional (i.e. district nurse or general practitioner)

b. Please conduct a cross validation of the model structure, model assumptions, model inputs, intermediate outcomes as well as final outcomes with other economic models focusing on a related decision problem. This includes the publications described in CS section B.3.1 as well as NICE TA358 (Tolvaptan for treating autosomal dominant polycystic kidney disease).

A *de novo* model was developed in this submission to estimate the costs and health outcomes of roxadustat for the treatment of symptomatic anaemia associated with CKD from a UK National Health Services (NHS) and Personal Social Services (PSS) perspective. There was no precedent and therefore no preferred methods to model this disease area as no previous Health Technology Assessment (HTA) submissions for treatments of anaemia associated with CKD were identified.

A collection of published cost-effectiveness models relevant for this submission, as highlighted in the question heading (CS Section B.3.1), were identified and detailed in CS Appendix G [13, 15-20, 34-38]. Given the characteristics of the models identified in terms of the population of interest, research question, and modelling approach (see CS Table 113), none of the identified models provided a cost-effectiveness analysis fully aligned with the decision problem covered in this submission. One model [38], described in CS Section B.3.1., did focus on patients not on dialysis, but did not model transition to dialysis, and implemented a time horizon of only 5 years. Therefore, in our view, the cross-validation exercise suggested would not offer a relevant or reliable exercise based on the differences in decision problems considered.

Regarding NICE TA358, the indication of interest in this submission was adults with autosomal dominant polycystic kidney disease (ADPKD). A patient level-simulation model was presented to investigate the cost-effectiveness of tolvaptan, applying a lifetime horizon of up to 80 years, and a cycle length of 1 year. The main focus of this model was ADPKD progression until the onset of end-stage renal disease (ESRD) in a first stage of the model, and from ESRD onwards in a second stage of the model. The main aspects modelled were movements between CKD stages, the incidence of renal failure (CKD stage 5), and the incidence of all-cause mortality. Anaemia was not considered or modelled in NICE TA358.

As roxadustat is a treatment for anaemia associated with CKD, and not CKD itself, a de novo model was needed to capture the treatment and associated outcomes of anaemia, within the usual progression of CKD. The lack of alignment between the clinical indication of interest and outcomes modelled in NICE TA358, and the focus of the current submission, as well as the validation described in C20a make, in our view, the cross-validation exercise unnecessary.

c. **Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using**

   i. **evidence used to develop the economic model.**

   ii. **evidence not used to develop the economic model.**

Please see responses to a) and b) above.

C21. Technical validation was conducted in a manner which is not sufficiently transparent for the ERG (detailed descriptions with results of the tests are missing in CS section B.3.9.1).

Please use the TECH-VER checklist (https://doi.org/10.1007/s40273-019-00844-y) to assess the technical verification of the economic model and report the results.

As highlighted to the ERG in our communication dated 26th July, unfortunately it has not been possible to undertake the technical validation using the checklist indicated in the allowed time. Please see response to question C20 for details on the model validation performed with external health economic and clinical experts.

C22. Several inconsistencies between costs in the CS and the economic model could be found. The first two items which have differing costs are "Long Term Stroke" which is valued at £4,767 and "Life Time Stroke" is valued at £4,873. The difference between these two items also correspond to the weighted cost of a stroke (~£106). The second pair of items which has differing costs are "MI Lifetime" and "Long Term MI" at £690 and £680 respectively,

a. **Please explain whether there are any inconsistencies between the model and the submission.**

A crosscheck between the model and submission resulted in the following inconsistencies:

- **Section B.3.5.1.4:**
  - Typo: The phrase in the CS Section B.3.5.1.4 “With an hourly cost of £119, and assuming a 15-minute appointment, each monitoring visits costs

£29.25” contains a typo not aligned with the model, where this value is correctly incorporated in cell 'Treatment Costs Breakdown'!E87.

- Corrected: The corrected phrase is “With an hourly cost of £119, and assuming a 15-minute appointment, each monitoring visits costs £29.75”

Section B.3.5.2.2.

- Typo: The values reported in Table 62 contain a typo are not aligned with the model, where these are correctly reported in sheet ‘Bl trans PopA!
- Corrected: Please see below the corrected Table 62.

Table 75. CS Table 62 corrected- Probability of receiving a blood transfusion

Health state	Total exposure time (weeks)	Weekly probability of needing a transfusion	Three-month probability of needing a transfusion
Roxadustat			
Hb <7	[redacted]	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]	[redacted]
Hb ≥ 13	[redacted]	[redacted]	[redacted]
ESA			
Hb <7	[redacted]	[redacted]	[redacted]
Hb 7.00 to 7.99	[redacted]	[redacted]	[redacted]
Hb 8.00 to 8.99	[redacted]	[redacted]	[redacted]
Hb 9.00 to 9.99	[redacted]	[redacted]	[redacted]
Hb 10.00 to 10.99	[redacted]	[redacted]	[redacted]
Hb 11.00 to 11.99	[redacted]	[redacted]	[redacted]
Hb 12.00 to 12.99	[redacted]	[redacted]	[redacted]
Hb ≥ 13	[redacted]	[redacted]	[redacted]

Abbreviations: Hb: haemoglobin; ESA: Erythropoiesis-stimulating agents.

Section B.3.5.2.3:

- Typo: Table 64 is missing the regression coefficients applied in the model relative to interaction effects between treatment of interest and Hb level.
- Corrected: Please see below Table 64 corrected:

Table 76. CS Table 64 corrected- Regression coefficients for proportion of patients receiving IV iron

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]
Diabetic - Yes	[redacted]	[redacted]	[redacted]
STUDY: OLYMPUS	[redacted]	[redacted]	[redacted]
STUDY: ANDES	[redacted]	[redacted]	[redacted]
STUDY: DOLOMITES	[redacted]	[redacted]	[redacted]
ESA arm			
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
Roxadustat arm			
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]

Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001.

Abbreviations: CVD: cardiovascular disease; ESA: erythropoiesis-stimulating agents; Hb: haemoglobin.

Section B.3.5.2.3:

- Typo: CS Table 66 values are incorrect and are not aligned with the values reported in the model submitted in cell 'Iron supp A'!K14:K15, which are correct
- Corrected: Please see below CS Table 66 corrected:

Table 77. CS Table 66 corrected- Dose of IV iron per administration

Intervention	Per cycle dose of IV iron (mg)
Roxadustat	[redacted]
ESA	[redacted]

Abbreviations: ESA: erythropoiesis-stimulating agents; IV: intravenous; mg: milligram.

Section B.3.5.3:

- Typo: In CS Table 68, the long-term stroke and long-term MI costs reported are incorrect and not aligned with the model submitted. The value reported in the model for long-term stroke in 'TRAE cost breakdown'!E28 and long-term MI in 'TRAE cost breakdown'!F44 are correct.
- Corrected: Please see below CS Table 68 corrected:

Table 78. CS Table 68 corrected-TRAE costs

TRAE	Unit cost	Source
Non-disabling stroke (acute)	£2,960	NHS Cost Collection [39]
Moderately disabling stroke (acute)	£3,999	
Severely disabling stroke (acute)	£6,912	
Long term stroke	£4,873	Xu et al. inflated with PSSRU index [40, 41]
Stroke total	£8,625*	
MI (acute)	£2,367	NHS Cost Collection [39]
Long term MI	£690	TA317, inflated with PSSRU index [41, 42]
MI total	£3,057	
VAT (acute)	£3,601	NHS Cost Collection [39]
Long term VAT	£0	Assumed
VAT total	£3,601	

Notes: *Applies proportions of 48.5%, 42.6% and 8.8% to non-disabling, moderately disabling and severely disabling stroke, respectively.

Abbreviations: MI: myocardial infarction; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; TA: technology appraisal; TRAE: Treatment-Related Adverse Event; VAT: Vascular Access Thrombosis.

b. If there are any inconsistencies, please reflect on where these inconsistencies may come from and correct the inconsistency.

All inconsistencies were due to outdated tables in the reported submission document. All inputs provided in the economic model were provided as intended. All inconsistencies were corrected in response to question a). It should be noted that no inconsistencies were identified in the results reported in the model and submission and correcting the inconsistencies did not have an impact in the results.

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Appendix A – detailed response to A23

a) ScHARRHud

Table 79 HCRU SLR search details (ScHARRHud)

	Original SLR	SLR Update
Interface / URL:	https://www.scharrhud.org.	
Database coverage dates:	n/a	
Search date:	22/01/19	22/01/2021
Retrieved records:	3	0

Original SLR

The following search was conducted (default 'Any field' selected):

anemi OR anaemi* = 3 records*

SLR Update

The following search was conducted (default 'Any field' selected):

anemi OR anaemi* = 0 records*

b) CEA Registry

Table 80 HCRU SLR search details (CEA Registry)

	Original SLR
Interface / URL:	https://cevr.tuftsmedicalcenter.org/databases/cea-registry
Database coverage dates:	n/a
Search date:	22/01/19
Retrieved records:	0

Original SLR

The following searches were conducted separately using the basic search interface: http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx.

The default 'Search for: Methods' was selected. Duplicates of records already retrieved from searches of other databases were excluded. All remaining returned results were assessed by the Information Specialist for relevance to the population of interest. Results assessed as not relevant were excluded.

anemi = 0 retrieved (18 results returned)

anaemi = 0 retrieved (8 results returned)

SLR update

Not performed given the CEA registry contains publications from 1976 to 2019 only.

c) NICE website

Table 81 HCRU SLR search details (NICE)

	Original SLR	SLR Update
Interface / URL:	https://www.nice.org.uk/	
Database coverage dates:	n/a	
Search date:	23/01/19	02/03/2021
Retrieved records:	2	1

Original SLR

A targeted search of the NICE website was conducted to identify Company Submissions to NICE, Assessment Reports and Final Appraisal Determination Documents for technology assessments (TAs) in adult patients with CKD and anaemia

1. The site search was used. The following search was conducted:

   (kidney OR kidneys OR renal OR nephropathy OR nephropathies OR nephropathic OR CKF OR CKD OR CRF OR CRD OR ESKD OR ESRD OR ESKF OR ESRF OR dialysis OR hemodialysis OR haemodialysis) AND (anemia OR anemias OR anemic OR anaemia OR anaemias OR anaemic) = 34 results returned.

For potentially relevant TAs, the History tab was used to locate Company Submissions to NICE, Assessment Reports and Final Appraisal Determination Documents.

One potentially relevant TA was identified (TA481). The Assessment Report and Final Appraisal Determination Document for the TA were downloaded.

The company submissions for the TA could not be identified on the NICE webpages. An e-mail was sent to NICE (nice@nice.org.uk) on the 23/01/19 asking them to send all company submissions for this TA. This guidance replaces NICE technology appraisal guidance 85, so NICE were also asked to send any separate company submissions for TA85. NICE confirmed that the relevant teams were looking into the request. Follow-up e-mails were sent to NICE on 07/02/19 and 27/02/19 to check on progress but as of 14/03/19 no company submissions had been received from NICE.

2. The following path was used to navigate to blood conditions:

NICE / NICE Guidance / Conditions and diseases / Blood and immune system conditions / Blood conditions.

Results were limited to TAs: https://www.nice.org.uk/guidance/conditions-and-diseases/blood-and-immune-system-conditions/blood-conditions/products?GuidanceProgramme=TA

19 results were browsed by the IS for relevance to adult patients with CKD and anaemia. 0 results were selected for further assessment.

3. The following path was used to navigate to acute kidney injury conditions:

NICE / NICE Guidance / Conditions and diseases / Kidney conditions

No TA results were found.

4. The following path was used to navigate to chronic kidney diseases

NICE / NICE Guidance / Conditions and diseases / Kidney conditions / Chronic kidney disease

Results were limited to TAs: https://www.nice.org.uk/guidance/conditions-and-diseases/kidney-conditions/chronic-kidney-disease/products?GuidanceProgramme=TA

Three results were identified but were not eligible.

5. The following path was used to navigate to Kidney conditions: general and other

NICE / NICE Guidance / Conditions and diseases / Kidney conditions / Kidney conditions: general and other

Results were limited to TAs: https://www.nice.org.uk/guidance/conditions-and-diseases/kidney-conditions/kidney-conditions--general-and-other/products?GuidanceProgramme=TA

2 results were identified> 1 result was excluded as a duplicate and 1 was not relevant.

SLR update

1. The site search was used. The following search was conducted:

(kidney OR kidneys OR renal OR nephropathy OR nephropathies OR nephropathic OR CKF OR CKD OR CRF OR CRD OR ESKD OR ESRD OR ESKF OR ESRF OR dialysis OR hemodialysis OR haemodialysis) AND (anemia OR anemias OR anemic OR anaemia OR anaemias OR anaemic) = 2 results returned.

d) Conference 'hand-searches'

Original SLR

The hand search performed was the same as described in Q A20.

SLR update

d) i ASN 2019, 2020

Search date: 26th February 2021

The following search terms were used, and the terms were searched separately:

anemi economic; anemi cost; anemi price; anemi pricing; anemi expenditure; anemi money; anemi budget; anemi burden; anemi resource; anemi visit; anemi appointment; anemi hospitalization; anemi hospitalisation; anemi hospitalised; anemi hospitalized; anemi admission; anemi admitted; anemi los; anemi bed day; anemi days hospital; anemi time hospital; anemi length

hospital; anemi duration hospital; anemi stay; anemi discharge; anemi home; anemi quality adjusted; anemi adjusted life year; anemi qaly; anemi qald; anemi qale; anemi qtime; anemi illness state; anemi utility; anemi utilities; anemi hui; anemi multiattribute; anemi multi attribute; anemi 5d; anemi eq-5; anemi eq5; anemi euro-qual; anemi euro qual; anemi euroqual; anemi quol; anemi qol; anemi euroqul; anemi eurqul; anemi quality of life; anemi sf36; anemi sf-36; anemi thirty; anemi short; anemi time trade off; anemi time tradeoff; anemi tto; anemi timetradeoff; anemi SF-12; anemi SF12; anemi 15-D; anemi 15D; anemi SF-6; anemi SF6; anemi 6D; anemi discrete choice; anemi choice experiment; anemi dce; anemi standard gamble; anemi sg; anaemi. A total of 1 record was retrieved

d) ii ISPOR 2019, 2020

Search date: 26th February 2021

The following search terms were used, and the terms were searched separately:

anemi; anaemi. A total of 2 records were retrieved

d) iii European Renal Association - European dialysis and Transplant Association (ERA EDTA) Congress, 2019, 2020

Search date: 26th February 2021

The following search terms were used, and the terms were searched separately:

anemi economic; anemi cost; anemi price; anemi pricing; anemi expenditure; anemi money; anemi budget; anemi burden; anemi resource; anemi visit; anemi appointment; anemi hospitalization; anemi hospitalisation; anemi hospitalised; anemi hospitalized; anemi admission; anemi admitted; anemi los; anemi bed day; anemi days hospital; anemi time hospital; anemi length hospital; anemi duration hospital; anemi stay; anemi discharge; anemi home; anemi quality adjusted; anemi adjusted life year; anemi qaly; anemi qald; anemi qale; anemi qtime; anemi illness state; anemi utility; anemi utilities; anemi hui; anemi multiattribute; anemi multi attribute; anemi 5d; anemi eq-5; anemi eq5; anemi euro-qual; anemi euro qual; anemi euroqual; anemi quol; anemi qol; anemi euroqul; anemi eurqul; anemi quality of life;

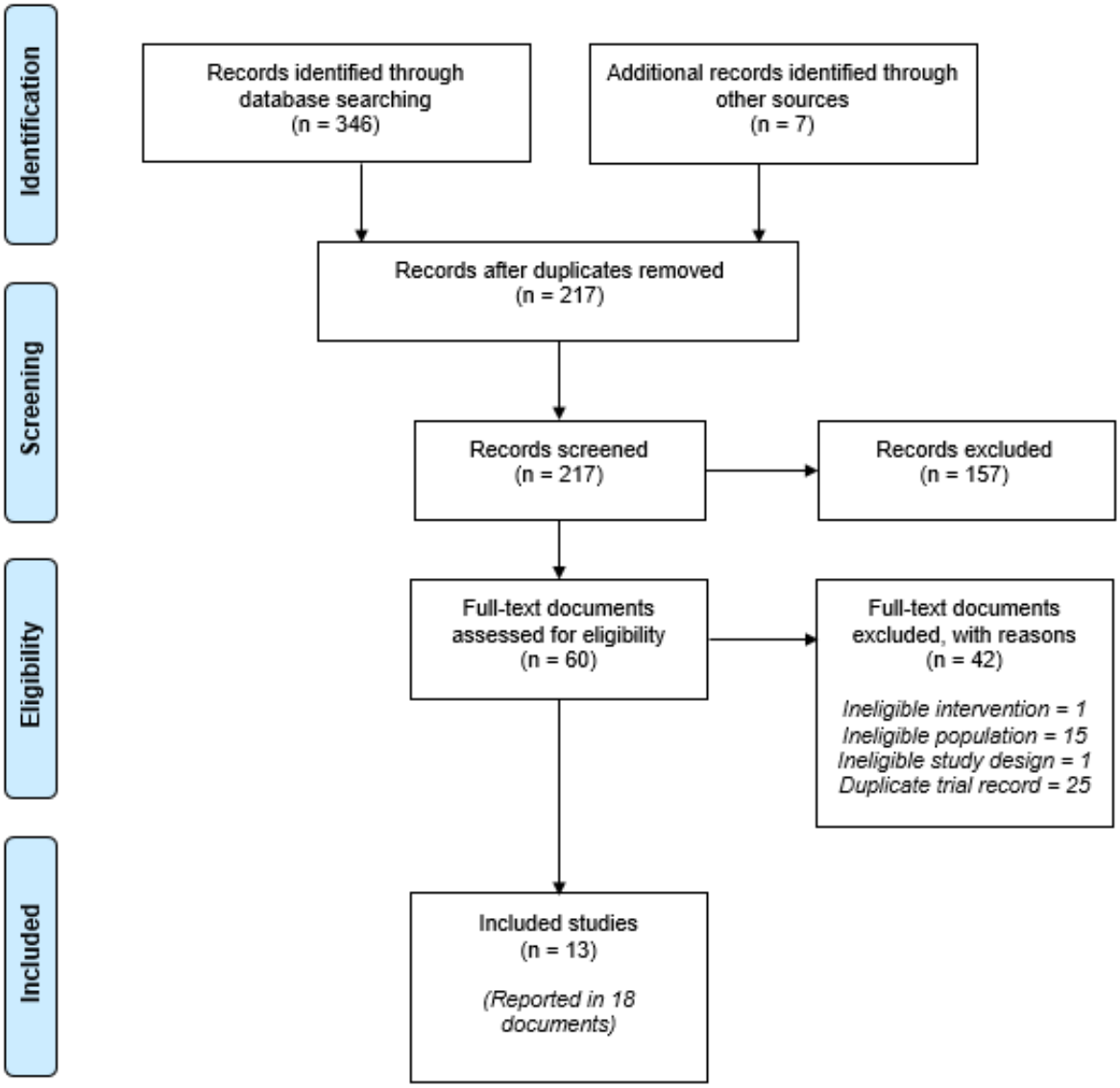
anemi sf36; anemi sf-36; anemi thirty; anemi short; anemi time trade off; anemi time tradeoff; anemi tto; anemi timetradeoff; anemi SF-12; anemi SF12; anemi 15-D; anemi 15D; anemi SF-6; anemi SF6; anemi 6D; anemi discrete choice; anemi choice experiment; anemi dce; anemi standard gamble; anemi sg; anaemi. A total of 2 records were retrieved

Appendix B – detailed response to B9

Original SLR

During the original SLR, 217 records were included for assessment. One-hundred and fifty-seven records were excluded following an assessment of titles and abstracts, leaving 60 records to be assessed at full text. Following full text review, 13 trials (reported in 18 documents) were included (Figure 27).

Figure 27. PRISMA flow diagram of study selection during clinical original SLR



Thirteen trials were identified that assessed roxadustat in patients with anaemia and CKD. There were:

- Four Phase II trials
- One Phase II/III extension trial
- Eight Phase III trials

The following tables (Table 82 to Table 84) provide the trial identifier, full reference (primary and associated references) and a summary of the treatment arms assessed in each trial. The tables are split by trials in dialysis and NDD patients.

Table 82 Phase II Trials

Trial Identifiers	References	Arms
Trials in non-dialysis patients		
NCT00761657 FGCL-SM4592-017 [43, 44]	Besarab A, Provenzano R, Hertel J, Zabaneh R, Klaus SJ, Lee T, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients. Nephrol Dial Transplant. 2015;30(10):1665-73.	Roxadustat Placebo
	Besarab A, Belo D, Diamond S, Martin E, Sun C, Lee T, et al. Evaluation of hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for hemoglobin correction and maintenance in non-dialysis chronic kidney disease patients for 16 and 24 weeks. Nephrol Dial Transplant. 2012;27(Suppl 2):ii133–ii45.	
	Phase 2 Study of FG-4592 in Subjects With Anemia and Chronic Kidney Disease Not Requiring Dialysis. Identifier: NCT00761657. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2008. Available from https://clinicaltrials.gov/show/NCT00761657.	
NCT01244763 FGCL-4592-041 [45]	Provenzano R, Besarab A, Sun CH, Diamond SA, Durham JH, Cangiano JL, et al. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. Clin J Am Soc Nephrol. 2016;11(6):982-91.	Roxadustat at various doses
	Study of FG-4592 in Non-Dialysis Chronic Kidney Disease Patients With Anemia. Identifier: NCT01244763. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://clinicaltrials.gov/show/nct01244763.	
Trials in dialysis patients		
NCT01147666 FGCL-4592-040 [46, 47]	Provenzano R, Besarab A, Wright S, Dua S, Zeig S, Nguyen P, et al. Roxadustat (FG-4592) versus epoetin alfa for anemia in patients receiving maintenance hemodialysis: A phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study. Am J Kidney Dis. 2016;67(6):912-24.	Roxadustat Epoetin alfa

Trial Identifiers	References	Arms
	Study of FG-4592 in Subjects With End-Stage Renal Disease Receiving Maintenance Hemodialysis. Identifier: NCT01147666. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://clinicaltrials.gov/show/nct01147666.	
	Provenzano R, Goodkin D, Klaus S, Linde P, Kazazi F, Lee T, et al. Evaluation of FG-4592, a novel oral hypoxia inducible factor prolyl hydroxylase inhibitor, to treat anemia in hemodialysis patients. Am J Kidney Dis. 2011;57(4):A80. [Interim results]	
NCT01414075 FGCL-4592-053	Study of FG-4592 to Correct Anemia in New Dialysis Patients. Identifier: NCT01414075. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2011. Available from https://clinicaltrials.gov/show/nct01414075.	Roxadustat at various doses

Table 83: Phase II/III

Trials Identifiers	Reference	Arms
NCT01630889 (open label extension study) FGCL-4592-059	Open Label Extension Study for the Long-term Efficacy and Safety of FG-4592 in Dialysis and Non-dialysis Chronic Kidney Disease Patients. Identifier: NCT01630889. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2012. Available from https://clinicaltrials.gov/show/NCT01630889.	Roxadustat at various doses

Table 84: Phase III trials

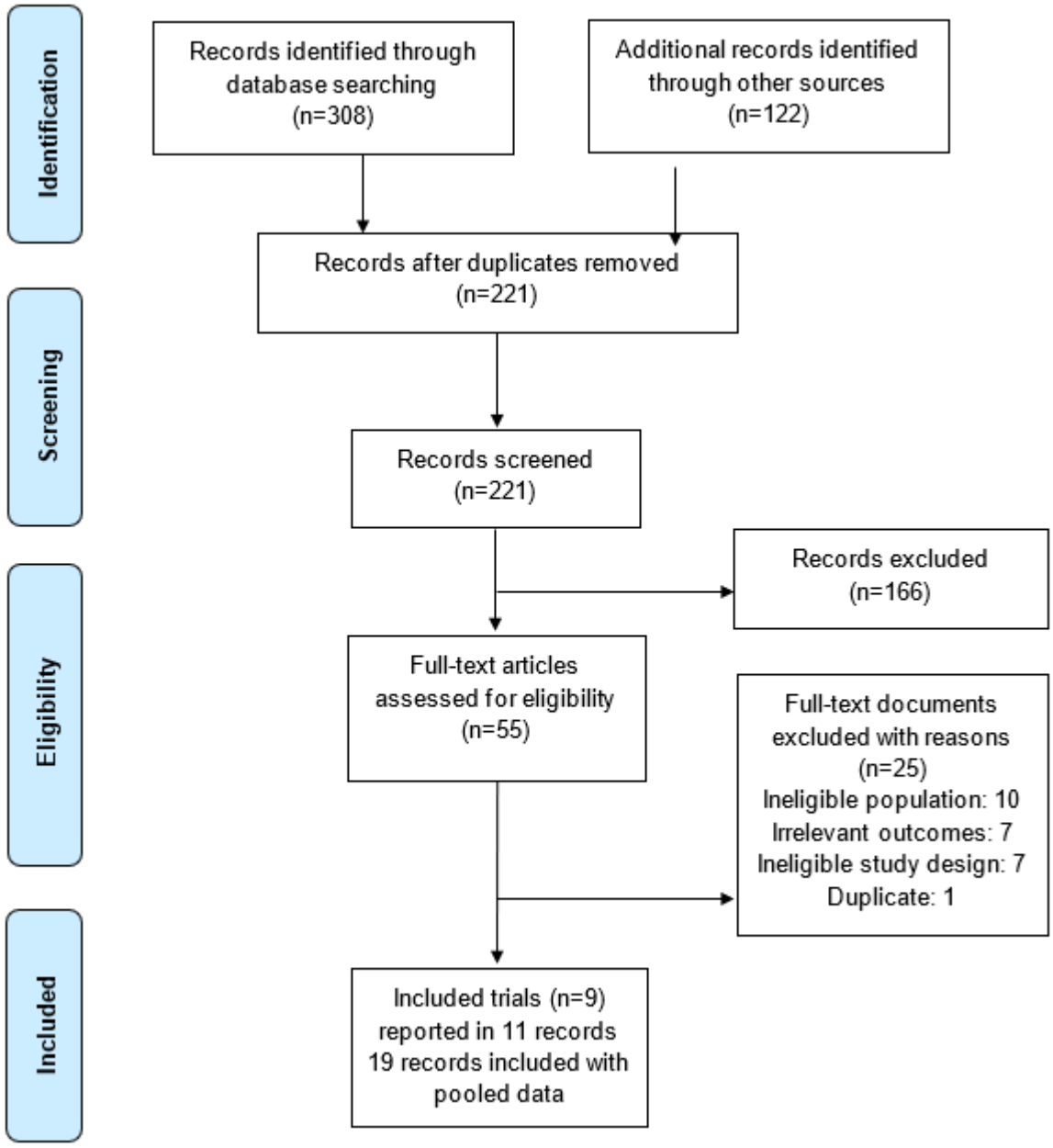
Trial Identifiers	Reference	Arms
Trials in non-dialysis patients		
DOLOMITES NCT02021318 1517-CL-0610 2013-000951-42	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa. Identifier: NCT02021318. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://clinicaltrials.gov/show/nct02021318.	Roxadustat Darbepoetin alfa
OLYMPUS NCT02174627 CTRI/2015/12/006412 D5740C00001 PERU 068-14	Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease (CKD), Not on Dialysis. Identifier: NCT02174627. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02174627.	Roxadustat Placebo
ANDES NCT01750190 FGCL-4592-060 KCT0001690 PERU 041-14	A Study of FG-4592 for the Treatment of Anemia in Chronic Kidney Disease Patients Not Receiving Dialysis. Identifier: NCT01750190. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2012. Available from https://clinicaltrials.gov/ct2/show/nct01750190.	Roxadustat Placebo

Trial Identifiers	Reference	Arms
ALPS NCT01887600 1517-CL-0608 2012-005180-27 PERU 058-15	Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis. Identifier: NCT01887600. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2013. Available from https://clinicaltrials.gov/show/nct01887600.	Roxadustat Placebo
Trials in dialysis patients		
HIMALAYAS NCT02052310 2013-002753-30 FGCL-4592-063/CFG13001 PERU 038-14	Safety and Efficacy Study for Treatment of Anemia in ESRD Newly Initiated Dialysis Patients. Identifier: NCT02052310. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02052310.	Roxadustat Epoetin alfa
ROCKIES NCT02174731 D5740C00002 PERU 067-14	Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease, on Dialysis. Identifier: NCT02174731. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/NCT02174731.	Roxadustat Epoetin alfa
SIERRAS NCT02273726 FGCL-4592-064	Evaluation of Efficacy and Safety of Roxadustat in the Treatment of Anemia in Stable Dialysis Subjects. Identifier: NCT02273726. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02273726.	Roxadustat Epoetin alfa
PYRENEES NCT02278341 EUCTR2013-001497-16-GB	Roxadustat in the Treatment of Anemia in End Stage Renal Disease (ESRD) Patients on Stable Dialysis. Identifier: NCT02278341. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2014. Available from https://clinicaltrials.gov/show/nct02278341.	Roxadustat Epoetin alfa / Darbepoetin alfa

SLR update

In the SLR update, 221 records were screened for inclusion. After title and abstract screening, 166 references were excluded against the eligibility criteria and 55 potentially relevant references were retrieved for full-text assessment. During the full-text review, further 25 records were excluded based on PICOS eligibility criteria. Following full text review, nine trials (reported in 11 documents) and 19 studies reporting pooled data from several randomised control trials (RCTs) were included in the current SLR update. The PRISMA diagram in Figure 28 presents the results of the search described above.

Figure 28. PRISMA flow diagram of study selection during clinical SLR update



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; n, number.

Nine trials (reported in 11 documents) were identified that assessed roxadustat in patients with anaemia associated with CKD. There were:

- One Phase Ib trial (FGCL-4592-039)
- Eight Phase III trials (ALPS, ANDES, DOLOMITES, OLYMPUS, HIMALAYAS, ROCKIES, SIERRAS, PYRENEES)

In addition, 19 studies were identified that reported pooled data from several Phase III RCTs comparing roxadustat to comparators.

Table 85 to Table 87 provide the trial identifier, full reference (primary and associated references) and a summary of the treatment arms assessed in each study.

Table 85: Phase Ib trial

Trial Identifiers	References	Arms
FGCL-4592-039 [48]	Provenzano, R., et al., Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor Roxadustat (FG-4592) for Treatment of Anemia in Chronic Kidney Disease: A Placebo-Controlled Study of Pharmacokinetic and Pharmacodynamic Profiles in Hemodialysis Patients. Journal of Clinical Pharmacology, 2020. 60(11): p. 1432-1440.	Roxadustat Placebo

Table 86: Phase III trials

Author, year	Trial(s)	References	Arms
NDD patients			
Fishbane 2019 [49]	OLYMPUS	Fishbane, S., et al., Olympus: A phase 3, randomized, double-blind, placebo-controlled, international study of roxadustat efficacy in patients with non-dialysis-dependent (NDD) CKD and anemia. Journal of the American Society of Nephrology, 2019. 30: p. 6.	Roxadustat Placebo
Pecoits 2020 [50]	OLYMPUS, ANDES, ALPS	*Pecoits-Filho, R., et al., Roxadustat treatment results in consistent improvements in hemoglobin (Hb) vs. placebo: An analysis of three multinational randomized clinical trials in patients with non-dialysis-dependent CKD (NDD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 2.	
Provenzano 2020 [51]	ALPS, ANDES	*Provenzano, R., et al., Roxadustat treatment of anemia in non-dialysis-dependent CKD is not influenced by iron status. Journal of the American Society of Nephrology, 2020. 31: p. 1.	
Coyne 2019 [52]	ANDES	Coyne, D.W., et al., Andes: A phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of roxadustat for the treatment of anemia in CKD patients not on dialysis. Journal of the American Society of Nephrology, 2019. 30: p. 822-823.	Roxadustat Placebo
Coyne 2020 [53]	ANDES	Coyne, D.W., et al., Roxadustat favourably modifies iron indices in patients with non-dialysis-dependent CKD-related anemia. Journal of the American Society of Nephrology, 2020.	

Author, year	Trial(s)	References	Arms
		31: p. 132.	
Barratt 2020 [54]	DOLOMITES	Barratt, J., et al., Roxadustat for the treatment of anemia in CKD patients not on dialysis (NDD): A phase 3, randomized, open-label, active-controlled study. Journal of the American Society of Nephrology, 2020. 31: p. 1.	Roxadustat Darbepoetin alfa
DD patients			
Provenzano 2019 [55]	HIMALAYAS	Provenzano, R., et al., Himalayas: A phase 3, randomized, open-label, active-controlled study of the efficacy and safety of roxadustat in the treatment of anemia in incident-dialysis patients. Journal of the American Society of Nephrology, 2019. 30: p. 5.	Roxadustat Epoetin alfa
Fishbane 2019 [56]	ROCKIES	Fishbane, S., et al., Rockies: An international, phase 3, randomized, open-label, active-controlled study of roxadustat for anemia in dialysis-dependent CKD patients. Journal of the American Society of Nephrology, 2019. 30: p. 6.	Roxadustat Epoetin alfa
Charytan 2019 [57]	SIERRAS	Charytan, C., et al., Sierras: A phase 3, open-label, randomized, active-controlled study of the efficacy and safety of roxadustat in the maintenance treatment of anemia in subjects with ESRD on stable dialysis. Journal of the American Society of Nephrology, 2019. 30: p. 822.	Roxadustat Epoetin alfa
NDD and DD patients			
Esposito 2019 [58]	ALPS, PYRENEES,	Esposito, C., et al., Two phase 3, multicentre, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis. Journal of the American Society of Nephrology, 2019. 30: p. 822.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa/ Darbepoetin alfa

Abbreviations: NDD, non-dialysis dependent; DD dialysis dependent

Table 87: Pooled data from phase III trials

Author, year/Trial Identifiers*	References	Arms
Pooled data from trials in non-dialysis dependent patients		
Roger 2020 [59]	Roger, S.D., et al., Efficacy and safety of roxadustat in patients with non-dialysis-dependent CKD, anemia, and heart failure. Journal of the American Society of Nephrology, 2020. 31: p. 648.	Roxadustat Placebo
Pollock 2020	Pollock, C.A., et al., Roxadustat increases hemoglobin in anemic non-dialysis-dependent (NDD) CKD patients	Roxadustat at various

Author, year/Trial Identifiers*	References	Arms
[60]	independent of inflammation. Journal of the American Society of Nephrology, 2020. 31: p. 132-133.	doses
Fishbane 2020 [61]	Fishbane, S., et al., Hemoglobin (HB) correction with roxadustat is associated with improved iron homeostasis in patients with non-dialysis-dependent CKD (NDD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 130.	Roxadustat Placebo
Fishbane 2020 [62]	Fishbane, S., et al., Associations between achieved hemoglobin and cardiovascular outcomes in the pooled phase 3 roxadustat studies of non-dialysis-dependent patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. B4.	Roxadustat
Coyne 2020 [63]	Coyne, D.W., et al., Subgroup analyses of efficacy of roxadustat for treatment of anemia in patients with non-dialysis-dependent CKD. Journal of the American Society of Nephrology, 2020. 31: p. 131-132.	Roxadustat Placebo
Coyne 2020 [64]	Coyne, D.W., et al., Health-related quality of life in roxadustat-treated patients with anemia and non-dialysis-dependent CKD. Journal of the American Society of Nephrology, 2020. 31: p. 131.	Roxadustat Placebo
Roger 2020 [65]	Roger, S.D., et al., Efficacy and safety of roxadustat in patients with non-dialysis-dependent CKD, anemia, and diabetes mellitus. Journal of the American Society of Nephrology, 2020. 31: p. 352.	Roxadustat Placebo
Pooled data from trials in dialysis dependent patients		
Provenzano 2020 [66]	Provenzano, R., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD and anemia on hemodialysis. Journal of the American Society of Nephrology, 2020. 31: p. 23.	Roxadustat Epoetin alfa
Pergola 2020 [67]	Pergola, P.E., et al., Hemoglobin (HB) correction with roxadustat is associated with improved iron homeostasis in patients with dialysis-dependent CKD (DD-CKD). Journal of the American Society of Nephrology, 2020. 31: p. 2.	Roxadustat Epoetin alfa
Coyne 2020 [68]	Coyne, D.W., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD, anemia, and heart failure. Journal of the American Society of Nephrology, 2020. 31: p. 648.	Roxadustat Epoetin alfa
Chan 2020 [69]	Chan, T.M.D., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD and anemia on peritoneal dialysis. Journal of the American Society of Nephrology, 2020. 31: p. 51.	Roxadustat Epoetin alfa
El-Shahawy 2020 [70]	El-Shahawy, M.A., et al., Roxadustat increases hemoglobin in anemic dialysis-dependent (DD) CKD patients independent of inflammation. Journal of the	Roxadustat at various doses

Author, year/Trial Identifiers*	References	Arms
	American Society of Nephrology, 2020. 31: p. 133	
Provenzano 2020 [71]	Provenzano, R., et al., Associations between achieved hemoglobin and cardiovascular outcomes in the pooled phase 3 trials of roxadustat in dialysis-dependent patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. B4-B5.	Roxadustat
Provenzano 2020 [72]	Provenzano, R., et al., Subgroup analyses of efficacy of roxadustat for treatment of anemia in patients with incident dialysis-dependent CKD. Journal of the American Society of Nephrology, 2020. 31: p. 131.	Roxadustat Epoetin alfa
Chan 2020 [73]	Chan, T.M.D., et al., Efficacy and safety of roxadustat in patients with dialysis-dependent CKD, anemia, and diabetes mellitus. Journal of the American Society of Nephrology, 2020. 31: p. 352.	Roxadustat Epoetin alfa
Pooled data from trials in both non-dialysis dependent and dialysis dependent patients		
Coyne 2020 [74]	Coyne, D.W., et al., Roxadustat is not associated with an increased risk of neoplasm in patients with CKD and anemia. Journal of the American Society of Nephrology, 2020. 31: p. 1-2.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa
Provenzano 2020 [75]	Provenzano, R., et al., Pooled analyses of the phase 3 roxadustat studies: Congestive heart failure hospitalisation rates in dialysis and non-dialysis patients with anemia treated with roxadustat vs. comparators. Journal of the American Society of Nephrology, 2020. 31: p. 41-42.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa
Chan 2020 [76]	Chan, T.M.D., et al., Roxadustat vs. Placebo or epoetin alfa has no clinically meaningful effect on blood pressure in patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. 649.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa
Roger 2020 [77]	Roger, S.D., et al., Roxadustat lowers low-density lipoprotein cholesterol in patients with anemia of CKD. Journal of the American Society of Nephrology, 2020. 31: p. 648-649.	Roxadustat vs. Placebo Roxadustat vs. Epoetin alfa

Note: *Trial identifiers not reported in the publications

Abbreviations: ESRD, end-stage renal disease; CKD, chronic kidney disease; DD-CKD, dialysis-dependent chronic kidney disease; NDD, non-dialysis-dependent; NDD-CKD, non-dialysis-dependent chronic kidney disease; vs., versus

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Kidney Care UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Care UK is the UK's leading kidney patient support charity providing advice, support and financial assistance to thousands every year. It is not a membership organisation, but it is in touch with thousands of kidney patients through its direct patient services (eg advocacy, counselling, facebook support group, patient grants), social media channels, telephone helpline and website.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	£32,055 to fund Kidney Care UK's Kidney Kitchen project https://www.kidneycareuk.org/about-kidney-health/living-kidney-disease/kidney-kitchen/ This is web based support to enable people with kidney disease to enjoy eating and drinking while following the diet plans given to them by their renal dietician. The funds covered costs including, staff time, filming costs, web development costs (more details available if required). Kidney Care UK also receives a grant of £200 per meeting for consultancy to an international think tank hosted by AZ which meets quarterly.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	n/a
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information and views represented in this submission has been gathered through a range of sources: Kidney Care UK advocacy services and Facebook support group, the views of Kidney Care Staff who are kidney patients, our Patient Advisory Group. We have also run regular surveys to explore the current challenges kidney patients are facing as well as the annual Patient Reported Experience Measures survey which reports on how kidney patients feel about their experience of care.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Many cases of CKD are mild or moderate and risks can be managed by patients and their GPs without ever visiting a hospital. However, for people with CKD that progresses and requires specialist input from the renal team it can be extremely serious and require life changing treatment. A diagnosis of CKD has huge implications for a person's quality of life. Challenges include the stress of coming to terms with a diagnosis of an incurable, progressive condition, as well as difficult decisions about treatment options and the strain of adjusting to new treatments. Many patients must also adhere to strict medication regimes and dietary restrictions. Symptoms include debilitating fatigue, significant pain, itching, swelling, restless leg syndrome, muscle cramps and sleep problems. People's capacity to stay in work, maintain relationships and quality of life can be severely compromised. There are almost 30,000 people receiving dialysis in the UK,[i] many of whom spend five hours a day, three days a week, every week, at hospital. Fiona Loud, our policy director and a kidney patient, explains "dialysis meant drinking just 500 ml of fluid a day, an almost impossible diet where chocolate, coffee, bananas, cheese, and so many others things are banned or restricted. And you must spend 5 or 6 hours in a hospital 3 days a week, with 2 big needles plunged into your arm, connected to a machine. And all this gives you just 10% of your normal kidney function, and you probably feel even sicker after treatment

	than you did before, your blood pressure has dropped way down and you may be bleeding from where those great big needles were for a long time. You may be too weak to walk and you are likely to be depressed and out of work. You have a day off, and then it all starts again…and again….and again." Unsurprisingly, CKD can take a huge toll on the mental health and emotional wellbeing of patients. Nearly half of in-centre haemodialysis patients experience some form of distress[ii] and up to 1 in 3 kidney patients will experience depression at some point. This in turn exacerbates physical ill health and a person's ability to manage their condition. Symptoms of depression in people with early stage kidney disease increases their risk of progressing to end-stage renal disease (requiring dialysis or a transplant) and death.[iii,iv] In transplant patients, depressive symptoms have been shown to increase the risk of death by 65%.[v] A carer's role will depend partly on the individual's stage of kidney disease, their symptoms (eg fatigue), comorbidities and the treatment they receive. Roles can include helping with activities of daily living and mobility, transportation, personal care, and support with treatment, for example adhering to the medication regime and also with dialysis (for example if the person has dialysis at home). As well as the physical demands of caring, it can be emotionally challenging as the carer and the person with kidney disease come to terms with the change in role and the impact of a life changing diagnosis. Caregiving demands in managing dialysis has proved to be taxing on the physical, social and emotional health of informal caregivers.[vi,vii] Anaemia is a common side effect of CKD in patients before dialysis, on dialysis and with a transplant. It further impacts on the quality of life of people already living with the challenges of CKD, as well as putting additional strain on the heart. Patients have shared with us the challenge of anaemia in CKD and how extreme fatigue and lacking energy for even simple tasks affects mental as well as physical health: "Living with CKD for over a decade has been very challenging, but with the added burden of anaemia associated CKD, impacted severely on the quality of my life. I only realised the severity of this during dialysis when it was at its worse. 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 because I had somewhat become dependent on my husband."

