Cochrane Library

Cochrane Database of Systematic Reviews

Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease (Review)

Natale P, Palmer SC, Jaure A, Hodson EM, Ruospo M, Cooper TE, Hahn D, Saglimbene VM, Craig JC, Strippoli GFM

Natale P, Palmer SC, Jaure A, Hodson EM, Ruospo M, Cooper TE, Hahn D, Saglimbene VM, Craig JC, Strippoli GFM.
Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease.
Cochrane Database of Systematic Reviews 2022, Issue 8. Art. No.: CD013751.
DOI: 10.1002/14651858.CD013751.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 8
OBJECTIVES 8
METHODS 8
RESULTS 11
Figure 1. 11
Figure 2. 14
Figure 3. 15
DISCUSSION 21
Figure 4. 22
AUTHORS' CONCLUSIONS 23
ACKNOWLEDGEMENTS 23
REFERENCES 24
CHARACTERISTICS OF STUDIES 38
DATA AND ANALYSES 200
Analysis 1.1. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 1: Cardiovascular death 203
Analysis 1.2. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 2: Death (any cause) 205
Analysis 1.3. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 3: Nonfatal myocardial infarction 206
Analysis 1.4. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 4: Fatal or nonfatal myocardial infarction (overall) 207
Analysis 1.5. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 5: Nonfatal stroke 208
Analysis 1.6. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 6: Fatal or nonfatal stroke (overall) 209
Analysis 1.7. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 7: Peripheral arterial events 210
Analysis 1.8. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 8: Transfusion 211
Analysis 1.9. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 9: Proportion reaching target haemoglobin 212
Analysis 1.10. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 10: Kidney failure 214
Analysis 1.11. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 11: Thrombosis 215
Analysis 1.12. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 12: Loss of unassisted patency (stenosis) 215
Analysis 1.13. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 13: Hyperkalaemia 216
Analysis 2.1. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 1: Cardiovascular death 218
Analysis 2.2. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 2: Nonfatal myocardial infarction 219
Analysis 2.3. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 3: Transfusion 219
Analysis 2.4. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 4: Proportion reaching target haemoglobin 220
Analysis 3.1. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 1: Cardiovascular death 225
Analysis 3.2. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 2: Fatigue 226
Analysis 3.3. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 3: Death (any cause) 227
Analysis 3.4. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 4: Nonfatal myocardial infarction 229
Analysis 3.5. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 5: Fatal or nonfatal myocardial infarction (overall) 230

Analysis 3.6. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 6: Nonfatal stroke 231
Analysis 3.7. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 7: Fatal or nonfatal stroke (overall) 232
Analysis 3.8. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 8: Nonfatal hospitalisation for heart failure 233
Analysis 3.9. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 9: Fatal or nonfatal hospitalisation for heart failure 233
Analysis 3.10. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 10: Peripheral arterial event 234
Analysis 3.11. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 11: Transfusion 235
Analysis 3.12. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 12: Proportion reaching target haemoglobin 237
Analysis 3.13. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 13: Kidney failure 239
Analysis 3.14. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 14: Thrombosis 240
Analysis 3.15. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 15: Loss of unassisted patency (occlusion/stenosis) 241
Analysis 3.16. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 16: Access intervention 242
Analysis 3.17. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 17: Cancer 243
Analysis 3.18. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 18: Infection 244
Analysis 3.19. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 19: Hyperkalaemia 245
Analysis 3.20. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 20: Pulmonary hypertension 247
Analysis 3.21. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 21: Diabetic retinopathy 248
Analysis 4.1. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 1: Cardiovascular death 250
Analysis 4.2. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 2: Fatigue 251
Analysis 4.3. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 3: Nonfatal myocardial infarction 252
Analysis 4.4. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 4: Nonfatal stroke 253
Analysis 4.5. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 5: Transfusion 254
Analysis 4.6. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 6: Proportion reaching target haemoglobin 255
Analysis 5.1. Comparison 5: Subgroup analysis: stage CKD (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin 256
Analysis 5.2. Comparison 5: Subgroup analysis: stage CKD (HIF versus ESA), Outcome 2: Thrombosis 257
Analysis 6.1. Comparison 6: Subgroup analysis: duration of therapy (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin 258
Analysis 6.2. Comparison 6: Subgroup analysis: duration of therapy (HIF versus ESA), Outcome 2: Thrombosis 259
Analysis 7.1. Comparison 7: Subgroup analysis: frequency of administration (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin 260
Analysis 7.2. Comparison 7: Subgroup analysis: frequency of administration (HIF versus ESA), Outcome 2: Thrombosis 261
Analysis 8.1. Comparison 8: Subgroup analysis: phase 2 versus phase 3 studies (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin 262
Analysis 8.2. Comparison 8: Subgroup analysis: phase 2 versus phase 3 studies (HIF versus ESA), Outcome 2: Thrombosis 263
APPENDICES 263
WHAT'S NEW 300
HISTORY 300

CONTRIBUTIONS OF AUTHORS 300
DECLARATIONS OF INTEREST 300
SOURCES OF SUPPORT 300
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 301
NOTES 301
INDEX TERMS 301

[Intervention Review]

Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease

Patrizia Natale[1,2,3], Suetonia C Palmer[4], Allison Jaure[2,5], Elisabeth M Hodson[2,6], Marinella Ruospo[1], Tess E Cooper[2,6], Deirdre Hahn[7], Valeria M Saglimbene[1,2], Jonathan C Craig[6,8], Giovanni FM Strippoli[1,2,6]

[1]Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy. [2]Sydney School of Public Health, The University of Sydney, Sydney, Australia. [3]Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy. [4]Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand. [5]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [6]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia. [7]Department of Nephrology, The Children's Hospital at Westmead, Westmead, Australia. [8]College of Medicine and Public Health, Flinders University, Adelaide, Australia

Contact: Giovanni FM Strippoli, giovanni.strippoli@uniba.it.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 9, 2022.

Citation: Natale P, Palmer SC, Jaure A, Hodson EM, Ruospo M, Cooper TE, Hahn D, Saglimbene VM, Craig JC, Strippoli GFM. Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease. *Cochrane Database of Systematic Reviews* 2022, Issue 8. Art. No.: CD013751. DOI: 10.1002/14651858.CD013751.pub2.

ABSTRACT

Background

Anaemia occurs in chronic kidney disease (CKD) and is more prevalent with lower levels of kidney function. Anaemia in CKD is associated with death related to cardiovascular (CV) disease and infection. Established treatments include erythropoiesis-stimulating agents (ESAs), iron supplementation and blood transfusions. Oral hypoxia-inducible factors (HIF) stabilisers are now available to manage anaemia in people with CKD.

Objectives

We aimed to assess the benefits and potential harms of HIF stabilisers for the management of anaemia in people with CKD.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 22 November 2021 through contact with the Information Specialist using search terms relevant to our review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

Randomised and quasi-randomised studies evaluating hypoxia-inducible factors stabilisers compared to placebo, standard care, ESAs or iron supplementation in people with CKD were included.

Data collection and analysis

Five authors independently extracted data and assessed the risk of bias. Treatment estimates were summarised using random effects pair-wise meta-analysis and expressed as a relative risk (RR) or mean difference (MD), with a corresponding 95% confidence interval (CI). Evidence certainty was assessed using GRADE.

Main results

We included 51 studies randomising 30,994 adults. These studies compared HIF stabilisers to either placebo or an ESA.

Compared to placebo, HIF stabiliser therapy had uncertain effects on CV death (10 studies, 1114 participants): RR 3.68, 95% CI 0.19 to 70.21; very low certainty evidence), and nonfatal myocardial infarction (MI) (3 studies, 822 participants): RR 1.29, 95% CI 0.31 to 5.36; I^2 = 0%; very low certainty evidence), probably decreases the proportion of patients requiring blood transfusion (8 studies, 4329 participants): RR 0.51, 95% CI 0.44 to 0.60; I^2 = 0%; moderate certainty evidence), and increases the proportion of patients reaching the target haemoglobin (Hb) (10 studies, 5102 participants): RR 8.36, 95% CI 6.42 to 10.89; I^2 = 37%; moderate certainty evidence).

Compared to ESAs, HIF stabiliser therapy may make little or no difference to CV death (17 studies, 10,340 participants): RR 1.05, 95% CI 0.88 to 1.26; I^2 = 0%; low certainty evidence), nonfatal MI (7 studies, 7765 participants): RR 0.91, 95% CI 0.76 to 1.10; I^2 = 0%; low certainty evidence), and nonfatal stroke (5 studies, 7285 participants): RR 1.06, 95% CI 0.71 to 1.56; I^2 = 8%; low certainty evidence), and had uncertain effects on fatigue (2 studies, 3471 participants): RR 0.80, 95% CI 0.56 to 1.16; I^2 = 0%; very low certainty evidence). HIF stabiliser therapy probably decreased the proportion of patients requiring blood transfusion (11 studies, 10,786 participants): RR 0.87, 95% CI 0.76 to 1.00; I^2 = 25%; moderate certainty evidence), but may make little or no difference on the proportion of patients reaching the target Hb (14 studies, 4601 participants): RR 1.00, 95% CI 0.93 to 1.07; I^2 = 70%; low certainty evidence), compared to ESA.

The effect of HIF stabilisers on hospitalisation for heart failure, peripheral arterial events, loss of unassisted dialysis vascular access patency, access intervention, cancer, infection, pulmonary hypertension and diabetic nephropathy was uncertain.

None of the included studies reported life participation. Adverse events were rarely and inconsistently reported.

Authors' conclusions

HIF stabiliser management of anaemia had uncertain effects on CV death, fatigue, death (any cause), CV outcomes, and kidney failure compared to placebo or ESAs. Compared to placebo or ESAs, HIF stabiliser management of anaemia probably decreased the proportion of patients requiring blood transfusions, and probably increased the proportion of patients reaching the target Hb when compared to placebo.

PLAIN LANGUAGE SUMMARY

Are hypoxia-inducible factor stabilisers effective for management of anaemia among people with chronic kidney disease?

What is the issue?

Anaemia (reduced levels of circulating red blood cells) is common in people with chronic kidney disease (CKD). Anaemia is linked to cardiovascular disease, infection and death. Hypoxia-inducible factors (HIF) stabilisers have now become available to manage anaemia and can be taken by mouth, thus avoiding injections.

What did we do?

We evaluated whether HIF stabilisers are beneficial for children and adults with CKD to manage anaemia. We evaluated all clinical studies for hypoxia-inducible factor stabilisers and summarised the results. We evaluated how certain we could be about the evidence related to hypoxia-inducible factors stabiliser using a system called "GRADE".

What did we find?

We included 51 studies randomising 30,994 adult patients. Patients in the studies were given a HIF stabiliser, a sugar pill (placebo), or erythropoietin treatment. The treatment they got was decided by random chance. The studies were generally short-term (over a few weeks). There were no studies in children or people who had received a kidney transplant.

HIF stabilisers decreased blood transfusions for people with CKD when compared to placebo or erythropoietin treatment. HIF stabilisers increased the number of patients reaching their haemoglobin target level when compared to placebo. HIF stabilisers have uncertain effects on life expectancy and the chance of heart disease in people with CKD.

Conclusions

HIF stabilisers decreased the need for a blood transfusion for people with CKD and increased the number of patients reaching their haemoglobin target level. We are not sure whether hypoxia-inducible factor stabilisers have any impact on life expectancy or life quality in people with CKD when compared to a placebo or other treatments for anaemia.

Summary of findings 1. Hypoxia-inducible factor (HIF) stabilisers versus placebo for people with chronic kidney disease (CKD)

HIF stabilisers versus placebo for people with CKD

Patient or population: people with CKD (including HD and PD)

Settings: multinational

Intervention: HIF stabilisers

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	HIF stabilisers				
Cardiovascular death Median follow-up: 16 weeks	**Low risk population (CKD)**		**RR 3.68** (0.19 to 70.21)	1114 (10)	⊕⊖⊖⊖ **very low** [1,2,3]	Studies were not designed to measure effects of HIF stabiliser management of anaemia on CV death compared with placebo in CKD and HD
	No events	3/607**				
	High risk population (HD)					
	No events	No events				
Fatigue	Not reported	Not reported	--	--	--	No studies reported this outcome
Life participation	Not reported	Not reported	--	--	--	No studies reported this outcome
Nonfatal myocardial infarction Median follow-up: 24 weeks	**Low risk population (CKD)**		**RR 1.29** (0.31 to 5.36)	822 (3)	⊕⊖⊖⊖ **very low** [1,2,4]	The effects of HIF stabiliser management of anaemia on nonfatal MI were uncertain compared with placebo in CKD
	8 per 1000	**2 more per 1000** (from 6 fewer to 35 more)				
Nonfatal stroke Median follow-up:	**Low risk population (CKD)**		Not estimable	228 (2)	⊕⊖⊖⊖ **very low** [1,2,4]	Studies were not designed to measure effects of HIF stabiliser management of anaemia on nonfatal stroke compared with placebo in CKD
	No events	No events				

21 weeks						
Proportion of patients requiring blood transfusion Median follow-up: 18 weeks	**Low risk population (CKD)**		**RR 0.51** (0.44 to 0.60)	4329 (8)	⊕⊕⊕⊖ **moderate** [1]	HIF stabiliser management of anaemia probably decreases the proportion of patients requiring blood transfusion compared to placebo in CKD and HD
	200 per 1000	**96 fewer per 1000** (from 112 fewer to 80 fewer)				
	High risk population (HD)					
	214 per 1000	**169 fewer per 1000** (206 fewer to 30 more)				
Proportion reaching target haemoglobin Median follow-up: 16 weeks	**Low risk population (CKD)**		**RR 8.36** (6.42 to 10.89)	5102 (10)	⊕⊕⊕⊖ **moderate** [1]	HIF stabiliser management of anaemia probably increases the proportion of patients reaching their Hb target compared to placebo in CKD and HD
	83 per 1000	**594 more per 1000** (424 more to 821 more)				
	High risk population (CKD and HD)					
	No events	63/141**				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** Event rate derived from the raw data. A 'per thousand' rate is non-informative in view of the scarcity of evidence and zero events in the control group

HD: haemodialysis; **PD:** peritoneal dialysis; **CI**: confidence interval; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Evidence certainty was downgraded by one level due to study limitations. Some studies had unclear risks for sequence generation and/or allocation concealment and the majority or all of them were not blinded (participant/investigator and/or outcomes assessor). All studies reported sources of funding
[2] Evidence certainty was downgraded by one level due to imprecision
[3] Evidence certainty was downgraded by one level due to indirectness in the study population
[4] Evidence certainty was downgraded by one level due to imprecision (optimal information size was not met and the included studies reported zero events)

Summary of findings 2. Hypoxia-inducible factor (HIF) stabilisers versus erythropoiesis-stimulating agent (ESA) for people with chronic kidney disease (CKD)

HIF stabilisers versus ESA for people with CKD

Patient or population: people with CKD (including HD and PD)

Settings: multinational

Intervention: HIF stabilisers

Comparison: ESA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ESA	HIF stabilisers				
Cardiovascular death Median follow-up: 28 weeks	**Low risk population (CKD)**		**RR 1.05** (0.88 to 1.26)	10,340 (17)	⊕⊕⊖⊖ **low** [1,2]	HIF stabiliser management of anaemia may have little or no difference on CV death compared with ESA in CKD
	34 per 1000	**6 more per 1000** (from 3 fewer to 18 more)				
	High risk population (HD and PD)					
	77 per 1000	**3 fewer per 1000** (from 19 fewer to 17 more)				
Fatigue Median follow-up: 57 weeks	**Low risk population (CKD)**		**RR 0.80** (0.56 to 1.16)	3471 (2)	⊕⊖⊖⊖ **very low** [1,2,3]	HIF stabiliser management of anaemia had uncertain effects on fatigue compared with ESA in CKD
	36 per 1000	**7 fewer per 1000** (from 16 fewer to 6 more)				
Life participation	Not reported	Not reported	--	--	--	No studies reported this outcome
Nonfatal myocardial	**Low risk population (CKD)**		**RR 0.91** (0.76 to 1.10)	7765 (7)	⊕⊕⊖⊖ **low** [1,2]	HIF stabiliser management of anaemia may have little or no difference on
	46 per 1000	**3 more per 1000**				

infarction Median follow-up: 26 weeks		(from 9 fewer to 18 more)				nonfatal MI compared with ESA in CKD, HD and PD
	High risk population (HD and PD)					
	80 per 1000	**16 fewer per 1000** (from 30 fewer to 2 more)				
Nonfatal stroke Median follow-up: 28 weeks	**Low risk population (CKD)**		**RR 1.06** (0.71 to 1.56)	7285 (5)	⊕⊕⊖⊖ **low** [1,2]	HIF stabiliser management of anaemia may have little or no difference on nonfatal stroke compared with ESA in CKD, HD and PD
	10 per 1000	**5 more per 1000** (from 1 fewer to 16 more)				
	High risk population (HD)					
	24 per 1000	**5 fewer per 1000** (from 12 fewer to 8 more)				
Proportion of patients requiring blood transfusion Median follow-up: 52 weeks	**Low risk population (CKD)**		**RR 0.87** (0.76 to 1.00)	10786 (11)	⊕⊕⊕⊖ **moderate** [1]	HIF stabiliser management of anaemia probably decreases the proportion of patients requiring blood transfusion compared to ESA in CKD, HD and PD
	121 per 1000	**4 fewer per 1000** (19 fewer to 16 more)				
	High risk population (HD)					
	154 per 1000	**31 fewer per 1000** (55 fewer to 2 more)				
Proportion reaching target haemoglobin Median follow-up: 27 weeks	**Low risk population (CKD)**		**RR 1.00** (0.93 to 1.07)	4601 (14)	⊕⊕⊖⊖ **low** [1,2]	HIF stabiliser management of anaemia may have little or no difference on the proportion of patients reaching their Hb target compared to ESA in CKD, HD and PD
	793 per 1000	**16 more per 1000** (79 fewer to 127 more)				
	High risk population (HD and PD)					
	540 per 1000	**11 fewer per 1000** (49 fewer to 32 more)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
HD: haemodialysis; **PD:** peritoneal dialysis; **CI**: confidence interval; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

---

[1] Evidence certainty was downgraded by one level due to study limitations. Some studies had unclear risks for sequence generation and/or allocation concealment and the majority or all of them were not blinded (participant/investigator and/or outcomes assessor). All studies reported sources of funding
[2] Evidence certainty was downgraded by one level due to imprecision
[3] Evidence certainty was downgraded by one level because similar studies assessed the outcomes

BACKGROUND

Description of the condition

Chronic kidney disease (CKD), reduced kidney function or structural changes in kidney tissue lasting longer than three months, affects approximately 0.7 billion people globally with 20 million additional people affected each year (Global Burden of Disease 2017). Reduced kidney function and raised levels of albumin in the urine are important risk factors for cardiovascular (CV) disease. CKD increases CV risk approximately two- to four-fold in excess of traditional CV risk factors (Gansevoort 2013). CKD is associated with fatigue (Mathias 2020) and lower quality of life (QoL), and incurred 61.3 million disability-affected years worldwide in 2017 (GBD Kidney Disease 2017; Global Burden of Disease 2017; Wyld 2019).

Anaemia (reduced levels of circulating red blood cells (RBC)) occurs as a result of the progression of CKD due to impaired kidney erythropoietin secretion, lower absorption of iron, macrophage sequestration of iron by uraemic inflammation, and shortened RBC survival (Babitt 2012). Anaemia is a critically important outcome for people with CKD (SONG 2017) and may worsen the impact of CKD on health-related (HR) QoL including decreased work productivity (van Haalen 2020). Anaemia prevalence is higher at lower levels of kidney function, affecting one in five people with moderate CKD (estimated glomerular filtration rate (eGFR) 30 to 59 mL/min/1.73 m^2) (El-Achkar 2005). Anaemia in CKD is associated with increased death, including death related to CV disease and infection (Ma 1999).

Description of the intervention

Treatments for anaemia caused by CKD include erythropoiesis-stimulating agents (ESAs), iron supplementation and blood transfusion. Clinical practice guidelines suggest that iron deficiency is corrected prior to initiation of ESA therapy, minimising RBC transfusions especially to avoid allosensitization, except when rapid correction of anaemia is required (KDIGO Clinical Practice Guideline Anemia 2012). ESAs to target higher haemoglobin (Hb) levels (> 130 g/L) in people with CKD increase the risk of death and adverse CV events (Phrommuntikul 2007), leading to clinical practice guidance that suggests ESA therapy is used to avoid Hb concentrations below 90 g/L (KDIGO Clinical Practice Guideline Anemia 2012). Hypoxia-inducible factors (HIF) are promising orally administered drugs to treat anaemia in people with CKD (Haase 2021).

How the intervention might work

HIF are transcription factors present in cells formed through binding of HIF-α and β subunits (Semenza 2011). The HIF-β subunit is expressed constitutively, while the HIF-α subunit is regulated through hydroxylation at proline residues by HIF-prolyl-hydroxylases. During tissue hypoxia, the HIF-prolyl-hydroxylase is inhibited, stabilising HIF-1 and HIF-2, which act to up-regulate expression of many genes, including those that promote erythropoiesis and angiogenesis as well as metabolic processes. HIF stabilisers inhibit HIF-prolyl-hydroxylase activity and stimulate erythropoiesis in people with CKD (Bernhardt 2010).

Oral HIF stabilisers correct anaemia in people with CKD in a dose-dependent manner (Provenzano 2016c). HIF suppresses hepcidin production, which is the main regulator of systemic iron homeostasis (Nemeth 2009), enabling ferroportin stabilisation and promoting intestinal uptake and iron mobilisation from the reticuloendothelial system (Liu 2012; Renassia 2019; Schwartz 2019). Although HIF stabilisation has potentially pleiotropic cellular effects, changes is vascular endothelial growth factor (VEG-F) have not been seen at doses used in randomised controlled trials (RCTs). Potential adverse consequences of HIF stabiliser treatment include tumour activity and angiogenesis (LaGory 2016). HIF stabilisers provide a potential oral therapy for sustained correction of anaemia in CKD, less dependent on iron (particularly intravenous (IV) supplementation. Although oral treatment adherence in a dialysis setting is still not clearly defined among nephrologists, oral HIF stabiliser therapy may be more acceptable to patients, including the potential to avoid the known adverse consequences of treatments with ESAs and blood transfusions. Several HIF stabilisers are available including roxadustat, vadadustat, daprodustat, desidustat, enarodustat and molidustat.

Why it is important to do this review

Evidence for HIF stabilisers to treat anaemia in people with CKD is emerging in RCTs. With data presented from phase 2 studies for competitive HIF stabilisers and preliminary data from phase 3 studies on roxadustat in patients requiring dialysis, sufficient evidence was available to determine the efficacy and safety of HIF stabilisers compared to other treatment strategies, including ESAs therapy. This Cochrane review evaluated the benefits and potential harms of HIF stabilisers in CKD and provide a summary of the certainty of available evidence for decision-makers including clinicians, patients, and policy-makers.

OBJECTIVES

We aimed to assess the benefits and potential harms of HIF stabilisers for the management of anaemia in people with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which treatment allocation was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the effects of HIF stabilisers versus other anaemia therapies, placebo or standard care in people with CKD were included.

Types of participants

Inclusion criteria

Adults and children with CKD were included. We defined CKD as those who are receiving any form of kidney replacement therapy (KRT), have a functioning kidney transplant, have impaired kidney function defined as a reduced eGFR < 60 mL/min/1.73 m^2, or the presence of other markers of kidney damage such as proteinuria (KDOQI stages 1-5) (KDIGO Clinical Practice Guideline CKD 2012), or elevated serum creatinine (SCr) (> 120 mmol/L), or as defined by study authors.

Types of interventions

We evaluated the following treatment comparisons:

1. HIF stabiliser versus placebo
2. HIF stabiliser versus standard care
3. HIF stabiliser versus ESA
4. HIF stabiliser versus iron supplementation

We evaluated HIF stabiliser therapy given orally at any frequency. We included RCTs regardless of the target Hb used to guide dose and frequency.

We investigated studies comparing different doses and phase 1 and 2 studies using subgroup analysis.

We excluded studies assessing head-to-head comparisons of HIF stabilisers.

We excluded studies with follow-up of less than eight weeks.

Types of outcome measures

We did not exclude studies based on non-reporting of outcomes of interest.

The outcomes selected included the relevant SONG core outcome sets as specified by the Standardised Outcomes in Nephrology initiative (SONG 2017).

Primary outcomes

- CV death
- Life participation
- Fatigue

Secondary outcomes

- CV disease (nonfatal myocardial infarction (MI), nonfatal stroke, peripheral arterial event, hospitalisation for heart failure (HF))
- Proportion of patients requiring blood transfusion
- Vascular access (including vascular access failure, early thrombosis (< eight weeks), loss of unassisted patency (combined data for stenosis/occlusions), access failure to attain suitability for dialysis, and need for access intervention (combined data for surgically or by radiological guided angioplasty))
- Cancer
- Kidney failure
- Infection
- Graft health (including graft loss, graft function, acute rejection and chronic rejection)
- Peritoneal dialysis (PD) infection
- PD failure
- Proportion of patients reaching the target Hb
- Adverse events (including pulmonary hypertension, deterioration of diabetic retinopathy, kidney and liver cysts and hyperkalaemia)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Register of Studies up to 22 November 2021 through contact with the Information Specialist using search terms relevant to our review. The Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals and the proceedings and abstracts from major kidney and transplant conferences
4. Searching the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies and a list of handsearched journals, conference proceedings and current awareness alerts are available on the Cochrane Kidney and Transplant website.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines
2. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies
3. Grey literature sources (e.g. abstracts, dissertations, and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, were also searched

Data collection and analysis

Selection of studies

The search strategies described were used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts were screened by five authors (PN, EH, MR, DH, VS) working independently, who discarded studies that were not applicable, however, studies and reviews that might include relevant data or information on studies were retained initially. Five authors (PN, EH, MR, DH, VS) independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which studies satisfy the inclusion criteria. Disagreements were resolved in consultation with another author (SP).

Data extraction and management

Data extraction was carried out independently by five authors (PN, EH, MR, DH, VS) using standard data extraction forms. Disagreements were resolved in consultation with another author (SC). Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together, and the publication with the most complete data were used in the analyses. Where relevant outcomes were only published in earlier versions these data were used. Any discrepancy between published versions was highlighted.

Assessment of risk of bias in included studies

Five authors (PN, EH, MR, DH, VS) independently assessed the following items using the risk of bias assessment tool (Higgins 2020) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are the study reports free of suggestion of selective outcome reporting (reporting bias)?
- Was the study free of other problems that could put it at risk of bias?

Measures of treatment effect

For dichotomous outcomes (death, CV disease, blood transfusion, vascular access, cancer, hospitalisation for HF, kidney failure, infection, graft health, PD infection, PD failure, proportion reaching Hb target, adverse events) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (life participation, fatigue) the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales have been used. Studies analysing change scores were included in meta-analyses together with studies including endpoint outcome data. Missing standard deviations were imputed.

Unit of analysis issues

For cross-over studies, we extracted data for the end of the first period of treatment.

Dealing with missing data

We requested any further information required from the original author by written correspondence (e.g. emailing corresponding author/s) and any relevant information obtained in this manner were included in the review. Evaluation of important numerical data such as screened, randomised patients, as well as intention-to-treat, as-treated and per-protocol population, were carefully performed. Attrition rates, for example, drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (e.g., last-observation-carried-forward) were critically appraised (Higgins 2020).

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test or a CI for I^2) (Higgins 2020).

Assessment of reporting biases

If possible, funnel plots were used to assess the potential existence of small study bias (Higgins 2020). We planned to generate funnel plots if at least 10 studies examining the same treatment comparison were included in the review and comment on whether any asymmetry in the funnel plot was due to publication bias or methodological or clinical heterogeneity of the studies.

Data synthesis

Data were pooled using the random-effects model, but the fixed-effect model was also used to ensure the robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We used subgroup analyses to explore possible sources of heterogeneity. Heterogeneity among participants could be related to the stage of kidney disease (stage 3-5 not requiring KRT, dialysis, kidney transplant) and the presence of comorbidities (CV disease, diabetes). Heterogeneity in treatments could be related to a prior agent(s) used, the Hb target during therapy, the type, and the frequency and the duration of therapy. Adverse effects were tabulated and assessed with descriptive techniques, as they were likely to be different for the various agents used. Where possible, the risk difference (RD) with 95% CI was calculated for each adverse effect, either compared to no treatment or another agent. Studies comparing different doses and phase 1 and 2 studies were investigated using subgroup analysis.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors on effect size:

- Repeating the analysis, excluding unpublished studies
- Repeating the analysis taking into account the risk of bias, as specified
- Repeating the analysis, excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2020a). The 'Summary of findings' tables also included an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. This was assessed by three authors (PN, EH, MR). The certainty of a body of evidence involves consideration of the within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates and risk of publication bias (Schunemann 2020b).