	"As a carer 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. He remembers me spending my days sleeping and taking a rest on the stairs due to breathlessness."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Many patients find having to inject themselves with EPO unpleasant, onerous and sometimes difficult. Some have to rely on family members to inject the treatment if they cannot do it themselves. Side effects of current treatment can also be unpleasant and impact on quality of life, particularly gastrointestinal issues. Patients have also reported giving themselves a hernia from constantly injecting in the right place. The following quotes illustrate challenges of the current treatment and thoughts about care: "I have suffered for many years with anaemia due to CKD. Have had numerous oral iron which has always caused abdominal discomfort and constipation." "In 2014 I became very ill with CKD and again required oral iron and EPO which I had to inject myself when I got home from hospital. My teenage daughter was horrified one day when I was injecting myself. She seemed to understand taking oral medication but barbaric to have an injection and give it to myself." "I struggled to inject myself. The needle was quite long and I often missed doses which impacted my health." "Having to take blood to monitor anaemia it would be great to do a prick test like they do at blood transfusion when obtaining blood from donors. It could save hospital appointments and laboratories fees."

8. Is there an unmet need for patients with this condition?	A treatment that avoids the need for home injections, for those patient who prefer oral medication.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The chief advantage of this technology for many patients is that it is an oral treatment rather than an injection. Many kidney patients would find this more convenient and easier to self-manage. Oral medication may be less traumatic and onerous than home injections of ESA treatment for patients and caregivers. Some patients are unable to administer injections themselves and have to rely on others to assist them. The new treatment could reduce reliance on others, as more people would be able manage oral medications. Avoiding the requirement for training for injections, as well as managing storage and disposal of sharps would all be advantages. An oral form of treatment would be easier to travel with than an injectable treatment, particularly given the requirement for storage and disposal of sharps. Reducing the need for iron infusions would be an advantage. Firstly to avoid the need for this additional treatment, and secondly, to avoid the risk of producing antibodies that might limit the donors a person could receive a transplant from.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	People on dialysis may prefer to receive treatment for anaemia intravenously via their dialysis machine, so as to reduce the number of tablets they are required to take. Patients also had questions about how quickly this oral treatment would work compared to injected form.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It may be that people on dialysis would prefer to receive ESA treatment for anaemia intravenously via their dialysis machine, rather than in tablet form, so as to reduce the number of oral medications they are required to take. The advantages and disadvantages should be discussed and choice offered.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**n/a**

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Anaemia is a common side effect of CKD in patients before dialysis, on dialysis and with a transplant.
- Extreme fatigue and lacking energy for even simple tasks affects mental as well as physical health
- The chief advantage of this technology for many patients is that it is an oral treatment rather than an injection
- The new treatment could reduce reliance on others, as more people would be able manage oral medications
- Some people on dialysis may prefer to receive anaemia treatment via their dialysis machines and choice to do so is important
- A treatment that reduced the need for iron infusion, and the associated risk of producing antibodies that impact on pool of compatible organs for transplant, would be welcomed by patients

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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[i] UK Renal Registry, 2020, UK Renal Registry 22nd Annual Report – data to 31/12/2018, Bristol, UK. Available from: renal.org/audit-research/annual-report

[ii] Seekles, M., Ormandy, P., & Kamerāde, D. (2020). Examining patient distress and unmet need for support across UK renal units with varying models of psychosocial care delivery: a cross-sectional survey study. BMJ open, 10(9), e036931. Available at: https://doi.org/10.1136/bmjopen-2020-036931

[iii] Tsai YC, Chiu YW, Hung CC, Hwang SJ, Tsai JC, Wang SL, et al. Association of symptoms of depression with progression of CKD. Am J Kidney Dis. 2012;60(1):54–61. Available at: https://www.ajkd.org/article/S0272-6386(12)00533-1/fulltext

[iv] Palmer SC, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Association between depression and death in people with CKD: a meta-analysis of cohort studies. Am J Kidney Dis. 2013;62(3):493–505. Available at: https://www.ajkd.org/article/S0272-6386(13)00589-1/fulltext

[v] Dew, M. A., Rosenberger, E. M., Myaskovsky, L., DiMartini, A. F., DeVito Dabbs, A. J., Posluszny, D. M., … Greenhouse, J. B. (2015). Depression and Anxiety as Risk Factors for Morbidity and Mortality after Organ Transplantation: A Systematic Review and Meta-Analysis. Transplantation, 100(5), 988– 1003. Available at: http://doi.org/10.1097/TP.0000000000000901

[vi] Belasco AG, Sesso R. Burden and quality of life of caregivers for hemodialysis patients. Am J Kidney Dis. 2002;39(4):805–12.

[vii] Tong A, Sainsbury P, Craig JC. Support interventions for caregivers of people with chronic kidney disease: a systematic review. Nephrol Dial Transplant. 2008;23(12):3960–5

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Renal Pharmacy Group**

3. Job title or position	**Renal Pharmacist**
4. Are you (please tick all that apply):	✓ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK Renal Pharmacy Group is a Forum to promote renal pharmacy, working in partnership with colleagues, including those from other specialties, both within the UK and internationally. The UK RPG also actively contributes to, and promotes, national guidance, pharmaceutical research, audit and innovation in renal medicine and pharmacy practice. **We are a non-profit organisation**.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat anaemia of CKD and maintain haemoglobin within the desired range of 100-120g/L without any adverse effects.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	To correct and maintain the haemoglobin within the desired target range of 100-120g/L and avoid the need for blood transfusions.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The current treatment for anaemia of chronic kidney disease is either oral or intravenous iron and / or subcutaneous (intravenous in haemodialysis patients) erythropoietin stimulating agents (ESAs). Oral iron is only effective if the patient is iron deficient and is often poorly tolerated or insufficient to meet the demands of erythropoiesis created by ESAs. The majority of non-haemodialysis patients require sub-cutaneous injection of ESAs at frequencies which vary from thrice weekly to monthly depending on the ESA preparation used. This is labour intensive for the healthcare professionals who need to train the patients / family members how to administer the ESA, patients and their families who administer the drug, and, if patients / families are unable to administer the ESA then the District Nurses and GP practice nurses become involved. This will then involve provision of an administration chart for the primary care team to administer the drugs. An oral preparation that addresses the lack of endogenous erythropoietin (EPO) in this patient group would be of considerable value. It would hopefully encourage patient compliance, decrease work load for both secondary care and primary healthcare professionals and primary care (District Nurses and GP practice nurses). It would not require cold chain storage which ESAs do. This would help with secondary care storage, patient's storage and decrease homecare delivery costs. It would also avoid unavoidable wasting secondary to power cuts. It would potentially decrease the requirements for intravenous iron which would decrease the use of healthcare resources – nursing staff to administer the iron, clerical staff to co-ordinate the appointments, hospital transport for those patients who need it, clinic space and time. It would also decrease time patients would spend having hospital appointments.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	By erythropoietin stimulating agents (ESAs) either sub-cutaneous or intravenous (in haemodialysis patients) injection together with oral or intravenous iron.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Chronic kidney disease: managing anaemia. NICE guideline [NG8] Published: 03 June 2015 Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease 2017
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway clearly defined in the above guidelines
• What impact would the technology have on the current pathway of care?	Dependant on cost but if cost neutral it could have considerable impact. It would potentially replace ESAs as first line treatment in the CKD non-haemodialysis population and certainly have a place in the treatment pathway for CKD non haemodialysis patients who are unable to self-inject ESAs
10. Will the technology be used (or is it already used) in	It would be initiated, monitored and dose titrated in secondary care by specialist anaemia services. Continued supply would depend on funding for anaemia services.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Current care involves a high use of healthcare resource in initiation of ESAs and provision of intravenous iron clinics. It also involves cold chain storage and disposal of the sharps following use. Initiation of ESAs – involves specialist renal healthcare professionals teaching patients and relatives to inject the ESA. Maintenance therapy– in those patients that cannot self-administer and do not have family members who can support them, other primary care healthcare professionals become involved such as Practice Nurses and District Nurses ESAs require cold chain storage and are bulky so require large fridge space in tertiary care settings where use is high. They require safe disposal both from hospital settings and patient settings. Patients using an ESA generally need regular administration of iv iron to support erythropoiesis. This requires a clinic space, clerical staff to appoint and arrange transport, ambulance transport, Pharmacy input in procurement and supply of iron product. In contrast roxadustat is an oral tablet administered three times a week. There would be no requirements to see patients and teach them how to use it. The use of intravenous iron with roxadustat appears to be lower that with ESAs so iron clinics would be reduced freeing up clinic time, healthcare staff and transport. It does not require cold chain storage or safe disposal as it doesn't involve sharps.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be initiated and monitored by Renal Services then depending on current practice either managed by the renal services or via shared care agreements involving joint renal services and primary care.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The only investment required would be in depth information about the product for healthcare professionals to read and information for patients. It should not require any specialist equipment or training of staff.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Not at this time. So far studies have showed non-inferiority compared with ESAs.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially. Patients will not have to inject themselves. They will not have to rely on family / healthcare professionals to administer the injections. Iron requirements potentially reduced necessitating less frequent clinic visits. One of the adverse effects of roxadustat is nausea which may have a negative effect on health-quality of life if experienced.
12. Are there any groups of people for whom the technology would be more or	More appropriate / effective for: Non haemodialysis patients. Especially those who are unable to self-inject. Potentially patients who are inflamed and exhibit ESA hypo-responsiveness. Patients that do not have fridges or have unreliable power sources and have frequent electricity power cuts in the winter storms Less appropriate for:

less effective (or appropriate) than the general population?	Unit haemodialysis patients. Seen to be a slightly higher event of clotting AVF dialysis access with roxadustat. Patient on haemodialysis have ESA administered by nursing staff often intravenously via the dialysis machine, compliance thereby assured.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology should be easier to use for both patients and health care professionals as it is an oral preparation as opposed to a sub-cutaneous injection: Patients and / or family members will not require training on sub-cutaneous administration as they do with current treatment. District nurses / Practice nurses will not be required to administer in the event the patients / family are unable to administer a sub-cutaneous injection. No special disposal requirements with roxadustat as opposed to sharps disposal with ESAs. No cold chain requirements for roxadustat as opposed to ESAs Monitoring requirements will be the same as current treatment Intravenous iron requirements should be lower (see above Q10 -less clinic space / time required, lower staffing resource, less demand on hospital transport)

	Patient acceptability would be predicted as being greater with roxadustat compared with current therapy. Prior to using roxadustat as with all new medications, information would be required for both health-care provider and patients
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with current treatment of anaemia of CKD the technology will be prescribed and monitored in accordance to guidelines.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unknown
16. Do you consider the technology to be innovative in its potential to make a	Yes. It is the first oral preparation to treat anaemia of CKD. It has been seen to be non-inferior to current treatment ESAs in the attainment of target haemoglobin and maintenance within the desired target range. Health related benefits would be due to a potential increase in patient compliance both due to intentional

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	non-compliance by the patient and inadvertent non-compliance due to having to reply on family members / healthcare professionals. There would also be a potential for a lower requirement of intravenous iron. Iron is an inflammatory substance with a potential association between labile iron and oxidative stress and has potential to cause well recognised hyper-sensitivity reactions necessitating it having to be administered in a hospital setting. An oral preparation would allow an increased number of patients to have treatment initiated sooner as there would be no need to book them into actual clinic to be taught how to use it. Patients could be counselled on the medication virtually or via the telephone. Due to not requiring cold-chain storage the tablets could be posted.
• Is the technology a 'step-change' in the management of the condition?	Potentially an additional step in the current treatment pathway. Prior to ESAs in appropriate population.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. There is currently no oral preparation to address a lack of endogenous EPO.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Nausea has been a side effect of this class of drugs, it's less with roxadustat but still occurs. This may affect tolerability and quality of life if experienced. A higher incidence of AVF dialysis access thrombosis has been seen with roxadustat than with ESA which may be a problem with use in haemodialysis patients.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Some of the trials had UK centres and therefore reflected UK practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Non-inferiority compared with standard treatment as seen in trials. A low incidence of adverse effects and zero serious adverse events. These were measured in trials but the real tolerability will become apparent most marketing.
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Unknown
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No
21. How do data on real-world experience compare with the trial data?	Unknown at this time

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Unknown
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • Only oral treatment to address endogenous EPO deficiency • Current treatment of subcutaneous ESAs for non-haemodialysis CKD patients is very labour intensive for both patients and healthcare professionals • Appears to decrease intravenous iron requirements and be less affected by inflammation than ESAs • Trial data suggests it is well tolerated • Could cause an increase in thrombosis in AVF dialysis access	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**UK Kidney Association**

3. Job title or position	**CONSULTANT NEPHROLOGIST**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	We are the leading professional body for the UK renal community, dedicated to improving lives by supporting professionals in the delivery of kidney care and research. We have over 1,200 doctors, scientists and multi-professional team members. Funded by membership fees and corporate sponsorship
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of	**NONE**

manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NONE**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	THE MAIN AIM OF ROXADUSTAT IS TO IMPROVE HAEMOGLOBIN CONCENTRATIONS IN PATIENTS WITH CHRONIC KDINEY DISEASE OR END STAGE KIDNEY DISEASE ON DIALYSIS WHILE MAINTAINING SAFETY. IT IS AN ORAL MEDICATION FOR USE IN PLACE ERYTROPOIETIN STIMULATING AGENTS.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. AS GOOD AS ERYHROPOITEN STIMULATING AGENTS (ESA) AT IMPROVING HAEMOGLOBIN TO THE TARGET RANGE 2. EFFECTIVE AT MAINTAINNG PATIENTS IN THE TARGET RANGE 3. SAFE WITH NO ADVERSE CARDIOVASCULAR DETRIMENT IN COMPARISON TO ESA. 4. REDUCTION IN THE NEED FOR INTRAVENOUS IRON

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	1. EFFECTIVE IN PATIENTS WITH CHRONIC INFLAMMATION AND ESA HYPORESPONSIVENESS – AREAS OF CLINICAL NEED FOR AN ALTERNATIVE AGENT. 2. USE IN PATIENTS WHO ARE NOT KEEN IN INJECTIONS.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	CURRENTLY GUIDELINES RECOMMEND IRON REPLETION FIRST WITH ORAL AND MORE LIKELY IV IRON THERAPY IN THOSE WHO HAVE NO CONTRAINDICATIONS. ONCE IRON REPLETE THE NEXT STEP TO ACHIEVE THE HAEMOGLOBIN IN THE TARGET RANGE (100-120G/L), IS USE OF SUBCUTANEOUS OR INTRAVENOUS ERYTHRPOIETIN STIMULATINE AGENTS. THESE CAN BE SHORT ACTING AGENTS GIVEN UP TO THREE TIMES A WEEK OR LONG ACTING AGENTS GIVEN WEEKLY OR EVEN LESS FREQUENTLY (MONTHLY).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	THIS IS WELL DOCUEMENTED IN THE CURRENT NICE AND KDIGO GUIDELINES (KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES) AND THE UKKA ANAEMIA GUIDELINES. THESE ARE ALL BROADLY SIMILAR WITH SLIGHT DIFFERENCE TO TARGET RANGES.
• Is the pathway of care well defined? Does it vary or are there differences of opinion	WELL DEFINED SOME DIFERECNES IN OPTIMISATION – FOR EXAMPLE THE RECENT PIVOTAL TRIAL HAS LED TO AN UPDATE ON OPTIMISATION OF IV IRON IN DIALYSIS PATIENTS – AS YET IT IS NOT CLEAR IF THIS

between professionals across the NHS? (Please state if your experience is from outside England.)	HAVE BEEN UNIVERSALLY ADOPTED BUT I AM CURRENTLY LOOKING INTO THIS VIA A UK WIDE SURVEY TO SEE HOW WELL IMPLEMENTED THESE NEW RECOMMENDATIONS ARE.
• What impact would the technology have on the current pathway of care?	THIS TECHNOLOGY WOULD ADD AN ADDITIONAL CHOICE TO CLINICIANS AND PATIENTS IN OPTIMISATION OF THEIR ANAEMIA. CHOICE IS CRITICAL. IT MAY SERVE TO MANAGE PARTICULAR GROUPS WHO DO NOT RESPOND TO ESA THERAPY OR WHERE IV IRON IS A CHALLENGE.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	YES IT WILL BE USED IN A SIMILAR FASHION TO ESA THERAPIES.
• How does healthcare resource use differ between the technology and current care?	NONE
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	SECONDARY CARE UNDER SPECIALIST NEPHROLOGY SERVICES, SIMILAR TO ESA USE

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	NO ADDITIONAL INVESTMENT APART FROM ONGOING EDUCATION IN THE FIELD OF ANEAMIA
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	THE TECHNOLOGY WITH BE AS EFFECTIVE IN PATIENTS WHO REQUIRE ESA THERAPY BOTH CHRONIC KIDENY DISEASE AND DIALYSIS PATIENTS. IT WOULD SEEM MORE ATTRACTIVE IN THOSE CHRONIC KIDNEY DISEASE PATIENTS, AS AN ORAL TABLET MAY BE PREFERRED TO AN INJECTION. IN DIALYSIS PATIENTS THIS IS LESS ATTRACTIVE AS CURRENTLY ESA THERAPY IS GIVNE IN THE DIALYIS MACHINE SO THERE IS NO INJECTION, AND THE ADDITIONAL TABLET MAY NOT BE ASS ATTRACTIVE. MEANINGFUL BENEFIT WILL BE RELATED TO PATIENT CHOICE AND OPTIONS AND IN THE GROUP OF 10-15% OF PATIENTS WHO DO NOT RESPOND TO ESA THERAPY.
• Do you expect the technology to increase length of life more than current care?	NO – COMPARABLE – THERE ARE NO LONG TERM DATA GREATER THAN 2 YEARS AND LIMITED HARD END POINT DATA. CURRENTLY MOST OF THIS DATA IS BASED ON EXPLORATIVE ANALYSIS OF THE CURRENTLY TRIALS WITH ROXADUXTAT.
• Do you expect the technology to increase health-related quality of life more than current care?	UNKNOWN AS DATA IS NOT AVAILABLE AND THE OFF TARGET EFFECTS REQUIRE MORE STUDY -FOR EXAMPLE THE REDUCTION IN LIPIDS AND POSSILE DELAY IN RENAL PROGRESSION BUT AGAIN THESE ARE POST HOC ANALYSIS AND NOT PRIMARY OUTCOMES

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	1. PATIENTS WITH CHRONIC INFLAMMATIOJN 2. PATIENTS HYPORESONSIVE TO ESA THERAPY 3. THESE WITH ESA ANTIBODIES AND ESA RESISTANCE
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	IT WILL POTENTIALLY BE EASIER TO USE AS IT IS A TABLET GIVEN 3 TIMES A WEEK. – THIS MIGHT PRESENT ISSUES WITH COMPLAINCE. THE THERAPY MAY LEAD TO A REDUCTION IN THE NEED FOR IV IRON THERAPY. MONITORING WILL BE SIMILAR TO CURRENT MONITORING FOR ANAEMIA MANAGEMENT

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	THERE ARE CERTAIN GROUPS WHICH MIGHT NEED TO BE EXCLUDED BASED ON THE TRIALS. FOR EXAMPLE CANCER PATIENTS – THIS IS SIMILAR TO ESA THERAPY MONITORING WILL BE NO DIFFERENT TO CURRENT PATHWAYS OF CARE.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	THERE IS LIMITED CLINICAL DATA AVAILABLE EXAMINING THIS BUT IT IS UNLIKELY TO DEMONSTRATE ANY substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current	THIS IS AN INNOVATE TECHNOLOGY WHICH HAS DEVELOPED FROM THE NOBEL PRIZE WINNING WORK Of THE OXFORD GROUP UNDER THE AUSPICES OF SIR PETER RADCLIFFE. THIS TECHNOLOGY WILL ADD TO ARMOURY IN THE EFFECTIVE MANAGEMENT OF CKD PATIENTS AND IN PARTICULAR THOSE WHO DO NOT RESPONDE TO ESA THERAPY. HEALTH RELATED BENEFITS DATA IS LIMITED AT PRESENT AND IT IS DIFFICULT TO COMMENT ON THIS

need is met?	AND IF THIS THERAPY WILL BE EBTTER THAN CURRENT THERAPIES.
• Is the technology a 'step-change' in the management of the condition?	YES – NOVEL AND THE MORE PHYSIOLOGICAL APPROACH MAY HAVE LONGER TERM BENEFITS. THE COMBINATION OF INCREASING HAEMOGLOBIN WITH ENDOGENOUS ERYTHROPOIETIN PRODUCTION AND IMPROVED IRON METABOLISM IS VERY ATTRACTIVE.
• Does the use of the technology address any particular unmet need of the patient population?	SEE ABOVE – CERTAIN GROUPS MAY PARTICULARILY BENEFIT FROM THIS THERAPY.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	SIDE AFFECTS ARE IMPORTANT AND NEED TO BE CONSIDERED WHEN PRESCRIBING. 1. INCREASED RISK OF HYPERTENSION – THIS MAY REQUIRE ADDITIONAL THERAPY 2. POTENTIAL INCREASED RISK OF VASCULAR ACCESS THROMBOSIS – MORE GRADUALLY INCREASE IN HAEMOGLOBIN MAY BE IMPORTANT TO OFFSET THIS 3. GASTRO-INTESTINAL SIDE AFFECTS 4. HEADACHE 5. OTHER THROMBOTIC EVENTS THIS MAY REQUIRE CARE IN THOSE "HIGH RISK GROUPS"

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	YES IN PART – HAEMOGLOBIN TARGET RANGES VARY.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. EFFICACY – MEASURED AGAINST COMPARATOR ESA 2. EFFICACY – MEASURED AGAINST PLACEBO – THIS MIGHT BE THE GROUP TO INITIALLY CONSIDER THERAPY AS THE GROUP IS NIAVE OF TEHRAPY 3. SAFETY OF DRUG AGAINST AN ACTIVE COMPARATOR – DATA DOES SHOW THIS AND THE POOLED ANALAYSIS DOES CONFRIM TO ADVERSE CARDIOVASCULAR RISK BUT ALSO NO ADDITIONAL BENEFIT.
• If surrogate outcome measures were used, do they adequately predict	NOT AT PRESENT

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	NONE THAT I AM AWARE OF THIS BUT AM AWARE THAT THE FDA DID NOT APPROVE THE DRUG WHILE THE EMA HAVE APPROVED.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO – THERE ARE STUDIES NOW ON 3 OTHER MOLECULES IN THE SAME FAMILY BUT THE QUESTION REMAINS CAN IT IS ASSUMMED THIS IS A CLASS AFFECT OR ARE THERE DIFFERENCES – I SUSPECT THERE MAYBE DIFFERENCES.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	NONE

21. How do data on real-world experience compare with the trial data?	REAL WORLD DATA IS SIMILAR BUT IS BASED ON NON UK DATA.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	NONE
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains	

uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- ROXADUSTAT REPRESENTS A NEW CLASS OF DRUG TO IMPORVE HAEMOGLOBIN LEVES SIMILAR TO ESA THERAPY
- ROADUSTAT REDUCE IRON REQUIREMENTS
- AN ORAL PREPARATION WHICH MIGHT HAVE ADDED BENEFITS
- SAFE WITH NO ADVERSE CARDIOVASCULAR RISK
- NEEDS TO BE USED IN CAUTION DUE TO VASCULAR ACCESS THROBOSIS, HYPERTENSION.

Thank you for your time.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Roxadustat for anaemia in chronic kidney disease [ID1483]

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Jeremy Howick and Robert Wolff acted as joint project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Thomas Otten and Charlotte Ahmadu acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Edyta Ryczek and Debra Fayter acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Sean Harrison acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ACM	All-cause mortality
AE	Adverse event
AiC	Academic in confidence
AIC	Akaike Information Criteria
ASN	American Society of Nephrology
BIC	Bayesian Information Criterion
BIW	Twice weekly
BL	Baseline
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CEM	Cost effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CFB	Change from baseline
CI	Confidence intervals
CiC	Commercial in confidence
CKD	Chronic kidney disease
CRP	C-reactive protein
CS	Company submission
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
DARE	Database of Abstracts of Reviews of Effects
DBP	Diastolic blood pressure
DD	Dialysis dependent
DRA	European Renal Association
DSA	Deterministic sensitivity analysis
EDTA	European Dialysis and Transplant Association Congress
EED	Economic Evaluation Database
eGFR	Estimated glomerular filtration rate
EOS	End of study visit
EOT	End of treatment
EQ-5D-3L	EuroQol five-dimension three level
EQ-5D-5L	EuroQol five-dimension five level
ERA EDTA	European Renal Association - European Dialysis and Transplant Association
ERG	Evidence Review Group
ESA	Erythropoiesis stimulating agent
EU	European Union
EUR	Erasmus University Rotterdam
FACT	Functional Assessment of Cancer Therapy
FAS	Full analysis set
GFR	Glomerular filtration rate
GLMM	Generalised linear mixed model
Hb	Haemoglobin

HbA1c	Glycated haemoglobin
HIF	Hypoxia-inducible factor
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ID	Identification
IPD	Individual participant data
IRT	Interactive response technology
ISN	International Clinical Trials Registry Platform
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney disease outcomes quality initiative
Kg	Kilogram
KSR	Kleijnen Systematic Reviews
LDL	Low density lipoprotein
LSM	Least squares mean
LY	Life year
MACE	Major adverse cardiovascular events
MACE+	A composite of all-cause mortality, myocardial infarction, stroke and hospitalisation for either unstable angina or congestive heart failure
MAP	Mean arterial pressure
MDRD	Modification of diet in renal disease
mg	Milligram
MI	Myocardial infarction
mL	Millilitre
mmol/l	Milli-moles per litre
MMRM	Mixed Model of Repeated Measures
MN	Miettinen & Nurminen
N/A	Not applicable
NCI CTCAE	National Cancer Institute- Common terminology criteria for adverse events
NDD	Non dialysis dependent
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NIHR	National Institute for Health Research
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
ONS	Office for National Statistics
PF	Physical function
PHI	Prolyl hydroxylases inhibitor
PPS	Per protocol set
PRESS	Peer Review of Electronic Search Strategies

PSS	Personal Social Services
QALY	Quality-adjusted life year
QW	Once weekly
RBC	Red blood cells
RCT	Randomised controlled trial
SAE	Serious adverse event
SAF	Safety analysis set
SBP	Systolic blood pressure
SC	Subcutaneous
SF-36	36-Item short form survey
SG	Standard gamble
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TIW	Thrice weekly
TRAE	Treatment related adverse events
TSAT	Transferrin saturation
Tx	Treatment
UK	United Kingdom
ULN	Upper limit of normal
UMC+	University Medical Center+
US	United States
USA	United States of America
VAS	Visual analogue scale
VAT	Vascular access thrombosis
VT	Vitality
WTP	Willingness to pay

Table of Contents

Abbreviations **3**

Table of Tables **8**

Table of Figures **10**

1. EXECUTIVE SUMMARY **11**

1.1 Overview of the ERG's key issues 11
1.2 Overview of key model outcomes 12
1.3 The decision problem: summary of the ERG's key issues 12
1.4 The clinical effectiveness evidence: summary of the ERG's key issues 13
1.5 The cost effectiveness evidence: summary of the ERG's key issues 15
1.6 Other key issues: summary of the ERG's view 17
1.7 Summary of the ERG's view 17

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM **19**

2.1 Population 24
2.2 Intervention 24
2.3 Comparators 24
2.4 Outcomes 25
2.5 Other relevant factors 25

3. CLINICAL EFFECTIVENESS **27**

3.1 Critique of the methods of review(s) 27
3.1.1 Searches 27
3.1.2 Inclusion criteria 28
3.1.3 Critique of data extraction 30
3.1.4 Quality assessment 30
3.1.5 Evidence synthesis 31
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these) 31
3.2.1 Details of included NDD-CKD RCTs 32
3.2.2 Statistical analysis of the included RCTs 38
3.2.3 Trial participant characteristics 42
3.2.4 Quality assessment of included RCTs 43
3.2.5 Efficacy results 44
3.2.6 Safety results 46
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 49
3.3.1 Details of included placebo-controlled trials 49
3.2.2 Placebo-controlled trial participant characteristics 50
3.4 Critique of the indirect comparison and/or multiple treatment comparison 52
3.5 Additional work on clinical effectiveness undertaken by the ERG 52
3.6 Conclusions of the clinical effectiveness section 52

4. COST EFFECTIVENESS **54**

4.1 ERG comment on company's review of cost effectiveness evidence 54
4.1.1 Searches performed for cost effectiveness section 54

4.1.2 Inclusion/exclusion criteria 56
4.1.3 Conclusions of the cost effectiveness review 58
4.2 Summary and critique of company's submitted economic evaluation by the ERG 58
4.2.1 NICE reference case checklist 58
4.2.2 Model structure 59
4.2.3 Population 61
4.2.4 Interventions and comparators 62
4.2.5 Perspective, time horizon and discounting 62
4.2.6 Treatment effectiveness and extrapolation 63
4.2.7 Adverse events 66
4.2.8 Health-related quality of life 67
4.2.9 Resources and costs 69

5. COST EFFECTIVENESS RESULTS 72

5.1 Company's cost effectiveness results 72
5.2 Company's sensitivity analyses 73
5.3 Model validation and face validity check 73
5.3.1 Face validity assessment 73
5.3.2 Technical verification 74
5.3.3 Comparisons with other technology appraisals 74
5.3.4 Comparison with external data used to develop the economic model 74
5.3.5 Comparison with external data not used to develop the economic model 74

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES 76

6.1 Exploratory and sensitivity analyses undertaken by the ERG 76
6.1.1 ERG base-case 76
6.1.2 ERG exploratory scenario analyses 77
6.1.3 ERG subgroup analyses 77
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG 80
6.3 ERG's preferred assumptions 81
6.4 Conclusions of the cost effectiveness section 81

7. END OF LIFE 84

8. REFERENCES 85

Table of Tables

Table 1.1: Summary of key issues 11

Table 1.2: Key issue 1: Population not in line with NICE scope (population restricted to NDD population, patients with CKD stages 1-2 excluded). 13

Table 1.3: Key issue 2. The outcomes are not in line with NICE scope 13

Table 1.4: Key issue 3: The cost effectiveness analysis in the CS relies upon pooled data across roxadustat arms of NDD ALPINE trials 14

Table 1.5: Key issue 4: Trial populations do not include UK patients 15

Table 1.6: Key issue 5: Model structure - justification for the Hb ranges and cut-off values used to define health states 15

Table 1.7: Key issue 6: Treatment effectiveness and extrapolation - time dependency and extrapolation of the multinomial logistic regression model 15

Table 1.8: Key issue 7: Adverse events 16

Table 1.9: Key issue 8: Model validation 16

Table 1.10: ERG base-case 17

Table 1.11: Deterministic scenario analyses (conditional on ERG base-case) 18

Table 2.1: Statement of the decision problem (as presented by the company) 19

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS) 27

Table 3.2: Eligibility criteria used in the systematic review of clinical effectiveness evidence 28

Table 3.3: Summary of the studies included in the CS 31

Table 3.4: Summary of trials included in clinical effectiveness evidence 34

Table 3.5: Sequential testing of primary and key secondary efficacy endpoints in the DOLOMITES trial 39

Table 3.6: Key inclusion and exclusion criteria for DOLOMITES 42

Table 3.7: Participant flow in DOLOMITES trial 43

Table 3.8: Risk of bias assessment 44

Table 3.9: Hb response during first 24 weeks without use of rescue therapy in DOLOMITES trial (PPS population) 45

Table 3.10: Summary of secondary outcomes in DOLOMITES trial 45

Table 3.11: Summary of early treatment discontinuation results for the DOLOMITES trial 47

Table 3.12: Summary of safety results for the DOLOMITES trial 47

Table 3.13: Key adverse events in the DOLOMITES trial (SAF population) 48

Table 3.14: Key inclusion and exclusion criteria for included trials 50

Table 4.1: Data sources for the health-related quality of life systematic review (as reported in CS) ... 54

Table 4.2: Data sources for the cost and healthcare resource identification, measurement and valuation systematic review (as reported in CS) 55

Table 4.3: Eligibility criteria for the systematic literature reviews 56

Table 4.4: NICE reference case checklist 58

Table 4.5: Key baseline patient characteristics used in the economic model 61

Table 4.6: Adverse events (probability per cycle) 66

Table 4.7: Utility decrements applied to age and gender adjusted general population utility values 67

Table 4.8: Hb level coefficients EQ-5D-3L 67

Table 4.9: Health state utility decrements 68

Table 4.10: ESA dose conversion rates 70

Table 4.11: Treatment cost per health state 70

Table 5.1: incremental results of roxadustat versus ESA for different time horizons 72

Table 5.2: Incremental results of roxadustat versus ESA using DOLOMITES data only versus base-case 73

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1) 78

Table 6.2: ERG base-case 80

Table of Figures

Figure 4.1: Model structure..... 60

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. Where possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report sections
1	The patient population in the company analysis differs somewhat from the final NICE scope. The company analysed data for a subgroup of the scope population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation, and those with CKD levels 3-5.	Section 2.1, 3.1.2
2	One of the outcomes (hospitalisation rates) is not in line with the NICE scope.	Section 2.4
3	The cost effectiveness analysis in the company submission relies upon pooled data across roxadustat arms of non dialysis dependent (NDD) ALPINE trials Some of these trials did not use comparators specified in the final NICE scope, and the resulting analysis is unanchored and indirect.	Sections 2.3, 3.2
4	The trials include very few participants from the United Kingdom (UK).	Section 2.1, 3.2.3
5	Model structure: justification for the Hb ranges and cut-off values to define health states is lacking.	Section 4.2.2
6	Treatment effectiveness and extrapolation: appropriateness of time dependency and extrapolation of the multinomial logistic regression model unclear.	Section 4.2.6
7	Potentially relevant adverse events were excluded.	Section 4.2.7
8	Model validation: lack of detail about face validity assessment, limited technical validation, limited cross- and external validation, and inconsistencies between the submission report and the model.	Section 5.3
CKD = chronic kidney disease; DD = dialysis dependent; Hb = haemoglobin; NDD = non dialysis dependent; NICE = National Institute for Health and Care Excellence; UK = United Kingdom		

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are 1) the inclusion of placebo comparators, 2) the exclusion of patients with chronic kidney disease (CKD) stages 1 and 2, the exclusion of dialysis dependent (DD) patients, and failure to measure hospitalisations directly.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

The company submission (CS) base-case cost effectiveness results (probabilistic) indicated that roxadustat is both [redacted] (incremental QALYs of [redacted]) and [redacted] ([redacted]) and thus [redacted] current care.

However, the 95% percentiles for the probabilistic incremental costs and QALYs were [redacted] and [redacted], respectively. The probability of roxadustat being cost effective, at a threshold of £20,000 per QALY gained, compared to erythropoiesis stimulating agents (ESAs) is 69%.

Overall, the technology is modelled to affect QALYs by:

- Increasing quality of life through favourable transitions between the haemoglobin (Hb) level health states.

Overall, the technology is modelled to affect costs by:

- Higher treatment costs than current care.
- Proportion of patients receiving the different ESA types.

The company performed and presented the results of deterministic sensitivity analyses (DSAs) as well as scenario analyses. The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) are:

- The proportion of patients with diabetes. This parameter ranged from 42% to 69% in the company's sensitivity analysis and resulted in the ICER changing from [redacted] to [redacted]. The weighted cost of the adverse events myocardial infarction (MI) and vascular access thrombosis (VAT) results in potentially large differences in costs. A change in the weighted cost of VAT could result in ICER ranges between [redacted] and [redacted]. A change in the weighted cost of MI could result in ICER ranges between [redacted] and [redacted].

The scenario analyses which had the greatest upward effect on the ICER were those relating to:

- The implementation of single ESA formulations for all patients. The largest cost increase was achieved by implementing 100% methoxy polyethylene glycol-epoetin beta use resulting in an ICER of [redacted]. The largest cost decrease was achieved by implementing 100% darbepoetin alfa use, resulting in roxadustat [redacted].

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the CS[1] is broadly in line with the final scope issued by NICE.[2] However, the evidence presented in the CS includes data from trials that have placebo comparators (see section 1.4) and patients from different populations from the one specified in the NICE scope, i.e., it excludes adult patients that are dialysis dependent, and those with CKD stages 1-2 (Table 1.2). In

addition, the evidence presented by the company does not include hospitalisations as a directly measured outcome (Table 1.3).

Table 1.2: Key issue 1: Population not in line with NICE scope (population restricted to NDD population, patients with CKD stages 1-2 excluded).

Report section	2.1
Description of issue and why the ERG has identified it as important	The NICE scope states that the population of interest is adults with anaemia associated with chronic kidney disease (CKD). The company analysed data for a subgroup of this population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation. In addition, the NICE scope states that the population of interest is adults with anaemia associated with chronic kidney disease (CKD).[2] The company analysed data for a subgroup of this population, namely those who have CKD stages 3-5.
What alternative approach has the ERG suggested?	In response to clarification, the company amended Table 1 of the CS to explicitly state that a narrower population was included in the CS.
What is the expected effect on the cost effectiveness estimates?	The cost effectiveness analyses apply to the population specified in the updated scope.
What additional evidence or analyses might help to resolve this key issue?	Current evidence restricted to narrower population. Further research should include patients with lower CKD stages.

Table 1.3: Key issue 2. The outcomes are not in line with NICE scope

Report section	2.3, 3.3 and 3.4
Description of issue and why the ERG has identified it as important	The NICE scope states that hospitalisation is a required outcome; hospitalisation rates were not measured directly.[2]
What alternative approach has the ERG suggested?	The ERG recommends including hospitalisation rates as outcomes.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	Directly measured hospitalisations should be reported and included in analyses.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified one major concern with the evidence presented on the clinical effectiveness, namely the inclusion of non-randomised comparisons between roxadustat and ESAs (Table 1.4). The ERG also noted that the evidence presented by the company includes very few UK patients (Table 1.5).

Table 1.4: Key issue 3: The cost effectiveness analysis in the CS relies upon pooled data across roxadustat arms of NDD ALPINE trials

Report section	**3.4**
Description of issue and why the ERG has identified it as important	The company submission states that there was no indirect treatment comparison. However, data from the roxadustat arms of four trials (3 placebo controlled and 1 with ESA as the comparator arm) were pooled to estimate clinical parameters, e.g. Hb level, with roxadustat and data from the only ESA arm was used to estimate the same clinical parameters with ESA. This therefore effectively constitutes an unanchored indirect treatment comparison. Any difference in effectiveness of roxadustat vs. ESA from such data is likely to be biased. This is because pooling the single roxadustat arms removes the effect of randomisation: patients from three trials in the pooled roxadustat dataset were not drawn randomly from the same population as those from the ESA arm. Therefore, effect modifiers and prognostic factors are no longer likely to be balanced across the two populations (the roxadustat arms of all ALPINE NDD trials and the ESA arm of the DOLOMITES trial). The company has not stated in either the CS or the clarification response that they made any attempt to make the pooled APLINE NDD roxadustat patients comparable to the ESA arm of the DOLOMITES trial. Therefore, any differences in the observed variables that are not balanced between these two populations (e.g. ethnicity, age, weight, sex, CVD history, diabetes, estimated glomerular filtration rate (eGFR)) could bias the cost effectiveness analysis. However, it is notable that even with matching or adjustment, unmeasured effect modifiers and prognostic factors would still bias the cost effectiveness analysis.
What alternative approach has the ERG suggested?	Using the DOLOMITES trial alone to inform the cost effectiveness analyses, as this trial provides direct evidence for the effectiveness of roxadustat and ESA in patients drawn randomly from the same population. Cost effectiveness analyses using only DOLOMITES trial data are presented in the clarification response (see section 4).
What is the expected effect on the cost effectiveness estimates?	An increase from an ICER of [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	An additional potential analysis that utilised data from all ALPINE NDD trials would be a network meta-analysis (NMA), if at least one RCT comparing ESA to placebo could be found. In this analysis, the direct evidence for roxadustat-ESA from the DOLOMITES trial would be supplemented by indirect evidence for roxadustat-placebo (from the three other ALPINE NDD trials) and ESA-placebo (from any additional trials). In addition to providing additional evidence, the NMA could also be used to assess heterogeneity and inconsistency, exploring whether the DOLOMITES trial is consistent with the other ALPINE NDD trials.

Table 1.5: Key issue 4: Trial populations do not include UK patients

Report section	2.1, 3.2.3, 3.6, 4.2.6
Description of issue and why the ERG has identified it as important	2% of patients in the ALPS trial and 11.5% of patients in the DOLOMITES trial on roxadustat were based in the UK, with the majority of patients coming from Central and Eastern Europe.[3] It is unclear whether the trial results are generalisable to a UK population.
What alternative approach has the ERG suggested?	Short of new UK-based trials, the ERG has no suggestions for an alternative approach.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is unclear.
What additional evidence or analyses might help to resolve this key issue?	An exploratory subgroup analysis with UK patients could be conducted.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in section 6.4 of this report. The company's cost effectiveness results are presented in section 5, the ERG's summary and detailed critique in section 4, and the ERG's amendments to the company's model and results are presented in section 6. The key issues in the cost effectiveness evidence are discussed in the Tables below.

Table 1.6: Key issue 5: Model structure - justification for the Hb ranges and cut-off values used to define health states

Report section	4.2.2
Description of issue and why the ERG has identified it as important	It was not thoroughly justified whether the eight health states, based on different Hb ranges, to model the anaemia status would properly reflect the treatment effect of roxadustat as compared to ESA.
What alternative approach has the ERG suggested?	The use of different cut-offs for the Hb ranges, and/or a smaller number of health states to model anaemia status in a sensitivity analysis.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	The use of different cut-offs for the Hb ranges, and/or a smaller number of health states to model anaemia status in a sensitivity analysis.

Table 1.7: Key issue 6: Treatment effectiveness and extrapolation: appropriateness of time dependency and extrapolation of the multinomial logistic regression model unclear

Report section	4.2.6
Description of issue and why the ERG has identified it as important	Time dependency and extrapolation of the multinomial logistic regression model used to estimate the proportion of patients in the Hb health states. It is unclear to what extent the time trends observed during the relatively short follow-up of the trials can be extrapolated for the 25-year time horizon, especially the interaction between treatment type

	and time. This was also raised as a concern during the clinical and health economic validation performed by the company.
What alternative approach has the ERG suggested?	To assess the impact, the ERG requested the company (clarification question C7c) to exclude time as a covariate and interaction term. Unfortunately, these analyses were not provided and thus the impact of including log(time + 1) in the multinomial logistic regression is unclear. Moreover, the ERG believes scenario analyses (as provided in the CS) with a shorter time horizon are informative (especially given the lack of survival difference this is a pragmatic approach to explore treatment waning scenarios).
What is the expected effect on the cost effectiveness estimates?	Although the analyses with restricted time horizon (clarification response Table 75) might indicate a minor impact, this depends on the extrapolation assumptions made and is thus not completely clear, e.g. the impact of including log(time + 1) in the multinomial logistic regression is unclear.
What additional evidence or analyses might help to resolve this key issue?	The appropriateness and impact of including log(time + 1) are unclear to the ERG. Hence, to assess the impact, the ERG requested the company (clarification question C7c) to exclude time as a covariate and interaction term. Unfortunately, these analyses were not provided and thus the impact of including log(time + 1) in the multinomial logistic regression is unclear. In addition further validation to support the inclusion of log(time + 1) as both a covariate as well as an interaction term (between log(time + 1) and treatment type) might be informative.

Table 1.8: Key issue 7: Adverse events

Report section	**4.2.7**
Description of issue and why the ERG has identified it as important	The company excluded potentially relevant adverse events with inconsistent reasoning.
What alternative approach has the ERG suggested?	The inclusion of additional adverse events (suggested: peripheral oedema, hyperkalaemia, nausea, hyperphosphatemia, muscle spasms, dyspnoea, headache, insomnia).
What is the expected effect on the cost effectiveness estimates?	The effect of the inclusion of the additional adverse events is unknown.
What additional evidence or analyses might help to resolve this key issue?	As requested in clarification question C8, the ERG would prefer additional adverse events to be included in the analysis.

Table 1.9: Key issue 8: Model validation

Report section	**5.3**
Description of issue and why the ERG has identified it as important	The model validation (cross-validation, external validation and technical validation) is limited.
What alternative approach has the ERG suggested?	The ERG suggests performing additional cross-validation and external validation and to complete the TECH-VER checklist for technical validation.

Report section	5.3
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Additional cross-validation and external validation and a completed TECH-VER checklist for technical validation will provide insight into the validity of the model.

1.6 Other key issues: summary of the ERG's view

None identified.

1.7 Summary of the ERG's view

The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in section 6.1, was [redacted]* per QALY gained. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of [redacted] and [redacted] at willingness to pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. The ERG did not identify errors that warranted fixing. The ERG did fix the violation related to the suboptimal pooling of the four NDD trials (Section 4.2.6). In the ERG base-case only the DOLOMITES trial data were used. The ERG identified matters of judgement which were incorporated in ERG scenario analyses (shortened time horizon, proportion per ESA type, proportion requiring ESA administration costs). The ERG base-case ICER increased most in the exploratory scenario analyses with alternative assumptions regarding the proportion of patients receiving each ESA agent.

* The company marked all results based on DOLOMITES only analyses in their response to clarification questions as commercial in confidence (CiC). As the ERG base case is conditional upon this analysis/model, the ERG now marked the ERG analyses also CiC. NICE usually does not accept ICERs to be CiC.

Table 1.10: ERG base-case

	Total costs	Total LYs	Total QALYs	Δ Costs	Δ LYs	Δ QALYs	ICER
Company base-case – deterministic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case – probabilistic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1) ERG base-case (using DOLOMITES data only) - deterministic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1) ERG base-case (using DOLOMITES data only) - probabilistic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ESA = erythropoiesis stimulating agent; ICER = incremental cost effectiveness ratio; LY = life year; N/A = not applicable; QALY = quality adjusted life year

Table 1.11: Deterministic scenario analyses (conditional on ERG base-case)

	Total costs	Total LYs	Total QALYs	Δ Costs	Δ LYs	Δ QALYs	ICER
1) ERG base-case (using DOLOMITES data only)							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2a) ERG base-case (using DOLOMITES data only) + 5 year time horizon							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2b) ERG base-case (using DOLOMITES data only) + 10 year time horizon							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3a) ERG base-case (using DOLOMITES data only) + all patients receive darbepoetin alfa							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3b) ERG base-case (using DOLOMITES data only) + all patients receive epoetin alfa							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3c) ERG base-case (using DOLOMITES data only) + all patients receive epoetin beta							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3d) ERG base-case (using DOLOMITES data only) + all patients receive epoetin beta (methoxy polyethylene glycol)							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3e) ERG base-case (using DOLOMITES data only) + all patients receive epoetin zeta							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4) ERG base-case (using DOLOMITES data only) + no patients require ESA administration costs							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG = Evidence Review Group; ESA = erythropoiesis stimulating agent; ICER = incremental cost effectiveness ratio; LY = life year; QALY = quality adjusted life year

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adult patients with anaemia associated with chronic kidney disease (CKD)	Adult patients with symptomatic anaemia associated with CKD who are non dialysis dependent (NDD) at the time of treatment initiation. For some of the analyses: patients with only CKD stages 3-5.	As stated in CS, section B.1.3.6: • Clinical experts stated that the oral mode of administration would offer additional benefit to patients who are NDD (as ESA and IV iron represent a much lesser burden for dialysis dependent [DD] patients).[4] In addition, in contrast to ESA, roxadustat does not require cold-chain storage and transit or refrigeration in the patient's home, thus offering additional convenience to patients with anaemia associated with CKD receiving treatment at home. Additional considerations related with sharps disposal from the patient home, also mean roxadustat offers additional benefits for patients receiving treatment at home (once syringes are used, they become biohazard material and require specific ways of disposal and destruction). Dialysis patients who are stable on ESA treatment should only be converted to roxadustat if there is a valid clinical reason[5] Data from the UK renal registry suggest	The NDD population considered in the CS differs from the population in the final NICE scope (which is all patients, including DD patients). Restricting the population to those with CKD stages 3-5 is problematic because patients with CKD stages 1 or 2 can also have anaemia.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			that over 90% of patients on dialysis are currently receiving an ESA[6]. As the roxadustat SmPC states that dialysis patients who are stable on ESA treatment should only be converted to roxadustat if there is a valid clinical reason, the company therefore anticipates that roxadustat will not be routinely initiated in dialysis patients. All four trials on NDD patients (ALPS, ANDES, OLYMPUS, DOLOMITES) allowed patients to continue treatment with roxadustat after initiation of dialysis[7-10] • A large proportion of patients enrolled in these trials started dialysis while receiving roxadustat and the clinical and cost-effectiveness results presented in this submission accounts for these patients. In line with this, throughout the submission, the term NDD is used in reference to the patient status at point of treatment initiation. The company anticipates NDD patients appropriately managed with roxadustat will be allowed to continue treatment after initiation of	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			dialysis, with no dose adjustment required.[1] As per the response to clarification letter (question B.3): • The prevalence of anaemia in patients with CKD increases as kidney function declines. A cross-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES) in the United States of America (USA) reported that anaemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%) Furthermore, the study found that the prevalence of anaemia in patients with stage 1 CKD was 8.4% and stage 2 was 12.2%. The NHANES study used the KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease for the definition of anaemia (< 12 g/dl in women and < 13 g/dl in men). Data for UK patients with anaemia and stages 1 or 2 CKD are limited. A UK study looking at the prevalence of anaemia in diabetic patients specifically, reported that prevalence of anaemia in patients	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			with eGFR > 60 ml/min/1.73m^2 was 9%.	
Intervention	Roxadustat	Roxadustat	N/A – in line with the NICE final scope.	The intervention is in line with the NICE scope
Comparator(s)	Erythropoietic stimulating agents (ESAs)	ESAs	No rationale provided as CS states that comparator is 'Per scope'.	The comparators as stated are in line with the NICE scope. However, it should be noted that the company included placebo-controlled trials and drew conclusions regarding the benefit of roxadustat vs. placebo, which does not inform the comparison with ESAs.
Outcomes	The outcome measures to be considered include: • haemoglobin response • maintenance of haemoglobin levels • use of additional therapy (including blood transfusion and intravenous iron) • hospitalisation • mortality • adverse effects of treatment including major adverse cardiovascular events • health-related quality of life	Per scope with the exclusion of hospitalisation.	Hospitalisation was not explicitly modelled in the economic model. Hospitalisation rates from the clinical trials were similar for roxadustat, placebo and ESA. Hospitalisation costs were indirectly captured through adverse event management, drug administration and monitoring.	Excluding hospitalisations explicitly (and using indirect measures such as adverse event management) is potentially problematic.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	In line with NICE scope	N/A – in line with the NICE final scope.	N/A
Subgroups to be considered	None specified	No subgroups considered		N/A
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	N/A

Based on Table 1 and pages 13 to 15 of the CS[1]

CKD = chronic kidney disease; CS = company submission; DD = dialysis dependent; eGFR = estimated glomerular filtration rate; ERG = Evidence Review Group; ESA = erythropoiesis stimulating agent; IV = intravenous; KDIGO = Kidney Disease Improving Global Outcomes; mL = Millilitre; N/A = not applicable; NDD = non dialysis dependent; NICE = National Institute for Health and Care Excellence; SmPC = Summary of Product Characteristics; UK = United Kingdom; USA = United States of America

2.1 Population

The population defined in the scope is: *"Adult patients with anaemia associated with Chronic Kidney Disease (CKD)"*.[2] The population in the company submission (CS) is limited to *"Adult patients with symptomatic anaemia associated with CKD who are non-dialysis dependent (NDD) at the time of treatment initiation"*.[1]

ERG comment: According to the company, the decision problem addressed in the company submission is slightly narrower than that specified in the final National Institute for Health and Care Excellence (NICE) scope, which does not specify that patients must be NDD. The broader population specified in the final scope may include patients that are DD. In their response to clarification questions, the company has amended the CS to reflect this difference in populations.[3]

In addition, included studies were restricted to patients with CKD stages 3-5. This population is narrower than the final NICE scope. Based on this difference, the ERG asked the company to amend their decision problem, provide additional justification for the modified population, and provide a supporting reference explaining whether patients with CKD stages 1 and 2 are likely to develop anaemia and what proportion of patients in the UK are likely to be affected.[11] In their response to the clarification letter, the company provided a reference indicating that the prevalence of anaemia increased from 8.4% in stage 1 CKD to 12.2% in stage 2.[3, 12] This shows that anaemia is more prevalent among patients with higher stages of CKD, but does not show that the prevalence of anaemia in patients with CKD stages 1-2 is low enough to warrant their exclusion (and deviation from NICE scope). The company has amended the CS to reflect this difference in populations.[11]

The ERG is also concerned about the generalisability to NHS patients in England and Wales (see sections 3.2.3, 3.6). It should be noted that roxadustat RCTs were considered as representative of UK clinical practice during the model clinical and health economic validation.

2.2 Intervention

The intervention (roxadustat) is in line with the scope.

Roxadustat is administered as an oral tablet three times a week and not on consecutive days. For patients initiating anaemia treatment not previously treated with ESA the recommended starting dose of roxadustat is 70 mg three times per week in patients weighing less than 100 kilograms (kgs) and 100 milligrams (mgs) three times per week in patients weighing 100 kg and over. This dose should be individualised to achieve and maintain target haemoglobin (Hb) levels of 10 to 12 g/dl. The individualised maintenance dose ranges from 20 mg to 400 mg (for dialysis dependent (DD) patients, maximum dose for NDD patients is 300 mg) three times per week.

For patients converting from an ESA, the recommended starting dose of roxadustat is based on the average prescribed ESA dose in the four weeks before conversion (see Summary of Product Characteristics (SmPC) for conversion table).[1]

2.3 Comparators

The description of the comparators in the NICE scope is as follows: *"Erythropoietic stimulating agents (ESAs)"*.[2]

ERG comment: Although the company stated that the comparators considered were the same as those in the final NICE scope, they included trials that compared roxadustat with placebo and drew conclusions regarding the effectiveness of roxadustat versus placebo. Therefore, the ERG asked the

company to perform separate analyses excluding the comparisons between roxadustat and placebo, using solely data from the DOLOMITES trial.[11] The company responded that they did not use the data from the placebo-controlled trials directly, but instead pooled the roxadustat data across studies.[3] They acknowledged limitations with this approach and claimed to temper these by using statistical models that *"accounted for any potential differences between clinical trials by using a hierarchical model structure and used each unique study identification (ID) to control for any impacts of "nesting" (i.e. patients from the same study are more likely to behave in a similar manner compared with patients from another study) where possible"*.[3] The ERG believes that the limitations of this approach are more serious than the company acknowledged (see sections 1.4, 2.3, and 3.3).

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- haemoglobin response
- maintenance of haemoglobin levels
- use of additional therapy (including blood transfusion and intravenous iron)
- hospitalisation
- mortality
- adverse effects of treatment including major adverse cardiovascular events
- health-related quality of life

The company stated that they evaluated all of these with the exclusion of hospitalisation (which they captured indirectly).

ERG comment: The ERG asked the company for a rationale for capturing hospital costs indirectly, and for a supporting reference for the similar hospitalisation rates for roxadustat, placebo and ESA.[11] The company responded that in order to model hospitalisation costs directly, a link between Hb level and hospitalisation rate (i.e. multinomial regression model) would be required to directly relate hospitalisations to the main anaemia progression factor (Hb level) captured in the cost effectiveness model. They also noted that *"a direct treatment effect of roxadustat in hospitalisations was not expected and the available evidence from the clinical studies was not enough to fit a robust statistical model, hospitalisations were not captured directly in relation to Hb level (i.e. anaemia progression)", and that "The main driver of hospitalisation costs in the cost-effectiveness model are adverse events. This is in line with the evidence from the clinical trials where for example, in ALPS[7] and DOLOMITES[10] around half of all hospitalisations were due to adverse events"*.[3] However, NICE guidance recommends using surrogate (indirect) outcomes only when direct outcomes is not posslble.[13] To confirm whether what the company expected was actually the case, it would be more robust to report hospitalisation directly. The DOLOMITES trial reported hospitalisations, and these could have been included.[10] Moreover, there are methodological problems with indirect outcome measures. For example, Kemp and Prasad state that "The factors outlined here lead us to conclude that surrogates should lead to practice change or drug approval only when robust validation studies demonstrate that a change in a specific surrogate has a reliable ability to predict changes in meaningful outcomes."[14]

2.5 Other relevant factors

According to the company, roxadustat is innovative because it can be taken orally, which represents a lower burden to patients who are NDD, notably because patients can be treated from home. In addition, roxadustat does not require cold-chain storage so is more easily transported and stored.

This appraisal does not fulfil the end-of-life criteria as specified by NICE because the life expectancy of patients eligible for roxadustat is well beyond 24 months (see section 7).

According to the company, no equality issues related to the use of roxadustat for the treatment of adults with anaemia related to CKD have been identified or are foreseen (CS, Section B.1.1).[1]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic review to evaluate the evidence on clinical effectiveness (efficacy and safety) of roxadustat for the treatment of patients with anaemia associated with CKD.[1] Section 3.1 critiques the methods of the review including: the search strategy; study inclusion criteria; data extraction; assessment of risk of bias; and data synthesis.

3.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[15] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[16] The ERG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the systematic literature review (SLR) conducted to identify the clinical evidence (efficacy and safety) of roxadustat and standard of care in the management of anaemia associated with CKD. The SLR was conducted in two stages: an initial SLR in January 2019 and an update in January - March 2021. The same search strategies were used in the original SLR and update.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date ranges	Dates searched
Electronic databases			
Medline	Ovid	1946-15/04/21 2019-27/01/21	29/04/19 27/01/21
Embase	Ovid	1974-25/4/19 2019-27/01/21	29/04/19 27/01/21
DARE	CRD	All years	29/04/19 27/01/21
HTA Database			
NHS EED			
CDSR	Wiley	Iss 5/12 May 2019 26/04/19-19/03/21	29/04/21 19/03/21
CENTRAL			
EconLit	Ovid	1886-20/04/19 2886-02/03/21	29/04/19 02/03/21
PubMed	Internet	All years	29/04/21
Conference proceedings			
ASN Kidney Week ERA EDTA Congress ISN	Internet	2016-2020 2016-2020 2016-2020	30/04/19; 26/02/21 30/04/19; 26/02/21 30/04/19; 26/02/21
Additional resources			
ClinicalTrials.gov ICTRP	Internet	to 2021	30/04/19; 26/02/21

Resource	Host/Source	Date ranges	Dates searched
ASN = American Society of Nephrology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effects; EED = Economic Evaluation Database; ERA EDTA = European Renal Association - European Dialysis and Transplant Association; HTA = Health Technology Assessment; ICTRP = International Clinical Trials Registry Platform; ISN = International Society of Nephrology; NHS = National Health Service			

ERG comment:

- Searches were undertaken to identify data published on the clinical effectiveness of roxadustat in the treatment of patients with anaemia in CKD. The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches. Issues with the original documentation of the searches were corrected in the Company's response to the ERG's clarification letter.
- A good range of databases, conference proceedings and clinical trials registers were searched.
- Searches were clearly documented and structured, making them transparent and reproducible.
- Results were not limited by publication date, language of publication or by study design.
- Searches were designed to identify all studies on roxadustat and appeared to use appropriate indexing terms and free-text synonyms.
- No attempts were made to search more broadly for the population of patients with anaemia in chronic kidney disease, or for the comparator treatment of erythropoiesis stimulating agents (ESAs).

3.1.2 Inclusion criteria

As stated above, the company performed a systematic review to evaluate the evidence on clinical effectiveness (efficacy and safety) of roxadustat for the treatment of patients with anaemia associated with CKD.[1] The study eligibility criteria for the systematic review are summarised in Table 3.2.

Table 3.2: Eligibility criteria used in the systematic review of clinical effectiveness evidence

	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years of age) with CKD (stage 3-5) and anaemia	Studies conducted in wholly Chinese or Japanese populations
Interventions & comparators	• Roxadustat • Best supportive care (BSC) • Placebo	Not provided
Outcomes	• Life years gained • Time to dialysis (in non-dialysis patients) • Proportion of patients with subsequent transplant <u>Change from baseline in the following parameters:</u> • Blood pressure • Cholesterol • Serum hepcidin • Serum ferritin • Transferrin Saturation (TSAT) • Glycated haemoglobin (HbA1c)	Not provided

	Inclusion criteria	Exclusion criteria
	• CRP HRQoL: • Patients' Global Impression of Change • EQ-5D-5L • SF-36 • FACT-An • FACT-fatigue Adverse events (AEs): • Proportion of patients with grade 3 or higher AEs • Proportion of patients with Serious AEs (SAEs) Specific cardiac adverse events including: • Ischaemic heart disease • Stroke • Myocardial infarction • Pulmonary embolism • Withdrawal due to AEs • Discontinuation due to any cause	
Study design	RCTs of any size and duration were eligible for inclusion. Crossover RCTs were included if data are presented at crossover	• Non-systematic reviews • Editorials • News stories
Language restriction	No language limits were applied	Not applicable
Date restriction	No date limits were applied	Not applicable

Based on Table 92 of the CS[1]
AEs = adverse events; CKD = chronic kidney disease; CRP = c-reactive protein; CS = company submission; EQ-5D-5L = EuroQol five-dimension five level; FACT = Functional Assessment of Cancer Therapy; HbA1c = Glycated haemoglobin; RCT = randomised controlled trial; SAEs = serious adverse events; SF-36 = 36-Item short form survey; TSAT = transferrin saturation

ERG comment: The population was restricted to patients who were CKD stages 3 to 5 which is narrower compared to the NICE scope. The comparators, however, are much broader than the NICE scope and include BSC and placebo.

ERG requested some clarification from the company regarding the inclusion and exclusion criteria for SLR:[11]

- The exclusion criteria for population states: *"studies conducted in wholly Chinese or Japanese populations"*. The response to the clarification letter noted that Japanese and Chinese patients baseline characteristics have been shown to differ from those in European countries which are likely to affect the progression and treatment of CKD.[3] Moreover, the company highlighted the differences in the clinical practice between those countries and the UK can weaken the applicability of the results to the current submission.[3]
- Outcomes includes in the SLR conducted by the company did not include all outcomes from the NICE scope. The company was asked in the clarification letter whether (1) use of additional

therapy (including blood transfusion and intravenous iron) and (2) mortality were included in the SLR. In the clarification letter response, the company stated *"(...) While the specific use of additional therapy and mortality were not stated as such in the SLR inclusion criteria, these were not excluded from the searches.(...)"*.[3] Moreover, the company argues that blood transfusions and IV usage were addressed partly by inclusion of BSC and mortality outcomes were included as part of life-years gained and discontinuation due to any cause (including death).

- The company was asked to provide some more information if the observational studies were considered for the inclusion in the SLR. In the response to the clarification letter, the company stated that *"The SLR did not exclude observational studies from consideration. However, in the absence of a marketing authorisation, no such studies were identified at the time of undertaking and updating the SLR"*.[3]
- The process of the study selection was not covered in the CS.[1] The company was asked in the clarification letter to provide more information about the process. In their response, the company stated that two independent reviewers screen title and abstracts and full texts for both the original and update of SLR.

The ERG considers justification for exclusion of wholly Chinese and Japanese populations as sufficient for this report. The process of the study selection is judged as adequate. However, the ERG does not agree with justification provided by the company regarding outcomes (i.e., use of additional therapy [including blood transfusion and intravenous iron] and mortality).

3.1.3 Critique of data extraction

There was no information about the process of data extraction in Appendix D of the CS.[1] The company did not include the template or summary of details extracted from the relevant articles. The data extraction was performed by a single reviewer and checked by a second reviewer.

ERG comment: The company provided more details regarding the data extraction process which was judged as adequate. However, the company did not provide the details of the data extraction form to see if all relevant outcomes were captured.

3.1.4 Quality assessment

The process of the quality assessment and the tool used was not covered by the CS.[1] However, in section B.2.5 of the CS,[1] the company stated that *"Overall, the ALPINE phase III clinical trials for roxadustat met all quality standards and followed good clinical practices. (...)"*.

ERG comment: In the clarification letter, the company was asked to provide more details about the tool used for the risk of bias assessment and the process of assessing the study quality.[11] The company responded *"A formal risk of bias assessment was not performed in the identification of relevant studies. We are therefore unable to offer commentary on the quality of studies identified in the literature review within the current timeframe. It is worth noting, that the purpose of the literature review was to identify relevant studies to the decision problem. Irrespective of the quality of studies identified, none of the findings or parameters were in turn used to inform any key modelling parameters, (...)"*.[3]

The ERG does not agree with the second part of the statement as the quality assessment of the included studies is important to assess the evidence in the clinical effectiveness section. The quality assessment of the included DOLOMITES trial is covered in section 3.2.4 below.

3.1.5 Evidence synthesis

The company presented the results of all studies covered by the CS separately for each outcome and there was no pooling of evidence across the efficacy outcomes. For the safety results, a meta-analysis of adjudicated major adverse cardiovascular events (MACE) and MACE+ (a composite of ACM, MI, stroke and hospitalisation for either unstable angina or congestive heart failure) events was conducted to synthesise the information from the roxadustat phase 3 trial (placebo arm and ESA separately). Key adverse events (myocardial infarction [MI], stroke and vascular access thrombolysis [VAT]) for the DOLOMITES trial was also reported separately.[1]

ERG comment: The company presented the results of the studies focused on NDD-CKD population in the main body of the CS and the results of studies focused on DD-CKD population in the Appendix H (see sections below for more details).[1] There was no pooling of the efficacy outcomes. For the safety results, the company provided the meta-analysis of the results, however, only the evidence from the eligible study (DOLOMITES) trial was used in this report.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified one roxadustat-ESA-controlled trial (DOLOMITES) and three roxadustat-placebo-controlled trials (ALPS, ANDES and OLYMPUS) relevant to this submission.

A summary of these studies can be found in Table 3.3.

ERG comment: Although four trials were identified as being relevant to this submission, given that the comparator is ESA, the ERG proposes that the DOLOMITES trial is solely relevant to this part of the ERG report.

Therefore, this section of the report presents the results of the DOLOMITES trial, while the ALPS, ANDES and OLYMPUS trials are discussed briefly in this section and again in section 3.3, as they form part of what is effectively an unanchored indirect treatment comparison.[17]

Table 3.3: Summary of the studies included in the CS

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
Study Design	Phase III, multicentre, randomised, double-blind, placebo-controlled trial.	Phase III, multicentre, randomised, double-blind, placebo-controlled trial.	Phase III, multicentre, randomised, double-blind, placebo-controlled trial.	Phase III, multicentre, randomised, open-label, active-controlled trial
Population	Patients with anaemia associated with Stage 3, 4 or 5 CKD not on dialysis.	Patients with anaemia associated with Stage 3, 4 or 5 CKD not on dialysis.	Patients with anaemia associated with Stage 3, 4 or 5 CKD not on dialysis.	Patients with anaemia associated with CKD who have not started dialysis treatment
Intervention	Roxadustat 70/100 mg[*ǂ] (N=391) orally TIW throughout treatment period (minimum 52 weeks up to	Roxadustat 70/100 mg[*ǂ] (N=616) orally TIW (except in patients who had already converted to BIW or QW	Roxadustat 70 mg[ǂ] (N=1,393) orally TIW throughout treatment period.	Roxadustat 70/100 mg[*] (N=323) orally TIW throughout treatment period (104 weeks).

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	maximum of 104 weeks or until the last patient randomised to treatment had completed 40 weeks of treatment).	dosing regimens as a result of being enrolled under previous protocol versions) throughout treatment period.		
Comparator(s)	Placebo (N=203) orally TIW throughout treatment period.	Placebo (N=306) orally TIW throughout treatment period.	Placebo (N=1,388) orally TIW throughout treatment period.	Darbepoetin alfa (N=293) SC or IV, dosed[ǂ] as per the EU SmPC throughout treatment period.
Supports market authorisation	Yes			
Used in economic model	Yes			
Rationale for use/non-use in the model	The study provides evidence of efficacy and safety of roxadustat in patients not on dialysis at the time of treatment initiation			
Key outcomes (specified in decision problem)	Hb response and maintenance Rescue medication Hospitalisation** Quality of life Safety (CV profile) Use of IV iron supplementation			

Based on Table 4 of the CS[1]

[*] The dose of roxadustat was adjusted based on patient's body weight; with patients weighing ≥45.0 kg to ≤70.0 kg receiving 70 mg while those weighing >70.0 kg to ≤160.0 kg receiving 100 mg. [**] Hospitalisations were not explicitly modelled in the cost-effectiveness model (CEM).
[ǂ] All dose adjustments were made to achieve a Hb target level of 11.0 g/dl and maintain patients' Hb levels between 10.0 g/dl and 12.0 g/dl.

BIW = twice weekly; CKD = chronic kidney disease; CS = company submission; CV = cardiovascular; ESA = erythropoiesis-stimulating agents; EU = European Union; HRQoL = Health-related quality of life; IV = intravenous; QW = once weekly; SC = subcutaneous; SmPC = Summary of Product Characteristics; TIW = thrice weekly

3.2.1 Details of included NDD-CKD RCTs

The CS identified four phase III, multicentre, randomised, open-label trials conducted in patients commencing on roxadustat when not on dialysis (NDD population), one of which, DOLOMITES, had an active-controlled study design (ESA), and three of which were of a placebo-controlled study design (ALPS, ANDES, and OLYMPUS).[1] DOLOMITES, investigated the efficacy and safety of roxadustat in NDD population of patients requiring escalation of treatment for anaemia associated with CKD beyond iron supplementation while the three placebo-controlled trials were conducted in anaemic patients with stage 3, 4 or 5 CKD and not on dialysis.[1] The NDD population referred to patients with

anaemia associated with CKD who are NDD only at the time of treatment initiation, whilst not excluding patients who start dialysis while receiving roxadustat or ESA.[1] All four RCTs of interest with the summary of each study methodology is presented in Table 3.4.

The active-controlled DOLOMITES trial consisted a screening period (up to six weeks), a treatment period (104 weeks) and a post-treatment follow-up period (four weeks).[1] Eligible patients were originally randomised 2:1 roxadustat: darbepoetin alfa (protocol v1.0)[1]. But from protocol v2.0 (dated 18 May 2015) onwards, patients were randomised in a 1:1 ratio to receive either roxadustat thrice weekly (TIW) or darbepoetin alfa via subcutaneous (SC) or IV injection, dosed as per the European Union (EU) SmPC.[1, 18] The placebo-controlled trials are discussed further in section 3.3, as they provide indirect evidence only.

Table 3.4: Summary of trials included in clinical effectiveness evidence

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
Location	Africa, Asia, Europe, North America, South America	Asia, North America, South America, Oceania	Asia, Europe, North America, South America	Asia, Europe
Settings and locations where data were collected	153 centres across 22 countries	163 sites	385 centres across 25 countries	156 centres across 28 countries
Trial Design	Phase 3, Multicentre, Randomised, Double-blind, Placebo-controlled Study	Phase 3, Multicentre, Randomised, Double-blind, Placebo-controlled Study	Phase 3, Multicentre, Randomised, Double-blind, Placebo-controlled Study	Phase 3, Multicentre, Randomised, Open-label, Active-controlled Study
Key eligibility criteria for participants	Eligible participants were at least 18 years of age with a diagnosis of CKD, with KDOQI stage 3, 4 or 5 who were not receiving dialysis (at baseline)	Eligible participants were at least 18 years of age with a diagnosis of CKD, with KDOQI Stage 3, 4 or 5 who were not receiving dialysis (at baseline)	Eligible participants were at least 18 years of age with a diagnosis of CKD, with KDOQI Stage 3, 4 or 5 who were not receiving dialysis (at baseline)	Eligible participants were at least 18 years of age Diagnosis of CKD, with KDOQI stage 3, 4 or 5 who were not receiving dialysis (at baseline)
Study drugs	Group 1: roxadustat 70/100 mg[*ǂ] TIW (N=391) Group 2: placebo TIW (N=203)	Group 1: roxadustat 70/100 mg[*ǂ] TIW (N=616) Group 2: placebo TIW (N=306)	Group 1: roxadustat mg[ǂ] TIW (N=1,393) Group 2: placebo TIW (N=1,388)	Group 1: roxadustat 70/100 mg[*] TIW (N=323) Group 2: darbepoetin alfa dosed as per the EU SmPC (N=293)
Permitted concomitant medications	• Statins and Other Substrates for OATP 1B1 • Phosphate Binders and Other Multivalent Cation-containing Drugs and Mineral Supplements • Antihypertensive Medications	• Statins • Phosphate binders • Therapeutic Phlebotomy	• Statins • Phosphate binders • Herbal medicines	• Statins and Other Substrates for Organic Anion Transporting Polypeptide 1B1 • Phosphate Binders and Other Multivalent Cation-containing Drugs and Mineral Supplements

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
				• Antihypertensive Medications
Primary outcome	Proportion of patients who achieve an Hb (g/dl) response* defined as: Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dl in any patient with baseline Hb >8.0 g/dl, or An increase from baseline Hb by ≥2.0 g/dl in any patient with baseline Hb ≤8.0 g/dl As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response			
Other outcomes	• Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period • Change from baseline in LDL (mmol/l) cholesterol to the average LDL cholesterol of weeks 12 to 28 • Use and time to first use of rescue therapy in the first 24 weeks of treatment (incidence rate per 100 patient years at risk) • Change from baseline in SF-36 VT subscore (points) to the average VT subscore of weeks 12 to 28 • Change from baseline in SF-36 PF subscore (points) to the average PF subscore of weeks 12 to 28	• Mean change from baseline in Hb averaged over eight-weeks of treatment at weeks 28 to 36 without rescue therapy • Mean change from baseline in Hb during the evaluation period (defined as week 28 until week 52) in patients with baseline CRP >ULN • Proportion of patients with Hb level ≥10 g/dl between week 28 to 36, without use of rescue therapy • Mean change from baseline in LDL cholesterol averaged over weeks 12 to 28 • Time to and proportion of patients who received rescue therapy	• Change in Hb from baseline to the average Hb from weeks 28-52 for patients with baseline high-sensitivity C-reactive protein (hsCRP) greater than the ULN • Proportion of total time of interpolated Hb values ≥10 (g/dl) from weeks 28 to 52 • Proportion of total time of interpolated Hb values 10-12 (g/dL) from weeks 28 to 52 • Mean change in LDL cholesterol (mmol/l) from baseline to week 24 • Time to first instance of receiving IV iron, RBC transfusions, or erythropoietin analogue as rescue therapy	• Hb (g/dl) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period • Change from baseline in LDL cholesterol (mmol/l) to the average LDL cholesterol of weeks 12 to 28 • Time to first use of IV iron in weeks 1–36 (per 100 patient years at risk) • Change from baseline in SF-36 PF subscore (points) in weeks 12–28 • Change from baseline in SF-36 VT subscore (points) in weeks 12–28 • Change from baseline in MAP (mmHg) to the average MAP value in weeks 20 to 28

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
	• Change from baseline in MAP (mmHg) to the average MAP value of weeks 20 to 28 • Occurrence and time to first occurrence of hypertension (defined as either systemic blood pressure >170 mmHg AND an increase from baseline ≥20 mmHg or as diastolic blood pressure >110 mmHg and an increase from baseline of ≥15 mmHg • Rate of progression of CKD measured by annualised eGFR slope over time	(composite of blood/RBC transfusion, ESA use, and IV iron) in the first 52 • Mean change from baseline in SF-36 VT subscore averaged over weeks 12 to 28 • Progression of CKD: rate of change in eGFR over time adjusted by baseline eGFR, censored at dialysis or kidney transplant • Time to and proportion of patients who received RBC transfusion in the first 52 weeks of treatment • Mean change from baseline in SF-36 VT subscore averaged over weeks 12 to 28 • Mean change from baseline in MAP averaged over weeks 20 to 28 • Time to (and proportion of patients with) worsened hypertension	• Time to and proportion of patients who received first administration of an RBC transfusion as rescue therapy • Change from baseline in SF-36 VT subscore (points) to the average VT subscore of weeks 12 to 28 • Rate of progression of CKD measured by annualised eGFR slope over time • Change from baseline in SF-36 PF subscore (points) to the average PF subscore of weeks 12 to 28	• Occurrence and time to first occurrence of hypertension (defined as [SBP ≥170 mmHg and SBP increase from BL ≥20 mmHg] or [DBP ≥110 mmHg and DBP increase from BL ≥15 mmHg]) during weeks 1 to 36

Study	ALPS	ANDES	OLYMPUS	DOLOMITES
Pre-planned subgroups	Subgroups were predefined based on the key baseline demographics and disease characteristics including: • Sex • Age • Race • Baseline weight, weight be gender-specific median (four groups), body-mass index • Geographical region • Baseline iron repletion status • CRP at baseline • Baseline HB value • Baseline eGFR value • Diabetes history • Baseline C-reactive protein • CKD stage • History of CVD			

Based on Table 5 of the CS[1]

[*] Distinct definitions of the primary endpoint (Hb response) for European Union (EU) and United States (US) were defined for the placebo-controlled trials (ALPS, ANDES and OLYMPUS), in accordance with the regulators. This submission only presents the definition and results for the EU-based primary endpoint.

BL = baseline; CKD = chronic kidney disease; CRP = C-reactive protein; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EOS = end of study; EOT = end of treatment; ESA = erythropoiesis-stimulating agent; EU = European Union; Hb = haemoglobin; HIF = hypoxia inducible factor; IV = intravenous; KDOQI = kidney disease outcomes quality initiative; LDL = low density lipoprotein; MAP = mean arterial pressure; MDRD = Modification of diet in renal disease; mmol/l = milli-moles per litre; PF = Physical functioning; PHI = prolyl hydroxylase inhibitor; RBC = red blood cells; SBP = systolic blood pressure; SF-36 = 36-Item short form survey; SmPC = summary of product characteristics; TIW = thrice weekly; TSAT = transferrin saturation; ULN = upper limit of normal; US = United States; VT = vitality

3.2.2 Statistical analysis of the included RCTs

As above, the ERG has restricted the focus of this report on the DOLOMITES trial only, as this was the sole trial used to inform the ERG preferred base-case.

Following the assumptions that for the primary endpoint, the proportion of patients with response in both the roxadustat and darbepoetin alfa (ESA) arm is the same, at least 80% and has a non-inferiority margin for the difference of proportions of 15%, the DOLOMITES trial was designed to provide at least 98% test power.[1] Thus, to demonstrate the statistical non-inferiority of roxadustat to ESA in the primary endpoint, the trial was designed with 248 participants in the roxadustat arm and 208 participants in the ESA arm.[1] The details of outcome classifications and definitions, population assessed, statistical methods used and testing (if for non-inferiority or superiority), have been outlined in Table 3.5.