We reported the following outcomes in the 'Summary of findings' tables.

- CV death
- Fatigue
- Life participation
- Nonfatal MI
- Nonfatal stroke
- Proportion of patients requiring blood transfusion
- Proportion of patients reaching the target Hb

RESULTS

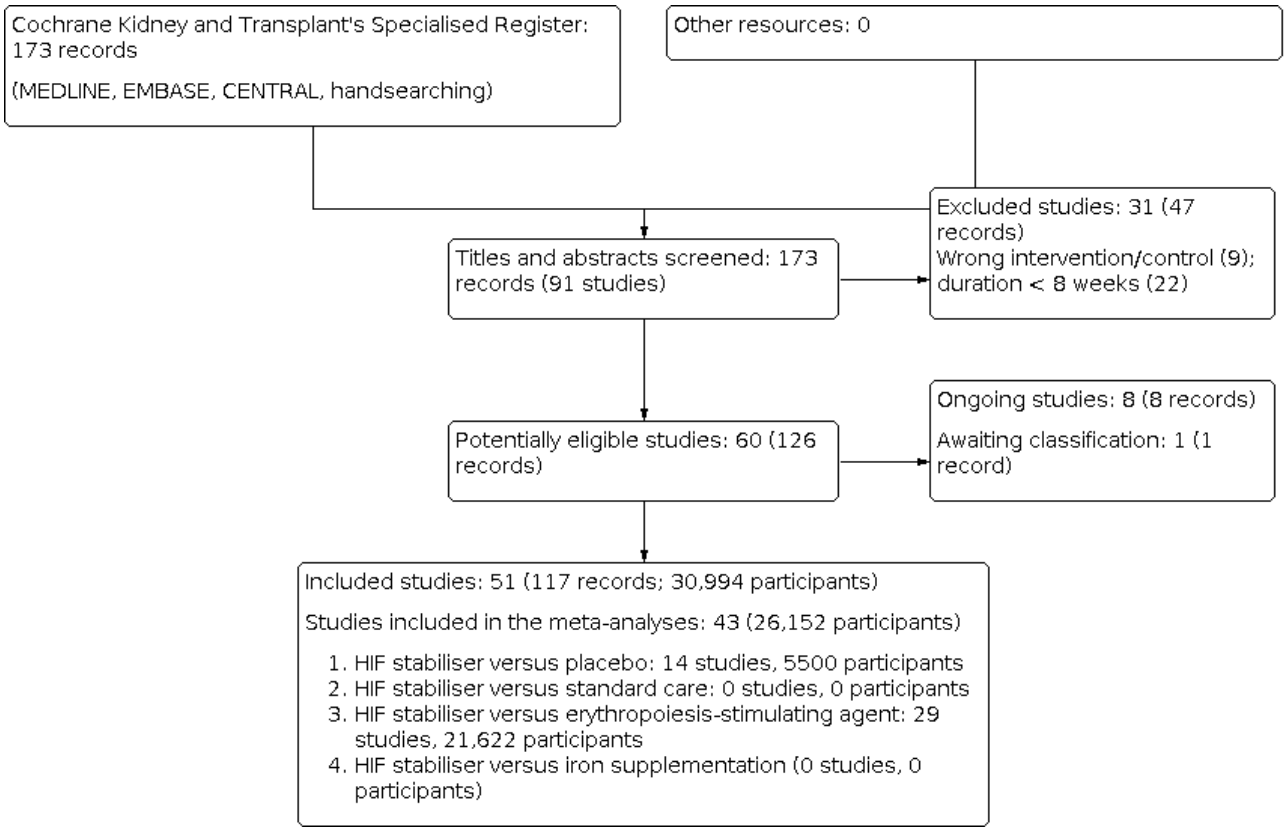
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies

Results of the search

After searching the Specialised Register, we identified 173 records. After screening titles, abstracts, and undertaking full-text review, 51 studies (117 records) were included, and 31 studies (47 records) were excluded. Eight ongoing studies were identified (ASCEND-FBF 2018; CTRI/2019/06/019635; DREAM-D 2019; NCT04027517; NCT04134026; NCT04313153; PER-038-14; SLCTR-2019-032) and one study was completed prior to publication; however, no results are as yet available (FO2RWARD-2 2019). These nine studies will be assessed in a future update of this review (Figure 1).

Figure 1. Flow diagram.



Included studies

We included 51 studies (117 records), randomising 30,994 participants. The characteristics of the participants and the interventions used are detailed in the Characteristics of included studies.

Study design, setting and characteristics

Study duration varied from 8 to 108 weeks, with a median of 28 weeks. No study had a cross-over or cluster-randomised design. Studies were conducted from 2013 to 2021 in China (Chen 2019; Chen 2019a; Chen DD 2017; Chen NDD 2017), Japan (Akizawa 2017; Akizawa 2019; Akizawa 2020a; Akizawa 2020c; Akizawa 2020f; Akizawa 2021; Hou 2021; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021; Nangaku 2021a; Nangaku 2021b; NCT01888445; NDD-CKD 2020; NDD-CKD 2020a; SYMPHONY HD 2021; SYMPHONY ND 2021), and the USA (Besarab 2015; Pergola 2016; Provenzano 2008; Provenzano 2016; Provenzano 2016a), or were multinational (ASCEND-D 2021; ASCEND-ID 2021; ASCEND-ND 2021; ASCEND-NHQ 2021; ASCEND-TD 2021; ALPS 2021; ANDES 2021; Brigandi 2016; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; DOLOMITES 2021; HIMALAYAS 2021; Holdstock 2019; Holdstock 2019a; INNO2VATE 2020; INNO2VATE 2020a; Meadowcroft 2019; OLYMPUS 2021; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; PYRENEES 2021; ROCKIES 2019;

SIERRAS 2021). All but three studies (Akizawa 2020f; Hou 2021; SYMPHONY ND 2021) received at least some funding from pharmaceutical companies. No studies were phase 1 studies, 19 studies (Akizawa 2017; Akizawa 2019; Besarab 2015; Brigandi 2016; Chen DD 2017; Chen NDD 2017; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; Holdstock 2019; Holdstock 2019a; NCT01888445; NDD-CKD 2020; NDD-CKD 2020a; Pergola 2016; Provenzano 2008; Provenzano 2016; Provenzano 2016a; SIERRAS 2021) were phase 2 studies, and 32 studies were phase 3 studies.

Study participants

The sample size varied from 51 (NDD-CKD 2020) to 3872 participants (ASCEND-ND 2021) (median of 223 participants). The mean study age ranged from 48 years (Chen 2019) to 72 years (MIYABI ND-C 2019; Nangaku 2021a) (median 63 years). No studies evaluated treatment in children or in recipients of a kidney transplant.

Twenty-five studies in people with CKD stages 3 to 5 not treated with dialysis (Akizawa 2019; Akizawa 2020f; ALPS 2021; ANDES 2021; ASCEND-ND 2021; ASCEND-NHQ 2021; Besarab 2015; Chen 2019a; Chen DD 2017; DIALOGUE 1 2019; DIALOGUE 2 2019; DOLOMITES 2021; Holdstock 2019; Holdstock 2019a; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021a; Nangaku 2021b; NDD-CKD 2020; OLYMPUS 2021; Pergola 2016; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; Provenzano 2008; SYMPHONY ND 2021), one study in people with CKD stages 3-5 including 5D (Brigandi 2016), 14 studies in people treated with haemodialysis (HD) (Akizawa 2017; Akizawa 2020a; Akizawa 2020c; ASCEND-TD 2021; Chen DD 2017; DIALOGUE 4 2019; Meadowcroft 2019; MIYABI HD-M 2019; Nangaku 2021; NCT01888445; NDD-CKD 2020a; Provenzano 2016; Provenzano 2016a; SYMPHONY HD 2021), one study in people with PD (Hou 2021), and 10 studies (ASCEND-D 2021; ASCEND-ID 2021; Chen 2019; HIMALAYAS 2021; INNO2VATE 2020; INNO2VATE 2020a; HIMALAYAS 2021; PYRENEES 2021; ROCKIES 2019; SIERRAS 2021) included people treated with HD and PD.

Seventeen studies reported information regarding the baseline eGFR in participants (Akizawa 2019; Akizawa 2021; ANDES 2021; Besarab 2015; Chen 2019a; Chen NDD 2017; DIALOGUE 1 2019; DIALOGUE 2 2019; Holdstock 2019; Holdstock 2019a; Nangaku 2021a; NDD-CKD 2020; OLYMPUS 2021; Pergola 2016; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; SYMPHONY ND 2021).

Fourteen studies enrolled people who were prescribed concomitant ESA (Akizawa 2020a; Akizawa 2020c; Akizawa 2020f; ASCEND-D 2021; ASCEND-ID 2021; ASCEND-ND 2021; ASCEND-TD 2021; DIALOGUE 2 2019; DIALOGUE 4 2019; Hou 2021; Nangaku 2021; Nangaku 2021a; Nangaku 2021b; SIERRAS 2021), three studies enrolled people who were prescribed iron supplements (Besarab 2015; Chen 2019a; NCT01888445), and four studies enrolled people who were also prescribed ESA, iron supplements or both (Akizawa 2017; PRO2TECT-CORRECTION 2021; SYMPHONY HD 2021; SYMPHONY ND 2021). One study enrolled people who did not receive ESA (ASCEND-NHQ 2021).

The target Hb levels in the included studies were as follows:

- One study reported the Hb target level ≥ 10 g/dL or an increase of at least 1.0 g/dL in people with a baseline Hb of 8.0 g/dL or more or an increase of at least 2.0 g/dL in people with a baseline Hb of less than 8.0 g/dL (Chen 2019a)
- Four studies reported the Hb target increase ≥ 1 g/dL (Besarab 2015; Chen 2019; Chen DD 2017; Provenzano 2008)
- One study reported either an increase in Hb ≥ 1 g/dL or Hb target ≥ 11.0 g/dL (Chen NDD 2017)
- One study reported an increase in Hb of 0.5 to 1.0 g/dL (Brigandi 2016)
- One study reported the Hb target increase of at least 0.5 to 2.0 g/dL (Akizawa 2017)
- Five studies reported the Hb target was10 to 11 g/dL (ASCEND-D 2021; ASCEND-ID 2021; ASCEND-ND 2021; ASCEND-TD 2021; DIALOGUE 4 2019)
- Two studies reported the Hb target was 10 to 11.5 g/dL (INNO2VATE 2020; Meadowcroft 2019)
- Seventeen studies reported the Hb target was 10 to 12 g/dL (Akizawa 2019; Akizawa 2020a; Akizawa 2020c; Akizawa 2021; DIALOGUE 2 2019; DOLOMITES 2021; MIYABI HD-M 2019; MIYABI ND-M 2019; Nangaku 2021; NCT01888445; NDD-CKD 2020; NDD-CKD 2020a; OLYMPUS 2021; PYRENEES 2021; ROCKIES 2019; SYMPHONY HD 2021; SYMPHONY ND 2021)
- One study reported the Hb target was 10 to 12 g/dL but also an increase of at least 1 g/dL (SIERRAS 2021)
- Two studies reported the Hb target was 11 g/dL and an increase of 1 g/dL if baseline Hb was > 8 g/dL or an increase of 2 g/dL if baseline Hb was < 8 g/dL (ANDES 2021; HIMALAYAS 2021)
- One study reported both an increase in Hb ≥ 1 g/dL or Hb target ≥ 11.0 g/dL (ALPS 2021)
- Five studies reported the Hb target 11 to 13 g/dL (MIYABI ND-M 2019; Nangaku 2021a; Nangaku 2021b; Provenzano 2016; Provenzano 2016a)
- One study reported the Hb target was 11 to 12 g/dL and an increase of 1 g/dL (ASCEND-NHQ 2021)
- One study reported the Hb target was 8 to 11 g/dL (Holdstock 2019a)
- One study reported the Hb target was 9 to 10.5 g/dL (Holdstock 2019)
- One study reported the Hb target was ≥ 11.0 g/dL (Pergola 2016)
- Three studies reported the Hb target in the USA was ≥ 10 to 11 g/dL and in the non-USA countries was ≥ 10 to 12 g/dL (INNO2VATE 2020a; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021)
- Three studies did not report a Hb target (Akizawa 2020f; ASCEND-D 2021; DIALOGUE 1 2019).

Interventions

- One study (Chen NDD 2017) compared three arms, including different doses of HIF stabiliser and placebo
- Seven studies (Akizawa 2019; Chen DD 2017; DIALOGUE 2 2019; Holdstock 2019; NCT01888445; NDD-CKD 2020; NDD-CKD 2020a) included different doses of HIF stabiliser and ESA (Chen DD 2017; DIALOGUE 2 2019; Holdstock 2019; NCT01888445), or different doses of HIF stabiliser and placebo (Akizawa 2019; NDD-CKD 2020; NDD-CKD 2020a)
- Five studies (Akizawa 2017; Besarab 2015; Brigandi 2016; DIALOGUE 4 2019; Provenzano 2016) compared five arms, including different doses of HIF stabiliser and ESA (DIALOGUE 4

2019; Provenzano 2016), or different doses of HIF stabiliser and placebo (Akizawa 2017; Besarab 2015; Brigandi 2016)
- One study (DIALOGUE 1 2019) compared six arms, including different doses of HIF stabiliser and placebo
- One study (Provenzano 2016a) compared seven arms, including different doses of HIF stabiliser and ESA

Forty-three studies (Akizawa 2017; Akizawa 2019; Akizawa 2020a; Akizawa 2020c; Akizawa 2021; ASCEND-D 2021; ASCEND-ND 2021; ALPS 2021; ANDES 2021; Besarab 2015; Brigandi 2016; Chen 2019; Chen 2019a; Chen DD 2017; Chen NDD 2017; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; DOLOMITES 2021; HIMALAYAS 2021; Holdstock 2019; Holdstock 2019a; Hou 2021; INNO2VATE 2020; INNO2VATE 2020a; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021; Nangaku 2021a; Nangaku 2021b; NCT01888445; NDD-CKD 2020; NDD-CKD 2020a; OLYMPUS 2021; Pergola 2016; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; Provenzano 2008; PYRENEES 2021; SIERRAS 2021; SYMPHONY HD 2021; SYMPHONY ND 2021) (26,152 participants) were included in the meta-analyses.

HIF stabilisers versus placebo

Sixteen studies (6330 participants) compared HIF stabiliser to placebo; 14 studies (5500 participants) could be meta-analysed.

- Daprodustat (2 studies, 147 participants) (Akizawa 2017; Brigandi 2016)
- FG2216 (1 study, 142 participants) (Provenzano 2008)
- Molidustat (1 study, 121 participants) (DIALOGUE 1 2019)
- Roxadustat (7 studies, 4769 participants) (Akizawa 2019; ALPS 2021; ANDES 2021; Besarab 2015; Chen 2019a; Chen NDD 2017; OLYMPUS 2021)
- Vadadustat (3 studies, 321 participants) (NDD-CKD 2020; NDD-CKD 2020a; Pergola 2016)

HIF stabilisers versus standard care

No studies compared HIF stabilisers to standard care.

HIF stabilisers versus erythropoiesis-stimulating agent

Thirty-four studies (23,141 participants) compared HIF stabilisers to ESA; 29 studies (21,406 participants) could be meta-analysed.

- Daprodustat versus not specified EPO (2 studies, 252 participants) (Holdstock 2019; Holdstock 2019a)
- Daprodustat versus darbepoetin alfa (3 studies, 4759 participants) (Akizawa 2020c; ASCEND-ND 2021; DOLOMITES 2021)
- Daprodustat versus darbepoetin alfa or EPO alfa (1 study, 2964 participants) (ASCEND-D 2021)
- Daprodustat versus mircera (1 study, 299 participants) (Nangaku 2021b)
- Enarodustat versus darbepoetin alfa (2 studies, 389 participants) (SYMPHONY HD 2021; SYMPHONY ND 2021)
- Molidustat versus epoetin alfa and beta (1 study, 199 participants) (DIALOGUE 4 2019)
- Molidustat versus darbepoetin alfa (4 studies, 679 participants) (DIALOGUE 2 2019; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019)
- Roxadustat versus epoetin alfa (4 studies, 2176 participants) (Chen 2019; Chen DD 2017; HIMALAYAS 2021; SIERRAS 2021)
- Roxadustat versus darbepoetin alfa (3 studies, 696 participants) (Akizawa 2020a; Akizawa 2021; NCT01888445)
- Roxadustat versus epoetin alfa and darbepoetin alfa (1 study, 838 participants) (PYRENEES 2021)
- Roxadustat versus not specified ESA (1 study, 129 participants) (Hou 2021)
- Vadadustat versus darbepoetin alfa (6 studies, 8026 participants) (INNO2VATE 2020; INNO2VATE 2020a; Nangaku 2021; Nangaku 2021a; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021).

HIF stabilisers versus iron supplementation

No studies compared HIF stabilisers with iron supplementation.

Excluded studies

We excluded 31 studies. The reasons for exclusion were:

- Follow-up less than eight weeks (22 studies: Akizawa 2019a; Akizawa 2019b; ASCEND:Fe 2018; ASCEND-BP 2017; Bailey 2019; Buch 2014; DD-CKD 2020; EudraCT2012-004049-34; EudraCT2012-004050-29; EudraCT2015-004790-32; Frohna 2007; Hartman 2014; Holdstock CKD 2016; Holdstock HD 2016; Martin 2017; NCT01971164; NCT03992066; Pai 2015; Parmar 2019; Provenzano 2011; Provenzano 2011a; Wiecek 2005)
- Wrong interventions (9 studies: Akizawa 2015a; Akizawa 2020g; Akizawa 2020; Akizawa 2020b; Besarab 2016; Haase 2016; NCT01679587; NCT04059913; Provenzano 2016b).

Ongoing studies

Our search identified eight studies that have yet to be completed.

- Daprodustat versus darbepoetin alfa (ASCEND-FBF 2018)
- Desidustat versus darbepoetin (CTRI/2019/06/019635; SLCTR-2019-032)
- Desidustat versus epoetin alfa (DREAM-D 2019)
- Enarodustat versus darbepoetin alfa (NCT04027517)
- Roxadustat versus epoetin alfa (NCT04134026; PER-038-14)
- Vadadustat versus darbepoetin alfa (NCT04313153)

Risk of bias in included studies

The risk of bias for studies overall are summarised in Figure 2 and the risk of bias in each study is shown in Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

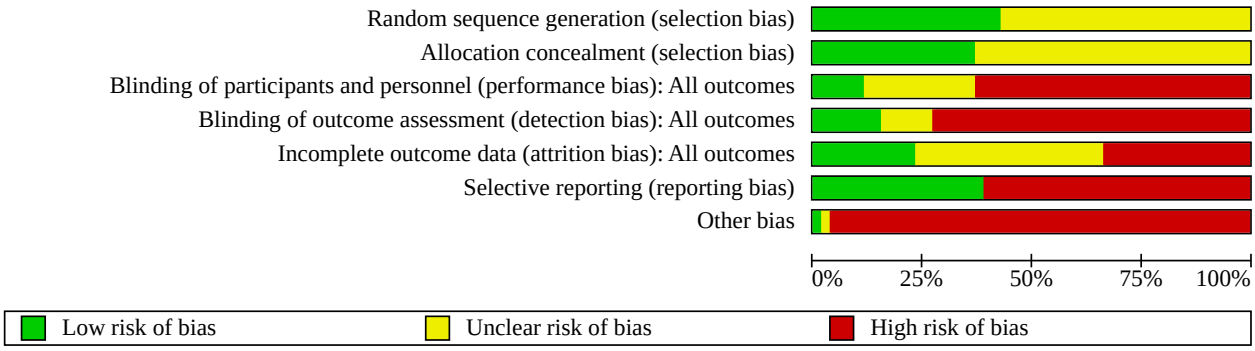


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

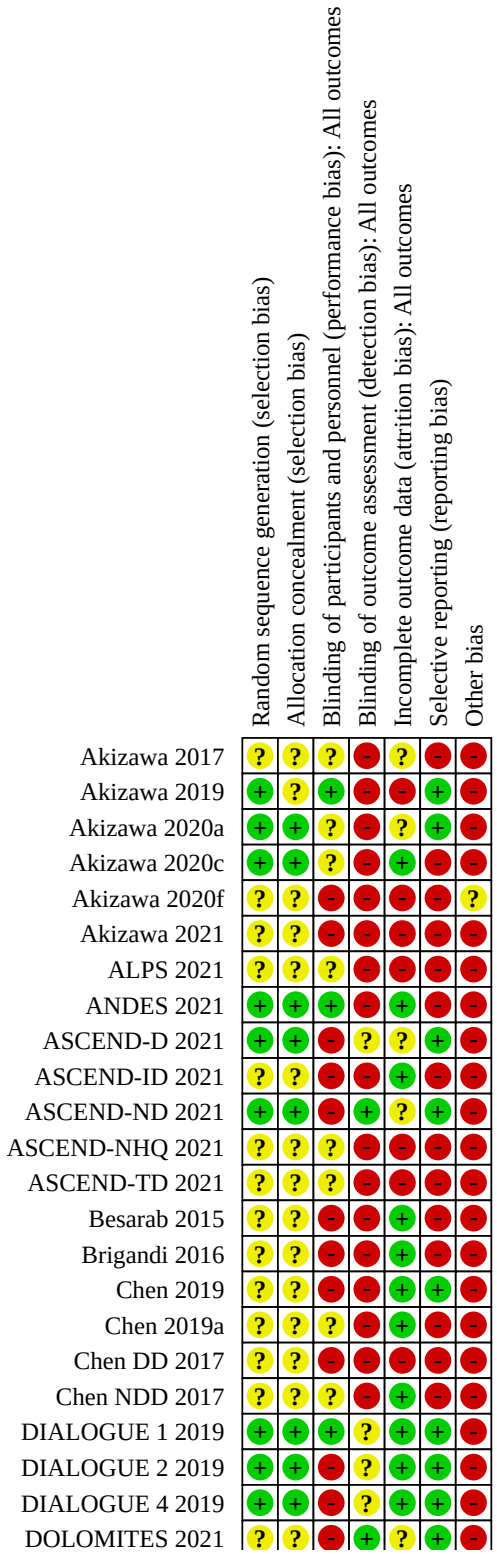
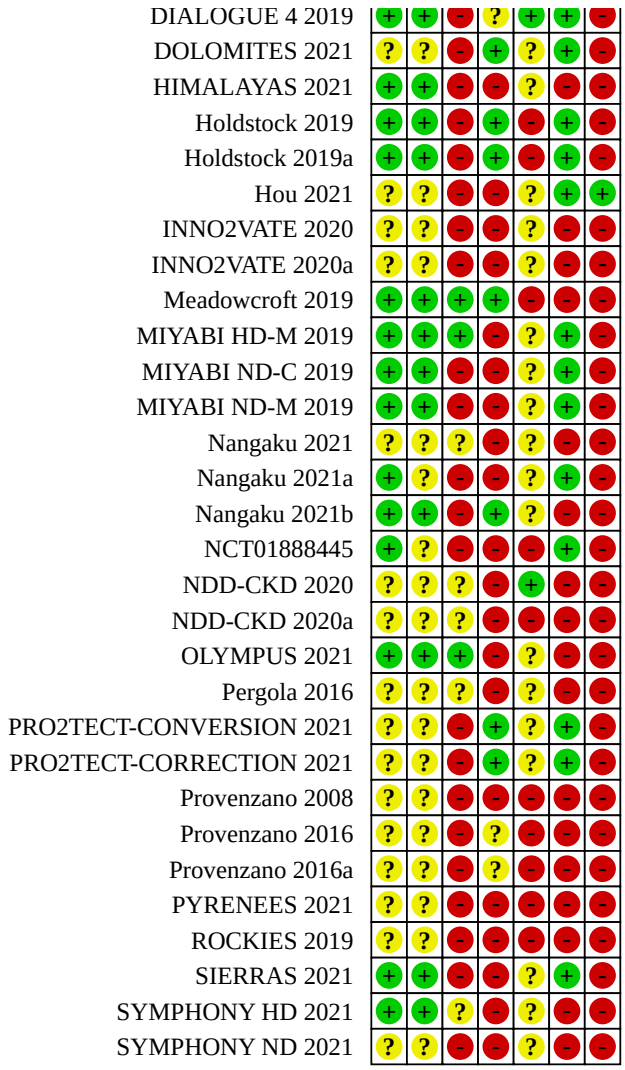


Figure 3. (Continued)



Allocation

Random sequence generation

Methods for generating the random sequence were at low risk of bias in 22 studies (Akizawa 2019; Akizawa 2020a; Akizawa 2020c; ANDES 2021; ASCEND-D 2021; ASCEND-ND 2021; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; HIMALAYAS 2021; Holdstock 2019; Holdstock 2019a; Meadowcroft 2019; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021a; Nangaku 2021b; NCT01888445; OLYMPUS 2021; SIERRAS 2021; SYMPHONY ND 2021). The method for generating the random sequence was unclear in 29 studies.

Allocation concealment

Allocation concealment was at low risk of bias in 19 studies (Akizawa 2020a; Akizawa 2020c; ANDES 2021; ASCEND-D 2021; ASCEND-ND 2021; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; HIMALAYAS 2021; Holdstock 2019; Holdstock 2019a; Meadowcroft 2019; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021b; OLYMPUS 2021; SIERRAS 2021; SYMPHONY ND 2021). The risk of bias for allocation concealment was unclear in 32 studies.

Blinding

Performance bias

Six studies (Akizawa 2019; ANDES 2021; DIALOGUE 1 2019; Meadowcroft 2019; MIYABI HD-M 2019; OLYMPUS 2021) included blinding to treatment allocation for participants and investigators. Thirty-two studies (Akizawa 2020f; Akizawa 2021; ASCEND-D 2021; ASCEND-ID 2021; ASCEND-ND 2021; Besarab 2015; Brigandi 2016; Chen 2019; Chen DD 2017; DIALOGUE 2 2019; DIALOGUE 4 2019; DOLOMITES 2021; HIMALAYAS 2021; Holdstock 2019; Holdstock 2019a; Hou 2021; INNO2VATE 2020; INNO2VATE 2020a; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021a; Nangaku 2021b; NCT01888445; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; Provenzano 2008; Provenzano 2016; Provenzano 2016a; PYRENEES 2021; ROCKIES 2019; SIERRAS 2021; SYMPHONY ND 2021) were not blinded to treatment allocation for participants and investigators. The risk of performance bias was unclear in 13 studies.

Detection bias

Eight studies (ASCEND-ND 2021; DOLOMITES 2021; Holdstock 2019; Holdstock 2019a; Meadowcroft 2019; Nangaku 2021b; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021) assessed outcomes based on objective laboratory assessments and were at low risk of bias. Thirty-seven studies (Akizawa 2017; Akizawa 2019; Akizawa 2020a; Akizawa 2020c; Akizawa 2020f; Akizawa 2021; ALPS 2021; ANDES 2021; ASCEND-ID 2021; ASCEND-NHQ 2021; ASCEND-TD 2021; Besarab 2015; Brigandi 2016; Chen 2019; Chen 2019a; Chen DD 2017; Chen NDD 2017; HIMALAYAS 2021; Hou 2021; INNO2VATE 2020; INNO2VATE 2020a; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021; Nangaku 2021a; NCT01888445; NDD-CKD 2020; NDD-CKD 2020a; OLYMPUS 2021; Pergola 2016; Provenzano 2008; PYRENEES 2021; ROCKIES 2019; SIERRAS 2021; SYMPHONY HD 2021; SYMPHONY ND 2021) were at high risk of bias for blinding of outcome assessment in reporting patient-centred outcomes, including adverse events. Six studies were considered at unclear risk of bias.

Incomplete outcome data

Twelve studies (Akizawa 2020c; ANDES 2021; ASCEND-ID 2021; Besarab 2015; Brigandi 2016; Chen 2019; Chen 2019a; Chen NDD 2017; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; NDD-CKD 2020) were at low risk of attrition bias. Seventeen studies (Akizawa 2019; Akizawa 2020f; Akizawa 2021; ALPS 2021; ASCEND-NHQ 2021; ASCEND-TD 2021; Chen DD 2017; Holdstock 2019; Holdstock 2019a; Meadowcroft 2019; NCT01888445; NDD-CKD 2020a; Provenzano 2008; Provenzano 2016; Provenzano 2016a; PYRENEES 2021; ROCKIES 2019) were at high risk of attrition bias as there was a differential loss to follow-up between treatment groups and/or high attrition rates in both treatment groups. Loss to follow-up was commonly due to withdrawal from the study or adverse events. The risk of attrition bias was unclear in 22 studies.

Selective reporting

Twenty studies (Akizawa 2019; Akizawa 2020a; ASCEND-D 2021; ASCEND-ND 2021; Chen 2019; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; DOLOMITES 2021; Holdstock 2019; Holdstock 2019a; Hou 2021; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021a; NCT01888445; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; SIERRAS 2021) reported expected and clinically-relevant outcomes and were at low risk of bias. Thirty-one studies did not report patient-centred outcomes of death or adverse events.

Other potential sources of bias

One study (Hou 2021) was assessed to be at low risk of bias, 49 studies (Akizawa 2017; Akizawa 2019; Akizawa 2020a; Akizawa 2020c; Akizawa 2021; ALPS 2021; ANDES 2021; ASCEND-D 2021; ASCEND-ID 2021; ASCEND-ND 2021; ASCEND-NHQ 2021; ASCEND-TD 2021; Besarab 2015; Brigandi 2016; Chen 2019; Chen 2019a; Chen DD 2017; Chen NDD 2017; DIALOGUE 1 2019; DIALOGUE 2 2019; DIALOGUE 4 2019; DOLOMITES 2021; HIMALAYAS 2021; Holdstock 2019; Holdstock 2019a; INNO2VATE 2020; INNO2VATE 2020a; Meadowcroft 2019; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021; Nangaku 2021a; Nangaku 2021b; NCT01888445; NDD-CKD 2020; NDD-CKD 2020a; OLYMPUS 2021; Pergola 2016; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; Provenzano 2008; Provenzano 2016; Provenzano 2016a; PYRENEES 2021; ROCKIES 2019; SIERRAS 2021; SYMPHONY HD 2021; SYMPHONY ND 2021) were assessed to be at high risk of bias due to the potential role of funding, and one study was assessed as unclear risk of bias for this domain (Akizawa 2020f).

Effects of interventions

See: **Summary of findings 1** Hypoxia-inducible factor (HIF) stabilisers versus placebo for people with chronic kidney disease (CKD); **Summary of findings 2** Hypoxia-inducible factor (HIF) stabilisers versus erythropoiesis-stimulating agent (ESA) for people with chronic kidney disease (CKD)

See Summary of findings 1 and Summary of findings 2.

HIF stabiliser versus placebo

Fourteen studies (Akizawa 2017; Akizawa 2019; ALPS 2021; ANDES 2021; Besarab 2015; Brigandi 2016; Chen 2019a; Chen NDD 2017; DIALOGUE 1 2019; NDD-CKD 2020; NDD-CKD 2020a; OLYMPUS 2021; Pergola 2016; Provenzano 2008) compared HIF stabiliser management of anaemia versus placebo in patients with CKD (stages 3, 4 or 5), including patients undergoing HD, during a median follow-up of 17 weeks. The certainty of the evidence was mainly low or very low (Summary of findings 1).

Primary outcomes

Cardiovascular death

Compared to placebo, HIF stabiliser therapy had uncertain effects on CV death (Analysis 1.1 (10 studies, 1114 participants): RR 3.68, 95% CI 0.19 to 70.21; very low certainty evidence) in people with CKD or undergoing HD.

Secondary outcomes

Death (any cause)

Compared to placebo, HIF stabiliser therapy may make little or no difference to death (any cause) (Analysis 1.2 (12 studies, 4469 participants): RR 1.12, 95% CI 0.97 to 1.30; I^2 = 0%; low certainty evidence) in people with CKD or undergoing HD.

Myocardial infarction

The effect of HIF stabiliser treatment on nonfatal MI was uncertain (Analysis 1.3 (3 studies, 822 participants): RR 1.29, 95% CI 0.31 to 5.36; I^2 = 0%; very low certainty evidence) compared with placebo in people with CKD.

When MI was reported as fatal or nonfatal events, HIF stabiliser therapy may make little or no difference to the numbers with fatal or nonfatal MI (Analysis 1.4 (5 studies, 4499 participants): RR 1.06, 95% CI 0.59 to 1.90; I^2 = 0%; low certainty evidence) compared with placebo in people with CKD.

Stroke

HIF stabiliser treatment had uncertain effects on nonfatal stroke (Analysis 1.5: 2 studies, 228 participants), as no events were reported in these two studies.

When stroke was reported as a fatal or nonfatal event, the effects of HIF stabiliser therapy on fatal or nonfatal stroke were uncertain (Analysis 1.6 (3 studies, 822 participants): RR 2.08, 95% CI 0.23 to 18.46; very low certainty evidence) compared with placebo in people with CKD.

Peripheral arterial events

DIALOGUE 1 2019 reported HIF stabilisers had uncertain effects on peripheral arterial events (Analysis 1.7 (1 study, 121 participants): RR 0.20, 95% CI 0.01 to 3.04) compared with placebo in people with CKD.

Proportion of patients requiring blood transfusion

HIF stabiliser treatment probably decreases the proportion of patients requiring blood transfusion (Analysis 1.8 (8 studies, 4329 participants): RR 0.51, 95% CI 0.44 to 0.60; I^2 = 0%; moderate certainty evidence) compared with placebo in people with CKD or undergoing HD.

Proportion of patients reaching the target haemoglobin

HIF stabiliser therapy probably increases the proportion of patients reaching the target Hb (Analysis 1.9 (10 studies, 5102 participants): RR 8.36, 95% CI 6.42 to 10.89; I^2 = 37%; moderate certainty evidence) compared to placebo in people with CKD or undergoing HD.

Kidney failure

HIF stabiliser therapy may make little or no difference to kidney failure (Analysis 1.10 (8 studies, 2228 participants): RR 1.22, 95% CI 0.98 to 1.51; I^2 = 0%; low certainty evidence) compared to placebo in people with CKD.

Thrombosis

HIF stabiliser therapy may increase thrombosis (Analysis 1.11 (3 studies, 3452 participants): RR 2.36, 95% CI 1.19 to 4.66; I^2 = 0%; low certainty evidence) compared to placebo in people with CKD or undergoing HD.

Loss of unassisted dialysis vascular access patency

The effect of HIF stabiliser therapy on the loss of unassisted dialysis vascular access patency was uncertain (Analysis 1.12 (2 studies, 157 participants): RR 1.18, 95% CI 0.13 to 10.31; I^2 = 0%; very low certainty evidence) compared to placebo in people undergoing HD.

Hyperkalaemia

HIF stabiliser therapy may increase hyperkalaemia (Analysis 1.13 (7 studies, 4845 participants): RR 1.29, 95% CI 1.01 to 1.64; I^2 = 18%; low certainty evidence) compared to placebo in people with CKD.

Subgroup analyses for HIF stabiliser versus placebo

Additional analyses were performed stratifying by stage of CKD.

- CV death
  - CKD: Analysis 2.1.1 (7 studies, 850 participants: RR 3.68, 95% CI 0.19 to 70.21; very low certainty evidence)
  - HD: Analysis 2.1.2 (2 studies, 157 participants: no reported events)
  - CKD and HD: Analysis 2.1.3 (1 study, 107 participants: no reported events)
- Nonfatal MI
  - CKD: Analysis 2.2.1 (3 studies, 822 participants: RR 1.29, 95% CI 0.31 to 5.36; I^2 = 0%; very low certainty evidence)
- Proportion of patients requiring blood transfusion
  - CKD: Analysis 2.3.1 (7 studies, 4271 participants: RR 0.52, 95% CI 0.44 to 0.60; I^2 = 0%; moderate certainty evidence)
  - HD: Analysis 2.3.2 (1 study, 58 participants: RR 0.21, 95% CI 0.04 to 1.14, very low certainty evidence)
- Proportion of patients reaching the target Hb
  - CKD: Analysis 2.4.1 (8 studies, 4931 participants: RR 8.18, 95% CI 6.13 to 10.93; I^2 = 50%, low certainty evidence)
  - CKD and HD: Analysis 2.4.2 (2 studies, 171 participants: RR 14.35, 95% CI 2.07 to 99.61; I^2 = 0%, very low certainty evidence)

Other subgroup analyses were not possible due to the limited number of studies and data.

Sensitivity analysis for HIF stabiliser versus placebo

Sensitivity analyses did not provide substantively different results or were not possible due to few data and studies.

HIF stabiliser versus erythropoiesis-stimulating agent

Twenty-nine studies (Akizawa 2020a; Akizawa 2020c; Akizawa 2021; ASCEND-D 2021; ASCEND-ND 2021; Chen 2019; Chen DD 2017; DIALOGUE 2 2019; DIALOGUE 4 2019; DOLOMITES 2021; HIMALAYAS 2021; Holdstock 2019; Holdstock 2019a; Hou 2021; INNO2VATE 2020; INNO2VATE 2020a; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021; Nangaku 2021a; Nangaku 2021b; NCT01888445; PYRENEES 2021; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; SIERRAS 2021; SYMPHONY HD 2021; SYMPHONY ND 2021) compared HIF stabiliser versus ESA management of anaemia in adults with CKD (stages 3, 4 or 5), including patients undergoing HD and PD, during a median follow-up of 52 weeks. The certainty of the evidence was mainly moderate or low (Summary of findings 2).

Primary outcomes

Cardiovascular death

HIF stabiliser therapy may make little or no difference to CV death (Analysis 3.1 (17 studies, 10,340 participants): RR 1.05, 95% CI 0.88 to 1.26; I^2 = 0%; low certainty evidence) compared to ESA in people with CKD, or those undergoing HD or PD.

Fatigue

The effect of HIF stabiliser management of anaemia on fatigue was uncertain (Analysis 3.2 (2 studies, 3471 participants): RR 0.80, 95% CI 0.56 to 1.16; I^2 = 0%; very low certainty evidence) compared with ESA in people with CKD.

Secondary outcomes

Death (any cause)

HIF stabiliser therapy probably makes little or no difference to death (any cause) (Analysis 3.3 (29 studies, 21,370 participants): RR 0.98, 95% CI 0.91 to 1.06; I^2 = 0%; moderate certainty evidence) compared to ESA in people with CKD, or those undergoing HD or PD.

Myocardial infarction

HIF stabiliser treatment may make little or no difference to nonfatal MI (Analysis 3.4 (7 studies, 7765 participants): RR 0.91, 95% CI 0.76 to 1.10; I^2 = 0%; low certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD.

When MI was reported as fatal or nonfatal events, HIF stabiliser treatment probably makes little or no difference to fatal or nonfatal

MI (Analysis 3.5 (15 studies, 14,183 participants): RR 0.95, 95% CI 0.80 to 1.12; I^2 = 0%; moderate certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD.

Stroke

HIF stabiliser treatment may make little or no difference to nonfatal stroke (Analysis 3.6 (5 studies, 7285 participants): RR 1.06, 95% CI 0.71 to 1.56; I^2 = 8%; low certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD.

When stroke was reported as a fatal or nonfatal event, HIF stabiliser treatment may make little or no difference to fatal or nonfatal stroke (Analysis 3.7 (7 studies, 8025 participants): RR 0.95, 95% CI 0.64 to 1.40; I^2 = 23%; low certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD.

Hospitalisation for heart failure

The effect of HIF stabiliser therapy on nonfatal hospitalisation for heart failure was uncertain (Analysis 3.8 (2 studies, 6836 participants): RR 1.23, 95% CI 1.00 to 1.52; I^2 = 0%; very low certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD.

The effect of HIF stabiliser therapy on fatal or nonfatal hospitalisation for heart failure was uncertain (Analysis 3.9 (3 studies, 7452 participants): RR 1.15, 95% CI 0.97 to 1.36; I^2 = 0%; very low certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD.

Peripheral arterial events

HIF stabiliser management of anaemia had uncertain effects on peripheral arterial events (Analysis 3.10: 2 studies, 323 participants), as no events were reported in the included studies.

Proportion of patients requiring blood transfusion

HIF stabiliser treatment probably decreases the proportion of patients requiring blood transfusion (Analysis 3.11 (11 studies, 10,786 participants): RR 0.87, 95% CI 0.76 to 1.00; I^2 = 25%; moderate certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD.

Proportion of patients reaching the target haemoglobin

HIF stabiliser treatment may make little or no difference to the proportion of patients reaching the target Hb (Analysis 3.12 (14 studies, 4601 participants): RR 1.00, 95% CI 0.93 to 1.07; I^2 = 70%; low certainty evidence) compared with ESA in people with CKD, or those undergoing HD or PD. There was moderate to high heterogeneity among the studies.

Kidney failure

HIF stabiliser treatment may make little or no difference to kidney failure (Analysis 3.13 (9 studies, 7312 participants): RR 1.02, 95% CI 0.91 to 1.15; I^2 = 0%; low certainty evidence) compared with ESA in people with CKD.

Thrombosis

HIF stabiliser therapy may make little or no difference to thrombosis (Analysis 3.14 (11 studies, 17,026 participants): RR 1.09, 95% CI 0.86 to 1.39; I^2 = 46%; low certainty evidence) compared with ESA in people with CKD, HD and PD. There was moderate heterogeneity among the studies.

Loss of unassisted dialysis access patency

HIF stabiliser therapy may have little or no difference on the loss of unassisted dialysis access patency (including stenosis and occlusions) (Analysis 3.15 (8 studies, 2945 participants): RR 1.16, 95% CI 0.85 to 1.59; I^2 = 0%; low certainty evidence) compared with ESA in people undergoing HD.

Access intervention

MIYABI ND-C 2019 reported that HIF stabiliser therapy made no difference to access interventions (Analysis 3.16 (1 study, 161 participants): RR 0.58, 95% CI 0.14 to 2.34) compared with ESA in people with CKD.

Cancer

HIF stabiliser therapy may make little or no difference to the number with cancer (Analysis 3.17 (7 studies, 1687 participants): RR 0.83, 95% CI 0.43 to 1.59; I^2 = 8%; low certainty evidence) compared with ESA in people with CKD or those undergoing HD.

Infection

Chen 2019 reported that HIF stabiliser treatment made no difference in the number with infection (Analysis 3.18 (1 study, 304 participants): RR 0.82, 95% CI 0.20 to 3.35) compared with ESA in people with HD and PD.

Hyperkalaemia

Twenty-one studies (Akizawa 2020a; Akizawa 2020c; Akizawa 2021; ASCEND-D 2021; ASCEND-ND 2021; Chen 2019; DOLOMITES 2021; HIMALAYAS 2021; Hou 2021; INNO2VATE 2020; INNO2VATE 2020a; MIYABI HD-M 2019; MIYABI ND-C 2019; MIYABI ND-M 2019; Nangaku 2021; Nangaku 2021a; Nangaku 2021b; PRO2TECT-CONVERSION 2021; PRO2TECT-CORRECTION 2021; PYRENEES 2021; SIERRAS 2021) reported hyperkalaemia without providing a clear definition.

HIF stabiliser treatment probably makes little or no difference to hyperkalaemia (Analysis 3.19 (21 studies, 20,177 participants): RR 0.92, 95% CI 0.82 to 1.04; I^2 = 10%; moderate certainty evidence) compared with ESA in people with CKD or those undergoing HD or PD.

Pulmonary hypertension

The effect of HIF stabiliser treatment on pulmonary hypertension was uncertain (Analysis 3.20 (7 studies, 8641 participants): RR 1.06, 95% CI 0.56 to 2.01; I^2 = 11%; very low certainty evidence) compared with ESA in people with CKD and HD.

Diabetic retinopathy

HIF stabiliser therapy may make little or no difference to the number with diabetic retinopathy (Analysis 3.21 (8 studies, 5036 participants): RR 1.26, 95% CI 0.71 to 2.22; I^2 = 0%; low certainty evidence) compared with ESA in people with CKD or those undergoing HD.

Subgroup analyses for HIF stabiliser versus ESA

Additional analyses to compare HIF stabiliser management versus ESA were performed stratifying by stage of CKD.

- CV death
  - CKD: Analysis 4.1.1 (7 studies, 5591 participants: RR 1.19, 95% CI 0.91 to 1.55; I^2 = 0%; low certainty evidence)

- HD: Analysis 4.1.2 (7 studies, 1352 participants: RR 0.98, 95% CI 0.23 to 4.19; I^2 = 0%; low certainty evidence)
- PD: Analysis 4.1.3 (1 study, 129 participants: RR 0.50, 95% CI 0.03 to 7.80)
- HD and PD: Analysis 4.1.4 (2 studies, 3268 participants: RR 0.96, 95% CI 0.75 to 1.23; low certainty evidence)

- Fatigue
  - CKD: Analysis 4.2.1 (2 studies, 3471 participants: RR 0.80, 95% CI 0.56 to 1.16; I^2 = 0%; very low certainty evidence)
- Nonfatal MI
  - CKD: Analysis 4.3.1 (2 studies, 3996 participants: RR 1.05, 95% CI 0.80 to 1.39; low certainty evidence)
  - HD: Analysis 4.3.2 (2 studies, 372 participants: RR 1.97, 95% CI 0.22 to 17.59; I^2 = 0%; very low certainty evidence)
  - PD: Analysis 4.3.3 (1 study, 129 participants: RR 1.52, 95% CI 0.06 to 36.48)
  - HD and PD: Analysis 4.3.4 (2 studies, 3268 participants: RR 0.80, 95% CI 0.62 to 1.03; I^2 = 0%; low certainty evidence)
- Nonfatal stroke
  - CKD: Analysis 4.4.1 (3 studies, 4122 participants: RR 1.43, 95% CI 0.82 to 2.48; low certainty evidence)
  - HD: Analysis 4.4.2 (1 study, 199 participants: RR 1.36, 95% CI 0.07 to 27.82)
  - HD and PD: Analysis 4.4.3 (1 study, 2964 participants: RR 0.82, 95% CI 0.51 to 1.34)
- Proportion of patients requiring blood transfusion
  - CKD: Analysis 4.5.1 (5 studies, 4933 participants: RR 0.97, 95% CI 0.84 to 1.13; I^2 = 0%; low certainty evidence)
  - HD and PD: Analysis 4.5.2 (6 studies, 5853 participants: RR 0.80, 95% CI 0.64 to 1.01; I^2 = 46%; very low certainty evidence)
- Proportion of patients reaching the target Hb
  - CKD: Analysis 4.6.1 (6 studies, 1369 participants: RR 1.02, 95% CI 0.90 to 1.16; I^2 = 79%; very low certainty evidence)
  - HD and PD: Analysis 4.4.2 (8 studies, 3232 participants: RR 0.98, 95% CI 0.91 to 1.06; I^2 = 59%; very low certainty evidence).

Other subgroup analyses were not possible due to the limited number of studies and data.

Subgroup analyses for proportion reaching Hb target: stratifying by stage of CKD

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.77), suggesting that different stages of CKD do not modify the effect of HIF stabiliser management of anaemia on the proportion reaching the Hb target (Analysis 5.1). However, a smaller number of participants contributed data to CKD and HD than to HD and PD subgroups, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analyses for thrombosis: stratifying by stage of CKD

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.99), suggesting that different stages of CKD do not modify the effect of HIF stabiliser management of anaemia on thrombosis (Analysis 5.2). However, a smaller number of participants and events contributed data to CKD and HD than to HD and PD subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analyses for proportion reaching Hb target: stratifying by the duration of therapy

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.78), suggesting that different duration of therapy does not modify the effect of HIF stabiliser management of anaemia on the proportion reaching the Hb target (Analysis 6.1). However, a smaller number of participants and events contributed data to the duration of therapy from 8 to 23 weeks and at least 54 weeks than from the 24 to 53 weeks subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analyses for thrombosis: stratifying by the duration of therapy

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.44), suggesting that different duration of therapy does not modify the effect of HIF stabiliser management of anaemia on thrombosis (Analysis 6.2). However, a smaller number of participants and events contributed data to the duration of therapy from 24 to 53 weeks subgroup than at least 54 weeks subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analyses for proportion reaching Hb target: stratifying by frequency of HIF stabiliser administration

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.43), suggesting that different frequency of HIF stabiliser administration does not modify the effect of HIF stabiliser management of anaemia on proportion reaching the Hb target (Analysis 7.1). However, a smaller number of participants and events contributed data to once/day administration than to three times/week administration subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analyses for thrombosis: stratifying by frequency of HIF stabiliser administration

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.17), suggesting that different frequency of HIF stabiliser administration does not modify the effect of HIF stabiliser management of anaemia on thrombosis (Analysis 7.2). However, a smaller number of participants and events contributed data to three times/week administration than the once/day administration subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analyses for proportion reaching Hb target: stratifying by type of study (phase 2 versus phase 3)

The test for subgroup differences indicates that there is no statistically significant subgroup effect (P = 0.26), suggesting that type of study does not modify the effect of HIF stabiliser management of anaemia on the proportion reaching the Hb target (Analysis 8.1). However, a smaller number of participants and events contributed data to phase 2 studies than phase 3 studies subgroup, meaning that the analysis may not be able to detect subgroup differences.

Subgroup analyses for thrombosis: stratifying by type of study (phase 2 versus phase 3)

The test for subgroup differences indicates no statistically significant subgroup effect (P = 0.96), suggesting that type of study does not modify the effect of HIF stabiliser management of anaemia on thrombosis (Analysis 8.2). However, a smaller number of participants and events contributed data to phase 2 studies than phase 3 studies subgroup, meaning that the analysis may not be able to detect subgroup differences.

Sensitivity analysis for HIF stabiliser versus ESA

Sensitivity analyses did not provide substantively different results or were not possible due to few data and studies.

HIF stabiliser versus standard care

No studies were designed to compare HIF stabiliser management of anaemia versus standard care.

HIF stabiliser versus iron supplementation

No studies were designed to compare HIF stabiliser management of anaemia with iron supplementation.

DISCUSSION

Summary of main results

We identified 51 studies randomising 30,994 adults evaluating HIF stabilisers for the treatment of anaemia in CKD (stages 3-5), including people receiving HD or PD. No studies were performed in children. No studies compared HIF stabiliser with standard care or iron supplementation. Most studies (29 studies randomising 21,622 participants) compared a HIF stabiliser management of anaemia with ESA for a median of 52 weeks. Risks of bias in the included studies were often high or unclear, and these risks combined with imprecision in effect estimates frequently led to low or very low certainty evidence.

HIF stabiliser management of anaemia had uncertain effects on CV death, fatigue and death (any cause). It is uncertain whether HIF stabiliser management of anaemia reduces nonfatal MI or nonfatal stroke. HIF stabilise management of anaemia probably decreased the proportion of patients requiring blood transfusion compared to placebo or ESA. HIF stabiliser management of anaemia probably increased the proportion of patients reaching their Hb target compared to placebo. The effects of HIF stabiliser management of anaemia on hospitalisation for HF, kidney failure, peripheral arterial event, thrombosis, loss of unassisted dialysis access patency, cancer, infection, pulmonary hypertension, and diabetic nephropathy were very uncertain. Subgroup analyses suggested that different stages of CKD, duration of therapy, frequency of HIF stabiliser administration and type of study (phase 2 or phase 3 studies) did not modify the effects of HIF stabiliser management of anaemia either on the proportion reaching the target Hb, or thrombosis. Adverse events were rarely reported; specifically, the definition of hyperkalaemia was not clearly stated.

Overall completeness and applicability of evidence

Evidence from the existing studies was frequently of low or very low certainty and not available to inform clinical care or policy. About half of the included studies were in people with CKD not treated with dialysis. Many studies compared different treatment doses. No studies were conducted on recipients of a kidney transplant or children.

Recently, the Food and Drug Administration (FDA) did not approve the use of roxadustat for the treatment of anaemia in people with CKD, including those requiring dialysis, due to the higher risk of thrombosis shown among HIF stabilisers compared to placebo or ESA (FDA Briefing Document 2021). HIF stabilisers could be considered second-choice drugs to treat anaemia in people undergoing dialysis who have been resistant to other drugs for anaemia (FDA Briefing Document 2021). In our review, most studies compared a HIF stabiliser management of anaemia with ESA, and clinically important outcome data were rarely reported. Nineteen studies were phase 2 studies that addressed drug efficacy rather than key clinical outcomes, such as death and adverse events. The majority of studies had a small sample size, were of short-term duration, had methodological limitations, or were primarily designed to evaluate surrogate measures of effect. Due to the included studies' short duration, no studies reported outcome data for life participation, PD infection, or PD technique longevity. Fatigue, hospitalisation due to HF, and infection were rarely reported. Adverse events related to treatment were not systematically reported (Appendix 3), preventing an adequate safety evaluation between HIF stabilisers and placebo or ESA.

No studies compared HIF stabilisers with standard care or iron supplementation.

Future studies on HIF stabilisers for treating anaemia should evaluate treatment outcomes as prioritised by stakeholders (patients, caregivers and health professionals) (SONG 2017) to inform clinical practice and decision making.

Quality of the evidence

We used standard risk of bias domains within the Cochrane tool and GRADE methodology (GRADE 2008) to assess the quality of study evidence. Based on low or very low certainty evidence for the majority of outcomes assessed, future studies might provide different results.

Some studies were at high or unclear risks of bias for most of the risk of bias domains assessment. The majority of studies did not report adequate allocation concealment, blinding or attrition. All but three studies received funding from pharmaceutical companies. Relevant clinical outcomes were rarely available for many of the included studies.

Heterogeneity in the reporting methods of many outcomes constrained data synthesis by meta-analysis. The targeted Hb values were wide heterogeneous. The limited number of studies prevented the exploration of other potential sources of heterogeneity in the analyses. Some subgroup and sensitivity analyses could not be conducted to explore for heterogeneity owing to insufficient data. Due to the limited number of studies, the assessment of adverse events was not possible.

Potential biases in the review process

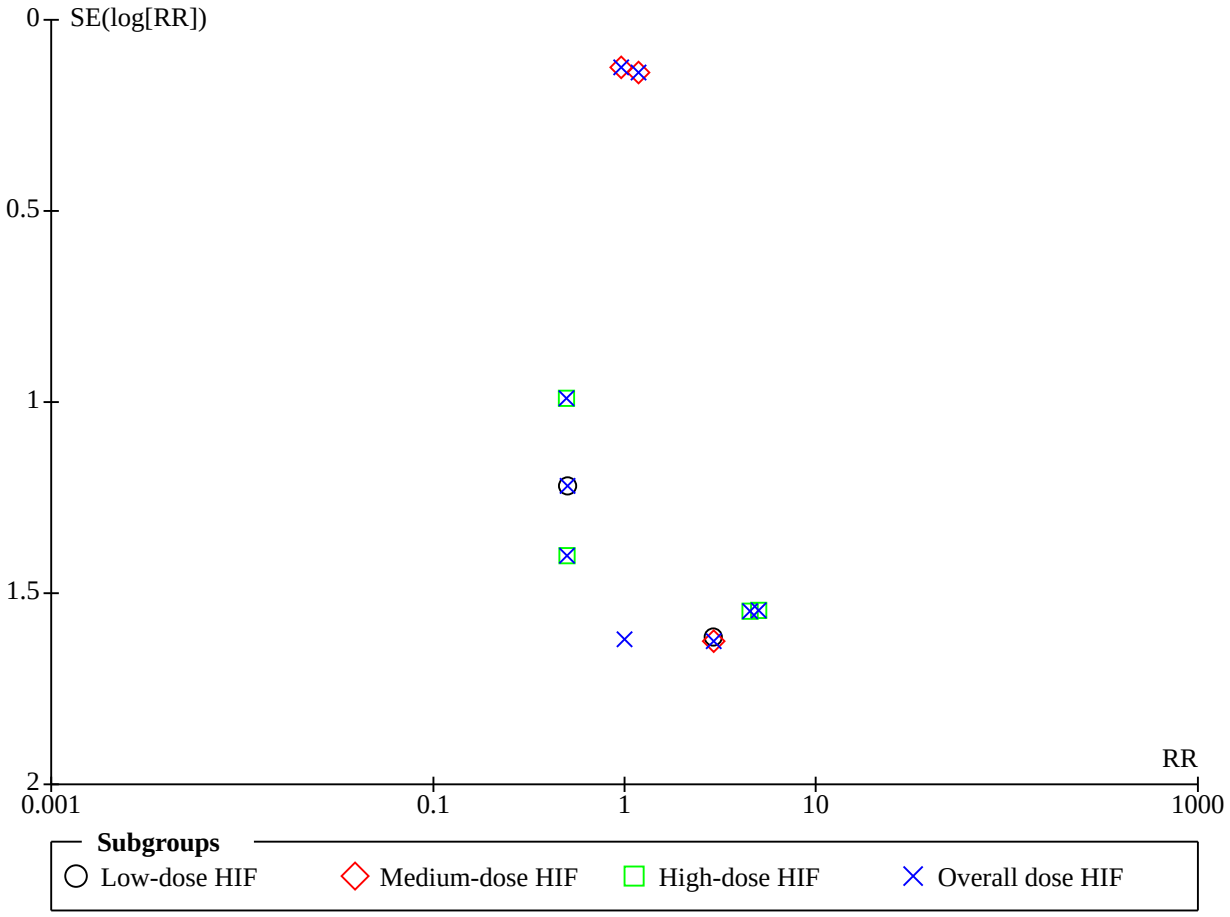
Our review was carried out using standard Cochrane methods. Each step was completed independently by at least two authors including a selection of studies, data management, and risk of bias assessment to minimise the risks of misclassification and adjudication of evidence. A highly sensitive search of the

Cochrane Kidney Transplant specialised register was undertaken in November 2021, without language restriction and including grey literature. Where possible, we contacted study authors to obtain further data. Many studies did not report key outcomes in a format suitable for meta-analysis.