Table 3.5: Sequential testing of primary and key secondary efficacy endpoints in the DOLOMITES trial

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
Primary endpoint				
Hb maintenance	Hb (g/dL) response defined as: • Hb ≥11.0 g/dl and a Hb increase from baseline Hb by ≥1.0 g/dl in any patient with baseline Hb >8.0 g/dl or • An increase from baseline Hb by ≥2.0 g/dl in any patient with baseline Hb ≤8.0 g/dL As measured at two consecutive visits separated by at least five days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response)	PPS	The proportion of responders in the primary efficacy variable was compared using a Miettinen & Nurminen (MN) approach, adjusting for covariates (Region, Baseline Hb values, History of cardiovascular, cerebro-vascular or thromboembolic diseases and Baseline eGFR) and comparing roxadustat to darbepoetin alfa. Alternatively, use of standard normal statistic proposed by Gart and Nam was also permitted.	Non-inferiority was concluded if the margin for the difference between groups is 0.15
Secondary endpoint(s)				
Hb maintenance	Hb (g/dl) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within six weeks prior to and during this eight-week evaluation period	PPS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL Hb, BL Hb by visit and BL eGFR as continuous covariates.	Non-inferiority was concluded if the lower bound of the 95% CI of the difference was LSM is >-0.75 g/dl
LDL cholesterol	Change from baseline in LDL cholesterol (mmol/l) to the average LDL cholesterol of weeks 12 to 28	FAS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by	Superiority

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
			treatment as categorical variables. BL LDL, BL Hb and BL eGFR as continuous covariates.	
Rescue medication	Time to first use of IV iron in weeks 1–36 (per 100 patient years at risk)	FAS	Method: Cox regression + Kaplan-Meier. Covariates: Stratified on Region, history of cardiovascular, cerebrovascular or thromboembolic disease and adjusted on BL Hb, BL eGFR as continuous covariates.	Superiority
HRQoL	Change from baseline in SF-36 PF subscore (points) in weeks 12–28	PPS	Analysis method: MMRM. Covariates: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 PF subscore and BL eGFR as continuous covariates.	Non-inferiority was concluded if the lower bound of the 95% CI of the difference of LSM was >-3 points
HRQoL	Change from baseline in SF-36 VT subscore (points) in weeks 12–28	PPS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 VT subscore and BL eGFR as continuous covariates	Non-inferiority was concluded if the lower bound of the 95% CI of the difference of LSM was >-3 points
CV profile	Change from baseline in MAP (mmHg) to the average MAP value in weeks 20 to 28	PPS	Analysis method: MMRM. Categorical variables: Treatment group, region, history of cardiovascular, cerebrovascular or thromboembolic disease, visits and visits by treatment as categorical variables. BL MAP, BL Hb and BL eGFR as continuous covariates.	Non-inferiority was concluded if the upper bound of the 95% CI of the difference of LSM was <1 mmHg

Classification	Outcome	Population assessed	Statistical method used	Testing (non-inferiority or superiority)
CV profile	Occurrence and time to first occurrence of hypertension (defined as [SBP ≥170 mmHg and SBP increase from BL ≥20 mmHg] or [DBP ≥110 mmHg AND DBP increase from BL ≥15 mmHg]) during weeks 1 to 36	PPS	Analysis Method: Cox regression + Kaplan-Meier. Covariates: Stratified on treatment group, region and history of cardiovascular, cerebrovascular or thromboembolic disease and adjusted on BL Hb, BL eGFR as continuous covariates.	Non-inferiority was concluded if the lower bound of the 95% CI of the difference was LSM is >-0.75 g/dl

Based on Table 11 of the CS[1]
BL = baseline; CI = confidence intervals; CS = company submission; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FAS = full analysis set; Hb = haemoglobin; HRQoL = health-related quality of life; ITT = intention-to-treat; IV = intravenous; LDL = low density lipoprotein; LSM = least squares mean; MAP = mean arterial pressure; MMRM = Mixed Model of Repeated Measures; MN =Miettinen & Nurminen; PF = physical function; PPS = per protocol set; SBP = systolic blood pressure; SF-36 = short form 36 health survey questionnaire; US = United States; VT = vitality

ERG comment: There were two substantial protocol amendments during the course of the DOLOMITES trial,[1] but in the ERG's view, these are unlikely to have a material effect on the trial outcomes. The inclusion and exclusion criteria seem reasonable, and the statistical analysis of the primary and secondary endpoints appear appropriate. As such, the ERG has no concerns about the statistical analysis of the DOLOMITES trial.

3.2.3 Trial participant characteristics

The key inclusion and exclusion criteria for the DOLOMITES trial are summarised in Table 3.6. All patients had to have been diagnosed with stage 3, 4 or 5 CKD and were not receiving dialysis when commencing on roxadustat therapy in the study.[1]

Table 3.6: Key inclusion and exclusion criteria for DOLOMITES

Key inclusion criteria for participants	• At least 18 years of age • Diagnosis of CKD, with KDOQI stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 ml/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's two most recent (prior to randomisation) Hb values during the screening period, obtained at least four days apart, was ≤10.5 g/dl, with a difference of ≤1.0 g/dl
Key exclusion criteria for participants	• ESA treatment within 12 weeks prior to randomisation • Treatment with IV iron within six weeks prior to randomisation • Patient had received an RBC transfusion within eight-weeks prior to randomisation • Known hereditary haematological diseases such as thalassaemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD • Known chronic inflammatory disease that could impact erythropoiesis

Based on Table 5 of the CS[1]
CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ESA = erythropoiesis-stimulating agent; Hb = haemoglobin; IV = intravenous; KDOQI = kidney disease outcomes quality initiative; MDRD = Modification of diet in renal disease; RBC = red blood cells

ERG comment: Participant flow in the DOLOMITES trial is reported in Table 3.7 below. A total of 424 participants (68.8%) completed the two year treatment, 215 (66.6%) in the roxadustat group and 209 (71.3%) in the darbepoetin alfa group.[1] The company was asked in the clarification letter to provide more information on the number of patients in the trial who were recruited in the UK: only 37 (11.5%) and 24 (8.2%) of the roxadustat and darbepoetin alfa arm, respectively.

The company also noted in their response to the clarification letter that, with respect to the DOLOMITES trial *"exclusion criteria for DOLOMITES was not considered to be consistent with current UK clinical practice in line with NICE guidelines requiring iron to be offered to patients receiving ESA therapy with respect to IV iron. However, with reference to blood transfusions the exclusion criteria was not considered inconsistent".*[11] In particular, the non-interventional, retrospective TUNE study found that [redacted] of UK patients receiving an ESA for anaemia associated with CKD received IV iron and [redacted] received oral iron, and the company states in the clarification letter response that this was not in line with the use of iron within the DOLOMITES study. Additionally, NICE guidelines stipulate that Hb levels of less than 11 g/dl should trigger investigation and possible treatment, larger than the 10.5 g/dl upper limit in the DOLOMITES trial. The DOLOMITES trial

population is only 9.9% from a UK population. There could be differences in populations, concomitant medications, and other factors between UK and non-UK populations. The company stated that a subgroup analysis of UK patients could not be conducted due to the small numbers and risk of *"reduced chance of detecting a true effect, low likelihood that a statistically significant result reflects a true effect, overestimated effect sizes, and low reproducibility"*.[11] This is correct, however, an exploratory analysis restricted to UK populations could provide tentative evidence. As such, and along with the restriction of the DOLOMITES trial to patients with CKD stages 3-5 and NDD, the generalisability of the DOLOMITES study results to the UK clinical population may be limited.

The company stated that "*In light of the Dmitrieva study discussed in the answer to B3, the inclusion of the placebo-controlled studies improves the generalisability to the UK population in terms of representing the prevalence of anaemia in various CKD stages, particularly in more advanced disease"*.[3] The ERG adds that the placebo comparisons are not in line with the final NICE scope and are problematic for other reasons (see above and sections 3.3 and 3.4). It should be noted that roxadustat RCTs were considered as representative of UK clinical practice during the model clinical and health economic validation.

Table 3.7: Participant flow in DOLOMITES trial

Total patients enrolled	Total patients randomised	Randomisation to each study arm	
		Roxadustat	Comparator*
930	616	323	293

Based on Table 12 of the CS[1]
Notes: *Comparator denotes placebo for ALPS, ANDES and OLYMPUS trials, and darbepoetin alfa for DOLOMITES trial.
CS = company submission

3.2.4 Quality assessment of included RCTs

The tool and methods used for quality assessment of included RCTs were not provided in the company submission, as addressed in section 3.1.4 of this report. Similarly, the results of quality assessments were not published and thus cannot be summarised in this report.

However, in section B.2.5 of the CS, the company states that, *"Overall, the ALPINE phase III clinical trials for roxadustat met all quality standards and followed good clinical practices. Randomisation in the trials was carried out appropriately such that baseline characteristics were well balanced across treatment arms. Patients and investigators remained blinded throughout the placebo-controlled studies*".[1]

ERG comment: As reported in section 3.1.4 that the ERG believes a quality assessment of included studies is an important part of the clinical effectiveness section, thus the ERG undertook a risk of bias (RoB) assessment of the DOLOMITES trial, previously identified by the ERG as the sole trial to be used to inform the ERG preferred base-case, using the Cochrane RoB tool as presented in Table 3.8.[10]

Table 3.8: Risk of bias assessment

Source of bias	Judgement (Low, Unclear or High risk of bias)	Support for judgement
Random sequence generation	Unclear risk	In Section 5.3.3 of the CSR, it is reported that [redacted] [10] However, no information on the randomisation technique used by the IRT was provided.
Allocation concealment	Unclear risk	As mentioned above, an IRT system was employed for randomisation and drug allocation. Although it is likely that a computer algorithm was employed using the IRT, a description of allocation concealment was not included in the CSR.
Blinding (performance bias)	High risk	The DOLOMITES trial was an open-label study, thereby the outcome is likely to have been influenced by lack of blinding.
Blinding (detection bias)	High risk	The DOLOMITES trial was an open-label study, thereby outcome assessments are likely to have been influenced by lack of blinding.
Incomplete outcome data/ assessment	Low risk	Sufficient reporting of data for all planned outcomes for all randomised patients included.
Selective reporting	Low risk	The study protocol and details of amendments were made available, and all study pre-specified outcomes appear to have been reported in the CSR.
Other bias	Low risk	The study appears to be free of other sources of bias

Cochrane risk of Bias Tool[10]
CSR = clinical study report; IRT = interactive response technology

3.2.5 Efficacy results

Tables 3.9 and 3.10 outline the primary and secondary outcomes, relevant to the NICE scope (see Table 2.1) in the DOLOMITES trial. As mentioned above, the results are presented only for the trial eligible to the NICE scope. Moreover, the company was asked to provide the results for the patients recruited in the UK only. However, the company argued that *"(...) no robust statistical analysis could be performed to provide the same clinical effectiveness endpoints as reported in section B.2 of the CS for the UK population (...)"*[3] and no results were provided.

Based on the results for the primary efficacy endpoint, roxadustat is non-inferior compared to darbepoetin alfa in terms of response to treatment in the first 24 weeks without rescue therapy with the difference in proportion of responders of 11.5% (95% confidence interval (CI) 5.7% to 17.4%).

Most of the secondary efficacy endpoints showed non-inferiority of roxadustat to darbepoetin alfa, including Hb change from baseline (CFB), health-related quality of life (HRQoL) endpoints, changes in mean arterial pressure (MAP) and occurrence of hypertension. Superiority was demonstrated for change in low density lipoprotein (LDL) cholesterol from baseline and time to first IV iron use.

Table 3.9: Hb response during first 24 weeks without use of rescue therapy in DOLOMITES trial (PPS population)

	Roxadustat (N=286)	Darbepoetin alfa (N=273)	Difference in proportion	Odds ratio
Number of responders, n (%)	256 (89.5%)	213 (78.0%)	11.51%	2.48
95% CI	85.4 to 92.8	72.6 to 82.8	5.66 to 17.36	1.53 to 4.04

Based on Table 22 of the CS[1]
CI = confidence interval; CS = company submission; Hb = haemoglobin; PPS = per protocol set

Table 3.10: Summary of secondary outcomes in DOLOMITES trial

Classification	Endpoint	Population assessed	Roxadustat vs. darbepoetin alfa	Conclusion
Hb maintenance	Hb (g/dl) change from baseline to week's 28–36; difference in LSM (95% CI)	PPS	0.015 (-0.132 to 0.161), P=0.844	Non-inferiority met
LDL cholesterol	LDL cholesterol (mmol/l) change from baseline to week's 12–28; difference in LSM (95% CI)	FAS	-0.404 (-0.510 to -0.297), P<0.001	Superiority met
Rescue medication	Time to first use of IV iron in weeks 1–36; incidence rate (per 100 patient years at risk); HR (95% CI)	FAS	0.46 (0.27 to 0.80), P=0.006	Superiority met
HRQoL	Change from baseline in SF-36 PF subscore (points) in weeks 12–28; difference in LSM (95% CI)	PPS	-1.280 (-2.420 to -0.141) P=0.028	Non-inferiority met
HRQoL	Change from baseline in SF-36 VT subscore (points) in weeks 12–28; difference in LSM (95% CI)	PPS	-0.420 (-1.622 to 0.781), P=0.492	Non-inferiority met
HRQoL	Change from baseline in the FACT-An AnS to the average of weeks 12 to 28	FAS	[redacted]	[redacted]
HRQoL	Change from baseline in the FACT-An total score to the average of weeks 12 to 28	FAS	[redacted]	[redacted]
HRQoL	Change from baseline to weeks 12 to 28 in the EQ-5D-5L VAS	FAS	[redacted]	[redacted]
CV profile	MAP (mmHg) change from baseline to average of weeks 20–28; difference in LSM (95% CI)	PPS	-0.362 (-1.577 to 0.852), P=0.558	Non-inferiority met
CV profile	Time to first occurrence of hypertension in weeks 1–36; incidence rate (per 100 patient years at risk) (95% CI)	PPS	HR: 0.827 (0.56 to 1.22), P=0.339	Non-inferiority met

Classification	Endpoint	Population assessed	Roxadustat vs. darbepoetin alfa	Conclusion
CV profile	MAP (mmHg) change from baseline to average of weeks 20–28; difference in LSM (95% CI)	FAS	[redacted]	[redacted]
CV profile	Time to first occurrence of hypertension in weeks 1–36; incidence rate (per 100 patient years at risk) (95% CI)	FAS	[redacted]	[redacted]

Based on Table 23 of the CS[1]
CI = confidence interval; CV = cardiovascular; EQ-5D-5L = EuroQol five-dimension five level; FACT = Functional Assessment of Cancer Therapy; FAS = full analysis set; Hb = haemoglobin; HR = hazard ratio; HRQoL = health-related quality of life; LDL = low density lipoprotein; LSM = least squares mean; MAP = mean arterial pressure; PF = physical functioning; PPS = per protocol set; SF-36 = 36-Item short form survey; VAS = visual analogue scale

3.2.6 Safety results

This section considers the information about adverse events provided in the CS for the DOLOMITES trial. Study discontinuation primarily due to death and adverse events were comparable on the intention-to-treat population of both roxadustat and darbepoetin arms (death: 33 [10.2%] vs. 34 [11.6%]; adverse event: 2 [0.6%] vs. 1 [0.3%]; Table 3.11).[1]

Based on Table 3.12, the overall incidence of treatment-emergent adverse events (TEAEs; 296 [91.6%] vs. 271 [92.5%]), TEAEs leading to death (34 [10.5%] vs. 34 [11.6%]) and overall death (40 [12.4%] vs. 37 [12.6%]) were comparable between the treatment arms of the DOLOMOTES trial.[1] However, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs and TEAEs leading to withdrawal of treatment, and drug-related TEAEs leading to withdrawal of treatment was higher on the roxadustat arm, when compared to the darbepoetin alfa arm.[1]

Based on Table 3.12, TEAEs occurring in ≥5% of trial participants were mostly comparable on both arms.[1] The most common TEAEs in roxadustat and darbepoetin alfa treatment groups were end-stage renal disease (33.4% versus 36.2%, respectively), hypertension (29.7% versus 33.8%, respectively), decreased glomerular filtration rate (GFR) (17.0% versus 16.7%, respectively), peripheral oedema (15.2% versus 12.3%, respectively) and hyperkalaemia (11.8% versus 14.3%, respectively). The difference of ≥3% or higher between treatment arms was reported for hypertension (29.7% and 33.8% for roxadustat and darbepoetin alfa arms, respectively), hyperphosphataemia (8.7% and 5.1%, respectively), dyspnoea (7.4% and 4.1%, respectively) and insomnia (5.9% and 2.7%, respectively).[1]

The results for key adverse events (i.e. MI and stroke) are comparable between treatment arms in the DOLOMITES trial. However, more patients in the roxadustat arm experienced vascular access thrombolysis (10 [3.1%] and 2 [0.7%]) when compared to ESA treatment arm, respectively (Table 3.13).[1]

Table 3.11: Summary of early treatment discontinuation results for the DOLOMITES trial

	Roxadustat (n=323)	Darbepoetin alfa (n=293)	Total (n=616)
Early treatment discontinuation up to two years			
Yes	73 (22.6%)	63 (21.5%)	136 (22.1%)
No	250 (77.4%)	230 (78.5%)	480 (77.9%)
Primary reason for discontinuation			
Completed	250 (77.4%)	230 (78.5%)	480 (77.9%)
Adverse event	2 (0.6%)	1 (0.3%)	3 (0.5%)
Death	33 (10.2%)	34 (11.6%)	67 (10.9%)
Lost to follow-up	3 (0.9%)	3 (1.0%)	6 (1.0%)
Progressive disease	0	1 (0.3%)	1 (0.2%)
Withdrawal by patient	30 (9.3%)	18 (6.1%)	48 (7.8%)
Study terminated by sponsor	0	0	0
Physician decision	3 (0.9%)	3 (1.0%)	6 (1.0%)
Pregnancy	0	0	0
Other	2 (0.6%)	3 (1.0%)	5 (0.8%)

Based on Table 107 of the CS[1]
CS = company submission; ITT = intention-to-treat

Table 3.12: Summary of safety results for the DOLOMITES trial

	Roxadustat (n=323) n (%)	Darbepoetin alfa (n=293) n (%)
Overview of TEAEs and death (SAF population)		
TEAE	296 (91.6%)	271 (92.5%)
Drug-related TEAE	78 (24.1%)	66 (22.5%)
Serious TEAE	209 (64.7%)	181 (61.8%)
Drug-related serious TEAE	18 (5.6%)	9 (3.1%)
TEAE leading to death	34 (10.5%)	34 (11.6%)
Drug-related TEAE leading to death	2 (0.6%)	0
TEAE leading to withdrawal of treatment	25 (7.7%)	11 (3.8%)
Drug-related TEAE leading to withdrawal of treatment	7 (2.2%)	1 (0.3%)
TEAE NCI-CTCAE Grades 3 or Higher	181 (56.0%)	164 (56.0%)
Death during the Safety Emergent Period	30 (9.3%)	31 (10.6%)
Death (Overall)	40 (12.4%)	37 (12.6%)
Summary of TEAEs occurring in ≥5% of patients in either treatment arm (SAF population)		
Overall	296 (91.6)	271 (92.5)
End-stage renal disease	108 (33.4)	106 (36.2)

	Roxadustat (n=323) n (%)	Darbepoetin alfa (n=293) n (%)
Hypertension	96 (29.7)	99 (33.8)
Glomerular filtration rate decreased	55 (17.0)	49 (16.7)
Oedema peripheral	49 (15.2)	36 (12.3)
Hyperkalaemia	38 (11.8)	42 (14.3)
Nausea	35 (10.8)	25 (8.5)
Viral upper respiratory tract infection	29 (9.0)	25 (8.5)
Diarrhoea	28 (8.7)	30 (10.2)
Hyperphosphataemia	28 (8.7)	15 (5.1)
Muscle spasms	25 (7.7)	15 (5.1)
Pneumonia	25 (7.7)	22 (7.5)
Dyspnoea	24 (7.4)	12 (4.1)
Bronchitis	22 (6.8)	18 (6.1)
Constipation	21 (6.5)	15 (5.1)
Headache	21 (6.5)	12 (4.1)
Iron deficiency	21 (6.5)	25 (8.5)
Urinary tract infection	21 (6.5)	27 (9.2)
Vomiting	21 (6.5)	19 (6.5)
Back pain	20 (6.2)	17 (5.8)
Pruritus	20 (6.2)	13 (4.4)
Insomnia	19 (5.9)	8 (2.7)
Arthralgia	18 (5.6)	14 (4.8)
Atrial fibrillation	18 (5.6)	12 (4.1)
Cardiac failure	18 (5.6)	18 (6.1)
Arteriovenous fistula thrombosis	16 (5.0)	10 (3.4)
Dizziness	16 (5.0)	15 (5.1)
Anaemia	14 (4.3)	19 (6.5)

Tables 108 and 109 of the CS[1]
CS = company submission; NCI CTCAE = National Cancer Institute - common terminology criteria for adverse events; SAF = safety analysis set; TEAE = treatment-emergent adverse event

Table 3.13: Key adverse events in the DOLOMITES trial (SAF population)

	DOLOMITES (SAF)	
	Roxadustat (N=323)	ESA (N=293)
MI	[redacted]	[redacted]
Stroke	[redacted]	[redacted]
Vascular access thrombosis (VAT)	[redacted]	[redacted]

Table 27 of the CS[1]
CS = company submission; MI: myocardial infarction, SAF: safety analysis set; VAT = vascular access thrombosis

ERG comment: The ERG does not have any major concerns related to safety results of the DOLOMITES trial.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company submission states that individual participant data (IPD) from patients in the roxadustat arms of the OLYMPUS, ANDES, ALPS and DOLOMITES studies were pooled and jointly analysed to estimate the clinical parameters, e.g. Hb level, in the cost effectiveness analysis.[1] This effectively implies and unanchored indirect treatment comparison:[17] the population used to inform the roxadustat treatment in the CEM comprises the roxadustat arms of all NDD ALPINE studies (of which DOLOMITES contributes 322 of 2,690 patients, 12.0%), whereas the population used to inform the ESA arm likely comprises solely patients in the ESA arm of the DOLOMITES trial.[1] It is not clear in the CS or the clarification responses whether the DOLOMITES trial provides all the evidence for ESA in the CEM, but it is unclear what further data could have been used.[1]

The OLYMPUS, ANDES and ALPS trials will be briefly described, though the results of these trials are not used in the ERG's preferred base-case.

3.3.1 Details of included placebo-controlled trials

The placebo-controlled ALPS study consisted of a screening period (up to six weeks), a treatment period (minimum 52 weeks up to a maximum of 104 weeks) and a post-treatment follow-up period (four weeks).[1] Eligible patients were randomised to receive roxadustat or placebo orally three times weekly (TIW) in a 2:1 ratio, with the initial roxadustat dose being based on a tiered, weight-based dosing scheme (Weight ≥45.0 kg to ≤70.0 kg: 70 mg).[1] Similarly, the ANDES study consisted of a screening period (up to six weeks), a treatment period (variable for individual patients – minimum treatment duration was 52 weeks with a maximum treatment duration of up to three years after the last patient was randomised) and a post-treatment follow-up period (four weeks).[1] Eligible patients were randomised (2:1) to receive roxadustat or placebo orally TIW (except in patients who had already converted to twice weekly (BIW) or once weekly (QW) dosing regimens because of being enrolled under previous protocol versions where this was maintained), with a similar weight-based initial dosing scheme as the ALPS trial.[1] The OLYMPUS trial consisted of a screening period (up to six weeks), a treatment period (variable for individual patients – treatment end date was defined based on when the target number of cardiovascular (CV) events was reached) and a post-treatment follow-up period (four weeks).[1] Eligible patients in this study were randomised (1:1) to receive roxadustat or placebo. Patients on the roxadustat arm were initially administered 70 mg of roxadustat orally TIW, with the dosing frequency on the placebo matched to that on the roxadustat arm (unless downward dose adjustment required a change to twice or once weekly dosing, permitted at four-week intervals from week 4, using a dosing algorithm).[1]

3.2.2 Placebo-controlled trial participant characteristics

The key inclusion and exclusion criteria for the ALPS, ANDES and OLYMPUS studies are summarised in Table 3.14. All patients must have been diagnosed with stage 3, 4 or 5 CKD and were not receiving dialysis when commencing on roxadustat therapy in the study.[1]

Table 3.14: Key inclusion and exclusion criteria for included trials

	ALPS	ANDES	OLYMPUS
Key inclusion criteria for participants	• At least 18 years of age • Diagnosis of CKD, with KDOQI stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 ml/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's three most recent Hb values during the screening period, obtained at least four days apart, was ≤10.0 g/dl, with a difference of ≤1.0 g/dl between the highest and the lowest values were included in the study • Prior to initiation the patient's ferritin level was ≥30 ng/ml (≥67.4 pmol/l) and transferrin saturation was ≥5%	• At least 18 years of age • Diagnosis of CKD, with KDOQI Stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 ml/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's three most recent Hb values during the screening period, obtained at least four days apart, was <10.0 g/dL, with a difference of ≤1.0 g/dl between the highest and the lowest values • Ferritin levels ≥30 ng/ml at randomisation and transferrin saturation ≥5%	• At least 18 years of age • Diagnosis of CKD, with KDOQI Stage 3, 4 or 5 who were not receiving dialysis (at baseline) • An eGFR <60 ml/min/1.73 m^2 estimated using the abbreviated 4-variable MDRD equation • Mean of the patient's two most recent Hb values during the screening period, obtained at least seven days apart, was <10.0 g/dl • Ferritin levels ≥50 ng/ml at randomisation and transferrin saturation ≥15% • Body weight of 45-160 kg
Key exclusion criteria for participants	• ESA treatment within 12 weeks prior to randomisation • Treatment with more than one dose of IV iron within 12 weeks prior to randomisation • Patient had received an RBC transfusion within eight weeks prior to randomisation • Known hereditary haematological diseases such as thalassaemia or sickle	• ESA treatment within 12 weeks of randomisation • More than one dose of IV iron within 12 weeks before randomisation • RBC transfusion within eight-weeks prior to randomisation • Known hereditary haematologic disease such as thalassaemia or sickle cell anaemia, pure red cell aplasia, or other	• ESA treatment within six weeks of randomisation • Known hereditary haematologic disease such as thalassaemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD • Patient had received an RBC transfusion during the screening period

	ALPS	ANDES	OLYMPUS
	cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD	known causes for anaemia other than CKD • Known chronic inflammatory disease that could impact erythropoiesis	

Table 5 of the CS[1]
CKD = chronic kidney disease; CS = company submission; eGFR = estimated glomerular filtration rate; ESA = erythropoiesis-stimulating agents; Hb = haemoglobin; IV = intravenous; KDOQI: kidney disease outcomes quality initiative; MDRD = Modification of diet in renal disease; RBC = red blood cells;

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company submission states that there was no indirect treatment comparison. However, data from the roxadustat arms of four trials (3 placebo controlled and 1 with ESA as the comparator arm) were pooled to estimate clinical parameters, e.g. Hb level, with roxadustat and data from the only ESA arm was used to estimate the same clinical parameters with ESA.[1] This therefore effectively constitutes an unanchored indirect treatment comparison.[17] The ERG would maintain that such a comparison presented in the company submission is likely to be severely biased, and therefore argues that the most appropriate analysis should be one using solely the DOLOMITES trial, which provides direct unbiased evidence for the effectiveness of roxadustat and ESA in patients drawn from the same population.

The largest problem with pooling single arms of several studies is that the effect of randomisation has been completely removed from the analysis: the patients are no longer drawn randomly from the same population, so effect modifiers and prognostic factors are no longer likely to be balanced across the two populations, here, the roxadustat arms of all ALPINE NDD trials and the ESA arm of the DOLOMITES trial. The analysis becomes an unanchored indirect comparison, and for such analyses to be unbiased, all effect modifiers and prognostic factors must be balanced across the populations. This is extremely unlikely to be the case, as the roxadustat arms of the ALPINE studies were drawn from distinct populations that likely have meaningful differences. For instance, the DOLOMITES trial included patients from Asia and Europe,[10] while the other ALPINE NDD trials included patients from North and South America, as well as in some cases Oceania and Africa.[19] Additionally, although the company states in the clarification responses that *"all patient characteristics used within the cost-effectiveness modelling were balanced between studies"*,[3] there are large differences in the percentage of the roxadustat trial populations who were diabetic: 37% in ALPS[7] versus 65% in ANDES.[8] These differences will likely extend to many unmeasured effect modifiers and prognostic factors, meaning the analysis is likely to be biased.

The company has not stated in either the company submission or the clarification response that they made any attempt to make the pooled APLINE NDD roxadustat patients comparable to the ESA arm of the DOLOMITES trial. Therefore, any differences in the observed variables that are not balanced between these two populations (e.g., ethnicity, age, weight, sex, CVD history, diabetes, eGFR) could bias the cost effectiveness analysis. However, it is notable that even with matching or adjustment, unmeasured effect modifiers and prognostic factors would still bias the cost effectiveness analysis (CEA).

These biases are not, however, present in the DOLOMITES trial, which directly compares roxadustat with ESA. Use of direct evidence such as this takes precedence over using indirect evidence (as in the CS). As such, the ERG base-case uses the results of the DOLOMITES trial alone, the results of which are likely to be much less biased than those of using the pooled roxadustat arms of the NDD ALPINE trials.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG undertook a quality assessment of the DOLOMITES trial (see section 3.2.4).

3.6 Conclusions of the clinical effectiveness section

The main evidence for the clinical effectiveness with the comparators (ESAs) required in the final NICE scope is the DOLOMITES trial.[1] The DOLOMITES trial is a phase III, multicentre, randomised, open-label, active-controlled trial, which includes patients with anaemia associated with CKD who have not started dialysis treatment. The trial consisted a screening period (up to six weeks), a treatment

period (104 weeks) and a post-treatment follow-up period (four weeks).[1] Eligible participants were originally randomised 2:1 roxadustat: darbepoetin alfa (protocol v1.0).[1] But from protocol v2.0 (dated 18 May 2015) onwards, patients were randomised in a 1:1 ratio to receive either roxadustat TIW or Darbepoetin alfa via subcutaneous (SC) or IV injection, dosed as per the European Union (EU) SmPC.[1, 18]

Four hundred and twenty-four (68.8%) patients completed the two year treatment, 215 (66.6%) in the roxadustat group and 209 (71.3%) in the darbepoetin alfa group.[1] Only 37 (11.5%) and 24 (8.2%) of the roxadustat and darbepoetin alfa arm, respectively, were based in the UK. The ERG assessed the risk of bias for the DOLOMITES trial and found that it was at an unclear risk of bias for random sequence generation and allocation concealment, at a high risk of bias for blinding, and at a low risk of bias for data assessment, and selective reporting.

Roxadustat was found to be non-inferior compared to darbepoetin alfa in terms of response to treatment in the first 24 weeks without rescue therapy with the difference in proportion of responders of 11.5% (95% CI 5.7% to 17.4%). Most of the secondary efficacy endpoints showed non-inferiority of roxadustat as well.

In terms of safety, study discontinuation primarily due to death and adverse events were comparable on the intention-to-treat population of both roxadustat and darbepoetin arms (death: 33 [10.2%] vs. 34 [11.6%]; adverse event: 2 [0.6%] vs. 1 [0.3%]; Table 3.11).[1]

The other three trials (ALPS, ANDES, OLYMPUS) did not use ESA comparators and therefore the ERG did not focus on them in the analysis as they were not relevant to the NICE scope. The ERG believes that pooling the roxadustat arms from these three trials with that from the DOLIMTES trial to inform the cost effectiveness analysis clinical parameters effectively constitutes an unanchored indirect treatment comparison and is likely to be severely biased. The ERG would therefore argue that the most appropriate analysis should be one using solely the DOLOMITES trial, which provides direct unbiased evidence for the effectiveness of roxadustat and ESA in patients drawn from the same population. As such, the ERG base-case uses the results of the DOLOMITES trial alone.

Finally, it is unclear to what extent the DOLOMITES trial is relevant to a contemporary NHS population, given the small number of UK participants in the trial. The company noted in their response to clarification questions that the additional placebo-controlled studies may have enhanced the generalisability of their results.[3] However, inferences about the generalisability of a comparison between roxadustat and ESAs cannot be reliably made on the basis of trials comparing roxadustat with placebo. It should be noted that roxadustat RCTs were considered as representative of UK clinical practice during the model clinical and health economic validation.

Overall, the DOLOMITES trial represents the best available evidence that attempts to compare roxadustat with the comparators listed in the NICE scope (ESAs). Nevertheless, there remains a substantial risk that the results lack applicability to the UK population.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

Three SLRs were performed with the objectives to identify and select relevant 1) health-related quality of life (HRQoL) studies (CS Appendix H); 2) costs and healthcare resource use studies (CS Appendix I) and 3) cost effectiveness analysis (CEA) studies (CS Appendix G).[1]

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[15] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[16, 20] The ERG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS states that studies included in the cost and healthcare resource use SLR and health-related quality of life SLR (detailed in Appendices H and I) were screened to identify cost effectiveness models relevant for this submission.[1] Separate searches were therefore not conducted to identify cost-effectiveness studies.

Appendix H of the CS provides details of the systematic literature review undertaken to identify and review published health utilities data in patients with anaemia in CKD.[1] Literature searches were conducted between 22 January 2019 and 10 February 2019. The search was subsequently updated between January to March 2021 using similar search strategies to capture any recently published evidence.

A summary of the sources searched is provided in Table 4.1

Table 4.1: Data sources for the health-related quality of life systematic review (as reported in CS)

Resource	Host/Source	Date range	Dates searched
Electronic databases			
Medline	OvidSP	2009-28/01/19 2019-27/01/21	30/01/19 07/01/21
Embase	OvidSP	2009-28/01/19 2019-29/01/21	30/01/19 29/01/21
DARE NHS EED HTA Database	CRD website	2009-2015 2009-2015 2009-2018	30/01/19
EconLit	OvidSP	2009-28/01/19 2019-02/03/21	30/01/19 02/03/21
PsycInfo	OvidSP	2009-JanWk3 2019 2019-29/01/21	30/01/19 29/01/21
PubMed	Internet	NA	23/01/19
Additional resources			
ScHARRHud	Internet	All years	22/01/19 22/01/21

Resource	Host/Source	Date range	Dates searched
CEA Registry	Internet	All years	22/01/19
NICE	Internet	All years	23/01/19 02/03/21
Conference proceedings			
ERA EDTA Congress ASN Kidney Week ISPOR		2016-2020	23/01/19 26/02/21

ASN = American Society of Nephrology; CEA = Cost Effectiveness Analysis Registry; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EED = NHS Economic Evaluation Database; ERA EDTA = European Renal Association - European Dialysis and Transplant Association; HTA = Health Technology Assessment; ISPOR = Professional Society for Health Economics and Outcomes Research

Appendix I of the submission provides details of the systematic literature review undertaken to identify and review published resource use data associated with the treatment of patients with anaemia in CKD.[1] Literature searches were conducted in January 2019. The search was subsequently updated between January to March 2021 using similar search strategies to capture any recently published evidence.

A summary of the sources searched is provided in Table 4.2.

Table 4.2: Data sources for the cost and healthcare resource identification, measurement and valuation systematic review (as reported in CS)

Resource	Host/Source	Date range	Dates searched
Electronic databases			
Medline	OvidSP	2009-28/01/19 2019-27/01/21	30/01/19 07/01/21
Embase	OvidSP	2009-29/01/19 2019-27/01/21	30/01/19 29/01/21
DARE NHS EED HTA Database	CRD website	2009-2015 2009-2015 2009-2018	30/01/19
EconLit	OvidSP	2009-24/01/19 2019-02/03/21	30/01/19 22/03/21
PsycInfo	OvidSP	2009-JanWk3 2019 2019-02/03/21	30/01/19 29/01/21
PubMed	Internet	All years	23/01/19
Additional resources			
ScHARRHUD	Internet	All years	22/01/19 22/01/21
CEA Registry	Internet	All years	22/01/19
NICE	Internet	All years	23/01/21 02/03/21
Conference proceedings			
ERA EDTA Congress ASN Kidney Week ISPOR		2016-2020	23/01/19 26/02/21

Resource	Host/Source	Date range	Dates searched
ASN = American Society of Nephrology; CEA = Cost Effectiveness Analysis Registry; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; EED = NHS Economic Evaluation Database; ERA EDTA = European Renal Association - European Dialysis and Transplant Association; HTA = Health Technology Assessment; ISPOR = Professional Society for Health Economics and Outcomes Research			

As the same searches were conducted for both the health-related quality of life systematic review (Appendix H) and the cost and healthcare resource identification, measurement and valuation systematic review (Appendix I), the following comments address both SLR searches.[1]

ERG comment:

- Searches were undertaken to identify data published on economic evaluations, health utilities data and resource use data for roxadustat in the treatment of patients with anaemia in CKD. The CS and the Company's response to the ERG's clarification letter provided sufficient details for the ERG to appraise the literature searches.
- A good range of electronic databases, conference proceedings and other resources were searched.
- Searches were extensive, using combinations of indexing terms and free-text synonyms for chronic kidney disease and anaemia.
- Searches were clearly documented and structured, making them transparent and reproducible.
- No language limits were applied.
- Search filters were applied to limit the results to economic evaluations, health utilities data and resource use data. Although the filters used were not cited as published filters, they appear comprehensive and likely to retrieve the relevant literature.
- Results for both the health-related quality of life systematic review and the cost and healthcare resource identification, measurement and valuation systematic review were limited to a publication date of 2009+. The ERG queried this date limit, and in the Company's response to the ERG's clarification letter, it was stated that "*a 2009 publication date limit was applied … as the company considered sufficient the evidence captured in the last 10 years at the time of conducting the SLR*".[3]

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on HRQoL studies and costs and resource use studies are presented in Table 4.3. According to the company's response to clarification question C3, no eligibility criteria are for the review on cost effectiveness studies.[3] For the latter, studies included in the HRQoL and cost and healthcare resource use reviews were screened to identify CEMs relevant for this submission. Additionally, seven studies were retrieved from a published review of cost effectiveness evidence in anaemia associated with CKD.

Table 4.3: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adult (≥18 years of age) patients with CKD (stage 3-5) with anaemia	Post renal transplant Non-anaemic CKD patients (without separate anaemic subgroup results)
Intervention	No restriction	
Comparator	No restriction	

	Inclusion criteria	Exclusion criteria
Outcomes(s) 1 (HRQoL studies)	Studies reporting on one of these preference-based quality of life measures, utilities and disutilities for the population of interest: • EuroQol five dimensions (EQ-5D) data (both EQ-5D-3L and EQ-5D-5L) • Short-Form (SF)-36, 6D and 15D • Health Utilities Index (HUI) • Discrete choice experiments, time trade off or standard gamble (SG) • Any other preference-based utility data Studies reporting utilities mapped from other tools Studies reporting on the mapping of quality of life/patient reported outcome measures to utility instruments	
Outcomes(s) 2 (Cost/resource use studies)	Direct medical costs (overall and specific costs) Indirect medical costs (overall and specific costs) Resource utilisation data	
Study design 1 (HRQoL studies)	The following types of study were eligible for inclusion: • Economic evaluations (cost effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses) • HTAs • Published models • Randomised controlled trials (RCTs) • Reports of utility elicitation exercises • Reports of utility validation exercises	News items, editorials, and case reports

	Inclusion criteria	Exclusion criteria
	• Mapped values studies Studies published as abstracts or conference presentations were eligible for inclusion if adequate information was provided. Studies reporting data used in economic evaluations were also followed-up and identified	
Study design 2 (Cost/resource use studies)	HTAs Costing studies Budget impact models Burden/cost of illness studies Studies reporting resource utilization and costs Observational studies Economic evaluations	Case reports Case studies
Based on CS Appendices H and I and clarification responses[1] CKD = chronic kidney disease; CS= company submission; EQ-5D = EuroQol five dimensions; EQ-5D-3L = EuroQol five-dimension three level; EQ-5D-5L = EuroQol five-dimension five level; HRQoL = health-related quality of life; HTA = health technology assessment; HUI = Health Utilities Index; RCT = randomised controlled trials; SF-36 = 36-Item short form survey		

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies.