Potential bias identified in our review included: 1) phase 2 studies may not be generalisable to phase 3 or real-world experience because they were of limited duration and not adequately controlled, and tested treatment strategies that may not then be subsequently used in phase 3 studies aimed at approval from regulatory agencies; 2) we pooled different HIF stabilisers agents which have yet to be established in significance; 3) we reported different rate of rise for each HIF stabiliser agent; 4) we pooled different frequency of administration; 5) we pooled major adverse CV events (MACE)-driven studies and not MACE-driven studies; 6) we precluded heterogeneity between treatment interventions due to the small number of data observations; 7) we did not exclude poor quality studies due to the small number of included studies; 8) the limited number of studies was a constraint on our ability to assess for potential reporting bias and selective outcome reporting; 9) the definition of Hb target varied across the eligible studies; 10) the effects of HIF stabilisers management of anaemia on longer-term outcomes were uncertain and the treatment endpoints were principally surrogate outcomes (e.g. blood pressure and laboratory parameters); 11) adverse events were rarely and inconsistently reported due to the short duration of the included studies; 12) no clear definition was provided for hyperkalaemia preventing the evaluation on different threshold; 13) the included studies were conducted in different geographical areas which translates to differences in underlying morbidity for patients.

Visual inspection of funnel plots for HIF stabilisers versus ESA did not suggest any evidence of small study effects indicating possible publication bias for CV death (Figure 4).

Figure 4. Funnel plot of comparison: 2 Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), outcome: 2.1 Cardiovascular death.



Agreements and disagreements with other studies or reviews

Few studies have examined the efficacy of HIF stabilisers in people with CKD, and the number of meta-analyses published in this field is limited.

Wang 2020 performed a meta-analysis of RCTs including only 2804 patients with CKD. The outcomes assessed included mainly surrogate outcomes and adverse events (hypertension, hyperkalaemia, CV events, vascular access thrombosis, headache, vomiting, nasopharyngitis, nausea, and diarrhoea). Our findings confirmed that HIF stabiliser management of anaemia may increase the risk of hyperkalaemia compared with placebo. Compared to our review, Wang 2020 did not investigate death in the included studies, excluded non-English studies and grey literature, and did not use GRADE to evaluate evidence certainty.

Zhong 2018 carried out a systematic review and meta-analysis of nine RCTs to assess the efficacy of HIF stabilisers in the treatment of anaemia in CKD. However, due to the limited studies and short follow-up, Zhong 2018 could not detect relevant clinical outcomes, including death and CV events, and focused mainly on surrogate outcomes (Hb, ferritin, hepcidin and total iron-binding capacity), preventing comparisons with our review. In addition, Zhong 2018 did not use GRADE to evaluate evidence certainty.

Li 2020 reviewed the findings from three clinical trials on roxadustat for treating kidney anaemia. Data were reported only for surrogate outcomes. The main differences with our review are the exclusion of other HIF stabilisers, such as daprodustat, molidustat and vadadustat, and the lack of data on mortality and safety outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

HIF stabilisers have uncertain effects on CV death, fatigue, death (any cause), nonfatal MI, nonfatal stroke, and kidney failure compared with placebo or ESA in people with CKD. HIF stabiliser management of anaemia probably decreases the proportion of patients requiring blood transfusion compared with placebo or ESA. HIF stabilisers probably increase the proportion of patients reaching their Hb target compared to placebo. There is scant evidence to inform decision-making in children and kidney transplant recipients. Adverse events were rarely and inconsistently provided.

Implications for research

In the near future, well-designed and adequately powered RCTs will be included to assess the benefits and harms of HIF stabilisers to treat anaemia in all stages of CKD, including people requiring any form of dialysis and kidney transplant recipients. The potential use of oral HIF stabilisers for anaemia may lead to higher compliance with the treatment in people with CKD and reduce the need for blood transfusion, although unwanted side effects could be a major concern in this population. Future real-world experience studies will assess the effects of HIF stabiliser regimen on the progression of CKD, and blood pressure and define the proper dose in people with and without iron supplementation. Future studies will evaluate whether HIF stabiliser effects are dependent on the CKD stage.

Our review has identified several ongoing and promising RCTs that could help to increase our knowledge and confidence in the findings, focusing on important outcomes, such as death and CV events. Further research is likely to change the estimated effects of treatments for anaemia in CKD and provide relevant information on HRQoL and patient-reported outcomes (including life participation and fatigue). Larger studies should be conducted in PD to address specific outcomes related to this population, including PD infection and PD technique longevity.

Future HIF stabiliser studies compared with standard care or iron supplementation will increase our certainty of the evidence based on the paucity of evidence in CKD.

Evaluation of cost-effectiveness for HIF stabilisers in the treatment of anaemia would assist decision-making by policy-makers and health care providers in this population.

ACKNOWLEDGEMENTS

The authors are grateful to the following peer reviewers for their time and comments: Anatole Besarab MD (Stanford University School of Medicine), Joshua M. Kaplan (Rutgers-New Jersey Medical School), Takeshi Hasegawa, MD, PH, PhD (Showa University), Ana Cabrita MD (Nephrology Department, Centro Hospitalar Universitário do Algarve-Faro).

REFERENCES

References to studies included in this review

Akizawa 2017 *{published data only}*

* Akizawa T, Tsubakihara Y, Nangaku M, Endo Y, Nakajima H, Kohno T, et al. Effects of daprodustat, a novel hypoxia-inducible factor prolyl hydroxylase inhibitor on anemia management in Japanese hemodialysis subjects. *American Journal of Nephrology* 2017;**45**(2):127-35. [MEDLINE: 27978511]

Endo Y, Kohno T, Imai Y, Kawase N, Hara K, Lepore JJ, et al. A 4 -week dose response study of the hypoxia inducible factor-prolyl hydroxylase inhibitor GSK1278863 in Japanese anemic haemodialysis subjects [abstract no: SA-PO819]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):818A.

NCT02019719. Study to evaluate the safety, efficacy and pharmacokinetics of GSK1278863 in Japanese hemodialysis-dependent subjects with anemia associated with chronic kidney disease [A 4-week, phase ii, randomized, double-blind, dose-ranging, placebo-controlled, parallel-group, multi-center study to evaluate the safety, efficacy and pharmacokinetics of GSK1278863 in Japanese hemodialysis-dependent subjects with anemia associated with chronic kidney disease]. clinicaltrials.gov/show/NCT02019719 (first received 24 December 2013).

Akizawa 2019 *{published data only}*

Akizawa T, Iwasaki M, Otsuka T, Reusch M, Misumi T. Roxadustat for the treatment of chronic kidney disease-associated anemia in Japanese patients not on dialysis [abstract no: FR-PO1142]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):7B.

* Akizawa T, Iwasaki M, Otsuka T, Reusch M, Misumi T. Roxadustat treatment of chronic kidney disease-associated anemia in Japanese patients not on dialysis: a phase 2, randomized, double-blind, placebo-controlled trial. *Advances in Therapy* 2019;**36**(6):1438-54. [MEDLINE: 30953333]

Akizawa 2020a *{published data only}*

Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Authors' Reply. *Journal of the American Society of Nephrology* 2021;**32**(4):1005-7. [MEDLINE: 33649099]

Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) conversion study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan [abstract no: TH-PO1151]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):B4.

* Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. *Journal of the American Society of Nephrology* 2020;**31**(7):1628-39. [MEDLINE: 32493693]

Akizawa T, Yamaguchi Y, Majikawa Y, Reusch M. Factors affecting the doses of roxadustat vs darbepoetin alfa for anemia treatment in hemodialysis patients. *Therapeutic Apheresis & Dialysis* 2021;**25**(5):575-85. [MEDLINE: 33200512]

Astellas1517-CL-0307. A study of intermittent oral dosing of ASP1517 in hemodialysis chronic kidney disease patients with anemia [A phase 3, multi-center, randomized, 2-arm parallel, double-blind, active-comparator (darbepoetin alfa) conversion study of intermittent oral dosing of ASP1517 in hemodialysis chronic kidney disease patients with anemia]. www.clinicaltrials.astellas.com/study/?pid=1517-CL-0307 (accessed 4 May 2022).

Liu F, Wang J, Ye Q, Fu H, Mao J. Roxadustat for renal anemia in ESRD from PKD patients: is it safe enough? *Journal of the American Society of Nephrology* 2021;**32**(4):1005. [MEDLINE: 33649100]

Nguyen QD, Sepah YJ, Yamaguchi Y, Otsuka T, Majikawa Y, Reusch M, et al. Ophthalmological effects of roxadustat in the treatment of anemia in dialysis-dependent and non-dialysis-dependent CKD patients: findings from two phase 3 studies [abstract no: PO0267]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):134. [EMBASE: 633698979]

Sepah Y, Nguyen QD, Yamaguchi Y, Majikawa Y, Reusch M, Akizawa T. Ophthalmological effects of roxadustat in the treatment of anaemia in chronic kidney disease patients on dialysis in a phase 3, randomised, double-blind, active-comparator conversion study [abstract no: MO002]. *Nephrology Dialysis Transplantation* 2020;**35**(Suppl 3):iii102. [EMBASE: 633421367]

Akizawa 2020c *{published data only}*

* Akizawa T, Nangaku M, Yonekawa T, Okuda N, Kawamatsu S, Onoue T, et al. Efficacy and safety of daprodustat compared with darbepoetin alfa in Japanese hemodialysis patients with anemia: a randomized, double-blind, phase 3 trial. *Clinical Journal of the American Society of Nephrology: CJASN* 2020;**15**(8):1155-65. [MEDLINE: 32723804]

Ozeki H, Akizawa T, Nangaku M, Yonekawa T, Okuda N, Kawamatsu S, et al. Efficacy and safety of daprodustat compared with darbepoetin alfa in Japanese hemodialysis patients with anemia: A randomized, double-blind, phase 3 trial [abstract no: SaO036]. *Nephrology Dialysis Transplantation* 2019;**34**(Suppl 1):a350. [EMBASE: 631305259]

Akizawa 2020f *{published data only}*

Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. A phase 3, multicenter, randomized, open-label, active comparator conversion study of roxadustat in non-dialysis-dependent (NDD) patients with anemia in chronic kidney disease (CKD) [abstract no: POS-244]. *Kidney International Reports* 2021;**6**(4 Suppl):S103. [EMBASE: 2011682459]

Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. A phase 3, multicenter, randomized, open-label, active comparator conversion study of roxadustat in non-dialysis-dependent (NDD) patients with anemia in CKD [abstract no: PO0269]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):134. [EMBASE: 633699036]

Nguyen QD, Sepah YJ, Yamaguchi Y, Otsuka T, Majikawa Y, Reusch M, et al. Ophthalmological effects of roxadustat in the

treatment of anemia in dialysis-dependent and non-dialysis-dependent CKD patients: findings from two phase 3 studies [abstract no: PO0267]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):134. [EMBASE: 633698979]

Akizawa 2021 *{published data only}*

* Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. Phase 3 study of roxadustat to treat anemia in non-dialysis-dependant CKD. *Kidney International Reports* 2021;**6**(7):1810-28. [MEDLINE: 34307976]

Akizawa T, Tanaka-Amino K, Otsuka T, Yamaguchi Y. Factors affecting doses of roxadustat versus darbepoetin alfa for anemia in nondialysis patients. *American Journal of Nephrology* 2021;**52**(9):702-13. [MEDLINE: 34628408]

ALPS 2021 *{published data only}*

Astellas 1517-CL-0608. Roxadustat in the treatment of anemia in chronic kidney disease patients not requiring dialysis [A phase 3, randomized, double-blind, placebo controlled study of the efficacy and safety of roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis]. www.trialsummaries.com/Study/StudyDetails?id=14384&tenant=MT_AST_9011 2019.

Esposito C, Csiky B, Tataradze A, Reusch M, Han C, Sulowicz W. Two phase 3, multicenter, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis [abstract no: SA-PO225]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):822. [EMBASE: 633767739]

Pecoits-Filho R, Chan TM, Hardy E, Yu KH, Fishbane S. 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) [abstract no: TH-OR05]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):2. [EMBASE: 633697943]

Rastogi A, Pecoits-Filho R, Fishbane S, Little DJ, Hardy E, Yu KH, et al. Roxadustat treatment corrects anemia to hemoglobin (HB) values ≥10 g/dL in the majority of patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) [abstract no: PO0264]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):133. [EMBASE: 633698803]

* Shutov E, Sulowicz W, Esposito C, Tataradze A, Andric B, Reusch M, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, double-blind, placebo-controlled study (ALPS). *Nephrology Dialysis Transplantation* 2021;**36**(9):1629-39. [MEDLINE: 33630072]

ANDES 2021 *{published data only}*

Coyne DW, Roger SD, Chou W, Besarab A, Leong R, Lee TT, et al. Roxadustat favorably modifies iron indices in patients with non-dialysis-dependent CKD-related anemia [abstract no: PO0262]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):132. [EMBASE: 633698686]

* Coyne DW, Roger SD, Shin S, Kim SG, Cadena AA, Moustafa MA, et al. Roxadustat for CKD-related anemia in non-dialysis patients. *Kidney International Reports* 2021;**6**(3):624-35. [MEDLINE: 33732977]

Coyne DW, Roger SD, Shin SK, Kim SG, Cadena AA, Moustafa MA, 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 [abstract no: SA-PO0228]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):822-3. [EMBASE: 633767955]

Pecoits-Filho R, Chan TM, Hardy E, Yu KHP, Fishbane S. 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) [abstract no: TH-OR05]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):2. [EMBASE: 633697943]

Rastogi A, Pecoits-Filho R, Fishbane S, Little DJ, Hardy E, Yu KH, et al. Roxadustat treatment corrects anemia to hemoglobin (HB) values ≥10 g/dL in the majority of patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) [abstract no: PO0264]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):133. [EMBASE: 633698803]

ASCEND-D 2021 *{published data only}*

Singh AK, Blackorby A, Cizman B, Carroll K, Cobitz AR, Davies R, et al. Study design and baseline characteristics of patients on dialysis in the ASCEND-D trial. *Nephrology Dialysis Transplantation* 2021;**37**(5):960-72. [MEDLINE: 33744933] [MEDLINE: 33744933]

Singh AK, Blackorby A, Cizman B, Cobitz AR, Godoy SA, Jha V, et al. Regional variation of erythropoietin-stimulating agent hyporesponsiveness in the global daprodustat dialysis study (ASCEND-D) [abstract no: TH-OR08]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):3. [EMBASE: 633698062]

* Singh AK, Carroll K, Perkovic V, Solomon S, Jha V, Johansen KL, et al. Daprodustat for the treatment of anemia in patients undergoing dialysis. *New England Journal of Medicine* 2021;**385**(25):2325-35. [MEDLINE: 34739194]

ASCEND-ID 2021 *{published data only}*

Singh AK. Daprodustat is noninferior to darbepoetin alfa in treating anemia in incident dialysis patients [abstract no: PO0465]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):184-5. [EMBASE: 636331207]

ASCEND-ND 2021 *{published data only}*

Perkovic V, Blackorby A, Cizman B, Carroll K, Cobitz A, Davies R, et al. ASCEND-ND: Study design and baseline characteristics. *Nephrology Dialysis Transplantation* 2021;**36**(Suppl 1):i334-5. [EMBASE: 635918331]

* Singh AK, Carroll K, McMurray JJ, Solomon S, Jha V, Johansen KL, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. *New England Journal of Medicine* 2021;**385**(25):2313-24. [MEDLINE: 34739196]

ASCEND-NHQ 2021 *{published data only}*

Johansen KL, Cobitz AR, Lopes RD, Singh AK, Obrador GT, Cizman B, et al. Effects of daprodustat on hemoglobin and quality of life in patients with CKD: results of the ascend-NHQ randomized, double-blind, placebo-controlled trial [abstract no: FR-OR53]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):36. [EMBASE: 636330656]

ASCEND-TD 2021 *{published data only}*

Coyne DW, Singh AK, Lopes RD, Bailey CK, Dimino TL, Huang C, et al. ASCEND-TD: A randomized, double-blind, active-controlled study of daprodustat administered three times weekly in hemodialysis patients [abstract no: PO0487]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):191. [EMBASE: 636329480]

Besarab 2015 *{published data only}*

Besarab A, Hutler HN, Klaus S, Lee TT, Lilienfeld DE, Neff TB, et al. FG-4592, a novel oral HIF prolyl hydroxylase inhibitor, elevates hemoglobin in anemic stage 3/4 CKD patients [abstract no: SA-FC416]. *Journal of the American Society of Nephrology* 2010;**21**(Abstract Suppl):95A.

* 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. *Nephrology Dialysis Transplantation* 2015;**30**(10):1665-73. [MEDLINE: 26238121]

Brigandi 2016 *{published data only}*

Brigandi RA, Johnson B, Oei C, Westerman M, Olbina G, de Zoysa J, et al. A novel hypoxia-inducible factor-prolyl hydroxylase inhibitor (GSK1278863) for anemia in CKD: a 28-day, phase 2a randomized trial. *American Journal of Kidney Diseases* 2016;**67**(6):861-71. [MEDLINE: 26827289]

Brigandi RA, Johnson B, Oei C, Westerman ME, Olbina G, Kumar S, et al. Induction of erythropoiesis in anemic patients by prolylhydroxylase inhibitor in a repeat dose, randomized placebo controlled trial [abstract no: SA-PO117]. *Journal of the American Society of Nephrology* 2012;**23**(Abstract Suppl):662A.

Brigandi RA, Westerman ME, Olbina G, Oei C, Russ SF, Kumar S. Modulation of hepcidin by prolylhydroxylase inhibitor in randomized trials [abstract no: SA-PO118]. *Journal of the American Society of Nephrology* 2012;**23**(Abstract Suppl):662A.

Chen 2019 *{published data only}*

Chen N, Hao C, Liu B, Lin HL, Caili W, Xing CY, et al. A phase 3, randomized, open-label, active-controlled study of efficacy and safety of roxadustat for treatment of anemia in subjects with CKD on dialysis [abstract no: TH-PO1152]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):B5.

* Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, et al. Roxadustat treatment for anemia in patients undergoing long-term dialysis. *New England Journal of Medicine* 2019;**381**(11):1011-22. [MEDLINE: 31340116]

Chen 2019a *{published data only}*

* Chen N, Hao C, Peng X, Lin H, Yin A, Hao L, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. *New England Journal of Medicine* 2019;**381**(11):1001-10. [MEDLINE: 31340089]

Chen N, Hao C, Peng X, Lin HL, Yin A, Hao L, et al. A phase 3, randomized, double-blind, placebo-controlled study of efficacy and safety of roxadustat (FG-4592) for treatment of anemia in subjects with CKD not on dialysis [abstract no: TH-PO1153]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):B5.

Chen DD 2017 *{published data only}*

Chen N, Qian J, Chen J, Yu X, Mei C, Hao C, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrology Dialysis Transplantation* 2017;**32**(8):1373-86. [MEDLINE: 28371815]

Chen NDD 2017 *{published data only}*

* Chen N, Qian J, Chen J, Yu X, Mei C, Hao C, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrology Dialysis Transplantation* 2017;**32**(8):1373-86. [MEDLINE: 28371815]

Qian JQ, Chen N, Chen J, Hao C, Lin HL, Ni D, et al. A randomized, double-blind, placebo controlled trial of FG-4592 for correction of anemia in subjects with chronic kidney disease in China [abstract no: FR-OR011]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):38A.

DIALOGUE 1 2019 *{published data only}*

Akizawa T, Macdougall IC, Berns JS, Bernhardt T, Taguchi M, Ogura E, et al. Iron regulation by molidustat, bay 85-3934, a daily oral hypoxia-inducible factor prolyl hydroxylase inhibitor in patients with chronic kidney disease [abstract no: SP334]. *Nephrology Dialysis Transplantation* 2018;**33**(Suppl 1):i457. [EMBASE: 622606520]

Akizawa T, Macdougall IC, Berns JS, Yamamoto H, Taguchi M, Iekushi K, et al. Iron regulation by molidustat, a daily oral hypoxia-inducible factor prolyl hydroxylase inhibitor, in patients with chronic kidney disease. *Nephron* 2019;**143**(4):243-54. [MEDLINE: 31387097]

Macdougall IC, Akizawa T, Berns J, Lentini S, Bernhardt T. Molidustat increases haemoglobin in erythropoiesis stimulating agents (ESA)-naive anaemic patients with chronic kidney disease not on dialysis (CKD-ND) [abstract no: SO036]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i16. [EMBASE: 72325954]

* Macdougall IC, Akizawa T, Berns JS, Bernhardt T, Krueger T. Effects of molidustat in the treatment of anemia in CKD [Erratum in: Clin J Am Soc Nephrol. 2019 Oct 7;14(10):1524]. *Clinical Journal of the American Society of Nephrology: CJASN* 2019;**14**(1):28-39. [MEDLINE: 30559105]

Macdougall IC, Berns JS, Akizawa T, Fishbane S, Bernhardt T. DIALOGUE phase 2 program for BAY85-3934 a HIF-PH inhibitor with daily oral treatment in anemic patients suffering from CKD/

ESRD [abstract no: FR-PO219]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):413A.

DIALOGUE 2 2019 *{published data only}*

Akizawa T, Macdougall IC, Berns JS, Yamamoto H, Taguchi M, Iekushi K, et al. Iron regulation by molidustat, a daily oral hypoxia-inducible factor prolyl hydroxylase inhibitor, in patients with chronic kidney disease. *Nephron* 2019;**143**(4):243-54. [MEDLINE: 31387097]

Macdougall IC, Akizawa T, Berns J, Lentini S, Bernhardt T, Kruger T. Safety and efficacy of molidustat in erythropoiesis stimulating agents (ESA) pre-treated anaemic patients with chronic kidney disease not on dialysis (CKD-ND) [abstract no: SP309]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i193. [EMBASE: 72326411]

Macdougall IC, Akizawa T, Berns J, Lentini S, Bernhardt T. Molidustat increases haemoglobin in erythropoiesis stimulating agents (ESA)-naive anaemic patients with chronic kidney disease not on dialysis (CKD-ND) [abstract no: SO036]]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i16. [EMBASE: 72325954]

* Macdougall IC, Akizawa T, Berns JS, Bernhardt T, Krueger T. Effects of molidustat in the treatment of anemia in CKD [Erratum in: Clin J Am Soc Nephrol. 2019 Oct 7;14(10):1524]. *Clinical Journal of the American Society of Nephrology: CJASN* 2019;**14**(1):28-39. [MEDLINE: 30559105]

Macdougall IC, Berns JS, Akizawa T, Fishbane S, Bernhardt T. DIALOGUE phase 2 program for BAY85-3934 a HIF-PH inhibitor with daily oral treatment in anemic patients suffering from CKD/ESRD [abstract no: FR-PO219]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):413A.

DIALOGUE 4 2019 *{published data only}*

Akizawa T, Macdougall IC, Berns JS, Yamamoto H, Taguchi M, Iekushi K, et al. Iron regulation by molidustat, a daily oral hypoxia-inducible factor prolyl hydroxylase inhibitor, in patients with chronic kidney disease. *Nephron* 2019;**143**(4):243-54. [MEDLINE: 31387097]

Macdougall IC, Akizawa T, Berns J, Lentini S, Bernhardt T. Molidustat increases haemoglobin in erythropoiesis stimulating agents (ESA)-naive anaemic patients with chronic kidney disease not on dialysis (CKD-ND) [abstract no: SO036]. *Nephrology Dialysis Transplantation* 2016;**31**(Suppl 1):i16. [EMBASE: 72325954]

* Macdougall IC, Akizawa T, Berns JS, Bernhardt T, Krueger T. Effects of molidustat in the treatment of anemia in CKD [Erratum in: Clin J Am Soc Nephrol. 2019 Oct 7;14(10):1524]. *Clinical Journal of the American Society of Nephrology: CJASN* 2019;**14**(1):28-39. [MEDLINE: 30559105]

Macdougall IC, Berns JS, Akizawa T, Fishbane S, Bernhardt T. DIALOGUE phase 2 program for BAY85-3934 a HIF-PH inhibitor with daily oral treatment in anemic patients suffering from CKD/ESRD [abstract no: FR-PO219]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):413A.

DOLOMITES 2021 *{published data only}*

Barratt J, Andric B, Tataradze A, Schoemig M, Reusch M, Valluri U, et al. Roxadustat for the treatment of anemia in CKD patients not on dialysis (NDD): a phase 3, randomized, open-label, active-controlled study [abstract no: TH-OR02]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):1. [EMBASE: 633697812]

* Barratt J, Andric B, Tataradze A, Schomig M, Reusch M, Valluri U, 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 (DOLOMITES). *Nephrology Dialysis Transplantation* 2021;**36**(9):1616-28. [MEDLINE: 34077510]

Barratt J, Andric B, Tataradze A, Schomig M, Reusch M, Valluri U, 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 [abstract no: MO001]. *Nephrology Dialysis Transplantation* 2020;**35**(Suppl 3):iii101. [EMBASE: 633423023]

Barratt J, Andric B, Tataradze A, Schomig M, Reusch M, Valluri U, et al. Roxadustat for the treatment of anemia in chronic kidney disease (CKD) patients not on dialysis (NDD): a phase 3, randomized, open-label, active-controlled study [abstract no: Pos-247]. *Kidney International Reports* 2021;**6**(4 Suppl):S104. [EMBASE: 2011683542]

HIMALAYAS 2021 *{published data only}*

Provenzano M, Evgeny S, Liubov E, Korneyeva S, Kathresal AA, Poole L, 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 [abstract no: TH-OR021]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):5. [EMBASE: 633771140]

* Provenzano R, Shutov E, Eremeeva L, Korneyeva S, Poole L, Saha G, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. *Nephrology Dialysis Transplantation* 2021;**36**(9):1717-30. [MEDLINE: 33629100]

Holdstock 2019 *{published data only}*

Cizman B, Ackert J, Meadowcroft A, Biswas N, Kelly D, Kleinman D, et al. Ocular safety profile of daprodustat: results of two 24 week studies [abstract no: SAO004]. *Nephrology Dialysis Transplantation* 2018;**33**(Suppl 1):i316. [EMBASE: 622604997]

* Holdstock L, Cizman B, Meadowcroft AM, Biswas N, Johnson BM, Jones D, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants with chronic kidney disease. *Clinical Kidney Journal* 2019;**12**(1):129-38. [MEDLINE: 30746140]

Holdstock L, Cizman B, Meadowcroft AM, Biswas N, Jones D, Johnson BM, et al. Daprodustat, a HIF-prolyl-hydroxylase inhibitor, increases and maintains hemoglobin over 24 weeks in anemic chronic kidney disease subjects [abstract no: TH-PO908]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):304A.

Holdstock 2019a *{published data only}*

Cizman B, Ackert J, Meadowcroft A, Biswas N, Kelly D, Kleinman D, et al. Ocular safety profile of daprodustat: results of two 24 week studies [abstract no: SAO004]. *Nephrology Dialysis Transplantation* 2018;**33**(Suppl 1):i316. [EMBASE: 622604997]

* Holdstock L, Cizman B, Meadowcroft AM, Biswas N, Johnson BM, Jones D, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants with chronic kidney disease. *Clinical Kidney Journal* 2019;**12**(1):129-38. [MEDLINE: 30746140]

Holdstock L, Cizman B, Meadowcroft AM, Biswas N, Jones D, Johnson BM, et al. Daprodustat, a HIF-prolyl-hydroxylase inhibitor, increases and maintains hemoglobin over 24 weeks in anemic chronic kidney disease subjects [abstract no: TH-PO908]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):304A.

Hou 2021 *{published data only}*

Hou YP, Mao XY, Wang C, Xu ZH, Bu ZH, Xu M, et al. Roxadustat treatment for anemia in peritoneal dialysis patients: a randomized controlled trial. *Journal of the Formosan Medical Association* 2021;**121**(2):529-38. [MEDLINE: 34167878]

INNO2VATE 2020 *{published data only}*

Chertow GM, Boudville N, Chowdhury P, Gonzalez C, Kooienga L, Luo W, et al. Vadadustat for treatment of anemia in patients with dialysis-dependent CKD receiving peritoneal dialysis [abstract no: PO0464]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):184. [EMBASE: 636331136]

* Eckardt KU, Agarwal R, Aswad A, Awad A, Block GA, Bacci MR, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. *New England Journal of Medicine* 2021;**384**(17):1601-12. [MEDLINE: 33913638]

Eckardt KU, Agarwal R, Farag YM, Jardine AG, Khawaja Z, Koury MJ, et al. Global Phase 3 programme of vadadustat for treatment of anaemia of chronic kidney disease: rationale, study design and baseline characteristics of dialysis-dependent patients in the INNO2VATE trials. *Nephrology Dialysis Transplantation* 2020;**36**(11):2039-48. [MEDLINE: 33188693]

Eckardt KU. Global phase 3 clinical trials of vadadustat vs. darbepoetin alfa for treatment of anemia in patients with dialysis-dependent CKD [abstract no: TH-OR01]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):1. [EMBASE: 633697781]

Parfrey PS, Luo W, Maroni B, Anders R, Vargo D, McCullough PA. Thromboembolic events with vadadustat vs. darbepoetin alfa for anemia treatment in patients with dialysis-dependent CKD [abstract no: PO0463]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):184. [EMBASE: 636331080]

Winkelmayer W, Tumlin JA, Fishbane S, Farag Y, Vargo D, Luo W, et al. Hematologic efficacy of vadadustat for anemia in patients with kidney failure on dialysis [abstract no: MO529]. *Nephrology Dialysis Transplantation* 2021;**36**(Suppl 1):i325-6. [EMBASE: 635917983]

Winkelmayer WC, Fishbane S, Tumlin JA, Farag YM, Luo W, Anders R, et al. Iron-related outcomes in patients with dialysis-dependent CKD randomized to vadadustat vs. darbepoetin alfa [abstract no: PO0457]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):182. [EMBASE: 636330773]

INNO2VATE 2020a *{published data only}*

* Eckardt KU, Agarwal R, Aswad A, Awad A, Block GA, Bacci MR, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. *New England Journal of Medicine* 2021;**384**(17):1601-12. [MEDLINE: 33913638]

Eckardt KU, Agarwal R, Farag YM, Jardine AG, Khawaja Z, Koury MJ, et al. Global Phase 3 programme of vadadustat for treatment of anaemia of chronic kidney disease: rationale, study design and baseline characteristics of dialysis-dependent patients in the INNO2VATE trials. *Nephrology Dialysis Transplantation* 2020;**36**(11):2039-48. [MEDLINE: 33188693]

Eckardt KU. Global phase 3 clinical trials of vadadustat vs. darbepoetin alfa for treatment of anemia in patients with dialysis-dependent CKD [abstract no: TH-OR01]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):1. [EMBASE: 633697781]

Winkelmayer WC, Fishbane S, Tumlin JA, Farag YM, Luo W, Anders R, et al. Iron-related outcomes in patients with dialysis-dependent CKD randomized to vadadustat vs. darbepoetin alfa [abstract no: PO0457]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):182. [EMBASE: 636330773]

Meadowcroft 2019 *{published data only}*

Cizman B, Ackert J, Meadowcroft A, Biswas N, Kelly D, Kleinman D, et al. Ocular safety profile of daprodustat: results of two 24 week studies [abstract no: SAO004]. *Nephrology Dialysis Transplantation* 2018;**33**(Suppl 1):i316. [EMBASE: 622604997]

Cobitz AR, Meadowcroft AM, Cizman B, Holdstock L, Biswas N, Jones D, et al. Daprodustat, a HIF-prolyl-hydroxylase inhibitor, maintains hemoglobin levels over 24 weeks in anemic hemodialysis subjects switching from recombinant human erythropoietin. [abstract no: SA-OR114]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):93A.

* Meadowcroft AM, Cizman B, Holdstock L, Biswas N, Johnson BM, Jones D, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants on hemodialysis. *Clinical Kidney Journal* 2019;**12**(1):139-48. [MEDLINE: 30746141]

MIYABI HD-M 2019 *{published data only}*

Akizawa T, Taguchi M, Matsuda Y, Iekushi K, Yamada T, Yamamoto H. Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: Design and rationale of three phase III studies. *BMJ Open* 2019;**9**(6):e026602. [MEDLINE: 31203241]

* Akizawa T, Yamada T, Nobori K, Matsuda Y, Hayashi Y, Hayasaki T, et al. Molidustat for Japanese patients with renal anemia receiving dialysis. *Kidney International Reports* 2021;**6**(10):2604–16. [MEDLINE: 34622100]

Akizawa T, Yamada T, Nobori K, Matsuda Y, Hayashi Y, Hayasaki T, et al. Results from a phase 3 study comparing the efficacy and safety of molidustat vs. Darbepoetin Alfa in patients receiving hemodialysis and treated with erythropoiesis-stimulating agents (ESAS) [abstract no: PO22623]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):B4. [EMBASE: 633697376]

MIYABI ND-C 2019 *{published data only}*

* Yamamoto H, Nobori K, Matsuda Y, Hayashi Y, Hayasaki T, Akizawa T. Efficacy and safety of molidustat for anemia in ESA-naive nondialysis patients: a randomized, phase 3 trial. *American Journal of Nephrology* 2021;**52**(10-11):871-83. [MEDLINE: 34569489]

Yamamoto H, Taguchi M, Matsuda Y, Iekushi K, Yamada T, Akizawa T. Molidustat for the treatment of renal anaemia in patients with non-dialysis-dependent chronic kidney disease: design and rationale of two phase III studies. *BMJ Open* 2019;**9**(6):e026704. [MEDLINE: 31203242]

Yamamoto H, Taguchi M, Nobori K, Matsuda Y, Iekushi K, Akizawa T. To investigate the efficacy and safety of molidustat in non-dialysis patients with renal anemia who are not treated with erythropoiesis stimulating agents: MIYABI ND-C [abstract no: P1866]. *Nephrology Dialysis Transplantation* 2020;**35**(Suppl 3):iii2177. [EMBASE: 633422996]

MIYABI ND-M 2019 *{published data only}*

* Yamamoto H, Nobori K, Matsuda Y, Hayashi Y, Hayasaki T, Akizawa T. Molidustat for renal anemia in nondialysis patients previously treated with erythropoiesis-stimulating agents: a randomized, open-label, phase 3 study. *American Journal of Nephrology* 2021;**52**(10-11):884-93. [MEDLINE: 34569482]

Yamamoto H, Taguchi M, Matsuda Y, Iekushi K, Yamada T, Akizawa T. Molidustat for the treatment of renal anaemia in patients with non-dialysis-dependent chronic kidney disease: design and rationale of two phase III studies. *BMJ Open* 2019;**9**(6):e026704. [MEDLINE: 31203242]

Yamamoto H, Taguchi M, Nobori K, Matsuda Y, Iekushi K, Akizawa T. To investigate the efficacy and safety of molidustat in non-dialysis patients with renal anemia who are treated with erythropoiesis stimulating agents: Miyabi ND-M [Abstract no: P1868]. *Nephrology Dialysis Transplantation* 2020;**35**(Suppl 3):iii2179. [EMBASE: 633423006]

Nangaku 2021 *{published data only}*

* Nangaku M, Kondo K, Ueta K, Kokado Y, Kaneko G, Matsuda H, et al. Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a phase 3, multicenter, randomized, double-blind study. *Nephrology Dialysis Transplantation* 2021;**36**(9):1731-41. [MEDLINE: 33650630]

Nangaku M, Kondo K, Ueta K, Kokado Y, Kaneko G, Matsuda H, et al. Randomized, double-blinded, active-controlled (darbepoetin alfa), phase 3 study of vadadustat in CKD patients with anemia on hemodialysis in Japan [abstract no: TH-OR024]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):6. [EMBASE: 633771357]

Nangaku 2021a *{published data only}*

Nangaku M, Kondo K, Kokado Y, Ueta K, Kaneko G, Shiosaka M, et al. Randomized, open-label, active-controlled (darbepoetin alfa), phase 3 study of vadadustat for treating anemia in non-dialysis-dependent CKD patients in Japan [abstract no: SA-PO229]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):823. [EMBASE: 633767995]

* Nangaku M, Kondo K, Kokado Y, Ueta K, Kaneko G, Tandai T, et al. Phase 3 randomized study comparing vadadustat with darbepoetin alfa for anemia in Japanese patients with nondialysis-dependent CKD. *Journal of the American Society of Nephrology* 2021;**32**(7):1779-90. [MEDLINE: 33883252]

Nangaku 2021b *{published data only}*

GSK201753. A 52-week, Phase III, open-label, multi-center study to evaluate efficacy and safety of GSK1278863 in Japanese non-dialysis and peritoneal dialysis subjects with anemia associated with chronic kidney disease [study protocol]. www.clinicaltrials.gov/ProvidedDocs/63/NCT02791763/Prot_000.pdf (accessed 9 May 2022).

* Nangaku M, Hamano T, Akizawa T, Tsubakihara Y, Nagai R, Okuda N, et al. Daprodustat compared with epoetin beta pegol for anemia in Japanese patients not on dialysis: a 52-week randomized open-label phase 3 trial. *American Journal of Nephrology* 2021;**52**(1):26-35. [MEDLINE: 33561857]

NCT01888445 *{published data only}*

* Astellas1517-CL-0304. A study to investigate the effect of ASP1517 after intermittent oral dosing in dialysis chronic kidney disease patients with anemia compared with darbepoetin as a reference drug [A Japanese, phase 2, multicenter, randomized, 4-arm parallel, double-blind (arms 1-3), open-label (arm 4), active-comparator (darbepoetin alfa) study of intermittent oral dosing of asp1517 in hemodialysis-dependent chronic kidney disease patients with anemia [1517-CL-0304 clinical study results report]]. www.trialsummaries.com/Study/StudyDetails?id=14175&tenant=MT_AST_9011; www.clinicaltrials.gov/ct2/show/NCT01888445 (first received 6 August 2018).

NDD-CKD 2020 *{published data only}*

* Nangaku M, Farag YM, deGoma E, Luo W, Vargo D, Khawaja Z. Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, for treatment of anemia of chronic kidney disease: two randomized Phase 2 trials in Japanese patients. *Nephrology Dialysis Transplantation* 2020 Jul 20 [epub ahead of print]. [DOI: 10.1093/ndt/gfaa060] [MEDLINE: 32719868]

Nangaku M, Khawaja Z, Luo W, Garafola S, De Goma E, Komatsu Y. Randomized, placebo-controlled phase 2 trials of vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), to treat anemia of CKD [abstract no: TH-PO228]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):171. [EMBASE: 633737146]

Solinsky C, Farag YM, Khawaja Z, Anders R, Luo W, Chavan A, et al. Impact of vadadustat on iron regulation in Japanese subjects with chronic kidney disease (CKD) [abstract no: 352]. *American Journal of Kidney Diseases* 2020;**75**(4):638-9. [EMBASE: 2005716872]

NDD-CKD 2020a *{published data only}*

* Nangaku M, Farag YM, deGoma E, Luo W, Vargo D, Khawaja Z. Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, for treatment of anemia of chronic kidney disease: two randomized Phase 2 trials in Japanese patients. *Nephrology Dialysis Transplantation* 2020 Jul 20 [epub ahead of print]. [DOI: 10.1093/ndt/gfaa060] [MEDLINE: 32719868]

Nangaku M, Khawaja Z, Luo W, Garafola S, deGoma E, Komatsu Y. Randomized, placebo-controlled phase 2 trials of vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), to treat anemia of CKD [abstract no: TH-PO228]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):171. [EMBASE: 633737146]

Solinsky C, Farag YM, Khawaja Z, Anders R, Luo W, Chavan A, et al. Impact of vadadustat on iron regulation in Japanese subjects with chronic kidney disease (CKD) [abstract no: 352]. *American Journal of Kidney Diseases* 2020;**75**(4):638-9. [EMBASE: 2005716872]

OLYMPUS 2021 *{published data only}*

AstraZeneca. A phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis [clinical study protocol V6; 31 August 2018]. www.clinicaltrials.gov/ProvidedDocs/27/NCT02174627/Prot_000.pdf (accessed 9 May 2022).

Eleftheriadis T, Pissas G, Liakopoulos V, Stefanidis I. On the increased event rate of urinary tract infection and pneumonia in CKD patients treated with roxadustat for anemia. *Journal of the American Society of Nephrology* 2021;**32**(6):1537. [MEDLINE: 33849917]

Fishbane S, El-Shahawy MA, Pecoits-Filho R, Van BP, Houser MT, Frison L, 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 [abstract no: TH-OR023]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):6. [EMBASE: 633771285]

* Fishbane S, El-Shahawy MA, Pecoits-Filho R, Van BP, Houser MT, Frison L, et al. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized phase 3 study. *Journal of the American Society of Nephrology* 2021;**32**(3):737-55. [MEDLINE: 33568383]

Fishbane S, El-Shahawy MA, Van BP, Little DJ. Authors' Reply. *Journal of the American Society of Nephrology* 2021;**32**(6):1537-8. [MEDLINE: 33849916]

Pecoits-Filho R, Chan TM, Hardy E, Yu KH, Fishbane S. 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) [abstract no: TH-OR05]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):2. [EMBASE: 633697943]

Rastogi A, Pecoits-Filho R, Fishbane S, Little DJ, Hardy E, Yu KH, et al. Roxadustat treatment corrects anemia to hemoglobin (HB) values ≥10 g/dL in the majority of patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) [abstract no: PO0264]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):133. [EMBASE: 633698803]

Pergola 2016 *{published data only}*

Haase VH, Spinowitz BS, Pergola PE, Farmer T, Maroni BJ, Hartman CS. AKB-6548 demonstrates controlled hemoglobin (HGB) response in a phase 2b study for the treatment of anemia in patients with chronic kidney disease not on dialysis (ND-CKD) [abstract no: TH-PO649]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):237A.

Haase VH, Spinowitz BS, Pergola PE, Khawaja Z, Chan J, Zuraw Q, et al. Efficacy and dose requirements of vadadustat are independent of systemic inflammation and prior erythropoiesis-stimulating agent(ESA) dose in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) [abstract no: TH-PO907]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):304A.

Pergola PE, Spinowitz B, Haase VH, Hartman CS, Farmer TM, Polu KR, et al. AKB-6548, a novel hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) for the treatment of anemia in patients with chronic kidney disease not on dialysis (ND-CKD) [abstract no: FO015]. *Nephrology Dialysis Transplantation* 2015;**30**(Suppl 3):iii8. [EMBASE: 72206296]

* Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney International* 2016;**90**(5):1115-22. [MEDLINE: 27650732]

Spinowitz BS, Pergola PE, Haase VH, Farmer TM, Hartman CS, Maroni BJ. Hemoglobin (HGB) response in a phase 2b study of AKB-6548 for the treatment of anemia in patients with non-dialysis dependant chronic kidney disease (NDD-CKD). [abstract no: TH-OR038]. *Journal of the American Society of Nephrology* 2015;**26**(Abstract Suppl):11A.

PRO2TECT-CONVERSION 2021 *{published data only}*

Bunn HF. Vadadustat for anemia in patients with dialysis-dependent or non-dialysis-dependent chronic kidney disease. *New England Journal of Medicine* 2021;**385**(16):e56. [MEDLINE: 34644481]

Chertow GM, Pergola PE, Agarwal R, Block GA, Farag YM, Jardine AG, et al. Cardiovascular safety and efficacy of vadadustat for the treatment of anemia in non-dialysis-dependent CKD: design and baseline characteristics. *American Heart Journal* 2021;**235**(5):1-11. [MEDLINE: 33129989]

* Chertow GM, Pergola PE, Farag YM, Agarwal R, Arnold S, Bako G, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *New England Journal of Medicine* 2021;**384**(17):1589-600. [MEDLINE: 33913637]

Chertow GM. Global phase 3 clinical trials of vadadustat vs. darbepoetin alfa for treatment of anemia in patients with non-dialysis-dependent CKD [abstract no: FR-OR54]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):B2. [EMBASE: 633697273]

Koury M, Pergola PE, Roy-Chaudhury P, Farag YM, Luo W, Anders R, et al. Iron-related outcomes in patients with non-dialysis-dependent CKD randomized to vadadustat vs. darbepoetin Alfa [abstract no: PO0482]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):190. [EMBASE: 636329134]

McCullough PA, Luo W, Anders R, Vargo D, Parfrey PS. Assessment of thromboembolic events with vadadustat vs. darbepoetin alfa for treatment of anemia in patients with non-dialysis-dependent CKD [abstract no: PO0462]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):184. [EMBASE: 636331039]

PRO2TECT-CORRECTION 2021 *{published data only}*

Bunn HF. Vadadustat for anemia in patients with dialysis-dependent or non-dialysis-dependent chronic kidney disease. *New England Journal of Medicine* 2021;**385**(16):e56. [MEDLINE: 34644481]

Chertow GM, Pergola PE, Agarwal R, Block GA, Farag YM, Jardine AG, et al. Cardiovascular safety and efficacy of vadadustat for the treatment of anemia in non-dialysis-dependent CKD: design and baseline characteristics. *American Heart Journal* 2021;**235**(5):1-11. [MEDLINE: 33129989]

* Chertow GM, Pergola PE, Farag YM, Agarwal R, Arnold S, Bako G, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *New England Journal of Medicine* 2021;**384**(17):1589-600. [MEDLINE: 33913637]

Chertow GM. Global phase 3 clinical trials of vadadustat vs. darbepoetin alfa for treatment of anemia in patients with non-dialysis-dependent CKD [abstract no: FR-OR5]. *Journal of the American Society of Nephrology* 2020;**31**(Abstract Suppl):B2. [EMBASE: 633697273]

Koury M, Pergola PE, Roy-Chaudhury P, Farag YM, Luo W, Anders R, et al. Iron-related outcomes in patients with non-dialysis-dependent CKD randomized to vadadustat vs. darbepoetin alfa [abstract no: PO0482]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):190. [EMBASE: 636329134]

McCullough PA, Luo W, Anders R, Vargo D, Parfrey PS. Assessment of thromboembolic events with vadadustat vs. darbepoetin alfa for treatment of anemia in patients with non-dialysis-dependent CKD [abstract no: PO0462]. *Journal of the American Society of Nephrology* 2021;**32**(Abstract Suppl):184. [EMBASE: 636331039]

Provenzano 2008 *{published data only}*

Provenzano R, Fadda G, Bernardo M, James C, Kochendoerfer G, Lee T, et al. FG2216, a novel oral HIF-PHI, stimulates erythropoiesis and increases hemoglobin concentration in patients with non-dialysis CKD [abstract no: 212]. *American Journal of Kidney Diseases* 2008;**51**(4):A80.

Provenzano R, Hulter H, Agarwal A, Klaus S, Lee T, Yu P, et al. Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor FG-2216 increases Hb without FE depletion in the absence of IV Fe [abstract no: 249]. *American Journal of Kidney Diseases* 2013;**61**(4):A78. [EMBASE: 71024073]

Provenzano 2016 *{published data only}*

Provenzano R, Besarab A, Dua SL, Nguyen PV, Wright SH, Zeig S, et al. FG-4592, a novel oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), maintains hemoglobin levels and lowers cholesterol in hemodialysis patients: phase 2 comparison with epoetin alfa [abstract no: FR-PO257]. *Journal of the American Society of Nephrology* 2012;**23**(Abstract Suppl):428A.

* 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. *American Journal of Kidney Diseases* 2016;**67**(6):912-24. [MEDLINE: 26846333]

Provenzano 2016a *{published data only}*

Provenzano R, Besarab A, Dua SL, Nguyen PV, Wright SH, Zeig S, et al. FG-4592, a novel oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), maintains hemoglobin levels and lowers cholesterol in hemodialysis patients: phase 2 comparison with epoetin alfa [abstract no: FR-PO257]. *Journal of the American Society of Nephrology* 2012;**23**(Abstract Suppl):428A.

* 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. *American Journal of Kidney Diseases* 2016;**67**(6):912-24. [MEDLINE: 26846333]

PYRENEES 2021 *{published data only}*

Astellas 1517-CL-0613. Roxadustat in the treatment of anemia in end stage renal disease (ESRD) patients on stable dialysis [A phase 3, randomized, open-label, active-controlled study to evaluate the efficacy and safety of roxadustat in the maintenance treatment of anemia in end stage renal disease patients on stable dialysis]. www.trialsummaries.com/Study/StudyDetails?id=14380&tenant=MT_AST_9011 (accessed 9 May 2022).

* Csiky B, Schomig M, Esposito C, Barratt J, Reusch M, Valluri U, et al. Roxadustat for the maintenance treatment of anemia in patients with end-stage kidney disease on stable dialysis: a European phase 3, randomized, open-label, active-controlled study (PYRENEES). *Advances in Therapy* 2021;**38**(10):5361-80. [MEDLINE: 34537926]

Esposito C, Csiky B, Tataradze A, Reusch M, Han C, Sulowicz W. Two phase 3, multicenter, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis. *Swiss Medical Weekly* 2020;**150**(Suppl 248):21-2S. [EMBASE: 634241523]

Esposito C, Csiky B, Tataradze A, Reusch M, Han C, Sulowicz W. Two phase 3, multicenter, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis [abstract no: SA-PO225]. *Journal of the*

American Society of Nephrology 2019;**30**(Abstract Suppl):822. [EMBASE: 633767739]

ROCKIES 2019 *{published data only}*

AstraZeneca. A phase 3, multicenter, randomized, open-label, active-controlled study of the safety and efficacy of roxadustat in the treatment of anemia in dialysis patients [Clinical study protocol v8.0 19 September 2018]. www.clinicaltrials.gov/ProvidedDocs/31/NCT02174731/Prot_000.pdf (accessed 10 May 2022).

Fishbane S, Pollock CA, El-Shahawy MA, Escudero ET, Rastogi A, Van BP, et al. ROCKIES: an international, phase 3, randomized, open-label, active-controlled study of roxadustat for anemia in dialysis-dependent CKD patients [abstract no: TH-OR022]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):6. [EMBASE: 633771219]

SIERRAS 2021 *{published data only}*

* Charytan C, Manllo-Karim R, Martin ER, Steer D, Bernardo M, Dua SL, et al. A randomized trial of roxadustat in anemia of kidney failure: SIERRAS study. *Kidney International Reports* 2021;**6**(7):1829-39. [MEDLINE: 34307977]

Charytan C, Manllo-Karim R, Martin ER, Steer D, Bernardo M, Dua SL, 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 [abstract no: SA-PO227]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):822. [EMBASE: 633767862]

SYMPHONY HD 2021 *{published data only}*

Akizawa T, Maeda K, Miyazawa Y, Koretomo R. Phase 3 study to compare the efficacy and safety of enarodustat (JTZ-951), an oral HIF-PH inhibitor, with darbepoetin alfa in anemic patients with CKD receiving maintenance hemodialysis [abstract no: TH-PO1186]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):B4.

Akizawa T, Nangaku M, Yamaguchi T, Koretomo R, Maeda K, Miyazawa Y, et al. A phase 3 study of enarodustat (JTZ-951) in Japanese hemodialysis patients for treatment of anemia in chronic kidney disease: SYMPHONY HD study. *Kidney Diseases* 2021;**7**(6):494-502. [EMBASE: 2013576033]

SYMPHONY ND 2021 *{published data only}*

Akizawa T, Nangaku M, Yamaguchi T, Koretomo R, Maeda K, Miyazawa Y, et al. A phase 3 study of enarodustat in anemic patients with CKD not requiring dialysis: the SYMPHONY ND study. *Kidney International Reports* 2021;**6**(7):1840-9. [MEDLINE: 34307978]

References to studies excluded from this review

Akizawa 2015a *{published data only}*

Akizawa T, Hanaki K, Arai M. JTZ-951, an oral novel HIF-PHD inhibitor, elevates hemoglobin in Japanese anemic patients with chronic kidney disease receiving maintenance hemodialysis [abstract no: FO019]. *Nephrology Dialysis Transplantation* 2015;**30**(Suppl 3):iii10. [EMBASE: 72206300]

Akizawa 2019a *{published data only}*

Akizawa T, Miyazawa Y, Matsui A, Koretomo R, Arai M. Enarodustat (JTZ-951) , an oral HIF-PH inhibitor, elevates and maintains hemoglobin levels over 30 weeks in Japanese anemic patients with CKD not on dialysis [abstract no: TH-PO225]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):171. [EMBASE: 633737010]

* Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Matsui A, et al. A placebo-controlled, randomized trial of enarodustat in patients with chronic kidney disease followed by long-term trial. *American Journal of Nephrology* 2019;**49**(2):165-74. [MEDLINE: 30699415]

Akizawa 2019b *{published data only}*

Akizawa T, Miyazawa Y, Maeda K, Koretomo R, Arai M. Enarodustat (JTZ-951), an oral HIF-PH inhibitor, maintains hemoglobin levels switching from ESAs over 30 weeks in Japanese anemic patients with CKD receiving maintenance hemodialysis [abstract no: TH-PO226]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):171. [EMBASE: 633737068]

* Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Maeda K, et al. Enarodustat, conversion and maintenance therapy for anemia in hemodialysis patients: a randomized, placebo-controlled phase 2b trial followed by long-term trial. *Nephron* 2019;**143**(2):77-85. [MEDLINE: 31117088]

Akizawa 2020 *{published data only}*

* Akizawa T, Otsuka T, Reusch M, Ueno M. Intermittent oral dosing of roxadustat in peritoneal dialysis chronic kidney disease patients with anemia: a randomized, phase 3, multicenter, open-label study. *Therapeutic Apheresis & Dialysis* 2020;**24**(2):115-25. [MEDLINE: 31222951]

Akizawa T, Otsuka T, Reusch M, Ueno M. Phase 3, multicenter, open-label study of intermittent oral roxadustat in peritoneal dialysis CKD patients with anemia [abstract no: SA-OR075]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):99. [EMBASE: 633736837]

Akizawa 2020b *{published data only}*

Akizawa T, Otsuka T, Yamaguchi Y, Reusch M. Phase 3, multicenter, randomized, open-label, non-comparative study of intermittent oral roxadustat in ESA-naive CKD patients not on dialysis in Japan [abstract no: SA-PO226]. *Journal of the American Society of Nephrology* 2019;**30**(Abstract Suppl):822. [EMBASE: 633767826]

Akizawa T, Yamaguchi Y, Otsuka T, Reusch M. A phase 3, multicenter, randomized, two-arm, open-label study of intermittent oral dosing of roxadustat for the treatment of anemia in Japanese erythropoiesis-stimulating agent-naive chronic kidney disease patients not on dialysis. *Nephron* 2020;**144**(8):372-82. [MEDLINE: 32580188]

Akizawa 2020g *{published data only}*

Akizawa T, Ueno M, Shiga T, Reusch M. Oral roxadustat three times weekly in ESA-naive and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: Results

from two phase 3 studies. *Therapeutic Apheresis & Dialysis* 2020;**24**(6):628-41. [MEDLINE: 31891449]

ASCEND:Fe 2018 *{published data only}*

NCT03457701. Anemia studies in CKD: erythropoiesis via a novel prolyl hydroxylase inhibitor (PHI) daprodustat-iron (ASCEND: Fe) [A repeat dose, open label, two period, randomized, cross over study to compare the effect of daprodustat to recombinant, human erythropoietin (rhEPO) on oral iron absorption in adult participants with anemia associated with chronic kidney disease who are not on dialysis]. www.clinicaltrials.gov/show/NCT03457701 (first received 7 March 2018).