4.1.3 Conclusions of the cost effectiveness review

The CS (Appendices G to I) provides an overview of the included cost effectiveness (13 studies), HRQoL (nine studies; utility values not used in the economic model according to CS Table 132) and resource use and costs studies (31 studies; utility values not used in the economic model according to CS Table 150), but no specific overall conclusion was formulated.[1]

ERG comment: The ERG has no comments about the searches related to the cost effectiveness review (see sections 3.1.1 and 4.1.1 for additional details). Eligibility criteria were suitable for the SLR performed.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.4: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with reference case
Perspective on costs	NHS and PSS	In line with reference case

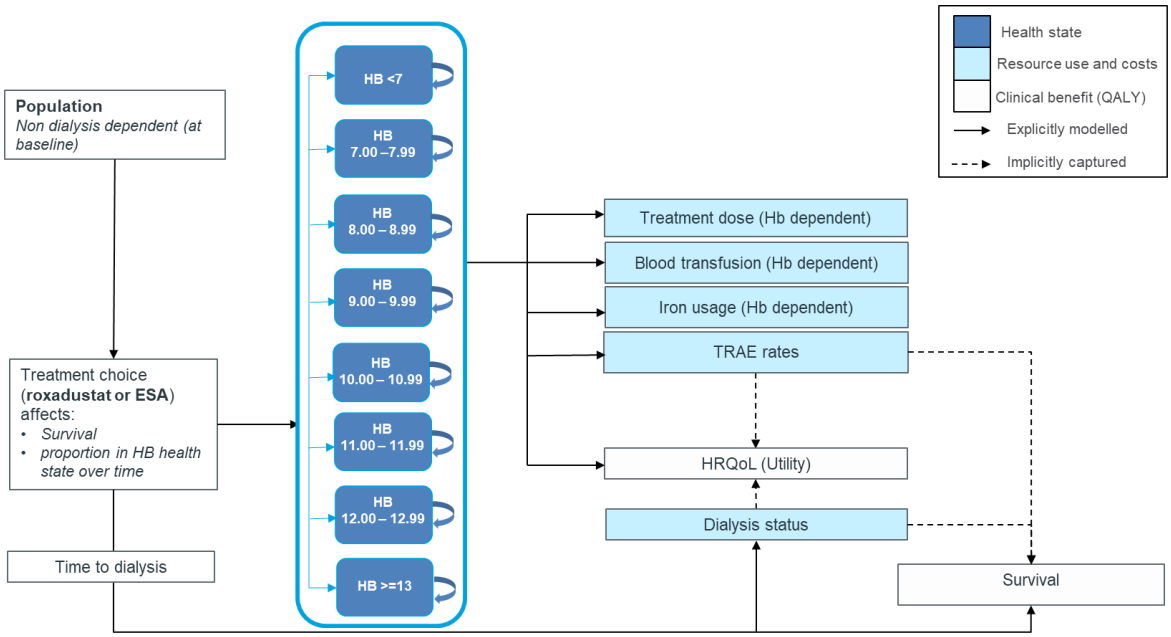
Element of health technology assessment	Reference case	ERG comment on company's submission
Type of economic evaluation	Cost utility analysis with fully incremental analysis	In line with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with reference case (at the end of the time horizon 2.5% is still alive but extending the time horizon only has a minor impact on the ICER, CS Tables 72 and 75)
Synthesis of evidence on health effects	Based on all non-dialysis trials.	Pooling of evidence is not in line with best practices.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	In line with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	In line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

EQ-5D = EuroQol five dimensions; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year

4.2.2 Model structure

The company developed a de novo health state transition cohort model, programmed in Microsoft® Excel, to conduct a cost-utility analysis. In addition to a death health state, eight alive health states were defined to reflect the anaemia status based on different ranges of Hb levels (Figure 4.1). Patients alive at the beginning of each cycle were distributed across the eight Hb health states using a multinomial logistic regression model. The treatment (roxadustat or ESA) impacted these transition probabilities over time. The proportion of patients alive at each cycle was estimated using a parametric function fitted to survival data. Another parametric function fitted to time to dialysis data was used to estimate the proportion of patients on dialysis. The relationships between dialysis status, survival and HRQoL, and between treatment related adverse events (TRAE), survival and HRQoL were not explicitly modelled.

Figure 4.1: Model structure



Based on Figure 8 of the CS[1]

Notes: Hb dependent: These outcomes are dependent on Hb level (i.e., dependent on the regression equation used to estimate Hb level)

CS = company submission; ESA = erythropoiesis-stimulating agent; Hb = haemoglobin; HRQoL = health-related quality of life; IV = intravenous; QALY = quality adjusted life year; TRAE = treatment-related adverse events; Tx = treatment

ERG comment: The main concerns of the ERG relate to: a) the modelling of anaemia status using eight health states, b) the implicit modelling of the impact of dialysis and cardiovascular events on HRQoL, costs and survival, c) not considering kidney transplant and CKD stages in the model, d) the justification for not using a cost-minimisation analysis.

a) The company used eight health states with ranges of Hb levels and death to model this condition. The ranges and cut-off points used for the Hb levels were not fully justified. It was also unclear why these health states would differ in terms of HRQoL, costs and survival. In response to clarification question C1a, the company explained that the ranges of Hb levels to define the health states were based on Yarnoff et al. 2016,[21] who used these ranges as a categorisation underlying their modelling of the risk of blood transfusion (based on Lawler et al. 2010[22]). The rationale behind this categorisation is not described in these publications. The company further argues that Finkelstein et al. 2009,[23] the source of utility values in Yarnoff et al. 2016,[21] demonstrated that as Hb levels increased in increments of 1 g/dl in Hb there were significant improvements in a variety of quality-of-life domains. According to the ERG, that was not demonstrated by Finkelstein et al. Finkelstein et al. 2009[23] is a narrative mini-review and merely summarises the findings of studies that show that anaemia impacts quality of life domains. Moreover, it needs to be emphasised that the model in Yarnoff et al. 2016[21] is a microsimulation which modelled quality of life impact via the (continuous) patient characteristic Hb level. That does not necessarily imply that 1 g/dl change in Hb level has a meaningful impact on quality of life. Additionally, during the clinical and health economic validation performed by the company concerns were also raised regarding the use of eight different Hb categories (the participating health economist queried *"The model might be more robust with less categories. Do the HB categories differ in terms of costs or HRQoL? What is*

the reasoning for 8 categories?" and the clinician responded *"Only 3 Hb target ranges are needed: Less than 10, 10-12 (UK target) and >12 (above UK target)."* [4]). To summarise, the rationale for the definition of the ranges of Hb levels in the model was not thoroughly justified. The impact of different cut-offs for the Hb ranges, and/or a smaller number of health states to model anaemia status on the results are difficult to predict.

b) A disadvantage of not explicitly modelling the relationship between dialysis status, survival and HRQoL, and between treatment related adverse events (TRAE), survival and HRQoL is that the relation might become implausible/flawed during extrapolation. Because extrapolated survival and time to dialysis do not differ between the treatments, in this model this does not substantially impact the incremental results.

c) While the population in the submission consists of patients with CKD and anaemia, kidney transplant and CKD stages were not considered in the model. In response to clarification question C1d the company argued that it was not necessary to model these aspects of the condition, because roxadustat and ESA do not impact CKD progression.[3] The ERG agrees that not modelling these aspects will not affect the incremental cost effectiveness results because the extrapolated time to death and time to dialysis do not differ between the treatments, but it might impact the absolute estimates of costs and QALYs.

d) The company conducted a cost-utility analysis, which is consistent with the NICE reference case. In the Decision Support Unit (DSU) report "The use of cost minimisation analysis for the appraisal of health technologies",[24] it is stated that the use of cost-minimisation analysis needs a strong rationale for clinical equivalence. The DOLOMITES trial showed non-inferiority on the primary outcome (difference in proportion with Hb response in first 24 weeks) for roxadustat versus darbepoetin alfa (while Hb is the main driver of difference in treatment effectiveness in the economic model). In response to clarification question C2 the company justified the use of a cost-utility analysis by stating roxadustat and ESA cannot be considered equivalent for reasons of observed differences in Hb response and use of IV iron (which both seem biologically plausible), and way of administration.[3] The ERG agrees that for this decision problem a cost-minimisation analysis would not be appropriate.

4.2.3 Population

In line with expected indication, the cost effectiveness analysis evaluates roxadustat for the treatment of adult patients with symptomatic anaemia associated with CKD who are not on dialysis at the time of treatment initiation. The NICE scope states that the population of interest is adults with anaemia associated with CKD. The company analysed data for a subgroup of this population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation. In addition, the NICE scope states that the population of interest is adults with anaemia associated with CKD. The company analysed data for a subgroup of this population, namely those who have CKD stages 3-5.[1]

The population is based on the four NDD trials (DOLOMITES, ALPS, ANDES, OLYMPUS). The baseline characteristics of these patients are listed in Table 4.5.

Table 4.5: Key baseline patient characteristics used in the economic model

Characteristics	Value
Number of individuals	4,847
Starting age of population (years)	63.0
Proportion of patients: male	42.5%
Proportion of patients: female	57.5%

Characteristics	Value
Proportion of patients with CVD history	38.3%
Proportion of patients with diabetes	55.5%
Median baseline eGFR	17.1
Proportion of patients from DOLOMITES	12.7%
Proportion of patients from ALPS	12.2%
Proportion of patients from ANDES	18.8%
Proportion of patients from OLYMPUS	56.3%

Based on CS Table 29[1]
CS = company submission; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate

ERG comment: The main concern of the ERG relates to the pooling of the population in the four NDD trials to obtain treatment effectiveness estimates. This is discussed in section 4.2.6.

4.2.4 Interventions and comparators

The intervention considered in the CS is roxadustat, a first in class oral hypoxia-inducible factor prolyl hydroxylases inhibitors (HIF-PHIs). The comparator of interest in the CS is ESA. ESAs were considered to have equal efficacy at equivalent doses and were modelled as a class. In the model, the company considered all available ESAs in the British National Formulary (BNF): epoetin alfa, epoetin beta, epoetin zeta, darbepoetin alfa and methoxy polyethylene glycol-epoetin beta.

In the DOLOMITES trial darbepoetin alfa was used as the comparator. In this trial, the initial roxadustat dose was based on a tiered, weight-based (weight at baseline) dosing scheme: weight ≥45.0 kg to ≤70.0 kg received 70 mg three times a week, and weight >70.0 kg to ≤160.0 kg received 100 mg three times a week. Subsequently, for both roxadustat and darbepoetin alfa, in DOLOMITES study treatment was dosed for Hb correction, until patients achieved Hb levels of ≥11.0 g/dl and Hb increase from baseline of ≥1.0 g/dl as measured at two consecutive study visits separated by at least five days. Once Hb correction was reached, patients entered the maintenance period. The aim of the maintenance period was to treat to a Hb target level of 11.0 g/dl by maintaining Hb levels between 10.0 g/dl and 12.0 g/dl. No stopping rule nor treatment discontinuation were applied, and patients were allowed to continue roxadustat after starting dialysis.

ERG comment: The main concern of the ERG related to modelling ESA as a class. According to the guidelines the different ESA have equal efficacy at equivalent doses.[25] The prices are however quite different. See section 4.2.9.

4.2.5 Perspective, time horizon and discounting

The analysis was performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length is three months with a lifetime time horizon (25 years) and a half-cycle correction is applied.

ERG comment: In the CS, the company stated a 25-year time horizon was used. At the end of the time horizon 2.5% of the patients are still alive, but extending the time horizon further only has a minor impact on the ICER, CS Tables 72 and 75).[1] This was therefore considered to represent a lifetime time horizon. The approach is in accordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for intervention and comparators are obtained via statistical analysis of the NDD trials (ALPS, ANDES, OLYMPUS, DOLOMITES). In short, a multinomial logistic regression model was used to estimate the proportion of patients in the Hb health states while time to dialysis and time to death were estimated using parametric survival models (with log-logistic and exponential distributions respectively).

4.2.6.1 Proportion of patients in the Hb health states

The alive patients in the economic model were distributed across the Hb health states. For the first cycle, the baseline distribution of patients in the NDD trials was used. Notably the majority of patients were allocated to the Hb 9.00-9.99 health state and no patient has Hb ≥11 at baseline (see CS Table 30).[1]

To distribute the proportions of alive patients across the Hb health states after the first cycle, a multinomial logistic regression model was used including the Hb health states as dependent (categorical) variables (with Hb 10.00-10.99 as reference). Included covariates were treatment type (placebo, ESA or roxadustat), log(time +1), CVD history at baseline, diabetic status at baseline, study ID (ALPS, ANDES, OLYMPUS, DOLOMITES) and an interaction between treatment type and log (time +1). Study ID was added to account for nesting effects. See CS Table 35 for the regression coefficients and CS Figures 10 and 11 for the proportion of patients in the Hb categories over time.[1]

4.2.6.2 Time to dialysis

Time to dialysis was estimated using parametric survival regression models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised Gamma). Included covariates were CVD history at baseline, diabetic status at baseline, study ID (ALPS, ANDES, OLYMPUS, DOLOMITES) and baseline eGFR (no covariate for treatment type was included consistent with clinical expert advice and data from the DOLOMITES trial).

The CS stated that the *"log-logistic distribution was found to be the best function in terms of long-term clinical plausibility, presenting a long tail capturing a fraction of patients who will never start dialysis"*.[1] Goodness-of-fit statistics (AIC/BIC) were very similar for the different distributions (CS Tables 36-37 and CS Figure 12).[1]

The proportion of patients that were estimated to be on dialysis was subdivided between haemodialysis (88%) and peritoneal dialysis (12%) based on DOLOMITES trial data (CS Table 31), clinical experts confirmed these proportions were in line with UK clinical practice.[1]

4.2.6.3 Time to death

Time to death was estimated using parametric survival regression models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised Gamma). Included covariates were treatment type (placebo, ESA or roxadustat), CVD history at baseline, diabetic status at baseline, study ID (ALPS, ANDES, OLYMPUS, DOLOMITES), baseline eGFR and an interaction between treatment type and baseline eGFR.

The CS stated that the *"the exponential function was found to be the best in terms of BIC score, as well as long term clinical plausibility and a good visual fit"*.[1] However, goodness-of-fit statistics (AIC/BIC) were very similar for the different distributions (CS Table 32).[1]

The roxadustat related coefficients (CS Table 33) were omitted and the mortality estimations for roxadustat were set equal to those for patients treated with ESA consistent with clinical expert advice and data from the DOLOMITES trial (treatment specific mortality is assumed in a scenario analysis).

Estimated survival was adjusted using annual mortality rates for the general population (sourced from Office for National Statistics (ONS) life tables) combined with a standardised mortality ratio (SMR) of 3.6 for NDD to ensure the all-cause mortality (ACM) rate predicted by the trial data was consistent with the expected mortality for the CKD population.

CS Figure 9 and CS Table 34 provide information on the estimated (long-term) survival as used in the model (i.e., constrained by the CKD adjusted general population mortality and assuming no treatment effect). The parametric survival curves are below the Kaplan-Meier curves due to integration of CKD adjusted general population mortality.

4.2.6.4 Extrapolation beyond the observed data period

The estimated regression models were extrapolated beyond the observed data period. For both time to dialysis and time to death, no difference between ESA and roxadustat was assumed while the estimated proportions of patients in the Hb health states (estimated using the multinomial logistic regression model) were extrapolated without assuming waning of the relative treatment effect.

ERG comment: The main concerns of the ERG relate to: a) the procedure(s) used to estimate the (multinomial logistic) regression model(s); b) using the pooled NDD data versus DOLOMITES only data; c) time dependency and extrapolation of the multinomial logistic regression model; d) validating extrapolations; e) pre-specification of the statistical analyses; f) diagnostics of the (multinomial logistic) regression model(s).

a) Based on the company's clarification responses it became clear that study ID was included as a fixed effect (i.e., covariate) to attempt to control for nesting in the regression models used for estimating effectiveness in the economic analyses (multinomial logistic regression model as well as the parametric survival models to estimate time to death and time to dialysis). This is a suboptimal approach to account for nesting effects that induces bias as it breaks randomisation between the studies and the results should be interpreted as an observational comparison (see also section 3.3). This is particularly concerning for the multinomial logistic regression model as this is the main driver of differences in effectiveness (i.e., quality-adjusted life year (QALY) gains for roxadustat). Therefore, the current analyses providing a comparison between roxadustat and ESA based on suboptimal pooling of the NDD trials provides potentially improved precision, but should not be interpreted as a randomised comparison.
b) According to the response to clarification question C7, the company preferred using pooled data from the NDD trials over using only data from the DOLOMITES trial *"given the representativeness to UK practice, improved statistical strength, and the optimised use of all available data obtained on roxadustat in accordance with NICE guidance"*.[3] Regarding the representativeness to UK practice, 1) the company noted that the results from clarification response Table 50 (NDD pooled analyses) are broadly aligned to what is expected for a UK population and that the results from clarification response Table 51 (DOLOMITES data only analyses) are not substantially different; 2) the time to death of the DOLOMITES data only analyses might be more in line with the 22nd UK renal registry report (see below) and; 3) the DOLOMITES trial is the only source (in the NDD population) to inform the relative effectiveness of roxadustat compared with ESA, which is the main driver of QALY differences.[1, 3] Adding the other NDD trials will not improve in the representativeness of the

estimated relative effectiveness. Although the above, might support the representativeness of the DOLOMITES data to UK practice (compared with the pooled NDD data), using all NDD trials likely improves the statistical strength (i.e. power of the analysis) for covariates other than the relative effectiveness. However, given that the methods used to pool the NDD trials are suboptimal (see above), this is a trade-off between imprecision (using the DOLOMITES trial only) and bias (using the pooled NDD trials). Therefore, the ERG has a strong preference for using the DOLOMITES trial only analyses (adopted in the ERG base-case).

c) To incorporate time dependency in the (extrapolation of the) multinomial logistic regression model, the company included log(time +1) as a covariate as well as an interaction term (between log (time +1) and treatment type). It is unclear to what extend the time trends observed during the relatively short follow-up of the trials can be extrapolated for the 25-year time horizon, especially the interaction between treatment type and time. This was also raised as a concern during the clinical and health economic validation performed by the company (*"can we predict Hb state occupancy over a 40 year period from a short-term duration trial?"*[4]). The appropriateness and impact of including log (time +1) are unclear to the ERG. Hence, to assess the impact, the ERG requested to company (clarification question C7c) to exclude time as a covariate and interaction term.[11] Unfortunately, these analyses were not provided and thus the impact of including log(time +1) in the multinomial logistic regression is unclear.

d) In clarification response C7d, the company stated that the health state occupancy within the CEM as estimated by the multinomial logistic regression model were confirmed with clinical experts (stating that these were in line with their expectations given the renal registry guidelines). In addition, the plausibility of the extrapolated time to death as well as time to dialysis were considered in response to clarification question C6. The estimated time to death was compared with external data from the 22nd UK renal registry report at five years (73% registry vs [redacted] economic model) and 10 years (56% registry vs [redacted] economic model). Notably the DOLOMITES only analyses provided estimated time to death that was closer to the registry data ([redacted] and [redacted]; clarification response Table 54),[3] supporting the representativeness of the DOLOMITES only analyses. In addition, the estimated time to dialysis was checked for face validity by the company (clarification response C6), stating that *"clinical experts deemed the long-term extrapolation values to be reasonable for a cohort with an average starting age of ~65 years old"*.[3]

e) In response to clarification question C5 the company provided further details regarding the procedure used to estimate the multinomial logistic regression model.[3] Clarifying that missing data was assumed to be missing completely at random (the amount and patterns of missingness is unclear). Moreover, based on the company's response to clarification question C6, it appears that covariates that were statistically not significant were retained in the economic model.[3] However, the exact decision criteria to select and exclude (candidate) covariates and interaction terms were unclear. In addition, the company highlighted that the analyses were specified a priori in a statistical analysis plan (SAP). However, the SAP was unfortunately not provided in response to the clarification questions, hence the ERG was unable to consider the detail of pre-specification of the statistical analyses as well as adherence to the pre-specified plan. Therefore, the impact of the decisions made for the data analyses are unclear. This is applicable to all regression models estimated for the economic model, e.g., the time-to-event models considered in clarification response C6.[3]

f) The difference in treatment effectiveness (i.e., QALY gains for roxadustat) is mainly driven by the multinomial logistic regression distributing the alive patients between the different Hb health states. In clarification response C5b,[3] the company indicated that the suitability of the

multinomial logistic regression was assessed visually by comparing the statistical model predictions to the observed data (CS Figure 10).[1] However, despite additional clarification provided in response C5c, the interpretation of CS Figure 10[1] and thus the suitability of the multinomial logistic regression model (next to the inappropriate controlling for nesting effects) is unclear to the ERG. Similarly, the diagnostic plots provided (e.g., considering residuals and multicollinearity) for the other regression models were not (always) reassuring that the regression was appropriate while for the analyses using DOLOMITES data only, these diagnostic plots were not available to the ERG.

4.2.7 Adverse events

Adverse events were applied according to their probabilities per cycle (as observed in DOLOMITES[10], ALPS[7], OLYMPUS[9], and ANDES[8] for roxadustat and in DOLOMITES[10] for ESA). Three key treatment emergent adverse events, stroke, myocardial Infarction (MI) and vascular access thrombosis (VAT) were included. Other adverse events were not explicitly modelled as the company expected these would have a substantially lower impact on patients' utility and NHS resource use. Adverse event probabilities per cycle can be found in Table 4.6. Strokes were further subdivided in non-disabling, moderately disabling, and severely disabling (48.5%, 42.6% and 8.8% respectively).

Table 4.6: Adverse events (probability per cycle)

Adverse event	ESA	Roxadustat
Stroke	[redacted]	[redacted]
MI	[redacted]	[redacted]
VAT	[redacted]	[redacted]
Based on CS Table 47,[1] based on 4 NDD trials for Roxadustat, based on DOLOMITES trial for ESA CS = company submission; MI = myocardial infarction; VAT = vascular access thrombosis		

ERG comment: The main concerns of the ERG relate to: a) the exclusion of potentially relevant adverse events b) the incidence rates of adverse events.

a) The company included only major adverse cardiovascular events as adverse events stating that these have special importance as they result in death, worsening disease and significantly reduce HRQoL. According to the company, other TRAEs had a low incidence or showed no significant difference between roxadustat and ESA arms and were therefore expected to have negligible impact on model outcomes.
   The ERG disagrees with the exclusion of further adverse events for two reasons. Firstly, several AEs have a difference in incidence between treatments: Appendix F.4 Table 109 summarises TEAEs occurring in ≥5% of patients for roxadustat and the ESA darbepoetin alfa.[1] The incidence of oedema peripheral (15.2% for roxadustat patients and 12.3% for darbepoetin alfa patients), hyperkalaemia (11.8% compared to 14,3%), nausea (10.8% compared to 8.5%), hyperphosphatemia (8.7% compared to 5.1%), muscle spasms (7.7% compared to 5.1%), dyspnoea (7.4% compared to 4.1%), headache (6.5% compared to 4.1%), and insomnia (5.9% compared to 2.7%) seem to differ by two percent or more. Secondly, the company argued that these were not included because the difference in the incidence between treatments was not significant. This is however also the case for the included major adverse cardiovascular events. The ERG therefore considers it inconsistent to use this argument to exclude other adverse events. The impact on the results is unclear.
b) No statistically significant differences were found in the incidence of the included MACEs. The ERG therefore requested a scenario analysis assuming equal incidence of adverse events. The

company complied by conducting an analysis setting all AE incidences to 0. This analysis [redacted], resulting in roxadustat [redacted] with a NMB (£20,000 per QALY) of [redacted]. The company argued that the driver of this change was that the incidence of VAT was higher in the roxadustat population in the company base-case and the weighted cost of VAT being a key driver of the model.[1, 3]

4.2.8 Health-related quality of life

Health-related quality of life was estimated using general population utility values adjusted for age, sex, CKD and dialysis status and further adding utility decrements related to Hb level, history of CVD, diabetic status and treatment emergent adverse events.

4.2.8.1 General population utilities

General population utility values were adjusted for age, sex, CKD and dialysis status. The utility decrements that were used to adjust for age and sex can be found in CS Table 38. The utility decrements used for baseline adjustment can be found in Table 4.7.

Table 4.7: Utility decrements applied to age and gender adjusted general population utility values

	Utility decrement (SE)	Source
CKD decrement	0.033	Derived from Kind et al.[26] and Ara R. and Brazier J.E.[27]
Haemodialysis	0.352 (0.041)	NICE TA358[28]
Peritoneal dialysis	0.262 (0.049)	
Based on CS Table 39 CKD = chronic kidney disease; CS = company submission; NICE = National Institute for Health and Care Excellence; SE = standard error: TA = technology appraisal		

4.2.8.2 Utility decrements related to Hb level, history of CVD, diabetic status

Utility decrements were estimated based on the NDD trials[7-10] which used the EQ-5D-5L instrument cross-walked to EQ-5D-3L values[29]. A generalised linear mixed model (GLMM) with a Gaussian distribution and an identity link was then conducted to estimate utilities for each Hb level controlling for CVD history and diabetic status at baseline. To incorporate nesting effects, study ID and subject were included as random factors (Table 4.8).

Table 4.8: Hb level coefficients EQ-5D-3L

Parameter	Coefficient	Standard error	p-value
Intercept	[redacted]	[redacted]	[redacted]
Hb level <7	[redacted]	[redacted]	[redacted]
Hb level 7-8	[redacted]	[redacted]	[redacted]
Hb level 8-9	[redacted]	[redacted]	[redacted]
Hb level 9-10	[redacted]	[redacted]	[redacted]
Hb level 11-12	[redacted]	[redacted]	[redacted]
Hb level 12-13	[redacted]	[redacted]	[redacted]
Hb level >13	[redacted]	[redacted]	[redacted]
History of CVD – Yes	[redacted]	[redacted]	[redacted]

Diabetic - Yes	[redacted]	[redacted]	[redacted]

Based on CS Table 40[1]
Notes: * P ≤0.050, ** P ≤0.010, *** P ≤0.001
CS = company submission; CVD = cardiovascular disease; EQ-5D-3L = EuroQol five-dimension three level; Hb = haemoglobin;

The health state utilities obtained by the regressions estimated from the clinical trial analysis and patient characteristics are presented in CS Table 41. Based on these health state utilities, health state decrements are calculated (Table 4.9) that were applied to the general population utility values (adjusted for age, sex, CKD and dialysis status).

Table 4.9: Health state utility decrements

Health state	Base-case Utility (IPD EQ5D-3L)	Measured Utility (IPD EQ5D-5L)	Yarnoff et al.[21] Utility
Hb <7	[redacted]	[redacted]	0.080
Hb 7.00 to 7.99	[redacted]	[redacted]	0.068
Hb 8.00 to 8.99	[redacted]	[redacted]	0.057
Hb 9.00 to 9.99	[redacted]	[redacted]	0.046
Hb 10.00 to 10.99	[redacted]	[redacted]	0.034
Hb 11.00 to 11.99	[redacted]	[redacted]	0.023
Hb 12.00 to 12.99	[redacted]	[redacted]	0.011
Hb ≥ 13	[redacted]	[redacted]	0

Based on CS Tables 42 and 44[1]
CS = company submission; EQ-5D-3L = EuroQol five-dimension three level; Hb = haemoglobin; IPD = individual participant data

4.2.8.3. Utility decrements related to treatment emergent adverse events

Health-related quality of life decrements were found in the literature. Utility decrements per adverse event can be found in CS Table 48.[1]

ERG comment: The main concerns of the ERG relate to: a) the application of health state decrements, b) a lack of detail of the procedure used to estimate the coefficients for the EQ-5D regression analysis, c) inconsistencies in Hb health state utility decrements, and d) the use of additive disutilities.

a) The ERG requested a scenario analysis applying EQ-5D regression analysis directly based on trial data while only capping the estimated health state utility values to not exceed the actual population norm values as there seem to be substantial differences between the two. The company did not comply with this request stating that their approach followed best practice and was more accurate as it explicitly took the age-adjustment and CKD status and dialysis treatment into account. The ERG agrees that the approach of the company in the base-case analysis can be considered good practice.
b) The ERG asked the company to describe in detail the procedure used to estimate the coefficients for the EQ-5D regression analysis; including an overview of the data included, how missing data were handled, how diagnostics of the regression model were assessed, how the (candidate)

covariates as well as interaction terms were selected (with rationale) and how the regression model accounted for nesting effects. The company answered with an elaboration on the regression analysis, including the statement that a SAP was used. Based on the elaboration, the procedure used to estimate the coefficients seemed correct. However, the SAP was not provided to the ERG so that there was no way of evaluating the extent of pre-specification and the consistency of implementation of the SAP.

Relating to the handling of missing data, the company stated all missing data were assumed 'missing at random'. Last observation carried forward was used to impute missing data on dosing and Hb level information. The amount or patterns in the missing data were not given. The ERG finds the 'missing at random' assumption questionable. An alternative plausible explanation of non-completion could be patients feeling unwell and therefore not completing the questionnaire, leading to biased utilities (too high). This could bias QALY measurements upwards, thereby benefitting the most effective treatment in the model. This could favour roxadustat, although the impact is likely to be relatively small considering the small differences in Hb state occupancy between the treatments.

c) The ERG requested an explanation concerning the fact that Hb health state utility decrements seemed to be inconsistent. The company explained that inconsistencies at Hb level >13 g/dl could stem from extreme Hb levels having fewer observations, therefore being subject to greater uncertainty and that Hb levels above the recommended target could lead to additional adverse events. The ERG agrees that this is a plausible explanation for the observed inconsistency. The impact of different Hb health state utilities which would seem more consistent is unknown but likely minor.
d) Disutilities were assumed to be additive, while using alternative approaches (multiplicative or min/max. values) were not explored. Upon request for justification by the ERG, the company referred to Yarnoff 2016[21] and Glenngard 2018[30] to establish that previous studies had used additive utility decrements. The ERG agrees the use of additive utility decrements is consistent with previous studies. However, literature suggests that a multiplicative approach might be preferable with reference to Miyamato et al. 1998.[31]

4.2.9 Resources and costs

Costs that were applied in the economic model were costs related to the treatment (i.e. roxadustat or ESA), dialysis, blood transfusion, IV iron supplementation, drug administration, monitoring and treatment emergent adverse events. Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU).

4.2.9.1 Treatment costs

In line with clinical practice, treatment was given in two phases: correction and maintenance phase. In the correction phase, the weight dependent starting dose is titrated depending on patient's response to treatment and evolution of Hb levels, which was modelled by taking the average treatment dosage (during the first three months) of all patients in the applicable NDD trials (only the DOLOMITES trial was use for ESA)[7-10]. The treatment dose for the maintenance phase was modelled using a GLMM with a Gamma distribution and a log link (estimated separately for roxadustat and ESA). Included covariates were Hb level, CVD history at baseline and diabetic status at baseline.

The drug acquisition cost was set to £0.25 per mg for roxadustat. For ESA drug acquisition costs equivalent dose of the various alternative ESAs had to be estimated using dose conversion rates reported in Table 4.10 (using darbepoetin alfa, used in the DOLOMITES[10] trial, as reference). The costs of the different types of ESA were taken from taken from the BNF.[32-36] The proportions of patients receiving

each ESA were derived from the UK population of the TUNE study. The overall treatment costs were then calculated by multiplying the use of the drug with the price and the conversion factor. The overview of treatment costs can be found in Table 4.11.

Table 4.10: ESA dose conversion rates

ESA	Dose conversion factor
Darbepoetin alfa	1.00
Epoetin alfa	1.40
Epoetin beta	1.11
Epoetin beta (methoxy polyethylene glycol)	0.62
Epoetin zeta	1.38
Based on CS[1] CS = company submission; ESA = erythropoiesis stimulating agent	

Table 4.11: Treatment cost per health state

	Hb <7.00	Hb 7.00 - 7.99	Hb 8.00 - 8.99	Hb 9.00 - 9.99	Hb 10.00-10.99	Hb 11.00-11.99	Hb 12.00-12.99	Hb ≥13
First cycle								
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent cycles (per cycle)								
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: Economic model ESA = erythropoiesis stimulating agent; Hb = haemoglobin								

Following expert opinion,[4] drug administration costs were added for 20% for patients receiving ESA without dialysis and would require assistance with the administration. Out of these, 15% were assumed to require a home distract nurse for the administration and 5% were assumed to require hospital administration. The company assumed a 15-minute appointment with prices reference to PSSRU[37] hourly costs of £21.00 for a home district nurse and £28.25 for hospital administration.

4.2.9.2 Health state costs

Monitoring costs

Four monitoring appointments were assumed in the first model cycle. After the first cycle, 1.5 monitoring 15-minute appointments were assumed per model cycle costing £119 per hour.

Dialysis costs

Dialysis prices were based on NHS reference prices (codes LD01A and LD02A for haemodialysis, codes LD11A and LD12A for peritoneal dialysis).[38] This resulted in a cost of £153.52 for haemodialysis applied to 78.3% of patients on dialysis and a cost of £70.72 for peritoneal dialysis for 21.7% of patients on dialysis.

Blood transfusion

The probability of patients receiving blood transfusion was implemented based on a GLMM with a binomial distribution and logit link. Included covariates were Hb level, treatment type (placebo, ESA or roxadustat), CVD history at baseline and diabetic status at baseline. This was used to calculate probabilities for needing a transfusion per model cycle (CS Table 62; corrected version of this Table is provided in response to clarification question C22).[3] The cost of blood transfusions was based on the weighted average of a day case and outpatient transfusion.[39]

IV iron supplementation

The proportion of patients requiring IV iron supplementation differed between roxadustat and ESA and was estimated using a generalised linear model with a binomial distribution and a log link. Included covariates were Hb level, treatment type (placebo, ESA or roxadustat), study ID (ALPS, ANDES, OLYMPUS or DOLOMITES), CVD history and diabetic status at baseline.

Statistical analysis and expert opinion agreed that Hb levels had no impact on the weekly IV iron dose. The same IV iron dose was therefore applied regardless of Hb levels. A GLMM with a binomial distribution and log link was used to predict treatment dependent IV iron dose per cycle resulting in a [redacted] per administration in every cycle for patients receiving roxadustat and [redacted] per administration in every cycle for patients receiving ESA (both values are the corrected values as provided in response to clarification question C22).

The cost per unit was derived from the BNF.[40, 41] Resource use was derived from observational data on the real-world use from the TUNE study.[42] The average cost per mg applied in the model was £0.17. Administration costs were calculated as a weighted average of healthcare resource group (HRG) codes SA04G to SA04L,[39] leading to a cost of £274.73.

4.2.9.3 Event costs

Event costs for stroke (weighted average incorporating different severities), MI and VAT were included in the model. The total costs, including both acute and long-term costs, per stroke and MI were £8,625 and £3,057 respectively (both values are the corrected values as provided in response to clarification question C22). For VAT no long-term costs were applied in line with expert opinion. The acute cost per incidence of VAT was £3,601.

ERG comment: The main concerns of the ERG relate to: a) the proportion of patients receiving the different ESA types; b) pre-specification and diagnostics of the regression models.

a) As highlighted in the CS, inputs/assumptions related to the calculation of ESA costs are influential. This includes the proportion of patients receiving each ESA type. This was informed using UK specific data from the TUNE (a non-interventional, retrospective cohort study of medical records selected based on a convenience sampling method).[42] In response to clarification question C15, the company highlighted that *"clinical expert opinion confirmed there was no reliable or clear source of data to inform the proportion of patients receiving each ESA in UK clinical practice"*.[3] Therefore, the ERG performed scenario analyses for this input parameter. Similarly, for the proportion of patients for whom ESA drug administration costs are added (based on expert opinion) is considered in the ERG scenario analyses.
b) The company states that for regression analyses an SAP was used, which was unfortunately not provided to the ERG. The ERG was therefore not able to consider the detail or implementation of the pre-specification made in the SAP. The quality of the regression analysis is therefore unclear. The impact of this lack of transparency is unclear.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The CS base-case cost effectiveness results (probabilistic) indicated that roxadustat is both [redacted] (incremental QALYs of [redacted]) and [redacted] (additional costs of [redacted]) and thus [redacted] current care. Moreover, the 95% percentiles for the probabilistic incremental costs and QALYs were [redacted] and [redacted] respectively. The probability of roxadustat being cost effective, at a threshold of £20,000 per QALY gained, compared to ESA is 69%. Table 5.1 details these results.

Overall, the technology is modelled to affect QALYs by:

- Increasing quality of life through favourable transitions between the Hb level health states.

Overall, the technology is modelled to affect costs by:

- Higher treatment costs than current care.
- Proportion of patients receiving the different ESA types.

The disaggregated incremental costs and QALYs for time horizons of 5, 10, 15, 25 (base-case) and 35 years were provided in Table 75 of the clarification responses and are shown in Table 5.1.

Table 5.1: incremental results of roxadustat versus ESA for different time horizons

Variable/Time horizon	5	10	15	Base-case	35
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment (drug)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment (administration)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV iron (drug)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV iron (administration)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Access Thrombosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood transfusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 75 of the clarification response[3]
ICER = incremental cost effectiveness ratio; IV = intravenous; MI = myocardial infarction; NMB = net monetary benefit; QALY = quality adjusted life year; VAT = vascular access thrombosis

ERG comment: The main concern of the ERG related to not including the uncertainty of some parameters in the probabilistic analysis. The company clarified this in response to question C17 and

submitted an updated model file.[3]The impact of the updated probabilistic analysis on the results was very minimal.

5.2 Company's sensitivity analyses

The company performed and presented the results of deterministic sensitivity analyses (DSA) as well as scenario analyses. The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) are:

- The proportion of patients with diabetes. This parameter ranged from 42% to 69% in the company's sensitivity analysis and resulted in the ICER changing from [redacted] to [redacted].
- The weighted cost of the adverse events MI and VAT. A change in the weighted cost of VAT could result in ICER ranges between [redacted] and [redacted]. A change in the weighted cost of MI could result in ICER ranges between [redacted] and [redacted].

The scenario analyses which had the greatest upward effect on the ICER were those relating to:

- The implementation of single ESA formulations for all patients. The largest cost increase was achieved by implementing 100% methoxy polyethylene glycol-epoetin beta use resulting in an ICER of [redacted]. The largest cost decrease was achieved by implementing 100% darbepoetin alfa use, resulting in roxadustat [redacted].

ERG comment: The main concerns of the ERG related a) the absence of a scenario analysis using only DOLOMITES data, b) to the counterintuitive results of the scenario analyses regarding different time horizons.

a) For concerns detailed in section 4.2.6 the ERG requested a scenario analysis using only DOLOMITES data instead of the pooled data of the four NDD trials, see Table 5.2.

Table 5.2: Incremental results of roxadustat versus ESA using DOLOMITES data only versus base-case

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	NMB
	Costs	QALYs	Costs	QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario DOLOMITES data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 47 of the clarification response[3]
ICER = incremental cost effectiveness ratio; NMB = net monetary benefit; QALY = quality adjusted life year

b) While shorter time horizons usually result in a larger ICER, in the company analysis the ICER for shorter time horizons was lower. In response to question C19 the company explained the mechanism that caused this (which was satisfactory) and presented disaggregated outcomes of these scenario analyses and the base case (Table 5.1)

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company stated that experts validated the model approach and assumptions resulting in no major structural or modelling aspects being highlighted.

5.3.2 Technical verification

In the CS, the company states that internal validity was checked using different methodologies identifying no issues with the computational accuracy of the model.

5.3.3 Comparisons with other technology appraisals

No information is given on cross validation with other technology appraisals.

5.3.4 Comparison with external data used to develop the economic model

The company states that the model approach and assumption has been validated by clinical and health economic experts during a series of meetings carried out during the first quarter of 2021. During these meetings, no structural or major modelling aspects were highlighted, and all other insights were incorporated into the clinical positioning and modelling approach. In addition, cross-checks against source data were conducted by the company.

5.3.5 Comparison with external data not used to develop the economic model

No information was given regarding comparisons with external data not used to develop the economic model.