ASCEND-BP 2017 *{published data only}*

NCT03029247. Anemia study in chronic kidney disease (CKD): erythropoiesis via a novel prolyl hydroxylase inhibitor (PHI) daprodustat-blood pressure (ASCEND-BP) [A randomized, open-label study to evaluate the effect of daprodustat on blood pressure in subjects with anemia associated with chronic kidney disease on hemodialysis switched from a stable dose of an erythropoiesis-stimulating agent]. www.clinicaltrials.gov/show/NCT03029247 (first received 24 January 2017).

Bailey 2019 *{published data only}*

Bailey CK, Caltabiano S, Cobitz AR, Huang C, Mahar KM, Patel V, et al. A 29-day safety, efficacy, and pharmacodynamic study of a hypoxia-inducible factor prolyl hydroxylase inhibitor, daprodustat, administered TIW in anemic subjects on hemodialysis (HD) [abstract no: SA-PO811]. *Journal of the American Society of Nephrology* 2017;**28**(Abstract Suppl):889. [EMBASE: 633698132]

Bailey CK, Caltabiano S, Cobitz AR, Huang C, Mahar KM, Patel VV. A randomized, 29-day, dose-ranging, efficacy and safety study of daprodustat, administered three times weekly in patients with anemia on hemodialysis. *BMC Nephrology* 2019;**20**(1):372. [MEDLINE: 31619187]

Besarab 2016 *{published data only}*

Besarab A, Chan DT, Dua SL, Franco M, Henry E, Leong R, et al. Hypoxia inducing factor prolyl hydroxylase inhibitor FG-4592 corrects anemia in peritoneal dialysis [abstract no: SA-OR087]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):91A.

Besarab A, Chernyavskaya E, Motylev I, Shutov E, Kumbar LM, Gurevich K, et al. Roxadustat (FG-4592): correction of anemia in incident dialysis patients. *Journal of the American Society of Nephrology* 2016;**27**(4):1225-33. [MEDLINE: 26494833]

Besarab A, Chernyavskaya EN, Motylev I, Evgeny S, Yampolskiy AF, Kumbar LM, et al. FG-4592, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, corrects anemia without iron supplementation in incident dialysis patients [abstract no: TH-OR096]. *Journal of the American Society of Nephrology* 2012;**23**(Abstract Suppl):21A.

Besarab A, Szczech L, Yu KH, Neff TB. Impact of iron regimen on iron indices and hepcidin during roxadustat anemia correction in incident dialysis patients [abstract no: TH-PO847]. *Journal of the American Society of Nephrology* 2014;**25**(Abstract Suppl):304a.

Buch 2014 *{published data only}*

Buch A, Farmer TM, Hartman C, Alcorn H, Shalwitz R. Hemodialysis has minimal impact on the pharmacokinetics of AKB-6548, a once-daily oral inhibitor of hypoxia inducible factor prolyl-hydroxylases (HIFPHs) for the treatment of anemia related to chronic kidney disease (CKD) [abstract no: FR-PO952]. *Journal of the American Society of Nephrology* 2014;**25**(Abstract Suppl):590A.

DD-CKD 2020 *{published data only}*

* Nangaku M, Farag YM, deGoma E, Luo W, Vargo D, Khawaja Z. Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, for treatment of anemia of chronic kidney disease: two randomized Phase 2 trials in Japanese patients. *Nephrology Dialysis Transplantation* 2020 Jul 28 [epub ahead of print]. [MEDLINE: 32719868]

Nangaku M, Khawaja Z, Luo W, Garafola S, deGoma E, Komatsu Y. Randomized, placebo-controlled phase 2 trials of vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), to treat anemia of CKD [abstract no: TH-PO228]. *Journal of the American Society of Nephrology* 2018;**29**(Abstract Suppl):171. [EMBASE: 633737146]

Solinsky C, Farag YM, Khawaja Z, Anders R, Luo W, Chavan A, et al. Impact of vadadustat on iron regulation in Japanese subjects with chronic kidney disease (CKD) [abstract no: 352]. *American Journal of Kidney Diseases* 2020;**75**(4):638-9. [EMBASE: 2005716872]

EudraCT2012-004049-34 *{published data only}*

2012-004049-34. A four-week, phase IIa, randomized, active-controlled, parallel-group, multi-center study to evaluate the safety, efficacy and pharmacokinetics of switching subjects from a stable dose of recombinant human erythropoietin to GSK1278863 in hemodialysis-dependent subjects with anaemia associated with chronic kidney disease - 4 week switch study in HD subjects. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004049-34 2013.

GSK116582. A 4 week phase IIa, randomized, active-controlled, parallel-group, multi-center study to evaluate the safety, efficacy and pharmacokinetics of switching subjects from a stable dose of recombinant human erythropoietin to GSK1278863 in hemodialysis-dependent subjects with anemia associated with chronic kidney disease. www.clinicaltrialsregister.eu/ctr-search/trial/2012-004049-34/results 2013.

EudraCT2012-004050-29 *{published data only}*

GSK116581. A four-week phase IIa, randomized, double-blind, placebo controlled, parallel-group, multi-center study to evaluate the safety, efficacy and pharmacokinetics of GSK1278863 in subjects with anemia associated with chronic kidney disease who are not taking recombinant human erythropoietin and are not undergoing dialysis. www.clinicaltrialsregister.eu/ctr-search/trial/2012-004050-29/results 2012.

EudraCT2015-004790-32 *{published data only}*

2015-004790-32. A 29-day, randomized, double-blinded, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of GSK1278863 in hemodialysis-dependent subjects with anemia associated with chronic kidney disease who are switched from a stable dose of an erythropoiesis-stimulating agent. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004790-32 2016 Jan 13.

Frohna 2007 *{published data only}*

Frohna PA, Milwee S, Pinkett J, Lee T, Moore-Perry K, Chou J, et al. Preliminary results from a randomized, single-blind, placebo-controlled trial of FG-4592, a novel hypoxia inducible factor prolyl hydroxylase inhibitor, in CKD anemia [abstract no: SU-PO806]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):763A.

Haase 2016 *{published data only}*

Haase VH, Khawaja Z, Chan J, Zuraw Q, Farzaneh-Far R, Maroni BJ, et al. Vadadustat maintains hemoglobin (Hb) levels in dialysis-dependent chronic kidney disease (DD-CKD) patients independent of systemic inflammation or prior dose of erythropoiesis-stimulating agent (ESA) [abstract no: TH-PO960]. *Journal of the American Society of Nephrology* 2016;**27**(Abstract Suppl):318A.

Hartman 2014 *{published data only}*

Hartman CS, Shalwitz IR, Shalwitz RA. Controlled hemoglobin response in a double-blind, placebo-controlled trial of AKB-6548 in subjects with chronic kidney disease [abstract no: SO051]. *Nephrology Dialysis Transplantation* 2014;**29**(Suppl 3):iii22. [EMBASE: 71491516]

Shalwitz R, Hartman C, Flinn C, Shalwitz I, Peters KG, Besarab A, et al. AKB-6548, a new hypoxia-inducible factor prolyl hydroxylase inhibitor, increases hemoglobin in chronic kidney disease patients without increasing basal erythropoietin levels [abstract no: FR-OR116]. *Journal of the American Society of Nephrology* 2012;**23**(Abstract Suppl):56A.

Holdstock CKD 2016 *{published data only}*

Holdstock L, Meadowcroft AM, Maier R, Johnson BM, Jones D, Rastogi A, et al. Four-week studies of oral hypoxia-inducible factor-prolyl hydroxylase inhibitor GSK1278863 for treatment of anemia. *Journal of the American Society of Nephrology* 2016;**27**(4):1234-44. [MEDLINE: 26494831]

Holdstock HD 2016 *{published data only}*

* Holdstock L, Meadowcroft AM, Maier R, Johnson BM, Jones D, Rastogi A, et al. Four-week studies of oral hypoxia-inducible factor-prolyl hydroxylase inhibitor GSK1278863 for treatment of anemia. *Journal of the American Society of Nephrology* 2016;**27**(4):1234-44. [MEDLINE: 26494831]

Meadowcroft AM, Holdstock L, Maier R, Jones D, Johnson B, Cobitz AR, et al. Four-week safety, efficacy and pharmacodynamic study of hypoxia-inducible factor (HIF)-prolyl inhibitor GSK1278863 in anemic hemodialysis subjects switching from recombinant human erythropoietin [abstract no: SA-PO1092]. *Journal of the American Society of Nephrology* 2013;**24**(Abstract Suppl):6B.

Martin 2017 *{published data only}*

Martin ER, Smith MT, Maroni BJ, Zuraw QC, deGoma EM. Clinical trial of vadadustat in patients with anemia secondary to stage 3 or 4 chronic kidney disease. *American Journal of Nephrology* 2017;**45**(5):380-8. [MEDLINE: 28343225]

NCT01679587 *{published data only}*

NCT01679587. Dose escalation study to investigate safety, tolerability, pharmacodynamics, and pharmacokinetics of BAY85-3934 in subjects with chronic kidney disease (CKD) [A multicenter, randomized, single-blind, placebo-controlled, combined 2-fold cross-over and group-comparison, dose-escalation study to investigate safety, tolerability, pharmacodynamics, and pharmacokinetics of single oral doses of BAY 85-3934 in subjects with chronic kidney disease (CKD)]. www.clinicaltrials.gov/show/NCT01679587 (first received 6 September 2012).

NCT01971164 *{published data only}*

Yamamoto H. Safety, tolerability, PK & PD study of JTZ-951 in anemic subjects with end-stage renal disease [Randomized, single-blind, placebo-controlled, multiple ascending dose study to evaluate safety, tolerability, pharmacokinetics & pharmacodynamics of JTZ-951 administered once daily for 15 days in anemic subjects with end-stage renal disease]. www.clinicaltrials.gov/show/NCT01971164 (first received 29 October 2013).

NCT03992066 *{published data only}*

NCT03992066. Study to evaluate the pharmacokinetics, pharmacodynamics, and safety of vadadustat in hemodialysis subjects with anemia associated with chronic kidney disease [A phase 1b, randomized, open-label study to evaluate the pharmacokinetics, pharmacodynamics, and safety of vadadustat in hemodialysis subjects with anemia associated with chronic kidney disease]. www.clinicaltrials.gov/show/NCT03992066 (first received 19 June 2019).

NCT04059913 *{published data only}*

NCT04059913. Evaluate the efficacy and safety of multiple roxadustat dosing regimens for the treatment of anemia in dialysis subjects with chronic kidney disease [A prospective, randomized, open-label, multi-center study to evaluate the efficacy and safety of multiple roxadustat dosing regimens for the treatment of anemia in dialysis subjects with chronic kidney disease]. www.clinicaltrials.gov/show/NCT04059913 (first received 16 August 2019).

Pai 2015 *{published data only}*

Pai S, Koretomo R, Tamaki S, Berg J, Marbury T, Galloway C, et al. JTZ-951, a novel HIF-PHD inhibitor, demonstrates increases in hemoglobin, iron mobilization, reproducible pharmacokinetics, and safety following once daily administration for 15 days in patients with anemia receiving hemodialysis [abstract no: FP658]. *Nephrology Dialysis Transplantation* 2015;**30**:iii293-4. [EMBASE: 72207075]

Parmar 2019 *{published data only}*

Parmar D, Kansagra K. A phase II trial to assess safety, tolerability and efficacy of phd-2 inhibitor (desidustat-zyan1) in the treatment of anemia in pre-dialysis chronic kidney disease

patients [abstract no: MON-318]. *Kidney International Reports* 2019;**4**(7 Suppl):S430. [EMBASE: 2002179966]

Parmar DV, Kansagra KA, Patel JC, Joshi SN, Sharma NS, Shelat AD, et al. Outcomes of desidustat treatment in people with anemia and chronic kidney disease: a phase 2 study. *American Journal of Nephrology* 2019;**49**(6):470-8. [MEDLINE: 31112954]

Provenzano 2011 *{published data only}*

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 [abstract no: 253]. *American Journal of Kidney Diseases* 2011;**57**(4):A80. [EMBASE: 70379812]

Provenzano 2011a *{published data only}*

* Provenzano R, Tumlin J, Zabaneh R, Chou J, Hemmerich S, Neff TB, 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):1432-40. [MEDLINE: 32603526]

Provenzano R, Tumlin J, Zabaneh R, Linde P, Chou J, Zhong M, et al. Pharmacokinetics of oral FG-4592 to treat anemia in hemodialysis (HD) patients (PTS) [abstract no: 254]. *American Journal of Kidney Diseases* 2011;**57**(4):A80. [EMBASE: 70379813]

Provenzano 2016b *{published data only}*

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 [abstract no: FP215]. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii144-5. [EMBASE: 70765709]

Besarab A, Provenzano R, Fishbane S, Sun CH, Belo DS, Neff TB, et al. FG-4592 oral hypoxia-inducible factor prolyl hydroxylase inhibitor corrects anemia in nondialysis CKD patients without IV iron [abstract no: TH-PO364]. *Journal of the American Society of Nephrology* 2011;**22**(Abstract Suppl):196A.

* 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. *Clinical Journal of the American Society of Nephrology: CJASN* 2016;**11**(6):982-91. [MEDLINE: 27094610]

Wiecek 2005 *{published data only}*

Wiecek A, Piecha G, Ignacy W, Schmidt R, Neumayer HH, Scigalla P, et al. Pharmacological stabilization of HIF increased hemoglobin concentration in anemic patients with chronic kidney disease [abstract no: MO24]. *Nephrology Dialysis Transplantation* 2005;**20**(Suppl 5):v195.

References to studies awaiting assessment

FO2RWARD-2 2019 *{published data only}*

NCT03799627. Study of vadadustat in hemodialysis patients with anemia switching from epoetin alfa (FO2RWARD-2) [Phase 2, randomized, open-label, active-controlled, efficacy, safety, pharmacokinetics, and pharmacodynamics study of oral vadadustat for the treatment of anemia in hemodialysis subjects converting from epoetin alfa (FO2RWARD-2)]. www.clinicaltrials.gov/show/NCT03799627 (first received 10 January 2019).

References to ongoing studies

ASCEND-FBF 2018 *{published data only}*

NCT03446612. Anemia study in chronic kidney disease (CKD) : erythropoiesis via a novel prolyl hydroxylase inhibitor (PHI) daprodustat -forearm blood flow (ASCEND-FBF) [A randomized, repeat dose, open label, parallel group, multi-center study to evaluate the effect of daprodustat compared to darbepoetin alfa on forearm blood flow in participants with anemia of chronic kidney disease that are not dialysis dependent]. www.clinicaltrials.gov/show/NCT03446612 (first received 27 February 2018).

CTRI/2019/06/019635 *{published data only}*

Kansagra K. Desidustat in the treatment of anemia in chronic kidney disease (CKD) [A phase 3, multicenter, multicountry, open-label, randomized, active-controlled clinical trial to evaluate the efficacy and safety of desidustat versus darbepoetin for the treatment of anemia in patients with chronic kidney disease (CKD) who are not on dialysis.]. ctri.nic.in/Clinicaltrials/showallp.php?mid1=33329&EncHid=&userName=CTRI/2019/06/019635 (first received 12 June 2019).

DREAM-D 2019 *{published data only}*

Kansagra K. Desidustat in the treatment of anemia in CKD. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=36915&EncHid=&userName=CTRI/2019/12/022312 (first received 11 December 2019).

NCT04027517 *{published data only}*

Lee JW. A study to evaluate efficacy and safety of JTZ-951 compared to darbepoetin alfa in Korean renal anemia patients receiving hemodialysis [A multi-center, randomized, open-label, active-controlled, parallel-group, phase iii study to compare the efficacy and safety of JTZ-951 with darbepoetin alfa in anemic patients with chronic kidney disease receiving maintenance hemodialysis]. www.clinicaltrials.gov/show/NCT04027517 (first received 22 July 2019).

NCT04134026 *{published data only}*

Liu H. Evaluate the efficacy and safety of roxadustat for the treatment of anemia and risks of cardiovascular and cerebrovascular events in ESRD newly initiated dialysis patients [Phase 4 multicenter, randomized, open-lable, active-controlled study of the efficacy and safty of roxadustat for the treatment of anemia and risks of cardiovascular and cerebrovascular events in incident-dialysis patients]. www.clinicaltrials.gov/show/NCT04134026 (first received 21 October 2019).

NCT04313153 *{published data only}*

NCT04313153. Trial evaluating the efficacy and safety of oral vadadustat once daily (QD) and three times weekly (TIW) for the maintenance treatment of anemia in hemodialysis subjects converting from erythropoiesis-stimulating agents (ESAs) [Phase 3b, randomized, open-label, active-controlled trial evaluating the efficacy and safety of oral vadadustat once daily (QD) and three times weekly (TIW) for the maintenance treatment of anemia in hemodialysis subjects converting from erythropoiesis-stimulating agents (ESAs)]. www.clinicaltrials.gov/show/NCT04313153 (first received 18 March 2020).

PER-038-14 *{published data only}*

PER-038-14. A phase 3, multicenter, randomized, open-label active-controlled study of the efficacy and safety of FG-4592 in the treatment of anemia in incident-dialysis patients. www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=038-14 (first received 11 December 2014).

SLCTR-2019-032 *{published data only}*

Nazar AL. A randomized, active-controlled clinical trial to evaluate the efficacy and safety of desidustat versus darbepoetin for the treatment of anemia in patients with chronic kidney disease (CKD) who are not on dialysis [A phase 3, multicenter, multi-country, open-label, randomized, active-controlled clinical trial to evaluate the efficacy and safety of desidustat versus darbepoetin for the treatment of anemia in patients with chronic kidney disease (CKD) who are not on dialysis]. slctr.lk/trials/slctr-2019-032 (first received 13 August 2019).

Additional references

Babitt 2012

Babitt JL, Lin HY. Mechanisms of anemia in CKD. *Journal of the American Society of Nephrology* 2012;**23**(10):1631-4. [MEDLINE: 22935483]

Bernhardt 2010

Bernhardt WM, Wiesener MS, Scigalla P, Chou J, Schmeider RE, Günzler V, et al. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *Journal of the American Society of Nephrology* 2010;**21**(12):2151-6. [MEDLINE: 21115615]

El-Achkar 2005

El-Achkar TM, Ohmit SE, McCullogh PA, Crook ED, Brown WW, Grimm R, et al. Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: The Kidney Early Evaluation Program. *Kidney International* 2005;**67**(4):1483-8. [MEDLINE: 15780101]

FDA Briefing Document 2021

US Food & Drug Administration. Cardiovascular and Renal Drugs Advisory Committee Meeting July 15, 2021 Roxadustat. www.fda.gov/media/150728/download (accessed 10 May 2022).

Gansevoort 2013

Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**(9889):339-52. [MEDLINE: 23727170]

GBD Kidney Disease 2017

GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;**395**(10225):709-33. [MEDLINE: 32061315]

Global Burden of Disease 2017

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017 [Erratum in: Lancet. 2019 Jun 22;393(10190):e44]. *Lancet* 2018;**392**(10159):1789-858. [MEDLINE: 30496104]

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

GRADE 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [MEDLINE: 21195583]

Haase 2021

Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. *Kidney Int Suppl (2011)* 2021;**11**(1):8-25. doi: 10.1016/j.kisu.2020.12.002.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2020

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

KDIGO Clinical Practice Guideline Anemia 2012

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney International Supplements* 2012;**2**(4):279-335. [https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf]

KDIGO Clinical Practice Guideline CKD 2012

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements* 2013;**3**(1):1-150. [https://kdigo.org/guidelines/ckd-evaluation-and-management/]

LaGory 2016

LaGory EL, Giaccia AJ. The ever expanding role of HIF in tumour and stromal biology. *Nature Cell Biology* 2016;**18**(4):356-65. [MEDLINE: 27027486]

Li 2020

Li ZL, Tu Y, Liu BC. Treatment of renal anemia with roxadustat: advantages and achievement. *Kidney Diseases* 2020;**6**(2):65–73. [MEDLINE: 32309288]

Liu 2012

Liu Q, Davidoff O, Niss K, Haase VH. Hypoxia-inducible factor regulates hepcidin via erythropoietin-induced erythropoiesis. *Journal of Clinical Investigation* 2012;**122**(12):4635–44. [MEDLINE: 23114598]

Ma 1999

Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. *Journal of the American Society of Nephrology* 1999;**10**(3):610-9. [MEDLINE: 10073612]

Mathias 2020

Mathias SD, Blum SI, Sikirica V, Johansen KL, Colwell HH, Okoro T. Symptoms and impacts in anemia of chronic kidney disease. *Journal of Patient-Reported Outcomes* 2020;**4**(1):64. [MEDLINE: 32728779]

Nemeth 2009

Nemeth E, Ganz T. The role of hepcidin in iron metabolism. *Acta Haematologica* 2009;**122**(2-3):78–86. [MEDLINE: 19907144]

Phrommuntikul 2007

Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet* 2007;**369**(9559):381-8. [MEDLINE: 17276778]

Provenzano 2016c

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. *Clinical Journal of The American Society of Nephrology: CJASN* 2016;**11**(6):982-91. [MEDLINE: 27094610]

Renassia 2019

Renassia C, Peyssonnaux P. New insights into the links between hypoxia and iron homeostasis. *Current Opinion in Hematology* 2019;**26**(3):125-30. [MEDLINE: 30855332]

Schunemann 2020a

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. www.training.cochrane.org/handbook.

Schunemann 2020b

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Schwartz 2019

Schwartz AJ, Das NK, Ramakrishnan SK, Jain C Jurkovic MT, Wu J, et al. Hepatic hepcidin/intestinal HIF-2α axis maintains iron absorption during iron deficiency and overload. *Journal of Clinical Investigation* 2019;**129**(1):336-48. [MEDLINE: 30352047]

Semenza 2011

Semenza GL. Oxygen sensing, homeostasis, and disease [Erratum in: N Engl J Med. 2011 Sep 8;365(10):968]. *New England Journal of Medicine* 2011;**365**(6):537-47. [MEDLINE: 21830968]

SONG 2017

SONG Initiative. The SONG Handbook Version 1.0. www.songinitiative.org/reports-and-publications/ 2017.

van Haalen 2020

van Haalen H, Jackson J, Spinowitz B, Milligan G, Moon R. Impact of chronic kidney disease and anemia on health-related quality of life and work productivity: analysis of multinational real-world data. *BMC Nephrology* 2020;**21**(1):88. [MEDLINE: 32143582]

Wang 2020

Wang B, Yin Q, Han YC, Wu M, Li ZL, Tu Y, et al. Effect of hypoxia-inducible factor-prolyl hydroxylase inhibitors on anemia in patients with CKD: a meta-analysis of randomized controlled trials including 2804 patients. *Renal Failure* 2020;**42**(1):912-25. [MEDLINE: 32869703]

Wyld 2019

Wyld ML, Morton RL, Calyton P, Wong MG, Jardine M, Polkinghorne K, et al. The impact of progressive chronic kidney disease on health-related quality of life: A 12-year community cohort study. *Quality of Life Research* 2019;**28**(8):2081-90. [MEDLINE: 30937731]

Zhong 2018

Zhong H, Zhou T, Li H, Zhong Z. The role of hypoxia-inducible factor stabilizers in the treatment of anemia in patients with chronic kidney disease. *Drug Design, Development & Therapy* 2018;**12**:3003-11. [MEDLINE: 30271115]

References to other published versions of this review

Natale 2020

Natale P, Palmer SC, Tong A, Ruospo M, Hodson EM, Cooper TE, et al. Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No: CD013751. [DOI: 10.1002/14651858.CD013751]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akizawa 2017

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: November 2013 to August 2014 • Duration of follow-up: 8 weeks (treatment phase 4 weeks + 4 weeks follow-up)
Participants	**General information** • Setting: multicentre (21 sites) • Country: Japan • Inclusion criteria: CKD with an eGFR ≤ 89 mL/min/1.73 m^2 not requiring dialysis for 3 months since study completion; mean of two Hb values at screening and Hb test (at least 1 week apart from the screening test) < 10.0 g/dL, with a difference of ≤ 1.0 g/dL between the two values; TSAT ≥ 5% and ferritin ≥ 30 ng/mL at screening; serum folate ≥ 4.0 ng/mL; vitamin B12 ≥ 180 pg/mL at screening • Exclusion criteria: proliferative retinopathy, age-related macular degeneration, retinal vein occlusion and/or macular oedema that is considered to require treatment; Immunological disease with severe inflammation as assessed by the Investigator; even if the inflammation is in remission (e.g. SLE, rheumatoid arthritis, Sjogren's syndrome, coeliac disease); history of gastric/intestinal resection considered influential on the absorption of the drug in the GI tract or evidence of active gastroparesis; uncontrollable hypertension (more than one third DBP > 100 mm Hg within 16 weeks prior to screening); congestive HF (NYHA classification III or higher); history of hospitalisation for stroke, MI or lung infarction within 24 weeks before screening; positive for anti-HCV Ab, HBsAg or HIV; anaemia other than anaemia due to low/absent renal production of EPO (e.g. iron deficiency anaemia, haemolytic anaemia, pancytopenia); using ESA, anabolic androgenic steroid, testosterone enanthate or mepitiostane within 6 weeks before screening • Target Hb: increase of at least 0.5 g/dL, 1.0 g/dL, 1.5 g/dL, and 2.0 g/dL **Baseline characteristics** • CKD stage: HD • Number (randomised/analysed): treatment group 1 (19/19); treatment group 2 (20/20); treatment group 3 (19/19); treatment group 4 (20/20); control group (19/18) ○ ITT, while participants assessed in the safety population analysis were: treatment group 1 (19/19); treatment group 2 (20/20); treatment group 3 (19/19); treatment group 4 (20/20); control group (19/19) • Mean age ± SD (years): treatment group 1 (61.6 ± 8.49); treatment group 2 (58.9 ± 9.90); treatment group 3 (66.0 ± 9.23); treatment group 4 (62.2 ± 11.13); control group (63.4 ± 8.98) • Sex (M, %): treatment group 1 (8, 42%); treatment group 2 (12, 60%); treatment group 3 (7, 37%); treatment group 4 (11, 55%); control group (12, 63%) • Time on dialysis: not reported • eGFR: not reported **Comorbidities** • CV disease: not reported • Heart disease: not reported • Hypertension: not reported

Akizawa 2017 *(Continued)*

- Diabetes (number, %): treatment group 1 (9, 47%); treatment group 2 (5, 25%); treatment group 3 (2, 11%); treatment group 4 (9, 45%); control group (6, 19%)
- Prior agents used (number, %): all participants took ESA before randomisation
  - Oral iron: treatment group 1 (2, 11%); treatment group 2 (1, 5%); treatment group 3 (1, 5%); treatment group 4 (1, 5%); control group (0, 0%)
  - IV iron: treatment group 1 (1, 5%); treatment group 2 (4, 20%); treatment group 3 (7, 37%); treatment group 4 (2, 10%); control group (5, 26%)

Interventions	**Treatment group 1 (low-dose)*** • Daprodustat (GSK1278863) (oral): 4 mg once/day for 4 weeks **Treatment group 2 (medium-dose)** • Daprodustat (GSK1278863) (oral): 6 mg once/day for 4 weeks **Treatment group 3 (medium dose)** • Daprodustat (GSK1278863) (oral): 8 mg once/day for 4 weeks **Treatment group 4 (high-dose)** • Daprodustat (GSK1278863) (oral): 10 mg once/day for 4 weeks **Control group** • Placebo (oral): once/day **Co-interventions** • Subjects could be receiving stable maintenance oral or IV iron supplementation (IV iron ≤ 100 mg/week); however, changing the iron regimen during the study was not permitted *Note: If data were not available to report HIF considering the dose (low, medium and high dose), the analyses have been performed considering the average dose > dose assessed according to Meadowcroft 2019
Outcomes	**Primary outcome** • Hb CFB* at week 4 criteria. Hb levels were measured at screening, day 1, each week during the study, early withdrawal, and follow-up (week 8) **Secondary outcomes** • Hb response at week 4 • Percentage who achieved Hb response at week 4 • Number who reached pre-defined Hb stopping criteria up to week 4 • Maximum observed CFB EPO up to week 4 • Maximum observed percent CFB in peak VEGF up to week 4 • Percent CFB in hepcidin up to week 4 • CFB in ferritin at week 4 • CFB in TIBC, UIBC and iron at week 4 • CFB in transferrin at week 4 • Percent CFB in TSAT at week 4 • Plasma pharmacokinetic concentration of GSK1278863 and metabolites at week 4 • Adverse events and serious adverse events on therapy • Chemistry and haematology data of potential clinical importance up to week 4 • SBP and DBP of potential clinical importance up to week 4 • Heart rate of potential clinical importance up to week 4 • Abnormal ECG findings up to week 4