ERG comment: The main concerns of the ERG relate to: a) lack of detail on the face validity assessment, b) limited technical validation, c) limited cross- and external validation, d) inconsistencies between the submission report and the model.

a) The ERG requested more details of the face validity assessment, which the company provided in response to clarification question C20. [3] The model has been validated by two clinical experts and one health economic expert at two occasions and the minutes of these meetings were provided.
b) The technical validation was conducted in a manner which was not sufficiently transparent for the ERG (detailed descriptions with results of the tests are missing in CS section B.3.9.1).[1]The ERG asked the company to use the TECH-VER checklist[43] to assess the technical verification of the economic model and report the results. The company stated they had unfortunately not been able to undertake the technical validation using the checklist indicated in the allowed time for the clarification response. The ERG notes that, as suggested by the authors, under a time constraint, the time to complete the TECH-VER checklist can be limited if a hierarchical approach is followed (starting with black-box tests and only performing white-box tests and replication-based tests if errors are detected).
c) The ERG asked for additional cross- and external validation of the model (clarification question C20).[11] More specifically, the ERG asked for cross validation of the model structure, model assumptions, model inputs, intermediate outcomes as well as final outcomes with other economic models focusing on a related decision problem. This included the publications described in CS section B.3.1 as well as NICE TA358 (Tolvaptan for treating autosomal dominant polycystic kidney disease), and external validation using data used and not used for the development of the model. In response, the company stated that none of the studies described in CS section B3.1 or NICE TA358 fully aligned with the decision problem in their submission.[3] For that reason, the company deemed the requested analyses not relevant/reliable/necessary. The ERG agrees that the studies mentioned do not align fully with the decision problem in the current submission, but nevertheless has the opinion that cross-validation and external validation can provide information on (aspects of) the robustness of the current evaluation.

d) The ERG noted several inconsistencies between the CS submission report and model. In response to clarification question C22 the company clarified that these were all due to outdated tables in the company submission report.[3]

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[44]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, the ERG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016)[45]:[45]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base-case

Adjustments made by the ERG, to derive the ERG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base-case. The 'fixing error' adjustments were combined and the other ERG analyses were performed also incorporating these 'fixing error' adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

Fixing errors

None identified. Inconsistencies identified by the ERG were resolved during the clarification phase. Notably, issues might be highlighted after the ERG report has been submitted given it was not possible for the company to undertake the technical validation using the TECH-VER checklist in the allowed time (clarification response C21; section 5.3).

Fixing violations

1. Suboptimal pooling of the NDD trials potentially inducing bias (Section 4.2.6)
   Only the DOLOMITES trial data were used (instead of pooling all four NDD trials). This was implemented by using the "ID1483 Roxadustat CEM C7 v0.1 02.08.21 [CIC].xlsm" model file submitted by the company (in response to clarification questions).

Matters of judgement

Although the ERG identified matters of judgement, these were not included in the ERG base-case. Either because these issues were not influential or because the issues were incorporated in ERG scenario analyses (shortened time horizon, proportion per ESA type, proportion requiring ESA administration costs).

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base-case.

Exploratory scenario analyses

2. Time dependency and extrapolation of the multinomial logistic regression model (section 4.2.6)
   This was implemented by adjusting cell E18 on the "Model set up" worksheet.
   a. Shorter time horizon of 5 year
   b. Shorter time horizon of 10 year
3. Proportion of patients receiving each ESA agent (Section 4.2.9)
   This was implemented by adjusting cells E250:E254 on the "Population" worksheet.
   c. All patients receive darbepoetin alfa
   d. All patients receive epoetin alfa
   e. All patients receive epoetin beta
   f. All patients receive epoetin beta (methoxy polyethylene glycol)
   g. All patients receive epoetin zeta
4. No patients require ESA administration costs (Section 4.2.9)
   This was implemented by adjusting cell E49 on the "Model set up" worksheet.

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER	Resolved in ERG base-case	Required additional evidence or analyses
It was not thoroughly justified whether the eight health states, based on different Hb ranges, to model the anaemia status would properly reflect the treatment effect of Roxadustat as compared to ESA	4.2.2	Bias / Unavailability	The use of different cut-offs for the Hb ranges, and / or a smaller number of health states	Unclear	No	None
Suboptimal pooling of the NDD trials	4.2.6	Methods	Either using appropriate methods to pool the NDD trials or only use the DOLOMITES trial data (as in the ERG base-case)	Substantial	Yes	None
Time dependency and extrapolation of the multinomial logistic regression model. It is unclear to what extend the time trends observed during the relatively short follow-up of the trials can be extrapolated for the 25 year time horizon.	4.2.6	Unavailability	Analyses requested in clarification question C7c to assess the impact of including log(time + 1) as a covariate and interaction term.	Unclear	No	Further validation to support the inclusion of log(time + 1) as both a covariate as well as an interaction term (between log(time + 1) and treatment type) might be informative.
The company excluded potentially relevant adverse events with inconsistent reasoning.	4.2.7	Bias	The inclusion of additional adverse events (clarification question C8)	Unclear	No	Include additional adverse events in the model as requested in clarification question C8.
Model validation was limited	5.3	Bias	Perform additional cross-validation and external validation and complete the TECH-	Unclear	No	Perform the model validity analyses requested in clarification question C20, C21, C22

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER	Resolved in ERG base-case	Required additional evidence or analyses
			VER checklist for technical validation.			
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio						

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Table 6.2 the ERG base-case was presented (as described in section 6.1). The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the ERG base-case. The analyses numbers in Tables 6.2 and 6.3 correspond to the numbers reported in section 6.1.

Table 6.2: ERG base-case

	Total costs	Total LYs	Total QALYs	Δ Costs	Δ LYs	Δ QALYs	ICER
Company base-case – deterministic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base-case – probabilistic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1) ERG base-case (using DOLOMITES data only) - deterministic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1) ERG base-case (using DOLOMITES data only) - probabilistic							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6.3: Deterministic scenario analyses (conditional on ERG base-case)

	Total costs	Total LYs	Total QALYs	Δ Costs	Δ LYs	Δ QALYs	ICER
1) ERG base-case (using DOLOMITES data only)							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2a) ERG base-case (using DOLOMITES data only) + 5 year time horizon							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2b) ERG base-case (using DOLOMITES data only) + 10 year time horizon							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3a) ERG base-case (using DOLOMITES data only) + all patients receive darbepoetin alfa							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3b) ERG base-case (using DOLOMITES data only) + all patients receive epoetin alfa							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3c) ERG base-case (using DOLOMITES data only) + all patients receive epoetin beta							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Total costs	Total LYs	Total QALYs	Δ Costs	Δ LYs	Δ QALYs	ICER
3d) ERG base-case (using DOLOMITES data only) + all patients receive epoetin beta (methoxy polyethylene glycol)							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3e) ERG base-case (using DOLOMITES data only) + all patients receive epoetin zeta							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4) ERG base-case (using DOLOMITES data only) + no patients require ESA administration costs							
Roxadustat	[redacted]	[redacted]	[redacted]				
ESA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 ERG's preferred assumptions

The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions highlighted in section 6.1, was [redacted] per QALY gained. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY gained. The ICER increased most in the exploratory scenario analyses with alternative assumptions regarding the proportion of patients receiving each ESA agent.

6.4 Conclusions of the cost effectiveness section

The company developed a de novo health state transition cohort model, programmed in Microsoft® Excel, to conduct a cost-utility analysis. In addition to a death health state, eight alive health states were defined to reflect the anaemia status based on different ranges of Hb levels. Patients alive at the beginning of each cycle were distributed across the eight Hb health states and the treatment (roxadustat or ESA) impacted transition probabilities between these states over time. Time to dialysis data were used to estimate the proportion of patients on dialysis. The relationships between dialysis status, survival and HRQoL, and between treatment related adverse events (TRAE), survival and HRQoL were not explicitly modelled. In line with expected indication, the cost effectiveness analysis evaluated roxadustat for the treatment of adult patients with symptomatic anaemia associated with CKD (stages 3-5) who are not on dialysis at the time of treatment initiation. This is a subpopulation of the population stated in the NICE scope. The intervention considered in the CS is roxadustat, a first in class oral HIF-PHI. The comparator of interest in the CS is ESA; ESAs were considered to have equal efficacy at equivalent doses and were modelled as a class. Perspective, discount rate and time horizon were in line with the reference case.

The company used the four NDD trials to model the effectiveness of roxadustat compared to ESA. Input parameters for costs were based on literature. Health-related quality of life was incorporated using general population utility values adjusted for age, sex, CKD and dialysis status (based on literature) and further adding utility decrements related to Hb level, history of CVD, diabetic status (based on the four NDD trials) and treatment emergent adverse events (based on literature). Costs were based on literature and the four NDD trials.

The CS base-case cost effectiveness results (probabilistic) indicated that roxadustat is both [redacted] (incremental QALYs of [redacted]) and [redacted] (additional costs of [redacted]) and thus [redacted] current care. Moreover, the 95% percentiles for the probabilistic incremental costs and QALYs

were [redacted] to [redacted] and [redacted] to [redacted], respectively. The probability of roxadustat being cost effective, at a threshold of £20,000 per QALY gained, compared to ESA is 69%. Overall, the technology is modelled to affect QALYs by increasing quality of life through favourable transitions between the Hb states. The technology is modelled to affect costs by higher treatment costs than current care, and the proportion of patients receiving the different ESA types. The CS base-case results are most sensitive to the proportion of patients with diabetes, and the weighted cost of the adverse events MI and VAT. The scenario analyses which had the greatest upward effect on the ICER were those relating to the implementation of single ESA formulations for all patients.

The key issues identified by the ERG are related to the model structure, the estimation of treatment effectiveness, the adverse events included in the analyses and model validation.

- According to the ERG, it was not thoroughly justified whether the eight health states, based on different Hb ranges, to model the anaemia status would properly reflect the treatment effect of roxadustat as compared to ESA. Specifically, there was suboptimal pooling of the NDD trials. The regression models used to estimate treatment effectiveness are potentially biased due to suboptimal pooling of the four NDD trials. The ERG believes that the most appropriate analysis should be one using solely the DOLOMITES trial, which provides direct evidence for the effectiveness of roxadustat and ESA in patients drawn from the same population. This potentially has a substantial impact on the estimated cost effectiveness.
- Furthermore, the ERG had concerns related to the time dependency and extrapolation of the multinomial logistic regression model used to estimate the proportion of patients in the Hb health states. It is unclear to what extent the time trends observed during the relatively short follow-up of the trials can be extrapolated for the 25-year time horizon, especially the interaction between treatment type and time. This was also raised as a concern during the clinical and health economic validation performed by the company. The company excluded potentially relevant adverse events with inconsistent reasoning, which could bias the results.
- Finally, the ERG considered the model validation to be suboptimal. The bias potentially caused by the model structure, the multinomial logistic regression model used to estimate the proportion of patients in the Hb health states, excluding adverse events, and a possible lack of model validity could not be quantified. To address the issue related to the pooling of the four NDD trials to estimate treatment effectiveness, the ERG used only the DOLOMITES trial data in their base case analysis.

The estimated ERG base-case ICER (probabilistic), based on the ERG preferred assumptions, highlighted in section 6.1, was [redacted] per QALY gained. The probabilistic ERG base-case analyses indicated cost effectiveness probabilities of [redacted] and [redacted] at WTP thresholds of £20,000 and £30,000 per QALY gained. The ERG did not identify errors that warranted fixing. The ERG did fix the violation related to the suboptimal pooling of the four NDD trials (section 4.2.6). In the ERG base-case only the DOLOMITES trial data were used. Although the ERG identified matters of judgement, these were not included in the ERG base-case. Either because these issues required substantial model adaptations (incorporating additional adverse events) or because the issues were incorporated in ERG scenario analyses (shortened time horizon, proportion per ESA type, proportion requiring ESA administration costs). The ERG base-case ICER increased most in the exploratory scenario analyses with alternative assumptions regarding the proportion of patients receiving each ESA agent.

In conclusion, the ERG's key issues related to the model structure, pooling of NDD trials, extrapolation of proportion of patients per Hb state, inclusion of AEs and model validity. Addressing the issue of pooling of the NDD trials, the ERG base case is based on the DOLOMITES trial data only, which

provides direct evidence for the effectiveness of roxadustat and ESA in patients drawn from the same population. This resulted in an ICER of [redacted]. The other issues could not be quantified so the direction of bias is unclear.

7. END OF LIFE

The CS did not include any statements regarding roxadustat meeting the end of life criteria defined by NICE, therefore this is not applicable.[1]

8. REFERENCES

[1] Astellas. *Roxadustat for treating anaemia in CKD patients [ID1483]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*: Astellas, 2021. 379p.

[2] National Institute for Health and Care Excellence. *Roxadustat for treating anaemia in adults with chronic kidney disease. Final scope*, 2021. 4p. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10610/documents

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 8 September 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Reference to inconsistencies between the submission report and model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 1.1 (Table 1.1, Issue 8), and Section 5.3.5. (Page 75), the ERG states one of the main problems identified in the submission are the *"(…) inconsistencies between the submission report and the model."* These issues have been effectively addressed by Astellas in the response to the ERG clarification questions and Astellas considers that this is no longer a key issue.	Astellas requests the ERG to remove the "*inconsistencies between the submission report and the model"* as a key issue from Section 1.1 (Table 1.1, Issue 8), and from Section 5.3.5 (Page 75, ERG comment d))	All inconsistencies have been addressed and resolved by Astellas in the response to the ERG clarification questions. Specifically, the inconsistencies the ERG is referring to, have been addressed in the response to the clarification question *C22*.	Not a factual inaccuracy.

Issue 2 Population: Generalisability to NHS patients in England and Wales

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG is concerned about the generalisability of the company's clinical evidence to NHS patients in England and Wales due to the number of UK patients contained in the roxadustat randomised controlled trials (RCTs). The ERG is overestimating the limitations derived from the size of this subpopulation and contradicts clinical experts'	Astellas requests the following amendments to be performed: 1. Removing from Section 1.1 (Table 1.1) Issue 4, detailed and underlined below: *"The trials include very few participants from the United Kingdom (UK)."* 2. Adding a statement mentioning experts positive opinion considering roxadustat RCTs as representative of UK clinical	This rationale contradicts the acceptance of the trials populations as representative of UK clinical practice by experts during model clinical and health economic validation.	Not a factual inaccuracy. The ERG feels the generalisability of the presented evidence to clinical practice in England and Wales is reflected adequately A statement regarding the opinion of experts were

opinion considering roxadustat RCTs as representative of UK clinical practice. In Section 1.1 (Table 1.1), Section 2.1 (Page 24), Section 3.2.3 (Page 42), Section 1.4 (Table 1.5), Section 3.2.3 (Page 42 and Page 43), Section 3.2.3 (Page 43)	practice in Section 2.1 (Page 24) as follows (text underlined): "*The ERG is also concerned about the generalisability to NHS patients in England and Wales (see sections 3.2.3, 3.6).* <u>It should be noted however, that roxadustat RCTs were considered as representative of UK clinical practice during the model clinical and health economic validation</u>" 3. Removing the word "only" when referring to the number of UK patients as this is a subjective interpretation by the ERG. See below (text underlined). - In Section 3.2.3 (Page 42): *"The company was asked in the clarification letter to provide more information on the number of patients in the trial who were recruited in the UK: <u>only</u> [redacted] ([redacted]%) and [redacted] ([redacted]%) of the roxadustat and darbepoetin alfa arm, respectively."* - In Section 3.2.3 (Page 43): *"The DOLOMITES trial population is <u>only</u> [redacted]% from a UK population."*		added to sections 2.1, 3.2.3, and 3.6.

Issue 3 Population: UK population subgroup analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Derived from the ERG concerns about the generalisability of clinical evidence contained in the CS to NHS patients in England and Wales, the ERG is suggesting a potential analysis of a subpopulation with only UK patients, despite recognising the limitations associated to this analysis. In Section 1.4 (Table 1.5), and Section 3.2.3 (Page 43).	Astellas requests the following amendments to be performed: 1. Removing the following phrase detailed below (text underlined) in Section 3.2.3 (Page 43): "This is correct, however, an exploratory analysis restricted to UK populations could provide tentative evidence." 2. Adding a statement highlighting the limitations of performing an exploratory analysis with only UK patients in Section 1.4 (Table 1.5) as follows (text underlined) "*An exploratory subgroup analysis with UK patients could be conducted.* However the weakness of performing such an analysis on a small subgroup should be noted. The limitations associated to the sample size would result in reduced chance of detecting a true effect, low likelihood that a statistically significant result reflects a true effect, overestimated effect sizes, and low reproducibility."	Roxadustat's RCTs ANDES and OLYMPUS studies did not enrol any patients in UK centres. Given the small number of patients in the ALPS and DOLOMITES studies, no robust statistical analysis could be performed to provide the same clinical effectiveness endpoints as reported in section B.2 of the CS for the UK population. Performing statistical analyses in samples with low-statistical power has different associated problems such as reduced chance of detecting a true effect, low likelihood that a statistically significant result reflects a true effect, overestimated effect sizes, and low reproducibility. Additionally, subgroups should have been defined in the scoping stage with consideration being given to the rationale for expecting a subgroup effect. Considering the ERG have accepted the highlighted limitations as correctly identified, the rationale of performing the analysis nevertheless is unjustified	Not a factual inaccuracy. The "ERG comment" in section 3.2.3 adequately reflects the view of the ERG while highlighting the view of the company.

		and is likely to introduce greater uncertainty.	

Issue 4 Population: Exclusion of CKD 1-2 patients from the submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG report states further research should be done regarding patients with low CKD levels (CKD 1-2). The ERG has suggested that the clinical trial population being in patients with CKD 3-5 has impacted the generalisability to the UK clinical population. In Section 1.3 (Table 1.2) and Section 3.2.3 (Page 43)	Astellas requests deleting the following statements (text underlined) 1. In Section 1.3 (Table 1.2): "Current evidence restricted to narrower population. Further research should include patients with lower CKD stages." 2. in Section 3.2.3 (Page 43) removing the reference to stages 3-5 limiting the generalisability to UK practice. See below (text underlined) "As such, and along with the restriction of the DOLOMITES trial to patients with CKD stages 3-5 and NDD, the generalisability of the DOLOMITES study results to the UK clinical population may be limited"	In line with the NICE scope, ESA are the relevant comparator for roxadustat and are only prescribed in secondary care. Patients with CKD 3-5 are the relevant patient population as, in line within the NICE Clinical Guideline for CKD, patients are referred into secondary care for treatment of anaemia associated with CKD from CKD stage 3 onward. Patients in the early stages of CKD have a lower prevalence and severity of anaemia. Patients with CKD 1-2 will be under the care of their GP and only receive oral iron as treatment for anaemia. Furthermore, the anaemia in patients with CKD 1-2 is unlikely to be due to reduced erythropoietin (EPO) in the body and therefore will not be treated with ESAs. (Mercadal, L et al. 2012) For these reasons, patients with CKD1-2 have not been considered as relevant in this appraisal. This choice is aligned with the decision	Not a factual inaccuracy. Section 2.1 of the ERG report correctly describes the issue, including the response given by the company in response to request for clarification.

		problem and is consistent with how roxadustat is expected to be used in clinical practice. Astellas does not consider this population to be a determinant factor in the submission.	

Issue 5 Population: Inaccuracy when referring to the population of interest for this submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG states the population included in this appraisal is in line with the expected indication. According to Astellas this is not accurate enough. In Section 6.4 (Page 81): *"In line with expected indication, the cost effectiveness analysis evaluated roxadustat for the treatment of adult patients with symptomatic anaemia associated with CKD (stages 3-5) who are not on dialysis at the time of treatment initiation"*	Astellas requests to rephrase the statement described in Section 6.4 (Page 81) detailed in the description of the problem by the following text: "Within roxadustat expected indication and aligned with roxadustat's decision problem, the cost effectiveness analysis evaluated roxadustat for the treatment of adult patients with symptomatic anaemia associated with CKD (stages 3-5) who are not on dialysis at the time of treatment initiation."	The population of interest addressed in this submission and cost-effectiveness analysis is within the expected indication of roxadustat, but narrower as it focuses in adult patients with symptomatic anaemia associated with CKD (stages 3-5) who are not on dialysis at the time of treatment initiation.	Not a factual inaccuracy.

Issue 6 Population: Inaccuracy when describing the population of roxadustat RCTs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
All roxadustat clinical trials include only CKD 3-5 patients. This is not reflected accurately in the ERG report. 1. In Section 2 (Table 2.1, Decision problem addressed in the company submission column, Population row): *"Adult patients with symptomatic anaemia associated with CKD who are non dialysis dependent (NDD) at the time of treatment initiation.* *For some of the analyses: patients with only CKD stages 3-5."* 2. In Section 2.1 (Page 24): *"In addition, some of the studies were restricted to patients with CKD stages 3-5."* 3. In Section 3.2 (Table 3.3, DOLOMITES column, Population row)	Astellas requests the following amendments to be performed: 1. In Section 2 (Table 2.1, Decision problem addressed in the company submission column, Population row) amend the text as detailed below: Adult patients with symptomatic anaemia associated with CKD 3-5 who are non-dialysis dependent (NDD) at the time of treatment initiation. 2. In Section 2.1 (Page 24), replace "some of the studies" with "all of the studies" as detailed below: In addition, all of the studies were restricted to patients with CKD stages 3-5. 3. In Section 3.2 (Table 3.3, DOLOMITES column, Population row) amend the text as detailed below: Patients with anaemia associated with Stage 3,4 or 5 CKD, who have not started dialysis treatment.	All roxadustat NDD RCTs (ALPS, ANDES, OLYMPUS, and DOLOMITES) were restricted to Stage 3, 4, or 5 CKD patients.	The ERG made changes in section 2.1.

“Patients with anaemia associated with CKD who have not started dialysis treatment”			

Issue 7 Roxadustat as an innovative intervention

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 2.5 (Page 25), the ERG states that according to the company, roxadustat is innovative because it can be taken orally: *"According to the company, roxadustat is innovative because it can be taken orally, which represents a lower burden to patients who are NDD, notably because patients can be treated from home. In addition, roxadustat does not require cold-chain storage so is more easily transported and stored."* This is misleading as implies roxadustat's innovation is solely based on its oral method of administration.	Astellas request the ERG to add roxadustat's mode of action as an argument sustaining the drug innovative character (text underlined above) In Section 2.5 (Page 25): *"According to the company roxadustat is innovative primarily* <u>because of, its mode of action; roxadustat is a first-in-class oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI), and</u> *because it can be taken orally, which represents a lower burden to patients who are NDD, notably because patients can be treated from home. In addition, roxadustat does not require cold-chain storage so is more easily transported and stored."*	Roxadustat is a first-in-class oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI). Roxadustat activates the oxygen-sensing HIF pathway to mimic the body's natural response to hypoxia by reversibly inhibiting HIF-PH enzymes that target HIFs for degradation under normal oxygen conditions. Through the inhibition of HIF-PH, it stimulates a coordinated erythropoiesis response that includes the increase of plasma erythropoietin (EPO) levels, regulation of iron transporter proteins and reduction of hepcidin. This results in improved iron bioavailability, increased haemoglobin production and increased red cell mass. Roxadustat's multidimensional mode of action is an innovative solution for treating anaemia associated with CKD's multifactorial causality.	Not a factual inaccuracy.

Issue 8 Modelling ESA as a class

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG states their concern about modelling ESA as a class. While there is an agreement in the assumption of equivalent efficacy among ESAs, the ERG concern is motivated by the difference in ESA prices. Precisely, the ERG states: In Section 4.2.4 (Page 62) *"The main concern of the ERG related to modelling ESA as a class. According to the guidelines the different ESA have equal efficacy at equivalent doses. The prices are however quite different. See section 4.2.9."*	Astellas requests to remove the ERG comment underlined flagging this aspect as an issue of concern. In Section 4.2.4 (Page 62) (text underlined) *"The main concern of the ERG related to modelling ESA as a class. According to the guidelines the different ESA have equal efficacy at equivalent doses. The prices are however quite different. See section 4.2.9."*	Astellas has considered and captured differences in ESA prices and dosing in an accurate way, allowing to group these as a class in the company cost-effectiveness model. The economic model has been designed with the capability of adjusting the proportion of patients being treated with each ESA type, ESA doses, and prices. The company cost-effectiveness model allows the user to set the proportion of patients being treated with each ESA type. These proportions are used to calculate the weighted average number of drug administrations per week. In the base case, data specific to the UK was used with values sourced from the TUNE study (a real world study of UK ND patients). In order to estimate equivalent doses for the different ESA types included in the company cost-effectiveness model, the model takes a pragmatic approach where the recommended weekly dose (in mcg) derived from the BNF was utilised to calculate equivalent dose	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		conversion ratios between the available ESA. In terms of prices, the unit cost per injection and per microgram (mcg) of each ESA was derived from the BNF, converting international units (IU) to mcg where required. The process described above, which is further detailed in the Company Submission (CS) Section B.3.5.1.2. Drug acquisition costs, accurately captures all dimensions of ESA costs, addressing the concern expressed by the ERG, and allows grouping ESAs as a class in the cost-effectiveness model.	

Issue 9 Model structure: Kidney transplant and CKD stages

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 4.2.2 (Page 61) ERG Comment c), the ERG flags kidney transplant and CKD stages have not been included in the model. The ERG agrees with the justification provided by Astellas in the response to the ERG clarification question *C1d.* Still, the ERG insists in the issue by stating that: *"it might impact the absolute estimates of costs and QALYs."*	Astellas requests deleting the following statement detailed below (text underlined). In Section 4.2.2 c) (Page 61): "(…) <u>but it might impact the absolute estimates of costs and QALYs.</u>"	Considering the ERG agreement with the response given by Astellas in the ERG clarification question *C1d*, the company considers inappropriate flagging the impact of this matter in absolute estimates of costs and QALYs as this would not have an impact in the incremental cost effectiveness results of both interventions of interest. Additionally, as already detailed in the response to the ERG clarification question *C1d* and reinforcing the company approach, this aspect is not considered given roxadustat and ESA are not treatments for CKD and are used only to correct anaemia, and kidney transplant was not captured in the clinical trials and was part of the criterion for discontinuation.	Not a factual inaccuracy.

Issue 10 Model structure: justification for the Hb ranges and cut-off values to define health states is lacking.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 1.1 (Table 1.1) and Section 4.2.2 (page 60), ERG Comment a), the ERG states a lack of justification for the Hb	Astellas request removing the following:	As previously stated in the response to the ERG clarification question *C1a*, the use of eight health states was based on a	Not a factual inaccuracy.

ranges and cut-off values applied to define health states in the company cost-effectiveness model. The company believes that explanation provided in clarification question response *C1a* adequately justifies the Hb ranges and cut-off values applied to define health states in the company cost-effectiveness model and that this issue has been addressed.	1. Section 1.1 (Table 1.1) Issue 5, as detailed and underlined below: "Model structure: justification for the Hb ranges and cut-off values to define health states is lacking." 2. the ERG comment a) detailed in Section 4.2.2 (page 60)	previously published cost-effectiveness model of anaemia treatment for people with CKD. The Hb categories used for the relative risks for blood transfusion in the model match the eight health states used in the company model. Yarnoff et al. 2016 also state the utility loss per 1 g/dL in Hb. This was based on previous works in the literature demonstrating significant improvements in a variety of quality of life domains with increasing Hb levels. Other studies have shown that utility values differ per 1 g/dL change in Hb levels (Glenngard AH, 2008). No significant impact of Hb on survival was shown in the economic analysis but the change in HRQoL in the literature justifies the use of the eight health states. Using a smaller number of health states could lead to granularity in time trends being lost between treatment arms. Using a model with eight health states shows the nuances which could be important to demonstrate in the economic analysis. The use of eight health states was also accepted by clinical experts.	

Issue 11 The cost effectiveness analysis in the CS relies upon pooled data across roxadustat arms of NDD ALPINE trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG argues Astellas based the cost-effectiveness analysis on pooled data across roxadustat arms of the relevant non-dialysis dependent (NDD) trials, but that since some of these trials did not use comparators specified in the final NICE scope (ESAs), the resulting analysis is unanchored and indirect. Astellas believes this and the implications derived from this reasoning such as using only the DOLOMITES trial to inform the ERG base case are fundamentally wrong In Section 1.1 (Table 1.1, Issue 3), Section 1.4 (Table 1.4), Section 1.7 (Page 17), Section 2.3 (Page 25), Section 3.2 (Page 31), Section 3.3 (Page 49), Section 3.4 (Page 52), Section 3.5 (Page 52), Section 3.6 (Page 52), Section 4.2.1 (Table 4.4, Synthesis of evidence on health effects), Section 4.2.3 (Page 61), Section 4.2.6 (Page 64, ERG comment b))	Astellas requests the following amendments to be performed: 1. In Section 1.1 (Table 1.1, Issue 3), remove Issue 3 as a key issue 2. In Section 1.4 (Table 1.4), delete the evidence presented on the clinical effectiveness, namely the inclusion of non-randomised comparisons between roxadustat and ESAs, as matter of major concern 3. In Section 1.7 (Page 17), reformulate the Summary of the ERG's according to the amendments requested by considering all roxadustat RCTs (ALPS, ANDES, OLYMPUS, and DOLOMITES) *4.* In Section 2.3 (Page 25), delete the following statement (text underlined): *"The ERG believes that the limitations of this approach are more serious than the company acknowledged (see sections 1.4, 2.3, and 3.3)."* 5. In Section 3.2 (Page 31), reconsider the trials relevant to this submission expanding these to all roxadustat RCTs	Astellas disagrees with the ERG's reasoning and does not believe that it justifies the exclusion of the ALPS, ANDES and OLYMPUS trials. This would result in the removal of relevant data from over 2,300 individuals from the analysis and subsequent decision-making. As can be seen from Table 10 in the response document to the ERG questions, individuals recruited into all four NDD studies were very similar in terms of potential baseline risk or treatment effect modifiers. While there may be differences in some variables, if these are not modifiers of baseline risk or treatment efficacy, we would argue that these differences do not justify the use of DOLOMITES only as one of the smallest of the four studies. Further, the roxadustat dose, dosing schedule and mode of delivery were the same in all four studies. This again suggests that it is appropriate to try and borrow strength from all four studies to inform decision making.	Not a factual inaccuracy. As discussed in the ERG report, e.g. sections 2.3 and 3.2.1, DOLOMITES is the only trial directly comparing roxadustat to the comparator of interest, namely ESA.

	(ALPS, ANDES, OLYMPUS, and DOLOMITES) 6. In Section 3.3 (page 39), delete the following statement (text underlined) *"(…) This effectively implies and unanchored indirect treatment comparison: the population used to inform the roxadustat treatment in the CEM comprises the roxadustat arms of all NDD ALPINE studies (of which DOLOMITES contributes 322 of 2,690 patients, 12.0%), whereas the population used to inform the ESA arm likely comprises solely patients in the ESA arm of the DOLOMITES trial. It is not clear in the CS or the clarification responses whether the DOLOMITES trial provides all the evidence for ESA in the CEM, but it is unclear what further data could have been used."* 7. In Section 3.4 (Page 52), adjust this section to the amendments requested by considering all roxadustat RCTs (ALPS, ANDES, OLYMPUS, and DOLOMITES) 8. In Section 3.5 (Page 52), adjust this section to the amendments requested by considering all roxadustat RCTs (ALPS, ANDES, OLYMPUS, and DOLOMITES) 9. In Section 3.6 (Page 52), adjust this section not the amendments requested by considering all roxadustat RCTs	As previously stated in response to clarification question *B20*, all analyses conducted in section B.2.10 of the submission dossier were conducted by pooling all participants of all studies together to create a "master dataset". It should be noted that the placebo and darbepoetin alfa outcome data are not pooled together. Instead, the roxadustat outcome data is pooled across studies using a hierarchical model (i.e. all roxadustat data is compared to its own within trial comparator but strength is borrowed from each study to inform the overall estimates for roxadustat). Using this methodology allows for more accurate roxadustat predictions as it leverages data from all 2,690 study participants. This means that any cost-effectiveness estimates are based on individual patient data from nearly 3,000 individuals (the total of all individuals who received roxadustat or darbepoetin alfa) rather than the 684 in DOLOMITES. This will lead to greater certainty around many model parameters and hence a more robust incremental cost-effectiveness ratio (ICER) for decision-making.	

	(ALPS, ANDES, OLYMPUS, and DOLOMITES 10. In Section 4.2.6.4 (Page 64, ERG comment b)). remove the following statement (text underlined): *"However, given that the methods used to pool the NDD trials are suboptimal (see above), this is a trade-off between imprecision (using the DOLOMITES trial only) and bias (using the pooled NDD trials). Therefore, the ERG has a strong preference for using the DOLOMITES trial only analyses (adopted in the ERG base-case)."* 11. In Section 6 (Page 76), adjust this section to the amendments requested. Specifically, Astellas requests the ERG using information from all relevant studies in their decision making and not just the DOLOMITES study. We suggest the ERG reconsidering their base-case as the violation detailed in Section 6.1.1 (Page 77) is not correct.	In essence we have performed an individual patient-level data (IPD)-meta analysis in order to borrow strength across the pooled studies to generate relative efficacy estimates for roxadustat compared to other treatments of interest (particularly darbepoetin alfa). It should be noted that the cost-effectiveness model does not compare placebo with darbepoetin alfa at any point (as these were never compared directly with any of the clinical trials). We would further like to point out that all statistical models accounted for any potential differences between clinical trials by using a hierarchical model structure and used each unique study ID to control for any impacts of "nesting" (i.e. patients from the same study are more likely to behave in a similar manner compared with patients from another study) where possible. Where it was not possible to conduct hierarchical models due to limitations in the available software (multinomial logistic regressions for proportion in state), study IDs were included as fixed effect variables. Although this is not an ideal approach to account for nesting effects, it was deemed	

		appropriate to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. Furthermore, imbalances in baseline patient characteristics that may be prognostic of outcome (e.g. age, sex, CVD history, diabetes and estimated glomerular filtration rate (eGFR)) were also controlled for within the statistical models, something that cannot be done using fixed/random effect meta-analyses. Meta-analyses do not adjust for any heterogeneity in study populations that may influence treatment outcomes. Apart from a potential increase in the proportion of patients with a history of CVD at baseline in DOLOMITES, all patient characteristics used within the cost-effectiveness modelling are broadly balanced between studies as shown in Table 10 in the response document to the ERG questions. Furthermore, the lability of the ICER to small changes in costs or QALYs in the DOLOMITES only analysis should be noted. For these reasons, Astellas believes discarding data from 2,300 patients is not justifiable, and the	

		analysis using all four NDD trials offers the most appropriate use of all available evidence and should therefore be used for decision-making purposes.	

Issue 12 Time dependency and extrapolation of the multinomial logistic regression model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 1.1 (Page 11), the ERG has categorised the time dependency and extrapolation of the multinomial logistic regression model as mistaken. The use of the adjective "mistaken" is not considered appropriate as is it not a "mistake" as such.	Astellas request removing the adjective "mistaken" when referring to the time dependency and extrapolation of the multinomial logistic regression. The specific text to be removed is detailed below (text underlined). In Section 1.1 (Page 11): "*Treatment effectiveness and extrapolation: time dependency and extrapolation of the multinomial logistic regression model <u>is mistaken</u>"*	Previous justification of the inclusion of time within the multinomial logistic regression model for extrapolation purposes has been discussed in response to clarification questions *C5e, C5f, C5g* and *C5h*. This was also presented in detail in section B.3.3 of the original CS. Additionally, the ERG states later in section 4.2.6 of the ERG report that *"The appropriateness and impact of including log (time +1) are unclear to the ERG*". Furthermore, the effects of time and extrapolation have been explored in ERG scenario analyses and have been accepted as matters of judgement in the ERG report therefore we do not feel that this warrants the description that it is "mistaken".	Consistent with the suggestion, "is mistaken" has been removed.

Issue 13 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 4.2.7. (Page 66), the ERG states relevant adverse events have been excluded using an inconsistent reasoning, given major adverse cardiovascular (MACE) events did not show a significant difference between treatments and these were included. Furthermore, the ERG have highlighted adverse events with a difference of two percent or more between treatment arms in DOLOMITES as a criteria for inclusion within the model. The choice of two percent is seemingly arbitrary and has no bearing on clinical or statistical significance.	Astellas requests removing the text detailed below (text underlined) In Section 4.2.7 (Page 66): "The ERG therefore considers it inconsistent to use this argument to exclude other adverse events. The impact on the results is unclear" "The incidence of oedema peripheral (15.2% for roxadustat patients and 12.3% for darbepoetin alfa patients), hyperkalaemia (11.8% compared to 14,3%), nausea (10.8% compared to 8.5%), hyperphosphatemia (8.7% compared to 5.1%), muscle spasms (7.7% compared to 5.1%), dyspnoea (7.4% compared to 4.1%), headache (6.5% compared to 4.1%), and insomnia (5.9% compared to 2.7%) seem to differ by two percent or more."	For the patient population considered in the model (i.e. NDD patients who are not adequately managed with IV iron alone and require an ESA), MACE are especially important as increased doses of ESA further expose patients to increased risk of adverse events. The model included three key treatment emergent adverse events (TEAE): two major cardiovascular adverse events (MACE) (stroke and MI) and vascular access thrombosis (VAT). Stroke and MI were chosen as adverse events due to the pre-existing literature noting their prevalence in CKD and ESRD populations and impact on HRQoL. Following read out of the clinical trials, it was noted that VAT occurred in a minority of patients. VAT was included because more of these events occur in the roxadustat arm compared with ESAs in the dialysis dependent clinical trials. In contrast, the rate of other adverse events were comparable	Not a factual inaccuracy.

		between roxadustat and ESA (see CS Appendix F). Therefore, they were not explicitly modelled and were expected to have a substantially lower impact in patients HRQoL and NHS resource use. The model was reviewed by three KOLs who agreed this choice of AEs was appropriate Therefore, Astellas believes there are consistent reasons for considering Stroke, MI and VAT in the cost-effectiveness model above other AEs.	

Issue 14 Disutilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 4.2.8 (Page 69), ERG comment d), "the ERG agrees with the justification for the modelling choice of assuming all disutilities are additive provided by Astellas in response to the ERG clarification question *C13*. Still, the ERG states: *"However, literature suggests that a multiplicative approach might*	Astellas requests removing the highlighted text detailed below (text underlined). In Section 4.2.8 (Page 69), ERG comment d): "However, literature suggests that a multiplicative approach might be preferable with reference to Miyamato et al. 1998"	Considering the ERG agreement with the response given by Astellas to the ERG clarification question *C13*, Astellas considers the statement of concern as inconclusive, adding uncertainty to the report. As detailed in the response to the ERG question *C13*, there are broadly three ways to apply utility	Not a factual inaccuracy.

be preferable with reference to Miyamato et al. 1998"		decrements in an economic model: additive, multiplicative or min/max values. To the best of the company's knowledge there is no consensus within the health economics community as to which one is preferred, with NICE not stating a preference for one of the three approaches over the other two in their methods guide or TSD 12 document. As such, the choice of which to use is often based on modeller preference. As previous studies in this disease area have shown that utility decrements are associated with 1 g/dL changes in Hb level (Finkelstein et al. 2009, Yarnoff 2016 and Glenngard AH. 2008), it was decided that the most appropriate way to capture Hb related utility decrements within the economic model was to use an additive approach, which the ERG has agreed with, hence justifying the removal of the highlighted statement.	

Issue 15 Hospitalisations and surrogate outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 1.1 (Table 1.1, Issue 2) and Section 2.4 (Page 25), the ERG questions the indirect modelling of hospitalisation in the	Astellas disagrees with the ERG proposition and requests to remove the Issue 2 detailed in Section 1.1 (Table 1.1) and its consequent argumentation detailed in Section 2.4 (Page	Astellas would like to highlight that a total of [redacted] and [redacted] hospitalisations occurred in the Roxadustat and ESA arm of the	Not a factual inaccuracy. Section 2.4 of the ERG report discussed this issue in detail.

cost-effectiveness model submitted, and suggests that modelling hospitalisations directly by using the DOLOMITES data would have been preferred	25). Specifically, Astellas asks to remove the text detailed below (text underlined): In Section 2.4 (Page 25) *" (…) However, NICE guidance recommends using surrogate (indirect) outcomes only when direct outcomes is not posslble. To confirm whether what the company expected was actually the case, it would be more robust to report hospitalisation directly. The DOLOMITES trial reported hospitalisations, and these could have been included. Moreover, there are methodological problems with indirect outcome measures. For example, Kemp and Prasad state that "The factors outlined here lead us to conclude that surrogates should lead to practice change or drug approval only when robust validation studies demonstrate that a change in a specific surrogate has a reliable ability to predict changes in meaningful outcomes."*	DOLOMITES study respectively. In the roxadustat arm, approximately [redacted]% of hospitalisations were related to adverse events compared to approximately [redacted]% in the ESA arm. Furthermore, Table 47 from the DOLOMITES study CSR outlines the characteristics of the hospitalisations for each treatment arm. In this table, it is possible to see that the mean number of hospitalisations ([redacted] versus [redacted]), mean total duration of hospital stay ([redacted] versus [redacted]), mean duration per hospitalisation ([redacted] versus [redacted]) and number of days in hospital per PEY ([redacted] versus [redacted]) was comparable across the roxadustat and ESA arms respectively. The economic model directly captures the serious adverse events of stroke, MI and VAT which are likely to result in costly hospitalisation episodes. The economic model uses a separate adverse event rate for both the roxadustat and ESA treatment arms. However, due to a lack of data it was not possible to derive a rate for these adverse events stratified by Hb level using a robust	

		regression analysis. However, the committee should be reassured that the impact of these adverse events is captured directly. Due to the similar characteristics of hospitalisations between both treatment arms and because the economic model directly captures the impact of the serious adverse events which are likely to result in a hospitalisation, the impact of including non-serious, non-related hospitalisations on the incremental results in the economic model would be marginal.	