Akizawa 2017 *(Continued)*

*CFB was calculated by subtracting the baseline value from the post-dose value at week 4

Notes	• Funding: GlaxoSmithKline • Conflicts of interest: "Y.E., T.K., N.K., and K.H. are employees of GSK, and H.N., J.L., and A.C. are employees of GSK and are GSK shareholders. Y.I. is a former GSK employee. T.A., Y.T., and M.N. (all external physicians) received a consultant fee from GSK as medical advisors"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind." Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. In the treatment groups were reported side effects that participants and/or investigators could know to be specific for one of the interventions. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. Reporting of some outcomes (adverse effects) were unlikely to be biased because outcome assessors were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "A total of 97 subjects were randomized, of whom 86 (89%) subjects completed the study. Across treatment groups, the predominant reasons for premature withdrawal were reaching protocol-defined stopping criteria and AEs." ITT: treatment group 1 (19/19); treatment group 2 (20/20); treatment group 3 (19/19); treatment group 4 (20/20); control group (19/18) Safety population: treatment group 1 (19/19); treatment group 2 (20/20); treatment group 3 (19/19); treatment group 4 (20/20); control group (19/19)
Selective reporting (reporting bias)	High risk	All of the planned outcomes on ClincialTrials.gov were not measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

Akizawa 2019

Study characteristics

Methods	• Study design: 2 phase parallel RCT (two different randomisations were performed in phase 1 and phase 2) • Time frame: 17 September 2013 (date of first randomisation) to 1 December 2015 (date of last evaluation) • Duration of follow-up: 24 weeks (phase 1: 6 weeks, phase 2: only patients in the intervention group were re-randomised to once or 3 times/week of drug administration for the following 18 weeks)
Participants	**General information** • Setting: multicentre (32 sites) • Country: Japan • Inclusion criteria: CKD with eGFR (as calculated by the Japanese GFR estimation equation) of ≤ 89 mL/min/1.73 m^2, and not requiring dialysis for 3 months since study completion; mean of two Hb values at screening and Hb test (at least one week apart from the screening test) < 10.0 g/dL, with a difference of ≤ 1.0 g/dL between the two values; TSAT ≥ 5% and ferritin ≥ 30 ng/mL at screening; serum folate ≥ 4.0 ng/mL and vitamin B12 ≥ 180 pg/mL at screening • Exclusion criteria: proliferative retinopathy, age-related macular degeneration, retinal vein occlusion and/or macular oedema that is considered to require treatment; immunological disease with severe inflammation as assessed by the Investigator, even if the inflammation is in remission, the subject is excluded (e.g. SLE, rheumatoid arthritis, Sjogren's syndrome, coeliac disease); history of gastric/intestinal resection considered influential on the absorption of the drug in the GI tract or evidence of active gastroparesis; uncontrollable hypertension (more than one third DBP > 100 mm Hg within 16 weeks prior to screening test including); congestive HF (NYHA classification III or higher); history of hospitalisation for stroke, MI or lung infarction within 24 weeks before screening; positive for any of the following: anti-HCV Ab; HBsAg; or HIV; anaemia other than anaemia due to low/absent renal production of EPO (e.g. iron deficiency anaemia, haemolytic anaemia, pancytopenia); using ESA, anabolic androgenic steroid, testosterone enanthate or mepitiostane within 6 weeks before screening • Target Hb: 10 to 12 g/dL **Baseline characteristics** • CKD stage: non-dialysis-dependent CKD • Number (randomised/analysed): treatment group 1 (27/27); treatment group 2 (26/26); treatment group 3 (27/27); control group (27/27) • Mean age ± SD (years): treatment group 1 (67.3 ± 7.7); treatment group 2 (60.8 ± 8.8); treatment group 3 (65.0 ± 8.5); control group (61.9 ± 10.6) • Sex (M, %): treatment group 1 (14, 51.9%); treatment group 2 (14, 53.8%); treatment group 3 (11, 40.7%); control group (11, 40.7%) • Time on dialysis: not applicable • eGFR (mL/min/1.73 m^2): treatment group 1 (15.8 ± 6.3); treatment group 2 (17.3 ± 9.5); treatment group 3 (15.9 ± 7.5); control group (16.3 ± 8.5) **Comorbidities** • CV disease: not reported • Heart disease: not reported • Hypertension: not reported • Diabetes (number, %): not reported • Prior agents used (number, %): not reported
Interventions	**Treatment group 1** • Roxadustat (ASP1517): 50 mg 3 times/week for 6 weeks. After 6 weeks were re-randomised to once/week or 3 times/week dosing ○ Quote: "The 24-week study consisted of two treatment periods. The ‘‘fixed-dose period’’ was a 6-week period during which patients were equally randomized 1:1:1:1 (i.e., first randomisation) to

Akizawa 2019 *(Continued)*

receive placebo or roxadustat (50, 70, or 100 mg) three times weekly. The subsequent ''titration period'' was an 18-week period during which dose was adjusted to maintain Hb at 10–12 g/dL, taking into consideration the current Hb level and change in Hb over the previous 4 weeks. Patients who met pre-defined criteria during the titration period (Hb between 11 and 12.5 g/dL and an increase of C 1 g/dL from baseline) were equally re-randomized 1:1 (i.e., second randomisation) to continue three times weekly treatment or switch to once weekly dosing as maintenance treatment"

Treatment group 2

- Roxadustat (ASP1517): 70 mg 3 times/week for 6 weeks. After 6 weeks were re-randomised to once/week or 3 times/week dosing
  - Quote: "The 24-week study consisted of two treatment periods. The ''fixed-dose period'' was a 6-week period during which patients were equally randomised 1:1:1:1 (i.e., first randomisation) to receive placebo or roxadustat (50, 70, or 100 mg) three times weekly. The subsequent ''titration period'' was an 18-week period during which dose was adjusted to maintain Hb at 10–12 g/dL, taking into consideration the current Hb level and change in Hb over the previous 4 weeks. Patients who met pre-defined criteria during the titration period (Hb between 11 and 12.5 g/dL and an increase of C 1 g/dL from baseline) were equally re-randomized 1:1 (i.e., second randomisation) to continue three times weekly treatment or switch to once weekly dosing as maintenance treatment"

Treatment group 3

- Roxadustat (ASP1517): 100 mg 3 times/week for 6 weeks. After 6 weeks were re-randomised to once/week or 3 times/week dosing
  - Quote: "The 24-week study consisted of two treatment periods. The ''fixed-dose period'' was a 6-week period during which patients were equally randomized 1:1:1:1 (i.e., first randomisation) to receive placebo or roxadustat (50, 70, or 100 mg) three times weekly. The subsequent ''titration period'' was an 18-week period during which dose was adjusted to maintain Hb at 10–12 g/dL, taking into consideration the current Hb level and change in Hb over the previous 4 weeks. Patients who met pre-defined criteria during the titration period (Hb between 11 and 12.5 g/dL and an increase of C 1 g/dL from baseline) were equally re-randomized 1:1 (i.e., second randomisation) to continue three times weekly treatment or switch to once weekly dosing as maintenance treatment"

Control group

- Placebo for 24 weeks
  - Quote: "In order to maintain blinding, dose adjustment and the second randomisation by the web registration system were performed in the placebo arm, but in actuality did not occur"

Co-interventions

- Concomitant use of oral iron was allowed
- IV iron was permitted only if TSAT was < 5% and serum ferritin was < 30 ng/mL

Outcomes

Primary outcome

- Rate of rise in Hb (g/dL/week) at week 6

Secondary outcomes

- Percentage of cumulative number of responder patients at 28 weeks after dosing
- Percentage of visits at which patients maintain Hb between 10.0 to 12.0 g/dL after achieving Hb ≥ 10.0 g/dL for each patient at 28 weeks after dosing
- Percentage of patients who maintain Hb between 10.0 to 12.0 g/dL at each visit (weeks 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 28)
- Change from baseline in Hb at weeks 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 28)
- Safety assessed as the incidence of adverse events (including death), vital signs, 12-lead ECGs and lab-tests at 28 weeks after dosing
- Initiation of dialysis during the study period

Notes

- Funding: Astellas Pharma Inc

Akizawa 2019 *(Continued)*

- Conflicts of interest: "Tadao Akizawa reports personal fees from Astellas during the conduct of the study, and personal fees from Kyowa Hakko Kirin, AbbVie Inc., JT Pharmaceuticals Corporate, Kissei Pharmaceutical, Nipro Medical, Ono Pharmaceutical, Bayer HealthCare, Chugai Pharmaceutical, Torii Pharmaceutical, Fuso Pharmaceutical, Teijin Pharma, and GlaxoSmithKline outside the submitted work. Michael Reusch is employed with Astellas Pharma Europe B.V. Tetsuro Otsuka is employed with Astellas Pharma Inc. Toshihiro Misumi was employed with Astellas Pharma Inc. during the conduct of the study. Manabu Iwasaki has nothing to disclose"
- Note: this study reported two phases
  - Phase 1: randomised to oral placebo or roxadustat (50, 70, or 100 mg) 3 times/week for 6 weeks
  - Phase 2: only in the roxadustat group patients achieving Hb between 11 to 12.5 g/dL and increased of at least 1 g/dL from baseline were re-randomised to 3 times/week or once/week dosing for 18 weeks. In this review we assessed only the second phase because it was longer that 8 weeks. No changes were reported for the placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Dynamic allocation was conducted using a biased-coin minimisation approach with the following factors for the first randomisation: study site, average Hb level at screening assessment and screening period, estimated glomerular filtration rate (eGFR) at screening assessment. For the second randomisation, the allocation factors were study site, roxadustat dose immediately before the second randomisation, and Hb."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A double-blind procedure for participants, care providers, and those assessing outcomes ensured that oral roxadustat and placebo capsules were indistinguishable in appearance and all treatments were coded."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "TEAEs were coded using the Medical Dictionary for Regulatory Activities version 15.1 terminology." Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. Reporting of some outcomes (adverse effects) were unlikely to be biased because outcome assessors were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "A total of 83 (77.6%) patients completed the 24-week study. The overall discontinuation rate was 40.7% for the placebo TIW group and 16.3% for the roxadustat TIW pooled group (50 mg, n = 9 [33.3%]; 70 mg, n = 0; 100 mg, n = 4 [14.8%]). Patients discontinued as a result of a TEAE (n = 7, 8.8% roxadustat TIW pooled; n = 2, 7.4% placebo TIW), progressive disease (n = 4, 5.0% roxadustat TIW pooled), Hb level\8 g/dL (n = 5, 18.5% placebo TIW), lack of efficacy (n = 4, 14.8% placebo TIW), withdrawal by patient (n = 1, 1.3% roxadustat TIW pooled), or other reason (n = 1, 1.3% roxadustat TIW pooled)." Lost to follow-up: > 5% with differences between groups
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups

Akizawa 2019 *(Continued)*

	Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

Akizawa 2020a

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: November 2016 to March 2018 • Duration of follow-up: 24 weeks
Participants	**General information** • Setting: multicentre (58 sites) • Country: Japan • Inclusion criteria: ≥ 20 years; diagnosed with CKD, had been receiving stable chronic maintenance HD 3 times/week for more than 12 weeks before the prescreening assessments, and were scheduled to undergo HD 3 times/week during the study period; patients with renal anaemia who had been receiving IV treatment of rHuEPO (twice/week or 3 times/week) or darbepoetin alfa within the doses approved in Japan for more than 8 weeks before the prescreening assessments; mean of 2 most recent Hb levels just before registration (before dialysis after the longest dialysis interval) during the screening period had to be 10.0 to 12.0 g/dL (2 Hb levels had to be measured with at least a week interval); TSAT ≥ 20% or serum ferritin of ≥ 100 ng/mL during the screening period; receiving HD via AVF or graft or subcutaneously fixed superficial artery ◦ Female patients (non-childbearing potential female patients) ■ Post-menopausal (defined as at least 1 year without any menses) prior to the prescreening assessments ■ Documented surgically sterile ◦ Childbearing potential female patients ■ Agreed not to try to become pregnant during the study after informed consent acquisition and for 28 days after the final study drug administration, ■ Negative pregnancy test at the prescreening assessments, ■ If heterosexually active, agreed to consistently use two forms of highly effective birth control (at least one of which had to be a barrier method) starting at screening and throughout the study period and for 28 days after the final study drug administration ■ Agree not to breast feed starting at screening and throughout the study period, and for 28 days after the final study drug administration ■ Not to donate ova starting at screening and throughout the study period, and for 28 days after the final study drug administration ◦ Male patients and their female spouse/partners who were of childbearing potential had to be using 2 forms of highly effective birth control (at least one of which had to be a barrier method) starting at screening and continue throughout the study period, and for 12 weeks after the final study drug administration ◦ Male patients not to donate sperm starting at screening and throughout the study period, and for 12 weeks after the final study drug administration • Exclusion criteria: any untreated retinal neovascular lesion; untreated macular oedema; uncontrolled hypertension; anaemia that was not CKD-related; concurrent autoimmune disease with inflammation that could have affected erythropoiesis; elevated AST, ALT, or total bilirubin • Target Hb: 10 to 12 g/dL **Baseline characteristics** • CKD stage: HD • Number (randomised/analysed): treatment group (151/150); control group (152/151)

Akizawa 2020a *(Continued)*

- Patients analysed in the intervention group: SAS (150); FAS (150); PPS (114)
- Patients analysed in the control group: SAF (152); FAS (151); PPS (131)

- Mean age ± SD (years): treatment group (64.6 ± 11.7); control group (64.9 ± 10.1)
- Sex (M, %): treatment group (101, 67.3%); control group (107, 70.9%)
- Time on dialysis (months): treatment group (92.77 ± 89.78); control group (99.66 ± 101.63)
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: treatment group (141, 93.4%); control group (138, 92%)
- Diabetes(number, %): treatment group (54, 36%); control group (54, 35.8%)
- Prior agents used(number, %): all participants took ESA before randomisation (both rHuEPO and darbepoetin)

Interventions	**Treatment group (high dose)***

- Roxadustat (ASP1517): 3 times/week, initial dose 70 mg and 100 mg
- Titration doses to maintain Hb between 10 to 12 g/dL
  - Roxadustat dose was not to exceed 3 mg/kg or 300 mg

Control group

- Darbepoetin alfa: once/week injections, initial dose 10 to 60 µg, titration doses to maintain Hb between 10 to 12 g/dL

Co-interventions

- The use of statins was allowed with the recommendation that doses not exceed the proposed maximum doses
- Phosphate binders were to be dosed at least 1 hour before or after roxadustat
- Based on Japanese treatment guidelines, concomitant IV iron was allowed in both arms at the discretion of the investigator only to maintain TSAT at least 20% and/or serum ferritin at least 100 ng/mL when TSAT was at least 20% or serum ferritin was lower 100 ng/mL
- Oral iron was allowed based on individual patient needs

*Note: dose assessed according to NCT01888445

Outcomes	**Primary outcome**

- Change from baseline of average Hb to weeks 18 to 24

Secondary outcomes

- Average Hb levels at weeks 18 to 24
- Maintenance rate of the target Hb level (proportion of patients who achieved the average Hb level of 10.0 to 12.0 g/dL for weeks 18 to 24)
- Proportion of patients who achieved the target Hb level (10.0 to 12.0 g/dL) at each week
- Change of Hb levels from week 0 to each week
- Proportion of measurement points that met the target Hb level (10.0 to 12.0 g/dL) from weeks 18 to 24
- Rate of rise in Hb levels (g/dL/week) from week 0 to at the earliest date of week 4, time of discontinuation, or time of dose adjustment
- HCT, reticulocytes, iron, ferritin, transferrin, total iron binding capacity, soluble transferrin receptor, TSAT, reticulocytes Hb content
- QoL survey (SF-36, EQ-5D-5L, and FACT-An)
- Number of hospitalisations and duration of hospitalisation
- Vital signs, and 12-lead ECG were assessed during the study period
- Hepcidin assessed during the study period

Akizawa 2020a *(Continued)*

- Plasma concentration of unchanged form of ASP1517 (ASP1517 arm only) assessed during the study period
- Adverse events assessed during the study period
- Ophthalmological examination (funduscopic photograph, optical coherence tomography, visual acuity) assessed during the study period

Notes	• Funding: Astellas Pharma, Inc. • Conflicts of interest: "Dr. Akizawa reports personal fees from Astellas, Bayer Yakuhin LD., GlaxoSmithKline, JT Pharmaceuticals, Kissei Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, and Chugai Pharmaceutical Co. Ltd during the conduct of the study and reports personal fees from Ono Pharmaceutical Co. Ltd., Fuso Pharmaceutical Industries, Ltd., Nipro Corporation, and Torii Pharmaceutical Co. Ltd. outside of the submitted work. Dr. Iwasaki has nothing to disclose. Dr. Yamaguchi and Dr. Majikawa are employees of Astellas Pharma Inc. Dr. Reusch is an employee of Astellas Pharma Europe B.V. and reports other from Astellas Pharma Europe B.V., outside the submitted work. Dr. Iwasaki has nothing to disclose"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Assignment was implemented by a web-based randomisation system."
Allocation concealment (selection bias)	Low risk	Quote: "Assignment was implemented by a web-based randomisation system."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blind." Quote: "To maintain blinding, a double-dummy design was used; only the drug assignment manager and designated staff had access to the randomisation code."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. Reporting of some outcomes (adverse effects) were unlikely to be biased because outcome assessors were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "303 were randomized to receive either roxadustat (n=151) or DA (n=152). A total of 250 (82.5%) patients (roxadustat, n=119 [78.8%]; DA, n=131 [86.2%]) completed the study and 53 (17.5%) patients (roxadustat, n=32 [21.2%]; DA, n=21 [13.8%]) discontinued. Across all randomised patients, the leading reasons for discontinuation were adverse events (roxadustat, n=12 [7.9%]; DA, n=8 [5.3%]), protocol deviations (roxadustat, n=7 [4.6%]; DA, n=4 [2.6%]), and withdrawal by the patient (roxadustat, n=5 [3.3%]; DA, n=4 [2.6%])." Patients analysed in the intervention group were: SAF (150), FAS (150), PPS (114); patients analysed in the control group were: SAF (1520, FAS (151), PPS (131)
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups

Akizawa 2020a *(Continued)*

	Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

Akizawa 2020c

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: November 2016 to July 2018 • Duration of follow-up: 52 weeks treatment phase + 2 weeks follow-up

Participants	**General information**
	• Setting: multicentre (50 sites)
	• Country: Japan
	• Inclusion criteria: ≥ 20 years; HD or HDF 3 times/week for at least 12 weeks prior to screening; use of one and the same ESA for 10 weeks prior to screening (darbepoetin alfa 10 to 60 µg/week, epoetin (including biosimilars) ≤ 9000 IU/week, or EBP ≤ 250 µg/4 weeks); Hb ≥ 9.5 g/dL and ≤ 12.5 g/dL; ferritin > 100 ng/mL or TSAT > 20%; informed consent; females or males
	  ○ Females of non-childbearing potential
	  ■ Pre-menopausal with at least one of the following and no plans to utilise assisted reproductive techniques (e.g. in vitro fertilisation or donor embryo transfer): history of bilateral tubal ligation or salpingectomy; history of hysteroscopic tubal occlusion and postoperatively documented bilateral tubal obstruction; history of hysterectomy; history of bilateral oophorectomy
	  ■ Postmenopausal: ≥ 60 years or < 60 years with 12 months of spontaneous amenorrhoea
	  ■ Females on HRT whose menopausal status is in doubt will be required to use one of the most effective contraception methods if they wish to continue their HRT during the study. Otherwise they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment
	  ○ Females of childbearing potential must agree to comply with one of the contraception methods listed as requirements in "GlaxoSmithKline (GSK) Listing of Most Effective Contraceptive Methods for Females of Childbearing Potential from 28 days prior to the first dose of study medication until the completion of the follow-up visit
	• Exclusion criteria: planned living-related kidney transplant during the study; history of bone-marrow hypoplasia or PRCA; other causes of anaemia (pernicious anaemia, thalassaemia, sickle cell anaemia, or myelodysplastic syndromes); GI bleeding; MI, acute coronary syndrome, stroke, or TIA (diagnosed within 10 weeks prior to screening or during a period from screening to day 1); HF: NYHA class IV HF; corrected QT (QTc) interval; liver disease (ALT > 2 times ULN; bilirubin > 1.5 times ULN); current unstable active liver or biliary disease (onset of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal/gastric varices, persistent jaundice, or cirrhosis); history of malignancy within 2 years prior to screening, currently receiving treatment for cancer, or complex kidney cyst > 3 cm; concomitant medication and other study treatment-related criteria; planned use of IV iron during the screening phase or during a period from day 1 to week 4); history of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product; use or planned use of any prescription or non-prescription drugs or dietary supplements that are prohibited during the study period (strong inducers and inhibitor of cytochrome P450); use of an investigational agent within 30 days or 5 half-lives of the investigational agent (whichever is longer); any prior treatment with daprodustat for a treatment duration of > 30 days; clinical or laboratory abnormality, or examination finding that the investigator (or sub investigator) considers would put the subject at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study
	• Target Hb: 10.0 to 12.0 g/dL
	
	Baseline characteristics

Akizawa 2020c *(Continued)*

- CKD stage: HD
- Number (randomised/analysed): treatment group (136/133); control group (135/134)
  - 271 participants were included in the safety evaluation and 267 in ITT
- Mean age ± SD (years): treatment group (64 ± 10); control group (64 ± 11)
- Sex (M, %): treatment group (91, 67%); control group (89, 66%)
- Time on dialysis (years): treatment group (7.9 ± 6.9); control group (7.9 ± 7.1)
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: treatment group (127, 93%); control group (125, 93%)
- Diabetes (number, %): treatment group (56, 41%); control group (52, 39%)
- Prior agents used (number, %): all participants took ESA before randomisation

Interventions

Treatment group (low dose)*

- Daprodustat (oral): 4 mg once/day
  - Median (25th percentile, 75th percentile) daprodustat doses during weeks 40 to 52 were 4.0 (2.7 to 6.0) mg, 6.0 (4.0 to 8.7) mg, and 6.0 (4.0 to 8.0) mg for the tertile 1, 2, and 3 ERI subgroups, respectively
  - Dose was adjusted every 4 weeks to achieve and/or maintain Hb within the target range (10.0 to 12.0 g/dL)
- Darbepoetin alfa-matching placebo: once/week

Control group

- Darbepoetin alfa (IV): 10 to 60 mg once/week
  - Dose was adjusted every 2 weeks
- Oral daprodustat-matching placebo: once/day

Co-interventions

- Gemfibrozil and rifampin were excluded medications from screening to 7 days after treatment completion
- In both groups, IV iron or dose change for oral iron were not allowed from screening to week 4. From week 4 onward, supplemental iron therapy including IV and oral could be administered if ferritin ≤ 100 ng/mL and TSAT ≤ 20%

*Note: dose assessed according to Meadowcroft 2019

Outcomes

Primary outcome

- Mean Hb during the primary efficacy evaluation period (weeks 40 to 52)

Secondary outcomes

- Percentage with mean Hb in the target range during the primary efficacy evaluation period (weeks 40 to 52)
- Hb change from baseline at week 4
- Percentage who had Hb change from baseline at week 4
- Distribution of daprodustat dose level by visit (day 1, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48)
- Distribution of darbepoetin alfa dose level by visit (day 1, weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50)
- Duration of treatment interruption due to Hb > 13 g/dL (up to week 52)
- Number of dose adjustments for daprodustat (up to week 52)
- Hb at each assessment visit (day 1, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52)

Akizawa 2020c *(Continued)*

- Change from baseline in Hb at each assessment visit (day 1, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52)
- Percentage of who had Hb within the target range at each assessment visit (day 1, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52)
- Percentage of time in Hb target range during the primary efficacy evaluation period (weeks 40 to 52)
- Number who had Hb < 7.5 g/dL (up to week 52)
- Number who had Hb increase > 2 g/dL over any 4 weeks (up to week 52)
- Number who had Hb > 13.0 g/dL (Up to week 52)
- Number of episodes with Hb > 13.0 g/dL (up to week 52)
- AUC of plasma daprodustat (0, 1, 2, 3, and 4 hours post-dose at weeks 12 and 24)
- Cmax of plasma daprodustat (0, 1, 2, 3, and 4 hours post-dose at weeks 12 and 24)
- Adverse events and serious adverse events during the study period
- Vital signs during the study period
- Comprehensive ophthalmologic exams (best corrected visual acuity, intraocular pressure, anterior segment examination, and funduscopic examination) were conducted at baseline, week 12, and week 48

Notes

- Funding: GlaxoSmithKline
- Conflicts of interest: "T. Akizawa is a consultant for Astellas Pharma, Bayer Yakuhin, GlaxoSmithKline, Japan Tobacco, Kyowa Kirin, Nipro Corporation, Otsuka Pharmaceuticals, Sanwa Chemical, and Torii Pharmaceutical. Lecture fees were received from Bayer Yakuhin, Chugai Pharmaceutical, Fuso Pharmaceutical Industries, Kissei Pharmaceutical, Kyowa Kirin, Ono Pharmaceutical, and Torii Pharmaceutical. M. Nangaku has received grants and personal fees from Astellas Pharma, Chugai Pharmaceutical, Daiichi Sankyo, GlaxoSmithKline, Kyowa Kirin, Mitsubishi Tanabe Pharma, and Torii Pharmaceutical; grants from Bayer Yakuhin, Ono Pharmaceutical, and Takeda Pharmaceutical Company; and personal fees from AstraZeneca and JT Pharmaceuticals. T. Yonekawa, S. Kawamatsu, T. Onoue, and K. Hara are employees of GlaxoSmithKline. N. Okuda, Y. Endo, and A. Cobitz are employees of and hold equity"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Company-validated system." Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent. In addition, a validated system could be considered at low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "A biostatistician generated the randomisation codes using a company-validated system." Quote: "Interactive Web Response System."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind study." Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. However, since interventions were different, it was possible that investigators and/or participants were aware of treatment allocation. In the treatment groups were reported side effects that participants and/or investigators could know to be specific for one of the interventions. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. Reporting of some outcomes (adverse effects) were unlikely to be biased because outcome assessors were blinded to treatment assignment

Akizawa 2020c *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 332 participants screened, 271 participants were randomized (136 daprodustat, 135 darbepoetin alfa). A total of 115 participants (85%) in the daprodustat group and 120 (89%) in the darbepoetin alfa group completed the study. The most common reasons for study withdrawal in both treatment groups were AEs (ten daprodustat, eight darbepoetin alfa)." Quote: "All 271 participants were included in the safety population, 267 participants (133 daprodustat, 134 darbepoetin alfa) were included in the ITT population, and 245 participants (120 daprodustat, 125 darbepoetin alfa) were included in the modified ITT population." Lost to follow-up: < 5%
Selective reporting (reporting bias)	High risk	All of the planned outcomes on ClincialTrials.gov were not measured or reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

Akizawa 2020f

Study characteristics	
Methods	• Study design: phase 3, parallel RCT • Time frame: not reported • Duration of follow-up: 24 weeks; future analyses will be reported on 52 weeks
Participants	**General information** • Setting: not reported • Country: Japan • Inclusion criteria: adult, non-dialysis-dependent patients with anaemia receiving darbepoetin alpha, rHuEPO, or EBP for ≥ 8 weeks before prescreening • Exclusion criteria: not reported • Target Hb: not reported **Baseline characteristics** • CKD stage: CKD not on dialysis • Number (randomised/analysed): treatment group (131/not reported); control group (131/not reported) • Mean age ± SD (years): not reported • Sex (M, %): not reported • Time on dialysis (years): not reported • eGFR: not reported **Comorbidities** • CVdisease: not reported

Akizawa 2020f *(Continued)*

- Heart disease: not reported
- Hypertension: not reported
- Diabetes(number, %): not reported
- Prior agents used(number, %): all participants took darbepoetin alpha, rHuEPO, or EBP before randomisation