Issue 16 Minor text inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 1.2 (Page 12), probabilistic results detailed are incorrect. Text underlined below *"However, the 95% percentiles for the probabilistic incremental costs and QALYs were ([redacted]) and ([redacted]) respectively"*	Astellas requests correction as detailed below: *However, the 95% percentiles for the probabilistic incremental costs and QALYs were ([redacted]) and ([redacted]) respectively*	To support the accuracy of the document.	This has been corrected.
In Section 1.2 (Page 12), results of deterministic sensitivity analyses obtained when varying	Astellas requests correction as detailed below:	To support the accuracy of the document.	This has been corrected.

the weighted cost of VAT are incorrect. Text underlined below "*A change in the weighted cost of VAT could result in ICER ranges between* [redacted] *and* [redacted]*"*	*A change in the weighted cost of VAT could result in ICER ranges between* [redacted] *and* [redacted]		
In Section 5.2 (Page 72), results of deterministic sensitivity analyses obtained when varying the weighted cost of VAT are incorrect. Text underlined below *"The weighted cost of the adverse events MI and VAT. A change in the weighted cost of VAT could result in ICER ranges between* [redacted] *and* [redacted]*"*	Astellas requests correction as detailed below: *The weighted cost of the adverse events MI and VAT. A change in the weighted cost of VAT could result in ICER ranges between £*[redacted] *and* [redacted]*.*	To support the accuracy of the document.	This has been corrected.

(please cut and paste further tables as necessary)

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Tuesday 19 October 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Astellas Pharma Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data, or analyses?	Response
Key issue 1: The patient population in the company analysis differs somewhat from the final NICE scope. The company analysed data for a subgroup of the scope population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation, and those with CKD levels 3-5.	**NO**	The population of interest for this submission is adult patients with symptomatic anaemia associated with chronic kidney disease (CKD) stages 3-5 who are non-dialysis dependent (NDD) at the time of treatment initiation. The decision problem was updated in the response to the clarification questions (Question B1) to reflect that the population of interest in the submission is narrower than the one detailed in the final NICE scope. Patients with CKD stages 3-5 are the relevant patient population as, in line within the NICE Clinical Guideline for CKD (NG208), patients are referred into secondary care for treatment of anaemia associated with CKD from stage 3 onward. Consistent with the NICE scope, ESA are the relevant comparator for roxadustat and are only prescribed in secondary care. Patients in the early stages of CKD have a lower prevalence and severity of anaemia. Patients with CKD 1-2 will be under the care of their general practitioner and generally receive oral iron as treatment for anaemia. Furthermore, the anaemia in patients with CKD 1-2 is unlikely to be due to reduced erythropoietin in the body and therefore not usually treated with erythropoiesis stimulating agents (ESA) (Mercadal, L et al. 2012). Hence, patients with CKD 1-2 are not considered relevant for in this appraisal.
Key issue 2: One of the outcomes (hospitalisation rates) is not in line with the NICE scope.	**NO**	Hospitalisation as an outcome is considered within the cost effectiveness model and has been modelled indirectly for several reasons: • The cost effectiveness model is based on health states tracking anaemia severity levels (haemoglobin [Hb] levels) and in order to model hospitalisation costs directly, a link between Hb level and hospitalisation rate (i.e. multinomial regression model in the context of our model) would be required to directly relate hospitalisations to the main anaemia progression factor (Hb level) captured in the cost-effectiveness model. The low number of total hospitalisations limited the feasibility of a multinomial regression model linking Hb level to hospitalisations. Since a direct treatment effect of roxadustat in hospitalisations was not expected and the available evidence from the

		clinical studies was not enough to fit a robust statistical model, hospitalisations were not captured directly in relation to Hb level. • Linking hospitalisation directly to Hb level would limit the ability to cost different types of hospitalisations as the data would not allow to link different types of hospitalisations to Hb level. This approach would require an average cost and utility score for all the different types of hospitalisation events captured in the roxadustat trials. • The majority of the hospitalisations in the roxadustat studies were due to adverse events so explicitly modelling hospitalisations and adverse events would effectively double count the costs and quality of life effects associated with these events. Hence, to include hospitalisations as an explicit outcome, adverse events would have to be removed from the model. • Evidence from the DOLOMITES study shows that hospitalisation rates were comparable between roxadustat and ESA with the mean number of hospitalisations per patient and average duration of hospitalisations similar between treatment groups. (evidence provided in response to clarification question B6b). Based on the reasons provided for hospitalisation (in the DOLOMITES CSR), approximately [redacted]% of hospitalisations in the roxadustat arm and [redacted]% in the ESA arm of the DOLOMITES were related to adverse events. As noted in the response to key issue 7, major cardiovascular events are of particular importance for the target population in this appraisal and the selection of adverse events was validated by experts. Considering the similarity of the hospitalisation rates between roxadustat and ESA observed in the DOLOMITES study, the approach to model hospitalisations implicitly through adverse events is justified and inclusion of hospitalisations within the model itself could overestimate costs within the economic analysis.
Key issue 3: The cost effectiveness analysis in the company submission relies upon pooled data across roxadustat arms of non dialysis dependent (NDD) ALPINE trials Some of these trials did not use comparators specified in the final NICE scope, and the resulting analysis is unanchored and indirect.	**NO**	All analyses were conducted by pooling all participants of the studies together to create a “master dataset”. However, it should be noted that the placebo and darbepoetin alfa outcome data are not pooled together and placebo is not considered a comparator within the economic analysis. Instead the roxadustat outcome data was pooled across studies. As a result of pooling the data at the individual patient level, it was possible to leverage the additional roxadustat data from the other trials when comparing roxadustat to darbepoetin. In essence, an individual patient-level data-meta analysis was performed in order to borrow strength across the pooled studies to generate relative efficacy estimates for roxadustat compared to darbepoetin alfa. All statistical models accounted for any potential differences between clinical trials by using a hierarchical model structure and used each unique study ID to control for any impacts of “nesting” (i.e. patients from the same study are more likely to behave in a similar manner compared with patients from another study) where possible. Where it was not possible to conduct hierarchical models due to limitations in the available software (multinomial logistic regressions for proportion in state), study IDs were included as fixed effect variables. This approach was chosen to adjust for any

potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all.

Imbalances in baseline patient characteristics that could be prognostic of outcome (e.g. age, sex, cardiovascular disease history, diabetes and estimated glomerular filtration rate) were controlled within the statistical models, something that cannot be done using fixed/random effect meta-analyses. Meta-analyses do not adjust for any heterogeneity in study populations that may influence treatment outcomes. Apart from a difference in the proportion of patients with a history of cardiovascular disease at baseline in DOLOMITES, all patient characteristics used within the cost-effectiveness modelling were broadly balanced between studies, as shown in the table below (provided in response to clarification question B2).

Table 1: Patient baseline characteristics used in the statistical analyses

Study ID	N	Treatment	Age years	Weight Kg	Male	CVD history	Diabetic	eGFR* ml/min/1.73m2
OLYMPUS	1,357	Placebo	62.40 (14.12)	70.53 (18.90)	44%	31%	58%	20.0 (11.8)
	1,371	Roxadustat	60.86 (14.67)	69.89 (18.46)	41%	30%	57%	19.7 (11.7)
ANDES	305	Placebo	64.84 (13.20)	71.23 (18.37)	43%	33%	65%	22.4 (11.4)
	608	Roxadustat	64.98 (12.59)	71.33 (19.46)	39%	34%	65%	21.9 (11.5)
ALPS	203	Placebo	61.71 (13.76)	76.50 (16.51)	49%	44%	44%	17.2 (11.7)
	389	Roxadustat	60.54 (13.55)	73.85 (16.50)	43%	36%	37%	16.5 (10.2)
DOLOMITES	292	ESA	65.75 (14.42)	78.45 (17.68)	44%	48%	47%	20.4 (10.7)
	322	Roxadustat	66.87 (13.57)	76.93 (16.35)	45%	47%	46%	20.3 (11.5)

While there may be differences in some variables, if these are not modifiers of baseline risk or treatment efficacy, we would argue that these differences do not justify the exclusion of three out of the four relevant clinical trials in favour of the sole use of one of the smallest of the four studies. Furthermore, roxadustat dose, dosing schedule and mode of delivery were the same in all four studies. This again suggests that it is appropriate to try and borrow strength from the roxadustat data from all four studies to best inform decision-making.

Using this methodology allows for more accurate roxadustat predictions as it leverages data from all 2,660 study participants assigned to this intervention. This means that cost-effectiveness estimates using the pooled analysis are based on individual patient data from nearly 3,000 individuals (the total of all individuals who received roxadustat or

		darbepoetin alfa) rather than the 684 patients in DOLOMITES. This will lead to greater certainty around many model parameters and hence a more robust incremental cost-effectiveness ratio (ICER) for decision-making. The lability of the ICER to small changes in costs or quality-adjusted life years (QALYs) in the DOLOMITES only analysis should also be noted, alongside the observation that all parameters were similar however given the smaller number of patients these were associated with greater uncertainty. Considering the representativeness of the pooled analysis to UK practice, the improved statistical strength, and the optimised use of all available data obtained on roxadustat in accordance with NICE guidance, discarding data from 2,300 patients is not justified, and the analysis using all four NDD trials offers the most appropriate evidence for decision-making purposes.
Key issue 4: The trials include very few participants from the United Kingdom (UK).	**NO**	Although the trials included a relatively small number of UK patients, which is not uncommon with global clinical trial programmes, the experts considered the population derived from the roxadustat trials representative of UK clinical practice. During the model clinical and health economic validation, baseline demographics and disease characteristics (including average starting age and the proportion of patients who were male/female, with CVD history and patients with diabetes were presented for the patient populations from each of the trials. Baseline characteristics for the pooled NDD population to be used in the economic model were also shared, with this pooled population considered the most representative sample of the UK population by clinical experts. The number of UK patients is not considered sufficient to produce robust results in sub-group analysis. The ALPS and DOLOMITES clinical trials enrolled 12 (2.0%) and 61 (9.9%) patients from the UK respectively while no UK patients were enrolled in the ANDES and OLYMPUS trials, Performing statistical analyses in samples with low-statistical power is associated with problems such as reduced chance of detecting a true effect, low likelihood that a statistically significant result reflects a true effect, overestimated effect sizes, and low reproducibility.
Key issue 5: Model structure: justification for the Hb ranges and cut-off values to define health states is lacking.	**NO**	The model structure with eight health states was based on a previously published, peer-reviewed, cost-effectiveness model of anaemia treatment for CKD patients which simulated complications (e.g. stroke, MI, blood transfusions), and quality of life reductions related to changes in Hb levels (Yarnoff et al. 2016). The Hb categories used for the relative risks for blood transfusion in the published model matched the eight health states used in the company model. Yarnoff et al. state the utility loss per 1 g/dL in Hb based on Finklestein et al. 2009 who demonstrated that as Hb levels increased in increments of 1 g/dL in Hb there were significant improvements in a variety of quality-of-life domains. The positive correlation between Hb levels and health-related quality of life (HRQoL)

		in CKD patients has also been recognised elsewhere in the literature, with another published cost-effectiveness analysis by Glenngård et. al. 2008 following a similar stratification of HRQoL by Hb level, in CKD anaemia patients. Changes in HRQoL based on patient's Hb level are the main drivers of QALYs accrued in the economic model based on the modelled treatment effect of roxadustat (effect on Hb level over time). The association between Hb level and HRQoL was also confirmed in the roxadustat clinical trial programme. The figure presented below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle) for utility values at increasing Hb levels. These data show that utilities increase with increments of 1 g/dL in the patient's Hb level and the statistical model provides a reasonable estimate for the average utility value stratified by Hb level (evidence previously provided in response to clarification question C10). *Figure 1: Utility values by increasing Hb level (showing observed data in red and predicted values in blue)* 

		A similar observation can be made for the trends in roxadustat and ESA treatment doses, which are key drivers of incremental costs in the economic analyses. Treatment starting doses are weight dependent, with maintenance doses titrated according to each patient's response to treatment, and evolution of Hb levels in clinical practice. Therefore, there is an intrinsic link between the treatment effect and the treatment dose associated with it. The figures below show the observed data within the clinical trials demonstrating a change in weekly treatment dose for both roxadustat and ESA with increasing Hb levels (shared previously in response to clarification question C14). *Figure 2: Mean roxadustat weekly dose (observed data)* 

		Figure 3: Mean ESA weekly dose (observed data)  Using fewer health states in the economic modelling would lead to a loss of granularity in time trends between treatment arms. Furthermore, as 1 g/dL increments in Hb level have been shown to be associated with differences in costs and utilities by both published literature and the clinical trial evidence, the use of eight health states is well justified, and demonstrates the nuances which could be important in demonstrating the value of roxadustat in the economic analysis.
Key issue 6: Treatment effectiveness and extrapolation: appropriateness of time dependency and extrapolation of the	**NO**	The rationale for including time within the statistical model was to be able to estimate the proportion in state for the patient cohort at any given time point. Initial exploration of the model showed that using the natural log of time resulted in more clinically plausible extrapolations compared with using time on a linear scale. Assuming a linear relationship with time meant that when extrapolated over a longer time horizon, patients continuously improved, which is not a

multinomial logistic regression model unclear.		realistic assumption. By using the log scale for time, the regressions ensure changes in the proportion in state tend towards a plateau rather than assuming a constant increase/decrease over time. As time includes baseline (time 0), it is not mathematically possible to include it in any model predictions using a natural log. As a result, by adding 1 to all time values in the statistical model we were able to use time 0 in the statistical model predictions. The rationale for including treatment type within the statistical model was to be able to adjust for any impact that treatment type had on the proportion in state. The second order interaction between time and treatment type was included to be able to analyse whether the relationship between time and Hb level differed by treatment type. The interaction term allows the relationship between proportion in state and time to differ by treatment arm. Removing the interaction term would still leave time and treatment type as individual predictors in the regression. This would mean treatment type would impact the intercept (i.e. increase/decrease the relative starting points of each treatment) but the changes in the proportion in each health state overtime would be identical for each treatment arm (i.e. the difference at baseline would be maintained throughout the entire model). The above variables were selected in the statistical analysis plan prior to conducting any statistical analyses and were validated by medical experts as being the most relevant predictors. It is biologically plausible that the longer a patient remains on a treatment, the more it will impact their Hb level. As roxadustat and ESA differ in their modes of action and delivery, it is plausible that the impact of long-term treatment of these medications differs, as supported by the economic model. The interaction coefficients in Table 35 of the company submission (Document B) show the change in Hb level over time that is unique to each treatment arm. Coefficients indicated that over time, patients on both ESA and roxadustat are more likely to be in lower Hb levels compared to Hb level 10-11 and less likely to be in the higher Hb levels compared to Hb level 10-11. However, it should be noted that interaction terms are complicated to interpret in isolation and must be considered in conjunction with the sum of their parts. Although the ESA and roxadustat coefficients do not alter the relationship between time and Hb level, they do significantly alter the starting point of each arm (i.e. patients are more likely to start in the higher health states and thus over time are likely to move to lower ones as they cannot move to higher ones). The model was built with the functionality to maintain the proportion in state at any given time point. This functionality allows the model to test the sensitivity of the results to changes in proportion in state over time. This functionality can be accessed via a switch on the model set-up page. We have conducted three scenarios to maintain proportion in state after 5, 10 and 15 years. Results show that by fixing the proportion in state over time (i.e. ignoring the impact of time after set points), roxadustat remains cost-effective, as demonstrated in the results provided in response to clarification

<table>
<tr><td></td><td></td><td>question C5h (table below). The results further show that the treatment benefit from roxadustat is accrued early in the model and does not require protracted extrapolations to demonstrate cost-effectiveness.

Table 2: Scenario analysis supporting clarification question c5

<table>
<tr><th rowspan="2">Scenario</th><th colspan="2">Roxadustat</th><th colspan="2">ESA</th><th rowspan="2">Δ Costs</th><th rowspan="2">Δ QALYs</th><th rowspan="2">ICER</th></tr>
<tr><th>Costs</th><th>QALYs</th><th>Costs</th><th>QALYs</th></tr>
<tr><td>Base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Scenario C5.1: Proportion in state fixed after 5 year</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Scenario C5.2: Proportion in state fixed after 10 year</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Scenario C5.3: Proportion in state fixed after 15 year</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

Furthermore, as the long-term plausibility of the model extrapolations have been validated with clinicians, the approaches taken are considered appropriate.</td></tr>
<tr><td>Key issue 7: Potentially relevant adverse events were excluded.</td><td>YES</td><td>Three adverse events were included in the economic model – stroke, myocardial infarction (MI) and vascular access thrombosis (VAT).

Patients with chronic kidney disease (CKD) and end stage renal disease (ESRD) are at high risk of major adverse cardiovascular events (MACE). MACEs are important in any cardiovascular model, as these either result in death or worsening disease, and significantly reduce HRQoL. MACEs are commonly used as composite endpoints in cardiac research. However, in the current model these events are modelled separately in order to apply appropriate costs and utility decrements to each event as they are economically distinct. For the patient population in the model, MACEs are especially important for those treated with ESAs.

Stroke and MI were chosen as adverse events due to the pre-existing literature noting their prevalence in CKD and ESRD populations. VAT was included following read out of the clinical trials, as it was noted that VAT occurred in a minority of patients and was associated with a high healthcare resource cost. The model was reviewed by three experts who agreed this choice of adverse events was appropriate.

In response to the concern about potentially relevant adverse events being excluded from the economic model, the impact of grade 3+ treatment-emergent adverse events that occurred in more than 3% of the trial population in the</td></tr>
</table>

DOLOMITES study (presented in Table 62 of the clinical study report) was explored. [redacted] adverse events were identified: [redacted]

To explore the potential impact of these adverse events on the current cost-effectiveness outcomes, a simplified estimation of the expected costs and utility loss from these adverse events (assigning costs and utility for the proportion of patients experiencing the adverse events) is provided in Table 3 below.

Table 3: Estimation of the expected costs and utility loss from grade 3+ TEAEs occurring in more than 3% of DOLOMITES participants

Adverse Event	% Patients		Per event (TA712/TA622)		Weighted cost		Weighted disutility	
	Roxadustat	ESA	Cost	Disutility	Roxadustat	ESA	Roxadustat	ESA
Cardiac failure	[redacted]	[redacted]	£2,964.21	-0.00290	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	£2,526.61	-0.00575	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	£364.49	-0.00440	[redacted]	[redacted]	[redacted]	[redacted]
Total					[redacted]	[redacted]	[redacted]	[redacted]
Incremental					[redacted]		[redacted]	

As described in the response to clarification question C11, quality of life from CKD progression is captured indirectly in the model through the utilities associated with Hb level and dialysis status, thus the effects of end stage renal disease and decreased glomerular filtration rate (indicator of kidney function) were not explicitly applied to avoid double counting any roxadustat treatment benefit and CKD progression costs and a quality of life. The costs and disutilities associated with pneumonia and hypertension were collected from NICE TA712 and those for cardiac failure were collected from NICE TA622. Both were applied to the rates observed in the DOLOMITES study.

The above table shows the difference between arms is minimal both in terms of costs and quality of life and the inclusion of these adverse events in the cost-effectiveness model is not expected to have an impact in final comparative results. Therefore, there are consistent reasons for considering stroke, myocardial infarction, and vascular access thrombosis in the cost-effectiveness model and the inclusion of further adverse events is not expected to impact the results of the cost effectiveness analysis.

Key issue 8: Model validation: lack of detail about face validity assessment, limited technical validation, limited cross-and external validation, and inconsistencies between the submission report and the model.	**NO**	Greater detail about the validation undertaken was provided in response to clarification questions C20, C21 and C22 with all inconsistencies between the submission report and the model also addressed. It was not possible to complete a technical verification of the economic model using the TECH-VER checklist at the time of responding to the clarification questions as requested. However, this has now been completed and was submitted to NICE on 20 September 2021.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

References:

Mercadal L, Metzger M, Casadevall N, Haymann JP, Karras A, Boffa JJ, Flamant M, Vrtovsnik F, Stengel B, Froissart M; NephroTest Study Group. Timing and determinants of erythropoietin deficiency in chronic kidney disease. Clin J Am Soc Nephrol. 2012 Jan;7(1):35-42. doi: 10.2215/CJN.04690511. Epub 2011 Nov 17. PMID: 22096037; PMCID: PMC3265349.

Yarnoff BO, Hoerger TJ, Simpson SA, Pavkov ME, Burrows NR, Shrestha SS, Williams DE, Zhuo X. The Cost-Effectiveness of Anemia Treatment for Persons with Chronic Kidney Disease. PLoS One. 2016 Jul 12;11(7):e0157323. doi: 10.1371/journal.pone.0157323. PMID: 27404556; PMCID: PMC4942058.

Finkelstein FO, Story K, Firanek C, Barre P, Takano T, Soroka S, Mujais S, Rodd K, Mendelssohn D. Perceived knowledge among patients cared for by nephrologists about chronic kidney disease and end-stage renal disease therapies. Kidney Int. 2008 Nov;74(9):1178-84. doi: 10.1038/ki.2008.376. Epub 2008 Jul 30. PMID: 18668024.

Glenngård AH, Persson U, Schön S. Cost-effectiveness analysis of treatment with epoietin-alpha for patients with anaemia due to renal failure: the case of Sweden. Scand J Urol Nephrol. 2008;42(1):66-73. doi: 10.1080/00365590701561994. Epub 2007 Sep 28. PMID: 17907051.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **[insert deadline for comments]**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with anaemia and current treatment options	
About you	
1. Your name	**Jonathan Barratt**
2. Name of organisation	**University of Leicester**
3. Job title or position	**Professor of Renal Medcine**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with anaemia? ☒ a specialist in the clinical evidence base for anaemia or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NIL**
The aim of treatment for anaemia	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve clinical symptoms of anaemia- tiredness, lack of energy, loss of life participation due to easy fatiguability. There may be benefit in correcting anaemia on cardiac structure and function but this is less well established. Even less well established is the effect of haemoglobin correction on slowing the rate of decline of kidney function loss
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Correcting and maintaining Hb between 10 and 12 g/dL Improvement in patients symptoms as listed above

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in anaemia?	Yes 1. All current ESAs have to be given by sc/iv injection 2. It remains unclear what the cardiovascular implications are of correcting haemoglobin with exogenous supraphysiological doses of EPO 3. Patients with ongoing inflammation are ESA resistant and it is very difficult to maintain haemoglobin within the target range
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Anaemia associated with CKD is managed exclusively by multiprofessional teams in Kidney Units in secondary/tertiary care centres (not by GPs) Therapy involves a combination of iron supplementation (oral/IV) and use of ESAs to achieve target levels of ferritin/TSR and haemoglobin
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	UK Renal Association, European Renal Association and KDIGO (International) all tend to align on key targets for treatment
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	On the whole relative uniform clinical practice for most patients (in line with UK guidelines), there will be subtle differences in terms of timing of initiation of treatment and acceptable target Hb-particularly for the young and active and the elderly. Also a difference in use of oral vs IV iron across units.

• What impact would the technology have on the current pathway of care?	Ability to use an oral agent which potentially reduces the requirement for IV iron is likely to have a significant impact on the patient experience and healthcare utilisation with: • Less need for home delivery of ESAs and associated plasticware (non-HD patients only) • No need to train patients to administer a sc injection (non-HD patients only) • Less requirement for in hospital administration of IV iron (nursing/patient time) (non-HD patients only) • Less requirement for administration of IV iron on HD (nursing/pharmacy etc time)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes Prescribed and response monitored by multiprofessional teams in Kidney Units in secondary/tertiary care centres (not by GPs)
• How does healthcare resource use differ between the technology and current care?	• No need for plasticware etc associated with administration of a sc/iv drug • No need to train patients for self administration (non-HD patients only) • Less requirement for in hospital administration of IV iron (nursing/patient time) (non-HD patients only) • Less requirement for administration of IV iron on HD (nursing/pharmacy etc time)
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In line with current use of ESAs and IV iron to treat anaemia of CKD Roxadustat use will be managed by multiprofessional teams in Kidney Units in secondary/tertiary care centres (not by GPs)
• What investment is needed to introduce the technology? (For example,	Nil

for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Current hard to manage patients are those with resistant anaemia unresponsive to ESAs who have ongoing inflammation – the mode of action of Roxadustat would suggest it could be of benefit in this patient group but this has not been formally evaluated to date.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients	Easier- ais a tablet vs an injection while monitoring will be the same.

or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Current anaemia guidelines will be applied when using Roxadustat-so at present no change in the threshold for treatment initiation or target range compared to currently available ESAs- there is a KDIGO controversies meeting in December to begin to look at whether international guidelines need to change when using HIF-PHIs but no change in the anaemia guideline is expected for at least 12 months
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	HIF PHIs offer a more physiological approach to managing anaemia of CKD and initial data supports a pleiotropic effect of drugs such as Roxadustat in terms of suppressing hepcidin, improving iron utilisation and reducing the need for iron supplementation. For the patient there is likely to be less need for attendance at hospital, less medicalisation of their home with no further need for home sc EPO administration. For hospitals it will mean less patients attending for IV iron infusions which means the healthcare resource can be redirected to deal with other tasks.
• Is the technology a 'step-change' in the management of the condition?	Yes- as above
• Does the use of the technology address any particular unmet need of the patient population?	Yes- no need for parenteral drug administration- particularly beneficial for patients not on haemodialysis who will usually administer the drug themselves at home
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Major concern is cardiovascular safety – there is significant evidence that correcting anaemia of CKD with high doses of EPO is associated with increased cardiovascular risk, particularly when the aim is to correct the haemoglobin to normal. Current guidelines are that the target haemoglobin should therefore be 10-12g/dL. It is untested whether achieving a Hb within this range with EPO impacts on cardiovascular risk in CKD. Current studies of HIF-PHIs have mostly shown non-inferiority to EPO in terms of cardiovascular endpoints (MACE, MACE+, ACM) and have failed to show superiority when achieving Hb between 10-12 g/dL. Therefore there is still concern that anaemia correction with HIF PHIs may be associated increased cardiovascular risk in patients with kidney disease.
Sources of evidence	

20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes They assess Roxadustat in the setting of anaemia correction in non-dialysis CKD and incident dialysis patients and during the maintenance phase in the ESA conversion studies in dialysis patients. For non-dialysis CKD patients – both placebo controlled and ESA controlled studies performed (majority of patients ESA naïve) For incident dialysis patients ESA controlled studies performed (majority of patients ESA naïve) For dialysis dependent patients ESA controlled studies performed (majority of patients had prior ESA exposure) Threshold for initiation of therapy and target HB levels are consistent with current UK guidelines. Exclusion criteria in all of the studies means a number of patients who would ordinarily be treated with an ESA were excluded (e.g those with significant elevations in CRP). Oral/IV iron protocols were largely consistent with UK practice/guidelines
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	**Efficacy** 1. Hb response compared to placebo and to ESA (measured) 2. Iron utilisation (measured)

	3. Patient Reported Outcomes/QoL (not systematically evaluated) **Safety** Cardiovascular outcomes (MACE, MACE+, ACM)- (adjudicated & measured but studies designed to demonstrate non-inferiority rather than superiority) Venous/vascular access thrombosis (measured) SAEs/TEAEs (measured)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	In essence haemoglobin is a surrogate for improved QoL and reduced symptoms for anaemic patients- the relationship between haemoglobin response and symptoms is poorly understood as there are many causes for the symptoms patients with CKD suffer outside of those caused by a low haemoglobin.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA323?	No
23. How do data on real-world experience compare with the trial data?	I think they are broadly similar
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Current therapy with home administration of sc EPO requires the patient to have a fridge, be willing and accepting of a home treatment and have the confidence and support to administer their own treatment- in my experience this is more challenging in patients on low incomes, those where English is not their first language and if they are elderly, live alone and have dexterity problems.
24b. Consider whether these issues are different from issues with current care and why.	See above- no such issues with a tablet medication.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
25. The patient population in the company analysis differs somewhat from the final NICE scope. The company analysed data for a subgroup of the scope population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation, and those with CKD levels 3-5.	For NDD patients it is appropriate to only include CKD3-5- we do not see patients with CKD1 and 2 who have anaemia attributable to kidney disease. Patients on dialysis represent a large population of patients with anaemia of CKD however their risk of cardiovascular events is significantly greater than NDD patients and to me it is reasonable to introduce Roxadustat as a new therapy first for ESA-naïve NDD patients as these patients are likely to have the lowest risk of cardiovascular disease. It would not be unreasonable with time, and further study, to consider Roxadustat for DD patients in the future.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
26. One of the outcomes (hospitalisation rates) is not in line with the NICE scope.	Personally I would not be concerned over the importance of addition of hospitalisations as these are multifactorial in patients with progressive CKD with many issues outside anaemia contributing to this (of course this would be accounted for by randomisation but I am not sure it adds to my interpretation of the efficacy and safety data). For me adjudicated MACE and MACE+, ACM and vascular access thrombosis are far more relevant in this patient group.
27. The cost effectiveness analysis in the company submission relies upon pooled data across roxadustat arms of non dialysis dependent (NDD) ALPINE trials Some of these trials did not use comparators specified in the final NICE scope, and the resulting analysis is unanchored and indirect. 27a. Are there any published clinical trials investigating erythropoiesis-stimulating	The big challenge with the current ESAs is that the comparable large placebo controlled studies were never performed as it was automatically assumed correcting anaemia was a good thing, it wasn't until the later ESA studies aiming for higher haemoglobins that the cardiovascular safety issues were identified and clinicians began to question ESA-safety.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
agents (e.g., darbepoetin alfa, epoetin alfa) compared to placebo that can be used to anchor the ALPINE trials in the indirect comparison?	
28. The trials include very few participants from the United Kingdom (UK).	This is not a concern to me- there are significant numbers of Caucasian Europeans in the Alpine studies and I think it is reasonable to extrapolate from this population to the UK.
29. Model structure: justification for the Hb ranges and cut-off values to define health states is lacking.	Agree this is a challenge for all-as previously mentioned the correlation between haemoglobin and symptoms is imperfectly understood and can vary over time within an individual. The bottom line is that we do not have an adequate tool to measure symptoms directly related to renal anaemia and so everything that is used is imperfect, including the current PROMs. The Hb ranges and cut-off values to define health states do in my view equate to my clinical experience of looking after patients with progressive CKD.
30. Treatment effectiveness and extrapolation: appropriateness of time dependency and extrapolation	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
of the multinomial logistic regression model unclear.	
31. Potentially relevant adverse events were excluded.	Looking at those adverse events with a difference < 2% between arms in the Dolomites study I have to agree that none of the listed AEs would be of clinical concern and from my point of view justify be added to the modelling.
32. Model validation: lack of detail about face validity assessment, limited technical validation, limited cross-and external validation, and inconsistencies between the submission report and the model.	
33. Are there any important issues that have been missed in ERG report?	No

PART 2 – Technical engagement questions for clinical experts
Issues arising from technical engagement
PART 3 -Key messages

34. In up to 5 sentences, please summarise the key messages of your statement:

- **Patient population**: NDD CKD 3-5 ESA-naïve an appropriate low-CV risk CKD population in which to introduce roxadustat
- Roxadustat offers a number of advantages over current sc ESA use in NDD CKD (ease of administration, no patient training etc)
- Roxadustat offers advantages over current ESAs in terms of iron utilisation which will improve patient QoL and utilisation of healthcare resources
- Cardiovascular safety remains a concern when correcting haemoglobin in CKD and while non-inferiority to ESA is reassuring superiority is what many nephrologists were hoping for
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **[insert deadline for comments]**

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Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with anaemia and current treatment options	
About you	
1. Your name	**Prof Sunil Bhandari**
2. Name of organisation	**Hull University Teaching Hospitals NHS Trust.** Organisation – UK Kidney Association
3. Job title or position	**Consultant Nephrologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with anaemia? ☐ a specialist in the clinical evidence base for anaemia or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None from the Tobacco Industry**
The aim of treatment for anaemia	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The key aim of hypoxia inducible factor – proply hydroxylase inhibitors such as ROXADUSTAT is to be part of the treatment of anaemia in patients with Chronic Kidney Disease not on dialysis and also those patients on regular renal replacement therapy and maintain the haemoglobin concentration within the current recommended range of 100-120g/L while maintaining safety with an acceptable side effect profile.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	1. As good as erythropoietin stimulating agents (ESA) at improving haemoglobin to the target range 2. Effective at maintaining patients in the target range 3. Safe with no adverse cardiovascular detriment in comparison to ESA therapy. 4. Reduction in the need for intravenous iron

or a reduction in disease activity by a certain amount.)	5. Reduction in the need for blood transfusions
10. In your view, is there an unmet need for patients and healthcare professionals in anaemia?	1. Effective in patients with chronic inflammation 2. ESA hyporesponsiveness patients – areas of clinical need where an alternative therapy is needed for this group of patients to improve their haemoglobin levels and hence quality of life. 3. Use in patients who are not keen or struggle with injections
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Currently guidelines recommend iron repletion first with oral and more likely iv iron therapy in those who have no contraindications. Once iron replete the next step to achieve the haemoglobin in the target range (100-120g/l), is use of subcutaneous or intravenous erythropoietin stimulating agents. Sub-cutaneous (CKD and PD patients) or intravenous (in haemodialysis patients) injection together with iron. ESA agents can be short acting agents given up to three times a week or long acting agents given weekly or even less frequently (monthly).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Chronic kidney disease: managing anaemia. NICE guideline [NG8] Published: 03 June 2015 and revised in August 2021 Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease 2017 Management is well documented in the current NICE and KDIGO guidelines (kidney disease improving global outcomes) and the UKKA anaemia guidelines. These are all broadly similar with slight difference to target Hb ranges.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current treatment for anaemia of CKD is 1. First, oral or intravenous iron – usually IV iron 2. Then subcutaneous (intravenous in haemodialysis patients) erythropoietin stimulating agents (ESAs). 3. Blood transfusions when the above fail or Hb is extremely low and the patient symptomatic. Oral iron can be used but is poorly tolerated and insufficient to meet the demands of erythropoiesis when patients are also on ESAs. In CKD stages 3 or worse anaemia is more common – affecting over 75% when eGFR is less than 15 ml/min and in the majority of haemodialysis patients. Choice of ESA used by sub-cutaneous injection is variable throughout the UK from short acting thrice weekly preparations to longer acting monthly preparations. This is based on contracts. The majority of treatment is given in secondary care and monitored by specialists. An oral preparation in place of ESA in this group of patients would be of considerable value. It would lead to reduced burdens on the NHS and health care staff. The reduced requirements for intravenous iron and hence day case use would free up resources for other treatments. Reduced hospital visits would minimise risk of exposure to COVID-19.
• What impact would the technology have on the current pathway of care?	This technology would add an additional choice to clinicians and patients in optimisation of their anaemia. Choice is critical as detailed by the Government and Health Education England Certain groups would particularly benefit: 1. ESA naive patients as their primary treatment after iron for anaemia 2. Patients who are unable to take ESA therapy 3. ESA hyperresponsiveness 4. Those unable to self-inject ESA therapy

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it will be used in a similar fashion to ESA therapies. One difference might be as it is a tablet, the delivery and management would be simpler and more robust.
• How does healthcare resource use differ between the technology and current care?	1. Injection versus a tablet 2. Differences in storage cold chain storage and disposal of the sharps following use of ESA 3. Training in administration of ESA versus none with technology 4. Training healthcare professionals such as district nurse to deliver if patient cannot. 5. Reduced need with the technology for IV iron and hence visits to hospital as a result of its action on improving iron absorption and mobilisation. 6. Minimum risk of infection as a result of use of sharps
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care under specialist nephrology services, similar to ESA use
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment apart from ongoing education in the field of anaemia

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The technology with be as effective in patients who require ESA therapy both chronic kidney disease and dialysis patients. It would seem more attractive in those chronic kidney disease patients, as an oral tablet may be preferred to an injection. In dialysis patients this is less attractive as currently ESA therapy is given in the dialysis machine so there is no injection, and the additional tablet may not be as attractive to that group of patients. In addition, early data suggests caution in switching patients from ESA to the new technology due in part to the increase in vascular access thrombosis – the life line of the patient. Meaningful benefit will be related to patient choice and options and in the group of 10-15% of patients who do not respond to ESA therapy.
• Do you expect the technology to increase length of life more than current care?	No data is available, but this would be unlikely. We know that improving Hb in patients with CKD reduces mortality and cardiovascular risk. The data available show comparable risk. Unknown as data is not available and the off target effects require more study -for example the reduction in lipids and possible delay in renal progression but again these are post hoc analysis and not primary outcomes.
• Do you expect the technology to increase health-related quality of life more than current care?	The current data suggests improved Quality of life compared to placebo but comparable benefits to ESA therapy.
14. Are there any groups of people for whom the technology would be more or less effective	More appropriate for: • Patients with chronic inflammation and a high CRP • Patients hyporesponsive to ESA therapy • Those with ESA antibodies and ESA resistance • CKD patients not on dialysis • Those who are unable to self-inject.

(or appropriate) than the general population?	Potentially less appropriate for: • Unit haemodialysis patients who get IV ESA in the dialysis machine • Those with fistula problems • Those with clotting disorders • Those with allergy to drug
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It will potentially be easier to use as it is a tablet given 3 times a week. – this might present issues with compliance. This will be easier for patients. The therapy may lead to a reduction in the need for iv iron therapy. Monitoring will be similar to current monitoring for anaemia. It will be more green with the reduced need for special disposal requirements that are needed for sharps with ESAs and need for cold chain storage requirements for ESAs.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	There are certain groups which might need to be excluded based on the trials. For example cancer patients; patients with polycystic kidney disease; abnormal liver function tests; myeloma patients – this is in part similar to ESA therapy for cancer patients.

Do these include any additional testing?	Monitoring will be no different to current pathways of care
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There is limited clinical data available examining this but it is unlikely to demonstrate any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is an innovate technology which has developed from the Nobel prize winning work of the oxford group under the auspices of Sir Peter Radcliffe. This technology will add to the nephrologist armoury in the effective management of CKD patients and in particular those who do not respond to ESA therapy. Health related benefits data is limited at present and it is difficult to comment on this and if this therapy will be better than current therapies; is all can say is that it is as effective and safety is comparable.
• Is the technology a 'step-change' in the management of the condition?	Yes – novel and the more physiological approach may have longer term benefits as yet not identified including its widespread pleotropic effects which may be positive as in lipids but also negative in other areas. The combination of increasing haemoglobin with endogenous erythropoietin production and improved iron metabolism is very attractive to simplify management.

• Does the use of the technology address any particular unmet need of the patient population?	See above – certain groups may particularly benefit from this therapy.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are important and need to be considered when prescribing. 1. Increased risk of hypertension – this may require additional therapy 2. Potential increased risk of vascular access thrombosis – more gradual increase in haemoglobin may be important to offset this effect 3. Gastro-intestinal side affects 4. Headache 5. Other thrombotic events This may require care in those "high risk groups"
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes in part – in CKD patients the current therapy is iron repletion then ESA. The three placebo controlled trials therefore are not reflective but the DOLOMITES trial is more reflective of therapy. The haemoglobin target ranges vary.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Efficacy – measured against the current active comparator - ESA Therapy 2. Efficacy – measured against placebo – this might be the group to initially consider therapy as the group is naive of therapy and iron replete. 3. Safety of drug against an active comparator – data does show this and the pooled analysis does confirm no increase adverse cardiovascular risk but also no additional benefit. 4. Health related quality of life – these were measured and comparable to active comparator 5. Primary outcome of CV events and death – not measured as a primary outcome but a secondary outcome and pooled analysis. We do have data on other HIF-PHI outcomes. One of the most important aspects of the patient pathway is the move to a more holistic approach based on individualised care with sufficient treatments available to cater for all patient groups. We know the better the Hb is prior to commencement of dialysis the better the outcomes.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not At Present

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of this but am aware that the FDA did not approve the drug while the EMA have approved the drug. This is at odds and it is not completely clear as I do not have sight of the submissions to compare, but one would assume the data is the same.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No – there are studies now on 3 other molecules in the same family, but the question remains can it is assumed this is a class affect or are there differences – I suspect there maybe differences due to actions on various proteins. A recent metanalysis from Chen of 21 placebo controlled trials and 17 ESA trials of which 20 were in non-dialysis CKD patients confirmed comparable effects of the molecules and safety.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA323?	None on this molecule but other molecules in the same family and Daprodustat is currently being presented this week at the American Society of Nephrology 2021 and more data on Roxadustat – which I have been involved in.
23. How do data on real-world experience compare with the trial data?	Real world data is similar but is based on non UK data as the UK population is limited.
Equality	
24a. Are there any potential equality issues that should be	None

taken into account when considering this treatment?	The Dolomites data was 95% Caucasian so limited data on Asian and black patients while the other CKD studies ANDES and ALPS had 44% Caucasian. Reassuringly over 40% of the population had diabetes.
24b. Consider whether these issues are different from issues with current care and why.	N/A

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
25. The patient population in the company analysis differs somewhat from the final NICE scope. The company analysed data for a subgroup of the scope population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation, and those with CKD levels 3-5.	1. Anaemia is significantly less common in CKD stages 1 and 2. Current therapy is usually iron therapy alone and ESA use is uncommon in early CKD. Therefore, in my opinion it is appropriate to exclude CKD stages 1 and 2 where numbers of patients are small and often respond to iron therapy alone as detailed in the current NICE recommendations. 2. Dialysis dependent is a group where the use of Roxadustat could be used but from a clinical perspective it might be more difficult to justify given that current therapy is given intravenously during the dialysis through the machine – hence patients may prefer not to switch. This would be in contrast to Non dialysis CKD (NDD) and peritoneal dialysis patients where a tablets maybe more preferable to an injection. The data however from the trials involving dialysis patients would be useful to include to ensure there is no unexpected safety issues and the drug is effective in this population.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
26. One of the outcomes (hospitalisation rates) is not in line with the NICE scope.	It would be important to include details of hospitalisation rates and the nature of these from a safety perspective to reassure both clinicians and patients. I would expect these to be added to the scope of the data and would expect to see this in the treatment emergent adverse effects. This would also be important from an economic perspective as a major advantage or Roxadustat being and oral preparation is the potential reduction in hospital visits.
27. The cost effectiveness analysis in the company submission relies upon pooled data across roxadustat arms of non dialysis dependent (NDD) ALPINE trials Some of these trials did not use comparators specified in the final NICE scope, and the resulting analysis is unanchored and indirect.	• Cost effectiveness would depend on the comparator but this is complex as the drug in question is not a direct comparator to ESA therapy due to its additional benefits on iron absorption and mobilisation. • A pure analysis as in Dolomites in CKD patients would give a reasonable assessment of cost effectiveness, while the other data adds important safety data, critical in an overall assessment of the drug in question. • We know Roxadustat is as effective as ESA with the added benefit of reduced iron requirements. • Regarding published clinical trials investigating ESAs versus placebo – this really dates back to the 1990s when ESA therapy was first introduced into clinical practice without an active comparator and the remaining trials compare achieving a Hb target range using ESA therapy – these were the 4 landmark studies. • *Macdougall et al., Lancet 1990; 335: 489-493* • Silverberg DS, et al. J Am Coll Cardiol 2000

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
27a. Are there any published clinical trials investigating erythropoiesis-stimulating agents (e.g., darbepoetin alfa, epoetin alfa) compared to placebo that can be used to anchor the ALPINE trials in the indirect comparison?	There was a Meta-analysis: Erythropoiesis-Stimulating Agents in Patients With Chronic Kidney Disease, Suetonia C. Palmer, MBChB, Sankar D. Navaneethan, MD, MPH et al Annals of Internal Medicine. https://doi.org/10.7326/0003-4819-153-1-201007060-00252 - this did look as ESA versus placebo. In general studies published before 1998 were placebo-controlled as detailed below • Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. BMJ. 1990;300:573-8. [PMID: 2108751] • Bahlmann J , Schöter KH , Scigalla P , Gurland HJ , Hilfenhaus M , Koch KM , et al. Morbidity and mortality in hemodialysis patients with and without erythropoietin treatment: a controlled study. Contrib Nephrol. 1991;88:90-106. [PMID: 2040200] • Clyne N , Jogestrand T . Effect of erythropoietin treatment on physical exercise capacity and on renal function in predialytic uremic patients. Nephron. 1992;60:390-6. [PMID: 1584314] • Kleinman KS , Schweitzer SU , Perdue ST , Bleifer KH , Abels RI . The use of recombinant human erythropoietin in the correction of anemia in predialysis patients and its effect on renal function: a double-blind, placebo-controlled trial. Am J Kidney Dis. 1989;14:486-95. [PMID: 2688405] • Kuriyama S , Tomonari H , Yoshida H , Hashimoto T , Kawaguchi Y , Sakai O . Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron. 1997;77:176-85. [PMID: 9346384] • Morris KP , Skinner JR , Hunter S , Coulthard MG . Short term correction of anaemia with recombinant human erythropoietin and reduction of cardiac output in end stage renal failure. Arch Dis Child. 1993;68:644-8. [PMID: 8323333]

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
	• Nissenson AR , Korbet S , Faber M , Burkart J , Gentile D , Hamburger R , et al. Multicenter trial of erythropoietin in patients on peritoneal dialysis. J Am Soc Nephrol. 1995;5:1517-29. [PMID: 7703390] • Revicki DA , Brown RE , Feeny DH , Henry D , Teehan BP , Rudnick MR , et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. Am J Kidney Dis. 1995;25:548-54. [PMID: 7702049] • Sikole A , Polenakovic M , Spirovska V , Polenakovic B , Masin G . Analysis of heart morphology and function following erythropoietin treatment of anemic dialysis patients. Artif Organs. 1993;17:977-84. [PMID: 8110072] • Watson AJ , Gimenez LF , Cotton S , Walser M , Spivak JL . Treatment of the anemia of chronic renal failure with subcutaneous recombinant human erythropoietin. Am J Med. 1990;89:432-5. [PMID: 2220877]
28. The trials include very few participants from the United Kingdom (UK).	The lack of UK patients does limit the generalisability of the data. The breadth of the CKD population should be sufficient to ensure efficacy and safety. We do know from previous studies of anaemia; management in Chinese populations differs from others with lower use if IV iron therapy but European and American populations are similar. However, guidelines do differ in the targets for iron use and Erythropoietin based on KDIGO and European Best Practice Guidelines which can often affect optimal use of medications. For example, the Hb target when ESA therapy is used is 100-120 g/L based on NICE while KDIGO is more conservate at 100-115g/L. The trials do detail the targets, so this is not a major concern. The Dolomites data is 95% Caucasian which may limit generalisability to the Asian and Black population but these groups are better represented in the other three NDD studies as is diabetes in all the studies.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
29. Model structure: justification for the Hb ranges and cut-off values to define health states is lacking.	The guidelines currently based on ESA therapy which I guess the is current active comparator; this gives a target range of Hb of 100-120 g/L which should be the current benchmark for any model. Regarding health states the current data is I agree lacking and somewhat subjective. Based on the mechanism of action one was hoping that by increasing endogenous ESA rather that giving high doses, this more physiological approach might allow one to consider higher Hb targets but this is currently not borne out in the data – this might be due to too rapid an increase in Haemoglobin over a short period of time.
30. Treatment effectiveness and extrapolation: appropriateness of time dependency and extrapolation of the multinomial logistic regression model unclear.	This is beyond my expertise to comment on.
31. Potentially relevant adverse events were excluded.	I would expect all adverse events to be included as part of a safety evaluation. The additional data requires inclusion for completeness in comparison to placebo and directly with ESA therapy.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
	There is increasing data from other similar molecules on safety – for example the 4 studies on Vadadustat in the NEJM in 2021 from Chertow and others. This gives good data on adverse effects as does the meta-analysis. Important adverse effects include – hypertension; vascular access thrombosis; cardiovascular adverse effects and effects significantly greater than comparator.
32. Model validation: lack of detail about face validity assessment, limited technical validation, limited cross-and external validation, and inconsistencies between the submission report and the model.	Again, outside my expertise
33. Are there any important issues that have been missed in ERG report?	No major omissions that I can see from the report – it appears comprehensive. The only question is whether one considers a class effect of HIF-PHI drugs as there are now 4 with a large amount of published data and 6 under study. This might be useful for reassurance of safety although Sir Peter Radcliff has said that he believes that there are potential differences between the drugs due to

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
	their differential effect of downstream targets; different half life's and selectivity for HIF 1 and 2 alpha targets and PHD isoform selectivity. It is critical to justify a change in guidelines if targets are to be changed but I do not think this is the case just simply another option to add to the clinician armoury and use where appropriate. This will generate real world data which will need reviewed and analysed to examine specific groups such as those with a high CRP on therapy. This will help refine and optimise our use in addition to obtaining experience in the use of HIF-PHIs in clinical practice. One final area to consider in cost effectiveness is the "green credentials" – reduced waste from sharps and their disposal; packaging; consumables; reduced travel to hospital in our drive to be more friendly on the impacts to climate change.
PART 3 -Key messages	
34. In up to 5 sentences, please summarise the key messages of your statement: • HIF-PHI represent a novel new therapy for anaemia in CKD to add to current therapies • HIF -PHI are oral and offer potential use in non dialysis patients; peritoneal dialysis patients	

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PART 2 – Technical engagement questions for clinical experts
Issues arising from technical engagement
• Use of these drugs allows a reduction in use of IV iron and improved bioavailability • Adverse profile is comparable to active comparator but caution regarding fistula thrombosis • Use in inflamed patients is as effective and potentially beneficial for that group of patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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Please return this form by **5pm** on **[insert deadline for comments]**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with anaemia and current treatment options	
About you	
1.Your name	**Guy Hill**
2. Are you (please tick all that apply):	☐ a patient with anaemia? **X**☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with anaemia? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Kidney Care UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement X☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement X☐ I agree with it and **will be** completing
5. How did you gather the information included in your	**x**☐ I am drawing from personal experience.

statement? (please tick all that apply)	☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with anaemia? If you are a carer (for someone with anaemia) please share your experience of caring for them.	I was diagnosed IGA Nephropathy in 1996, CKD 2-5 in less than 2 years and PD dialysis for 2 years Transplant for 8 years , HHD for 4 years , Transplant 2 for 4 years , HHD for 3 years , Transplant 3 for 2 years to date. Throughout this time I have experienced anaemia and use of EPO and Iron to bring the HB up from 7 and all its issues of tiredness etc to 11+ and also the issues of too much HB , getting iron transfusions in a very busy renal service.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for anaemia on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I am very impressed with EPO and its effectiveness at relieving anaemia , especially at a time during CKD when the body is deteriorating in so many ways leaving patients very anxious and concerned about their medical future and QOL . It is the only treatment during CKD that appears to make a dramatic difference during this period and is critical in allowing a patient to make quality decisions on their future dialysis options. From my experience of being a patient advocate for 20 years , nearly all patients believe that EPO treatment is critical to their ESRF treatment path as it removes tiredness, confusion and anxiety and allows patients to develop a positive attitude to dialysis . Injection is certainly of concern for CKD patients at onset but soon becomes routine as the

	drug has such an impressive change to ones well being.once on dialysis in HD the epo is injected via the lines and not an issue. The main frustration is when EPO does not appear to work for some patients and there is a great sense of disappointment as their appears to be no alternatives.
8. If there are disadvantages for patients of **current NHS treatments** for anaemia (for example how erythropoiesis-stimulating agents or other treatments is given or taken, side effects of treatment etc) please describe these	Refrigeration and injection is not ideal for any patient to arrange. Very few patients are aware of the stroke issue if the HB becomes too high and removing blood is an organisational issue at clinic level. Very few patients report side effects at the time of injection or afterwards The biggest issue for EPO or roxadustat is not the drugs but keeping the iron stores up for both CKD and now dialysis patients , especially home based as we can no longer do our own injections and must have a nurse led infusion. This takes a lot of patient and clinic organisation and the infusion is too slow to allow the volume of patients needing it to be adequately monitored. THIS is where we need a new treatment.
Advantages of this treatment	
9a. If there are advantages of roxadustat over current treatments on the NHS, please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most	No injection and refrigeration is an advantage as quite a few doses are sent and can take a significant part of a below counter fridge. Both treatments seem to offer equal QOL advantages of which anaemia control is critical for successful completion of ESRF pathways. Its stated improvement on stabilising iron stores and potentially reducing infusions will certainly help a patient's organisational issues in their renal care. If all things are equal in a medical sense, then any patient would rather take a pill than self-inject if offered the choice 9c clearly as a pill roxadustat offers that advantage . However its medical effect on anaemia

important, and why? 9c. Does roxadustat help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	needs to be as good as EPO in terms of patient response across all states of ESRF and range of co morbidities and need for iron stores. From what I read there may be an iron advantage to standard EPO in medical terms and could be significant as a pill with less clinical organisational issues and stated cost benefit issues accordingly.
Disadvantages of this treatment	
10. If there are disadvantages of roxadustat over current treatments on the NHS please describe these? For example, are there any risks with roxadustat? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Roxadustat needs to have the same variation of quantity and time of dosing that EPO regimes have and certainly have control of not taking HB beyond 15 and into stroke territory
Patient population	
11. Are there any groups of patients who might benefit more from roxadustat or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with	Taking a pill is certainly a simpler process for patients with dexterity or caring issues , as often the carer will inject a CKD/ ESRF patient . Many diabetic /renal patients have sight –loss issues. Also a significant number of renal patients are 65+ and will therefore have greater dexterity issues.

mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering anaemia and roxadustat? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-	**I cannot see gender equality issues relating to medical propensity to getting renal disease and therefore needing more anaemia control . Although ther is a higher proportion of men with renal disease than women** However economic/social disadvantage that makes anaemia issues far more distressing for a patient in ESRF both QOL and problems of income generation . BAME populations in renal patients certainly find it harder economically and have a higher prevalence of diabetes and poor control leading to renal failure.

read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. The patient population in the company analysis differs somewhat from the final NICE	Yes CKD patients 1-3 have a very different clinical pathway to CKD 5 patients, mainly primary care and remote clinics. CKD 4/5 who will be engaged in the pre- dialysis programme and receive more attentive care.

scope. The company analysed data for a subgroup of the scope population, namely those who are not dialysis dependent at the time of treatment initiation, and those with CKD levels 3-5. 14a. Is the patient population identifiable in clinical practice?	
15. One of the outcomes (hospitalisation rates) is not in line with the NICE scope. 15a. What are the most important outcomes for patients? 15b. Are hospitalisation themselves or the cause of hospitalisations important	Anaemia tiredness is very disabilitating for patients QOL Quick reduction of Anaemia issues No patient wants to go to hospital , mainly because of the drama of entry to hospital and not getting medical ownership once in hospital. Any issue that can be dealt with at specialised clinics is better

outcomes?	
16. The cost effectiveness analysis in the company submission relies upon pooled data across roxadustat arms of non-dialysis dependent ALPINE trials. Some of these trials did not use comparators specified in the final NICE scope, and the resulting analysis is unanchored and indirect. 16a. Are there any published clinical trials investigating erythropoiesis-stimulating agents (e.g., darbepoetin alfa, epoetin alfa) compared to placebo that can be used to anchor the ALPINE trials in the	

indirect comparison?	
17. The trials include very few participants from the United Kingdom. 17a. Are patients with anaemia from other countries (e.g., Europe) similar to patients with anaemia in the United Kingdom?	During ESRF the severity of your pathway to ESRF depends a lot on your original disease. Therefore the likelihood of anaemia issues for one patient over another is the prevalence of the disease in that culture.
18. Model structure: justification for the haemoglobin ranges and cut-off values to define health states is lacking. 18a. Are haemoglobin cut off ranges recognised by patients as key outcomes in clinical practice?	This is probably beyond a standard patient knowledge and will be clinically led .

19. Treatment effectiveness and extrapolation: appropriateness of time dependency and extrapolation of the multinomial logistic regression model unclear. 19a. How long is anaemia associated chronic kidney disease treated with roxadustat?	
20. Potentially relevant adverse events were excluded. 20a. What are common adverse events experienced by patients with anaemia?	Tiredness is the main adverse outcome Higher doses to get the same effect . Too high HB and blood transfusions to take blood out.
21. Model validation: lack of detail about face validity assessment, limited technical	

validation, limited cross-and external validation, and inconsistencies between the submission report and the model.	
22. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

23. In up to 5 sentences, please summarise the key messages of your statement:

- Anaemia control is the single most important issue in CKD and on any dialysis therapy with regard to patient QOL
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Tuesday 19 October 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Astellas Pharma Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data, or analyses ?	Response	ERG comment
Key issue 1: The patient population in the company analysis differs somewhat from the final NICE scope. The company analysed data for a subgroup of the scope population, namely those who are not dialysis dependent (NDD) at the time of treatment initiation, and those with CKD levels 3-5.	**NO**	The population of interest for this submission is adult patients with symptomatic anaemia associated with chronic kidney disease (CKD) stages 3-5 who are non-dialysis dependent (NDD) at the time of treatment initiation. The decision problem was updated in the response to the clarification questions (Question B1) to reflect that the population of interest in the submission is narrower than the one detailed in the final NICE scope. Patients with CKD stages 3-5 are the relevant patient population as, in line within the NICE Clinical Guideline for CKD (NG208), patients are referred into secondary care for treatment of anaemia associated with CKD from stage 3 onward. Consistent with the NICE scope, ESA are the relevant comparator for roxadustat and are only prescribed in secondary care. Patients in the early stages of CKD have a lower prevalence and severity of anaemia. Patients with CKD 1-2 will be under the care of their general practitioner and generally receive oral iron as treatment for anaemia. Furthermore, the anaemia in patients with CKD 1-2 is unlikely to be due to reduced	Overall, the ERG agrees with these comments. Nonetheless, it should be emphasized that the decision problem has been updated to reflect the narrower scope. Whereas the final NICE scope states that the population of interest is “Adults with anaemia associated with CKD” (and does not specify a particular stage of CKD or whether they are dialysis dependent or not), the evidence in the company submission applies to “patients with stage 3-5 CKD who are not dialysis dependent”.

		erythropoietin in the body and therefore not usually treated with erythropoiesis stimulating agents (ESA) (Mercadal, L et al. 2012). Hence, patients with CKD 1-2 are not considered relevant for in this appraisal.	
Key issue 2: One of the outcomes (hospitalisation rates) is not in line with the NICE scope.	**NO**	Hospitalisation as an outcome is considered within the cost effectiveness model and has been modelled indirectly for several reasons: • The cost effectiveness model is based on health states tracking anaemia severity levels (haemoglobin [Hb] levels) and in order to model hospitalisation costs directly, a link between Hb level and hospitalisation rate (i.e. multinomial regression model in the context of our model) would be required to directly relate hospitalisations to the main anaemia progression factor (Hb level) captured in the cost-effectiveness model. The low number of total hospitalisations limited the feasibility of a multinomial regression model linking Hb level to hospitalisations. Since a direct treatment effect of roxadustat in hospitalisations was not expected and the available evidence from the clinical studies was not enough to fit a robust statistical model, hospitalisations were not captured directly in relation to Hb level. • Linking hospitalisation directly to Hb level would limit the ability to cost different types of hospitalisations as the data would not allow to link different types of hospitalisations to Hb level. This approach would require an average cost and utility score for all the different types of hospitalisation events captured in the roxadustat trials. • The majority of the hospitalisations in the roxadustat studies were due to adverse events so explicitly modelling hospitalisations and adverse events would effectively double count the costs and quality of life effects associated with these events. Hence, to include hospitalisations as an	The ERG does not believe that the comments amount to a sufficient reason for excluding directly measured hospitalisation rates (stated in the final NICE scope). • With respect to the comment that "a direct treatment effect of roxadustat in hospitalisations was not expected," the ERG notes that it is important to explore unexpected as well as expected potential adverse events. • The ERG acknowledges that "Linking hospitalisation directly to Hb level would limit the ability to cost different types of hospitalisations as the data would not allow to link different types of hospitalisations to Hb level." Despite that, the issue is not whether hospitalisation rates should be linked to Hb levels, but whether hospitalisation rates should be measured directly. • The ERG acknowledges that "The majority of the hospitalisations in the roxadustat studies were due to adverse events so explicitly modelling hospitalisations and adverse events would effectively double count the costs and quality of life effects associated with these events. Hence, to include hospitalisations as an explicit outcome, adverse events would have to be removed from the model." Despite this,

		explicit outcome, adverse events would have to be removed from the model. • Evidence from the DOLOMITES study shows that hospitalisation rates were comparable between roxadustat and ESA with the mean number of hospitalisations per patient and average duration of hospitalisations similar between treatment groups. (evidence provided in response to clarification question B6b). Based on the reasons provided for hospitalisation (in the DOLOMITES CSR), approximately [redacted] of hospitalisations in the roxadustat arm and [redacted] in the ESA arm of the DOLOMITES were related to adverse events. As noted in the response to key issue 7, major cardiovascular events are of particular importance for the target population in this appraisal and the selection of adverse events was validated by experts. Considering the similarity of the hospitalisation rates between roxadustat and ESA observed in the DOLOMITES study, the approach to model hospitalisations implicitly through adverse events is justified and inclusion of hospitalisations within the model itself could overestimate costs within the economic analysis.	not all hospitalisation rates were due to adverse events that were already counted in the modelling. And, since this comment implies that the reasons for hospitalisation can be known, it is possible to include hospitalisations that were not due to adverse events that have already been counted. • The ERG acknowledges that hospitalisation rates related to AEs were comparable between Roxadustat and ESA arms in the DOLOMITES trial, namely approximately [redacted] of hospitalisations in the roxadustat arm and [redacted] in the ESA arm of the DOLOMITES. Since this implies that between [redacted] and [redacted] of hospitalisations were not due to adverse events that were accounted for in the analysis, the ERG believes that this is evidence that the hospitalisations (certainly those that were not due to adverse events that were accounted for elsewhere in the analysis) should be measured and included in the analysis. • In short, the ERG believes that measuring hospitalisation rates directly (at least those that did not overlap with other adverse events), and that this issue (Key Issue 2 in the report) remains important.
Key issue 3: The cost effectiveness analysis in the company submission relies upon pooled data	**NO**	All analyses were conducted by pooling all participants of the studies together to create a “master dataset”. However, it should be noted that the placebo and darbepoetin alfa outcome data are not pooled together and placebo is not considered a comparator within the economic analysis. Instead	• The ERG believes that the limitations of the company’s approach (combining the outcomes from roxadustat arms of four different trials together with outcomes from darbepoeitin alfa in a single trial)

across roxadustat arms of non dialysis dependent (NDD) ALPINE trials Some of these trials did not use comparators specified in the final NICE scope, and the resulting analysis is unanchored and indirect.		the roxadustat outcome data was pooled across studies. As a result of pooling the data at the individual patient level, it was possible to leverage the additional roxadustat data from the other trials when comparing roxadustat to darbepoetin. In essence, an individual patient-level data-meta analysis was performed in order to borrow strength across the pooled studies to generate relative efficacy estimates for roxadustat compared to darbepoetin alfa. All statistical models accounted for any potential differences between clinical trials by using a hierarchical model structure and used each unique study ID to control for any impacts of "nesting" (i.e. patients from the same study are more likely to behave in a similar manner compared with patients from another study) where possible. Where it was not possible to conduct hierarchical models due to limitations in the available software (multinomial logistic regressions for proportion in state), study IDs were included as fixed effect variables. This approach was chosen to adjust for any potential differences in outcomes between different studies by using fixed effects rather than making no adjustment for study ID at all. Imbalances in baseline patient characteristics that could be prognostic of outcome (e.g. age, sex, cardiovascular disease history, diabetes and estimated glomerular filtration rate) were controlled within the statistical models, something that cannot be done using fixed/random effect meta-analyses. Meta-analyses do not adjust for any heterogeneity in study populations that may influence treatment outcomes. Apart from a difference in the proportion of patients with a history of cardiovascular disease at baseline in DOLOMITES, all patient characteristics used within the cost-effectiveness modelling were broadly balanced between studies, as shown in the table below (provided in response to clarification question B2). *Table 1: Patient baseline characteristics used in the statistical analyses* **Study ID** / **N** / **Treatment** / **Age** / **Weigh** / **Male** / **CVD his** / **Diabetic** / **eGFR* ml/min/1.73m2**	relative to the unbiased estimate of an RCT remain unacknowledged. Statistical models that attempt to account for potential differences notwithstanding, the combination of patients from different roxadustat arms amounts to a non-randomised (lower quality) comparison, and inferences drawn from this evidence need to be tempered accordingly. • The company states: "While there may be differences in some variables, if these are not modifiers of baseline risk or treatment efficacy, we would argue that these differences do not justify the exclusion of three out of the four relevant clinical trials in favour of the sole use of one of the smallest of the four studies" In response, the ERG notes that it is not possible to know whether the differences (some of which are listed in Table 1) are in fact modifiers of the outcome, and therefore the solution is to do a randomised comparison. • The ERG acknowledges the points made about the advantages and limitations of fixed and random effects meta-analyses. The ERG believes that this misses the point of the key issue, which is not about pooling data *per se*, but about the limitations of pooling data from non-overlapping intervention and control arms. • The ERG therefore maintains that this Key Issue (3 in the report) remains important as the arguments in the ERG report are still applicable and no new

				years	**t Kg**		**tory**			compelling arguments-/evidence has been provided by the company
		OLYMPUS	1,357	Placebo	62.40 (14.12)	70.53 (18.90)	44%	31%	58%	20.0 (11.8)
			1,371	Roxadustat	60.86 (14.67)	69.89 (18.46)	41%	30%	57%	19.7 (11.7)
		ANDES	305	Placebo	64.84 (13.20)	71.23 (18.37)	43%	33%	65%	22.4 (11.4)
			608	Roxadustat	64.98 (12.59)	71.33 (19.46)	39%	34%	65%	21.9 (11.5)
		ALPS	203	Placebo	61.71 (13.76)	76.50 (16.51)	49%	44%	44%	17.2 (11.7)
			389	Roxadustat	60.54 (13.55)	73.85 (16.50)	43%	36%	37%	16.5 (10.2)
		DOLOMITES	292	ESA	65.75 (14.42)	78.45 (17.68)	44%	48%	47%	20.4 (10.7)
			322	Roxadustat	66.87 (13.57)	76.93 (16.35)	45%	47%	46%	20.3 (11.5)

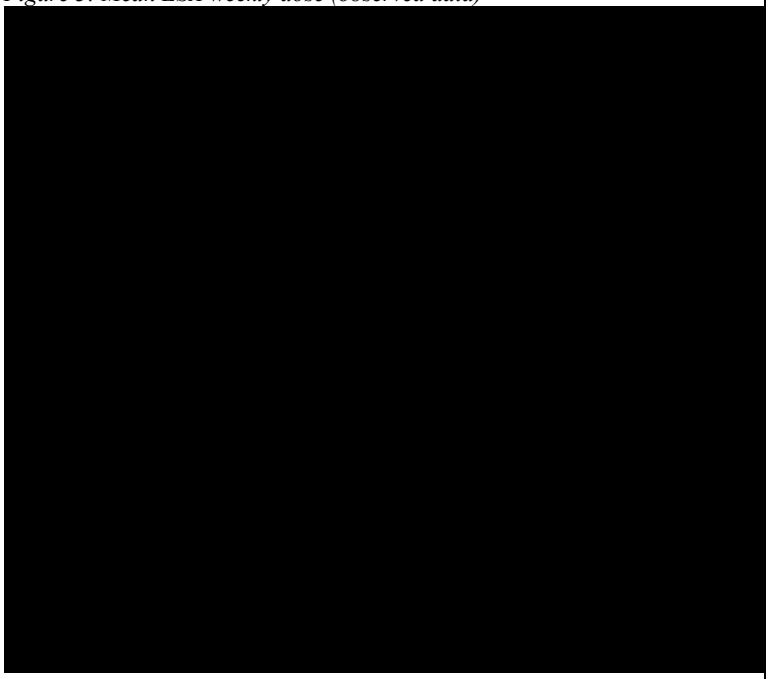
		While there may be differences in some variables, if these are not modifiers of baseline risk or treatment efficacy, we would argue that these differences do not justify the exclusion of three out of the four relevant clinical trials in favour of the sole use of one of the smallest of the four studies. Furthermore, roxadustat dose, dosing schedule and mode of delivery were the same in all four studies. This again suggests that it is appropriate to try and borrow strength from the roxadustat data from all four studies to best inform decision-making. Using this methodology allows for more accurate roxadustat predictions as it leverages data from all 2,660 study participants assigned to this intervention. This means that cost-effectiveness estimates using the pooled analysis are based on individual patient data from nearly 3,000 individuals (the total of all individuals who received roxadustat or darbepoetin alfa) rather than the 684 patients in DOLOMITES. This will lead to greater certainty around many model parameters and hence a more robust incremental cost-effectiveness ratio (ICER) for decision-making. The lability of the ICER to small changes in costs or quality-adjusted life years (QALYs) in the DOLOMITES only analysis should also be noted, alongside the observation that all parameters were similar however given the smaller number of patients these were associated with greater uncertainty. Considering the representativeness of the pooled analysis to UK practice, the improved statistical strength, and the optimised use of all available data obtained on roxadustat in accordance with NICE guidance, discarding data from 2,300 patients is not justified, and the analysis using all four NDD trials offers the most appropriate evidence for decision-making purposes.	
Key issue 4: The trials include very few	**NO**	Although the trials included a relatively small number of UK patients, which is not uncommon with global clinical trial	The ERG notes that even if the known baseline characteristics of the non-UK patients are similar to UK patients, our concern about generalisability to the UK

participants from the United Kingdom (UK).		programmes, the experts considered the population derived from the roxadustat trials representative of UK clinical practice. During the model clinical and health economic validation, baseline demographics and disease characteristics (including average starting age and the proportion of patients who were male/female, with CVD history and patients with diabetes were presented for the patient populations from each of the trials. Baseline characteristics for the pooled NDD population to be used in the economic model were also shared, with this pooled population considered the most representative sample of the UK population by clinical experts. The number of UK patients is not considered sufficient to produce robust results in sub-group analysis. The ALPS and DOLOMITES clinical trials enrolled 12 (2.0%) and 61 (9.9%) patients from the UK respectively while no UK patients were enrolled in the ANDES and OLYMPUS trials, Performing statistical analyses in samples with low-statistical power is associated with problems such as reduced chance of detecting a true effect, low likelihood that a statistically significant result reflects a true effect, overestimated effect sizes, and low reproducibility.	setting remains due to (among other things): unknown baseline characteristics may not have been controlled for, and concomitant care differs across countries in ways that could influence outcomes.
Key issue 5: Model structure: justification for the Hb ranges and cut-off values to define health states is lacking.	**NO**	The model structure with eight health states was based on a previously published, peer-reviewed, cost-effectiveness model of anaemia treatment for CKD patients which simulated complications (e.g. stroke, MI, blood transfusions), and quality of life reductions related to changes in Hb levels (Yarnoff et al. 2016). The Hb categories used for the relative risks for blood transfusion in the published model matched the eight health states used in the company model. Yarnoff et al. state the utility loss per 1 g/dL in Hb based on Finklestein et al. 2009 who demonstrated that as Hb levels increased in increments of 1 g/dL in Hb there were significant improvements in a variety of quality-of-life domains. The positive correlation between Hb levels and health-related quality of life (HRQoL) in CKD	The additional Figures provided by the company are informative. These Figures seemingly illustrate that there is a relation between Hb and dose and Hb and utility. However, the claim of the necessity of modelling Hb in these (small) categories is not supported. Based on these data a smaller number of categories would potentially already capture meaningful differences (consistent with the comments raised during the clinical and health economic validation performed by the company). The company did not provide additional compelling arguments, the requested

		patients has also been recognised elsewhere in the literature, with another published cost-effectiveness analysis by Glenngård et. al. 2008 following a similar stratification of HRQoL by Hb level, in CKD anaemia patients. Changes in HRQoL based on patient's Hb level are the main drivers of QALYs accrued in the economic model based on the modelled treatment effect of roxadustat (effect on Hb level over time). The association between Hb level and HRQoL was also confirmed in the roxadustat clinical trial programme. The figure presented below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle) for utility values at increasing Hb levels. These data show that utilities increase with increments of 1 g/dL in the patient's Hb level and the statistical model provides a reasonable estimate for the average utility value stratified by Hb level (evidence previously provided in response to clarification question C10). *Figure 1: Utility values by increasing Hb level (showing observed data in red and predicted values in blue)*	analyses or additional evidence to resolve this key issue. The ERG comments in the ERG report are still applicable. Most importantly that the rationale for the definition of the ranges of Hb levels in the model was not thoroughly justified and the expected impact of different cut-offs/fewer Hb health states is unclear. The ERG therefore maintains that this key issue remains important.

		 A similar observation can be made for the trends in roxadustat and ESA treatment doses, which are key drivers of incremental costs in the economic analyses. Treatment starting doses are weight dependent, with maintenance doses titrated according to each patient's response to treatment, and evolution of Hb levels in clinical practice. Therefore, there is an intrinsic link between the treatment effect and the treatment dose associated with it. The figures below show the observed data within the clinical trials demonstrating a change in weekly treatment dose for	

		both roxadustat and ESA with increasing Hb levels (shared previously in response to clarification question C14). *Figure 2: Mean roxadustat weekly dose (observed data)* 	

		Figure 3: Mean ESA weekly dose (observed data)  Using fewer health states in the economic modelling would lead to a loss of granularity in time trends between treatment arms. Furthermore, as 1 g/dL increments in Hb level have been shown to be associated with differences in costs and utilities by both published literature and the clinical trial evidence, the use of eight health states is well justified, and demonstrates the nuances which could be important in demonstrating the value of roxadustat in the economic analysis.	
Key issue 6: Treatment effectiveness and extrapolation:	**NO**	The rationale for including time within the statistical model was to be able to estimate the proportion in state for the patient cohort at any given time point. Initial exploration of the model showed that using the natural log of time resulted in more	The company did not provide additional compelling arguments, the requested

appropriateness of time dependency and extrapolation of the multinomial logistic regression model unclear.		clinically plausible extrapolations compared with using time on a linear scale. Assuming a linear relationship with time meant that when extrapolated over a longer time horizon, patients continuously improved, which is not a realistic assumption. By using the log scale for time, the regressions ensure changes in the proportion in state tend towards a plateau rather than assuming a constant increase/decrease over time. As time includes baseline (time 0), it is not mathematically possible to include it in any model predictions using a natural log. As a result, by adding 1 to all time values in the statistical model we were able to use time 0 in the statistical model predictions. The rationale for including treatment type within the statistical model was to be able to adjust for any impact that treatment type had on the proportion in state. The second order interaction between time and treatment type was included to be able to analyse whether the relationship between time and Hb level differed by treatment type. The interaction term allows the relationship between proportion in state and time to differ by treatment arm. Removing the interaction term would still leave time and treatment type as individual predictors in the regression. This would mean treatment type would impact the intercept (i.e. increase/decrease the relative starting points of each treatment) but the changes in the proportion in each health state overtime would be identical for each treatment arm (i.e. the difference at baseline would be maintained throughout the entire model). The above variables were selected in the statistical analysis plan prior to conducting any statistical analyses and were validated by medical experts as being the most relevant predictors. It is biologically plausible that the longer a patient remains on a treatment, the more it will impact their Hb level. As roxadustat and ESA differ in their modes of action and delivery, it is plausible that the impact of long-term treatment of	analyses or additional evidence to resolve this key issue. Therefore, the ERG comments in the ERG report are still applicable (see also ERG report section 4.2.6) and this key issue remains important.

these medications differs, as supported by the economic model.

The interaction coefficients in Table 35 of the company submission (Document B) show the change in Hb level over time that is unique to each treatment arm. Coefficients indicated that over time, patients on both ESA and roxadustat are more likely to be in lower Hb levels compared to Hb level 10-11 and less likely to be in the higher Hb levels compared to Hb level 10-11. However, it should be noted that interaction terms are complicated to interpret in isolation and must be considered in conjunction with the sum of their parts. Although the ESA and roxadustat coefficients do not alter the relationship between time and Hb level, they do significantly alter the starting point of each arm (i.e. patients are more likely to start in the higher health states and thus over time are likely to move to lower ones as they cannot move to higher ones).

The model was built with the functionality to maintain the proportion in state at any given time point. This functionality allows the model to test the sensitivity of the results to changes in proportion in state over time. This functionality can be accessed via a switch on the model set-up page. We have conducted three scenarios to maintain proportion in state after 5, 10 and 15 years. Results show that by fixing the proportion in state over time (i.e. ignoring the impact of time after set points), roxadustat remains cost-effective, as demonstrated in the results provided in response to clarification question C5h (table below). The results further show that the treatment benefit from roxadustat is accrued early in the model and does not require protracted extrapolations to demonstrate cost-effectiveness.

Table 2: Scenario analysis supporting clarification question c5

Scenario	Roxadustat	
	Costs	QALYs
Base case	[redacted]	[redacted]

		Scenario C5.1: Proportion in state fixed after 5 year [redacted] Scenario C5.2: Proportion in state fixed after 10 year [redacted] Scenario C5.3: Proportion in state fixed after 15 year [redacted] Furthermore, as the long-term plausibility of the model extrapolations have been validated with clinicians, the approaches taken are considered appropriate.	
Key issue 7: Potentially relevant adverse events were excluded.	**YES**	Three adverse events were included in the economic model – stroke, myocardial infarction (MI) and vascular access thrombosis (VAT). Patients with chronic kidney disease (CKD) and end stage renal disease (ESRD) are at high risk of major adverse cardiovascular events (MACE). MACEs are important in any cardiovascular model, as these either result in death or worsening disease, and significantly reduce HRQoL. MACEs are commonly used as composite endpoints in cardiac research. However, in the current model these events are modelled separately in order to apply appropriate costs and utility decrements to each event as they are economically distinct. For the patient population in the model, MACEs are especially important for those treated with ESAs. Stroke and MI were chosen as adverse events due to the pre-existing literature noting their prevalence in CKD and ESRD populations. VAT was included following read out of the clinical trials, as it was noted that VAT occurred in a minority of patients and was associated with a high healthcare resource cost. The model was reviewed by three experts who agreed this choice of adverse events was appropriate. In response to the concern about potentially relevant adverse events being excluded from the economic model, the impact of grade 3+ treatment-emergent adverse events that occurred in more than 3% of the trial population in the DOLOMITES study (presented in Table 62 of the clinical study report) was explored. [redacted] adverse events were identified: [redacted]	Based on the additional analyses provided by the company, the impact of adverse events seems minor. Hence, the ERG believes that this key issue should be regarded as a minor issue (i.e. not a key issue).

[redacted].

To explore the potential impact of these adverse events on the current cost-effectiveness outcomes, a simplified estimation of the expected costs and utility loss from these adverse events (assigning costs and utility for the proportion of patients experiencing the adverse events) is provided in Table 3 below.

Table 3: Estimation of the expected costs and utility loss from grade 3+ TEAEs occurring in more than 3% of DOLOMITES participants

Adverse Event	% Patients		Per event (TA712/TA622)		Weighted cost		Weighted disutility	
	Roxadustat	ESA	Cost	Disutility	Roxadustat	ESA	Roxadustat	ESA
Cardiac failure	[redacted]	[redacted]	£2,964.21	-0.00290	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	£2,526.61	-0.00575	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	£364.49	-0.00440	[redacted]	[redacted]	[redacted]	[redacted]
Total					[redacted]	[redacted]	[redacted]	[redacted]
Incremental					[redacted]		[redacted]	

As described in the response to clarification question C11, quality of life from CKD progression is captured indirectly in the model through the utilities associated with Hb level and dialysis status, thus the effects of end stage renal disease and decreased glomerular filtration rate (indicator of kidney function) were not explicitly applied to avoid double counting any roxadustat treatment benefit and CKD progression costs and a quality of life. The costs and disutilities associated with pneumonia and hypertension were collected from NICE TA712 and those for cardiac failure were collected from NICE TA622.

		Both were applied to the rates observed in the DOLOMITES study. The above table shows the difference between arms is minimal both in terms of costs and quality of life and the inclusion of these adverse events in the cost-effectiveness model is not expected to have an impact in final comparative results. Therefore, there are consistent reasons for considering stroke, myocardial infarction, and vascular access thrombosis in the cost-effectiveness model and the inclusion of further adverse events is not expected to impact the results of the cost effectiveness analysis.	
Key issue 8: Model validation: lack of detail about face validity assessment, limited technical validation, limited cross-and external validation, and inconsistencies between the submission report and the model.	**NO**	Greater detail about the validation undertaken was provided in response to clarification questions C20, C21 and C22 with all inconsistencies between the submission report and the model also addressed. It was not possible to complete a technical verification of the economic model using the TECH-VER checklist at the time of responding to the clarification questions as requested. However, this has now been completed and was submitted to NICE on 20 September 2021.	The ERG received the completed TECH-VER checklist on October 29th. This checklist supports the internal validity of the economic model. However, key issue 8 also entailed additional cross-validation and external validation (see also ERG report section 5.3). The ERG therefore maintains that this key issue remains important.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

References:

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