Interventions	**Treatment group** • Roxadustat **Control group** • Darbepoetin alfa **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Change of average Hb from baseline to weeks 18 to 24 **Secondary outcome** • Adverse events assessed during the study period
Notes	• Funding: not reported • Conflicts of interest: not reported • Abstract-only publications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported in sufficient detail to permit judgement
Selective reporting (reporting bias)	High risk	Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	Unclear risk	Baseline characteristics, or different non-randomised co-interventions were not reported between groups Funder and conflicts of interest were not reported

Akizawa 2021

Study characteristics

Methods	• Study design: phase 3, parallel RCT • Time frame: not reported • Duration of follow-up: 24 weeks

Participants	**General information**
	• Setting: multicentre
	• Country: Japan
	• Inclusion criteria: non-dialysis CKD not to require KRT during the study period; receiving ESA and whose Hb values are considered stable; mean of 2 most recent Hb values before randomisation must be ≥ 10.0 g/dL and ≤ 12.0 g/dL; TSAT ≥ 20% or serum ferritin ≥ 100 ng/mL
	  ○ Female subjects of non-childbearing potential
	  ■ Post-menopausal, or documented surgically sterile
	  ○ Female subjects of childbearing potential
	  ■ Agree not to try to become pregnant during the study and for 28 days after the final study drug administration And have a negative urine pregnancy test at pre-screening And, if heterosexually active, agree to consistently use two forms of highly effective birth control* (at least one of which must be a barrier method) starting at pre-screening and throughout the study period and continued for 28 days after the final study drug administration
	  ■ Must agree not to breast feed starting at pre-screening and throughout the study period, and continued for 28 days after the final study drug administration
	  ■ Female subject must not donate ova starting at pre-screening and throughout the study period, and continued for 28 days after the final study drug administration
	  ○ Male subjects and their female spouse/partners who are of childbearing potential must be using two forms of highly effective birth control (at least one of which must be a barrier method) starting at pre-screening and continue throughout the study period, and for 12 weeks after the final study drug administration
	  ○ Male subjects must not donate sperm starting at pre-screening and throughout the study period and, for 12 weeks after the final study drug administration
	• Exclusion criteria: concurrent retinal neovascular lesion untreated or macular oedema untreated, and any condition that significantly compromises the ability to visualize the retina; concurrent autoimmune disease with inflammation that could impact erythropoiesis; history of gastric/intestinal resection considered influential on the absorption of drugs in the GI tract (excluding resection of gastric or colon polyps) or concurrent gastro-paresis; uncontrolled hypertension; concurrent congestive HF (NYHA Class III or higher); history of hospitalisation for treatment of stroke, MI, or pulmonary embolism within 12 weeks before the pre-screening assessment; positive HBsAg or HCV Ab at the pre-screening assessment, or positive HIV in a past test; concurrent other form of anaemia than renal anaemia; history of PRCA; received treatment with protein anabolic hormone, testosterone enanthate, or mepitiostane within 6 weeks before the pre-screening assessment; AST, ALT, or total bilirubin > the criteria, or previous or concurrent another serious liver disease at pre-screening assessment; previous or current malignant tumour (no recurrence for at least 5 years is eligible); undergone red blood transfusion and/or a surgical procedure consider to promote anaemia and/or ophthalmological surgery within 4 weeks before the pre-screening assessment; undergone a kidney transplantation; history of serious drug allergy including anaphylactic shock; previous history of treatment with ASP1517 or participation in this study; participation in another clinical study or post-marketing clinical study (including that of a medical device) within 12 weeks before informed consent acquisition
	• Target Hb: 10 to 12 g/dL
	Baseline characteristics
	• CKD stage: non-dialysis CKD
	• Number (randomised/analysed): treatment group (132/131); control group (131/131)
	• Mean age ± SD (years): treatment group (68.9 ± 11.6); control group (70.9 ± 10.2)
	• Sex (M, %): treatment group (83, 63.4%); control group (75, 57.3%)

Akizawa 2021 *(Continued)*

- Time on dialysis: not applicable
- eGFR(mL/min/1.73 m^2): treatment group (17.9 ± 8.2); control group (18.2 ± 8.8)

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes: treatment group (68/131); control group (68/131)
- Prior agents used(number, %): not reported

Interventions	**Treatment group (high dose)***

- Roxadustat (ASP1517): 3 times/ week for 24 weeks; treated within the dose range of 20 to 200 mg, usually the doses were 70 to 100 mg
- Subjects converting from rHuEPO or darbepoetin alfa to ASP1517

Control group

- Darbepoetin alpha (SC): once every 2 weeks for 24 weeks
- Subjects converting from rHuEPO or darbepoetin alfa to darbepoetin alfa

Co-interventions

- Rescue therapy, such as RBC transfusions, were prohibited

*Note: dose assessed according to NCT01888445

Note: patients receiving rHuEPO or darbepoetin alfa before conversion were randomised to roxadustat or darbepoetin alpha (comparative arms). Patients who had used EBP before conversion were allocated to roxadustat (reference arm) - in this review we focused only on patients randomised reported in the comparative group

Outcomes	**Primary outcome**

- Change from baseline in average Hb (baseline and weeks 18 to 24)

Secondary outcomes

- Average Hb (week 18 to 24)
- Number who achieve target Hb level from week 18 to 24
- Proportion of Hb values within the target value in each post-dosing time point (up to end of treatment)
- Change from baseline in Hb to each post-dosing time point (up to end of treatment)
- Proportion of time points that achieve the target Hb level from weeks 18 to 24
- QoL assessed by SF-36, EQ-5D-5L, WPAI:ANS and FACT-An (up to end of treatment)
- Number with abnormal vital signs and/or adverse events related to treatment (up to end of treatment)
- Safety assessed by body weight, incidence of adverse events, and standard 12-lead ECG (up to end of treatment)
- Safety assessed by ophthalmological examination: fundoscopy optical coherence tomography, and visual acuity (up to week 24
- Number with abnormal laboratory values and/or adverse events related to treatment (up to end of treatment)
- Plasma concentration of unchanged ASP1517 (up to week 24)

Notes	

- Funding: Astellas Pharma Inc, FibroGen
- Conflicts of interest: "MR is an employee of Astellas Pharma Europe B.V. TA has received personal fees from Astellas, Bayer, Chugai, Fuso, GSK, JT Pharmaceuticals, KKC, Kissei, Nipro Corporation, Ono, Otsuka, Torii, and Sanwa Chemical Industrial Co., Ltd."

Akizawa 2021 *(Continued)*

- Note: the original study reported another treatment group that was assigned but not randomised - Roxadustat (ASP1517) for 52 weeks. This was out of the scope of our review and these data were not included here

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However, due to the difference in the interventions, blinding was unlikely
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "At the end of Week 24, 109 [82.6%] participants in the roxadustat [comparative] group, 121 [92.4%] in the DA [comparative] group, completed the 24-week treatment period." Loss to follow-up: > 5%
Selective reporting (reporting bias)	High risk	All of the planned outcomes on ClincialTrials.gov were not measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

ALPS 2021

Study characteristics

Methods	• Study design: parallel RCT • Time frame: September 2013 to November 2017 • Duration of follow-up: 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) and post-treatment follow-up period (4 weeks)
Participants	**General information** • Setting: multicentre (153 sites)

ALPS 2021 *(Continued)*

- Country: multinational (Belgium, Bulgaria, Belarus, Colombia, Dominican Republic, Estonia, Georgia, Greece, Guatemala, Hungary, Italy, Panama, Peru, Poland, Romania, Russian Federation, Serbia, South Africa, Spain, Turkey, Ukraine, UK)
- Inclusion criteria: ≥ 18 years; CKD (stage 3, 4 or 5); anaemic and not receiving dialysis (eGFR < 60 mL/min/1.73 m^2); ferritin ≥ 30 ng/mL; TSAT ≥ 5%; eGFR < 60 mL/min/1.73 m^2 (MDRD equation); serum folate ≥ LLN at screening; serum vitamin B12 ≥ LLN at screening; ALT, AST ≤ 3 times ULN; total bilirubin ≤ 1.5 times ULN; Body weight range 45.0 kg to 160.0 kg
- Exclusion criteria: received any ESA treatment within 12 weeks prior to randomisation; more than one dose of IV iron within 12 weeks prior to randomisation; RBC transfusion within 8 weeks prior to randomisation; known history of myelodysplastic syndrome or multiple myeloma; known hereditary hematologic disease such as thalassaemia or sickle cell anaemia, PRCA, or other known causes for anaemia other than CKD; known haemosiderosis, haemochromatosis, coagulation disorder, or hypercoagulable condition; chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; anticipated to have elective surgery that is expected to lead to significant blood loss or anticipated elective coronary revascularization; active or chronic GI bleeding; received any prior treatment with roxadustat or a HIF-PHI; treated with iron-chelating agents within 4 weeks prior to randomisation; history of chronic liver disease (e.g. cirrhosis or fibrosis of the liver); known NYHA class III or IV congestive HF; MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (e.g. pulmonary embolism) within 12 weeks prior to randomisation; uncontrolled hypertension or two or more SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg confirmed by repeat measurement within 2 weeks prior to randomisation; diagnosis or suspicion (e.g. complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma on renal ultrasound within 12 weeks prior to randomisation; history of malignancy (except cancers determined to be cured or in remission ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps); positive for HIV, HBsAg, or anti-HCV Ab'; active clinically significant infection manifested by WBC > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection within one week prior to randomisation; known untreated proliferative diabetic retinopathy, diabetic macular oedema, macular degeneration and retinal vein occlusion; any prior organ transplant (that has not been explanted) or a scheduled organ transplantation; participated in any interventional clinical study or has been treated with any investigational drugs within 30 days or 5 half-lives or limit set by national law, whichever is longer, prior to the initiation of screening; anticipated use of dapsone in any dose amount or chronic use of acetaminophen (paracetamol) > 2.0 g/day during the treatment or follow-up period of the study; history of alcohol or drug abuse within 2 years prior to randomisation
- Target Hb: ≥ 11.0 g/dL and Hb increase from baseline of ≥ 1.0 g/dL at 2 consecutive study visits separated by at least 5 days

Baseline characteristics

- CKD stage: stage 3, 4 or 5 CKD not on dialysis
- Number (randomised/baseline data/analysed): treatment group (394/391/389); control group (203/203/203)
- Mean age ± SD (years): treatment group (60.6 ± 13.5); control group (61.7 ± 13.8)
- Sex (M, %): treatment group (169, 43.2%); control group (99, 48.8%)
- Time on dialysis: not applicable
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Interventions	**Treatment group (medium dose)***

- Roxadustat
  - People ≥ 45 to ≤ 70 kg: 70 mg

ALPS 2021 *(Continued)*

- People > 70 to ≤ 160 kg: 100 mg
- The dose steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250 and 300 mg

Control group

- Placebo: red-coated, oval tablets for oral administration marked as 20, 50 and 100 mg

Co-interventions

- Not reported

*Note: dose assessed according to NCT01888445

Outcomes

Primary outcomes

- Percentage with Hb response to treatment at two consecutive visits during the first 24 weeks without rescue therapy prior to Hb response
- Hb change from baseline to the average Hb in weeks 28 to 52 regardless of rescue therapy

Secondary outcomes

- Hb change from baseline to the average Hb in weeks 28 to 36 without receiving rescue therapy within 6 weeks prior to and during 8-week evaluation period
- Change from baseline in LDL cholesterol (regardless of fasting status) to the average LDL cholesterol of weeks 12 to 28
- Time to first use of rescue therapy to week 104: composite of RBC transfusions, ESA use, and IV iron
- Change from baseline in SF-36 vitality sub-score to the average sub-score of weeks 12 to 28
- Change from baseline in SF-36 physical functioning sub-score to the average sub-score of weeks 12 to 28
- Change from baseline in MAP to the average MAP of weeks 20 to 28
- Time to first occurrence of hypertension
- Rate of progression of CKD: annualised eGFR (slope over time)
- Average Hb over weeks 28 to 36 without receiving rescue therapy within 6 weeks prior to and during 8-week evaluation period
- Average Hb over weeks 44 to 52 without receiving rescue therapy within 6 weeks prior to and during 8-week evaluation period
- Average Hb over weeks 96 to 104 without receiving rescue therapy within 6 weeks prior to and during 8-week evaluation period
- Time to achieve first Hb response without rescue therapy, as defined by primary endpoint to week 24
- Hb Change from baseline to each post-dosing time point (weeks 1, 2, 4,6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104)
- Hb Change from baseline to the average Hb of weeks 28 to 36 regardless of rescue therapy
- Hb Change from baseline to the average Hb of weeks 44 to 52 regardless of rescue therapy
- Hb Change from baseline to the average Hb of weeks 96 to 104 regardless of rescue therapy
- Percentage of Hb values within 10.0 to 12.0 g/dL in weeks 28 to 36 regardless of rescue therapy
- Percentage of Hb values within 10.0 to 12.0 g/dL in weeks 44 to 52 regardless of rescue therapy
- Percentage of Hb values within 10.0 to 12.0 g/dL in weeks 96 to 104 regardless of rescue therapy
- Time to first hospitalisation
- Number of days of hospitalisation/patient exposure year
- Time to first use of rescue therapy: composite of RBC transfusions, ESA use, and IV iron in the first 24 weeks of treatment
- Time to first use of RBC transfusions (to week 104)
- Mean monthly number of RBC packs (to week 104)
- Mean monthly volume of blood transfused (to week 104)
- Time to first use of ESA rescue therapy (to week 104)
- Time to first use of IV iron (to week 104)

ALPS 2021 *(Continued)*

- Change from baseline to each post-dosing visit in total cholesterol (weeks 4, 8, 12, 20, 28, 36, 44, 52, 68, 84, 104)
- Change from baseline to each post-dosing visit in LDL/HDL ratio (weeks 4, 8, 12, 20, 28, 36, 44, 52, 68, 84, 104)
- Change from baseline to each post-dosing visit in non-HDL cholesterol (weeks 4, 8, 12, 20, 28, 36, 44, 52, 68, 84, 104)
- Change from baseline to each post-dosing visit in ApoA1 (weeks 4, 8, 12, 20, 28, 36, 44, 52, 68, 84, 104)
- Change from baseline to each post-dosing visit in ApoB (weeks 4, 8, 12, 20, 28, 36, 44, 52, 68, 84, 104)
- Change from baseline to each post-dosing visit in ApoB/ApoA1 (weeks 4, 8, 12, 20, 28, 36, 44, 52, 68, 84, 104)
- Percentage with mean LDL cholesterol < 100 mg/dL calculated over weeks 12 to 28
- Percentage who achieved antihypertensive treatment goal in CKD participants over weeks 12 to 28
- Change from baseline to the average value of weeks 12 to 8 in QoL SF-36 physical component score
- Change from baseline to the average value of weeks 12 to 28 in anaemia subscale FACT score
- Change from baseline to the average value of weeks 12 to 28 in total FACT-An score
- Change from baseline to the average value of weeks 12 to 28 in the EQ-5D 5L VAS score
- Change from baseline to the average value of weeks 12 to 28 in WPAI anaemic symptoms
- Percentage of participants in each category in Patients' Global Impression of Change (weeks 12 to 28)
- Change from baseline to each study visit in serum hepcidin (weeks 4, 12, 20, 36, 52, 104)
- Change from baseline to each study visit in serum ferritin (weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 104)
- Change from baseline to each study visit in serum TSAT (weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 104)
- Change from baseline to each study visit in serum HbA1c (weeks 12, 28, 36, 44, 60, 84, 104)
- Change from baseline to each study visit in fasting blood glucose (weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 104)
- Change from baseline to each study visit in UACR (weeks 12, 24, 36, 52, 64, 76, 88,104)
- Change from baseline to each study visit in SCr (weeks 4, 8, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 104)
- Time to doubling of SCr or chronic dialysis or kidney transplant (to week 108)
- Time to CKD progression: composite of doubling SCr, chronic dialysis or kidney transplant, and death (to week 108)
- Time to at least 40% decrease in eGFR from baseline, chronic dialysis or kidney transplant (to week 108)
- Physical examination (end of treatment)
- 12-lead ECG (end of treatment)
- Vascular access thrombosis (end of treatment)

Notes

- Funding: Astellas Pharma Europe B.V, FibroGen
- Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Double-blind"

ALPS 2021 *(Continued)*

All outcomes		Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. Reporting of some outcomes (adverse effects) were unlikely to be biased because outcome assessors were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of 597 patients randomized into 1 of 2 treatment groups: 394 to the roxadustat group and 203 to the placebo group, 3 patients in the roxadustat treatment group were excluded due to GCP violations. Of 391 patients that received roxadustat, 114 discontinued during the first year and 146 discontinued up to 2 years with a total of 245 patients completing 2 years of treatment. Of the 203 patients that received placebo, 87 discontinued during the first year and 114 discontinued up to 2 years with a total of 89 patients completed 2 years of treatment." Quote: "Overall, 18.5% of patients discontinued study treatment with the reason given as “withdrawal by patient” (14.8% roxadustat, 25.6% placebo), 9.3% of patients overall were considered to have discontinued treatment due to the event of death (10.0% roxadustat, 7.9% placebo) and 5.1% withdrew due to AEs (5.4% roxadustat, 4.4% placebo). The incidence of treatment discontinuations with time was lower overall for patients in the roxadustat treatment group compared with the placebo treatment group." ITT analyses were not reported, some analyses were performed on 389/391 participants in the intervention group versus 203/203 in the placebo group (lost to follow-up > 5%, differences between groups)
Selective reporting (reporting bias)	High risk	All of the planned outcomes on ClincialTrials.gov were not measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were not reported

ANDES 2021

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: November 2012 to September 2018 • Duration of follow-up: minimum treatment duration may be less than 52 weeks, with a maximum treatment duration of up to 3 years + 4 weeks follow-up
Participants	**General information** • Setting: multicentre (163 sites)

ANDES 2021 *(Continued)*

- Country: international (USA, Argentina, Australia, Chile, Colombia, Hong Kong, Korea, Malaysia, New Zealand, Peru, Philippines, Puerto Rico, Singapore, Taiwan, Thailand)
- Inclusion criteria: CKD stage 3, 4, or 5 not receiving dialysis; Adults with eGFR < 60 mL/min/1.73 m^2; Hb ≤ 10.0 g/dL, ferritin ≥ 30 ng/mL, and TSAT ≥ 5%; anaemia qualified by measurements of Hb values during screening; additional blood work must be in a safe range for study entry; body weight 45 to 160 kg; willingness to use contraception if of child-bearing potential
- Exclusion criteria: treatment with an ESA within 12 weeks prior to study participation; more than one dose of IV iron within 12 weeks prior to study participation; blood transfusion within 8 weeks prior to study participation; active infection; chronic liver disease; severe congestive HF; recent heart attack, stroke, seizure, or blood clot; uncontrolled BP within 2 weeks prior to study participation; renal cell carcinoma; history of malignancy, including multiple myeloma or other myelodysplastic syndrome; chronic inflammatory disease that could impact RBC production; any prior organ transplant, or a scheduled organ transplantation; anticipated elective surgery that is expected to lead to significant blood loss, or anticipated elective heart procedure; GI bleeding; any prior treatment with FG-4592 or a HIF-PHI; recent use of an investigation drug or treatment, or participation in an investigation study; > 1 IV iron dose; RBC transfusion within 8 weeks of randomisation
- Target Hb
  - Baseline > 8.0 g/dL: ≥ 11 g/dL and an increase of ≥ 1.0 g/dL
  - Baseline ≤ 8.0 g/dL: ≥ 11 g/dL and an increase ≥ 2.0 g/dL

Baseline characteristics

- CKD stage: stage 3, 4, or 5 not receiving dialysis
- Number (randomised/analysed): treatment group (616/616); control group (306/306)
- Mean age ± SD (years): treatment group (64.9 ± 12.6); control group (64.8 ± 13.2)
- Sex (M, %): treatment group (241, 39.1%); control group (176, 42.5%)
- Time on dialysis: not applicable
- eGFR (mL/min/1.73 m^2): treatment group (21.9 ± 11.5); control group (22.4 ± 11.4)

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: treatment group (583, 94.6%); control group (292, 95.4%)
- Diabetes (number, %): treatment group (398, 64.6%); control group (200, 65.4%)
- Prior agents used (number, %): not reported

Interventions

Treatment group (medium dose)*

- FG-4592 (Roxadustat) (oral): weight-based starting doses of 70 mg or 100 mg, 3 times/week
  - Dose was titrated to achieve a Hb level ≥ 11 g/dL, followed by titration for maintenance
  - Patients weighing 45 to < 70 kg received 70 mg roxadustat or placebo, and those weighing ≥ 70 kg received 100 mg

Control group

- Placebo

Co-interventions

- Oral iron was encouraged

*Note: dose assessed according to NCT01888445

Outcomes

Primary outcome

- Efficacy of roxadustat in achieving Hb correction and maintenance (52 weeks)

Secondary outcomes

- Change in LDL cholesterol (28 weeks)

ANDES 2021 *(Continued)*

- Evaluate HRQoL benefits, as measured by SF-36 (28 weeks)
- Proportion who received rescue therapy (composite of RBC transfusion, ESA use, and IV iron) (52 weeks)
- Change in MAP and effect on reducing hypertension (52 weeks)
- Adverse events, serious adverse events, vital signs, ECG and physical exams (minimum of 52 weeks)
- Laboratory parameters (minimum of 52 weeks)
- Death occurred during the study

Notes

- Funding: FibroGen, Astellas Pharma Europe B.V., AstraZeneca
- Conflicts of interest: "DWC is a consultant for FibroGen, AstraZeneca, Vifor Pharma, GSK, Akebia, and FMC-RTG. SDR has received travel fees for investigator meetings and honoraria for serving on advisory boards for FibroGen, AstraZeneca, ZS Pharma, Vifor Pharma, and Amgen. TMC is an employee of the University of Hong Kong, and he has consulted for Novartis, Visterra, and UCB Biosciences. He has received research funding from Astellas Pharma and Baxter. AAC receives research funding from FibroGen. AB is consultant to FibroGen. WC, CB, ME, RL, TL, LS and K-HPY are employees of FibroGen, Inc. and hold stock and/or stock options in FibroGen, Inc. SGK, SKS, and MAM have no conflicts of interest to disclose"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization schedules were prospectively prepared, and automated randomisation and treatment assignments were provided by an interactive web response system."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization schedules were prospectively prepared, and automated randomisation and treatment assignments were provided by an interactive web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind study" Quote: "The investigator, study site staff, patient, sponsor, and designees were all blinded to the study drug assignment—but not the dose—which was achieved by using identical roxadustat and placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. Reporting of some outcomes (adverse effects) were unlikely to be biased because outcome assessors were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In the roxadustat group, 43.3% (267/616) of patients discontinued treatment, while 68.0% (208/306) of placebo-treated patients discontinued. This between-group difference in discontinuations was largely due to the lack of efficacy among patients in the placebo group. The primary reasons for discontinuations in the placebo group were withdrawal of consent and lack of efficacy. The primary reasons for discontinuations in the roxadustat group which occurred a lesser rates were adverse events or death and withdrawal of consent." All participants were included in the ITT analysis
Selective reporting (reporting bias)	High risk	All of the planned outcomes on ClincialTrials.gov were not measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported

ANDES 2021 *(Continued)*

Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Quote: "FibroGen employees and subcontractors had a role in study design, data collection, data analysis, data interpretation, and writing of the manuscript." Funder influenced data analysis and study reporting or interpretation Authors declared conflicts of interest

ASCEND-D 2021

Study characteristics

Methods	• Study design: phase 3, parallel RCT • Time frame: November 2016 to August 2018 • Duration of follow-up: 52 weeks + 6 weeks follow-up
Participants	**General information** • Setting: multicentre (431 sites) • Country: international (USA, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, India, Italy, Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, Russian Federation, Singapore, South Africa, Spain, Sweden, Taiwan, Turkey, Ukraine, UK) • Inclusion criteria: Aged 18 to 99 years; use of any approved ESA for at least the 6 weeks prior to screening and between screening and randomisation; Hb 8 to 11 g/dL and receiving at least the minimum ESA dose; on dialysis > 90 days prior to screening and continuing on the same mode of dialysis from screening (week 8) through to randomisation (day 1) (HD ≥ 2 times/week and PD ≥ 5 times/week, home HD ≥ 2 times/week); ≥ 80% and ≤ 120% compliance with placebo during run-in period; informed consent (screening only); capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol • Exclusion criteria: planned living-related or living-unrelated kidney transplant within 52 weeks after study start (day 1); ferritin ≤100 ng/mL (≤100 µg/L at screening); TSAT ≤ 20% at screening; history of bone marrow aplasia or PRCA; untreated pernicious anaemia, thalassaemia major, sickle cell disease or myelodysplastic syndrome; evidence of actively bleeding gastric, duodenal, or oesophageal ulcer disease or clinically significant GI bleeding ≤ 4 weeks prior to screening through to randomisation (day 1); MI or acute coronary syndrome ≤ 4 weeks prior to screening through to randomisation (day 1); stroke or TIA ≤ 4 weeks prior to screening through to randomisation (day 1); chronic NYHA Class IV HF; current uncontrolled hypertension as determined by the investigator that would contraindicate the use of rHuEPO; QTcB (day 1) >500 msec, or QTcB > 530 msec in subjects with bundle branch block; ALT >2 times ULN at screening; bilirubin > 1.5 times ULN at screening; current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis; history of malignancy within the 2 years prior to screening through to randomisation (day 1) or currently receiving treatment for cancer, or complex kidney cyst; history of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product, or epoetin alfa or darbepoetin alfa; use of strong inhibitors of CYP2C8 (e.g. gemfibrozil) or strong inducers of CYP2C8 (e.g. rifampin/rifampicin); use of other investigational agent or device prior to screening through to randomisation (day 1); any prior treatment with daprodustat for treatment duration of > 30 days, subject is pregnant, breastfeeding, or subject is of reproductive potential and does not agree to follow one of the contraceptive options listed in the List of Highly Effective Methods for Avoiding Pregnancy; any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (e.g. intolerance to rHuEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study

ASCEND-D 2021 *(Continued)*

- Target Hb: 10 to 11 g/dL

Baseline characteristics

- CKD stage
  - HD: treatment group (1316, 88.5%); control group (1308, 88.6%)
  - PD: treatment group (171, 11.5%); control group (169, 11.4%)
- Number (randomised/analysed): treatment group (1487/1487); control group (1477/1477)
- Mean age ± SD (years): not reported
- Sex (M, %): treatment group (851, 57.2%); control group (847, 57.3%)
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CV disease: treatment group (666/1478); control group (665/1477)
- Heart disease: not reported
- Hypertension: not reported
- Diabetes: treatment group (615/1478); control group (617/1477)
- Prior agents used (number, %)
  - ESA: treatment group (1478/1478); control group (1477/1477)

Interventions

Treatment group (medium dose)*

- Daprodustat (oral): once/day
- The starting dose of daprodustat was between 4 and 12 mg daily, according to the patient's previous ESA dose, and stepped changes in the dose from 1 to 24 mg were available for dose adjustments

Control group

- rHuEPO: participants on PD will be administered SC darbepoetin alfa and participants on HD will be administered IV epoetin alfa

Co-interventions

- Supplemental iron therapy if ferritin is ≤ 100 ng/mL or TSAT is ≤ 20%; investigator will choose the route of administration and dose of iron

*Note: dose assessed according to Meadowcroft 2019

Outcomes

Primary outcomes

- Time to the first occurrence of adjudicated MACE to end of study (event-driven, up to 3.3 years)
- Mean change in Hb between baseline and efficacy period (mean over weeks 28 to 52)

Secondary outcomes

- Time to first occurrence of adjudicated MACE or a thromboembolic event (vascular access thrombosis, symptomatic DVT or symptomatic pulmonary embolism) (event-driven, up to 3.3 years)
- Time to first occurrence of adjudicated MACE or a hospitalisation for HF (event-driven, up to 3.3 years)
- Average monthly IV iron dose mg/subject up to and including week 52
- Time to first occurrence of death (any cause), CV death, fatal or non-fatal MI, fatal or non-fatal stroke (event-driven, up to 3.3 years)
- Time to first occurrence of MACE or hospitalisation for HF (recurrent events analysis) (event-driven, up to 3.3 years)
- Time to first occurrence of CV death or non-fatal MI incidences (event-driven, up to 3.3 years)
- Time to first occurrence of all-cause hospitalisation (event-driven, up to 3.3 years)
- Time to first occurrence of all-cause hospital re-admission within 30 days (event-driven, up to 3.3 years)

ASCEND-D 2021 *(Continued)*

- Time to first occurrence of MACE or hospitalisation for HF or thromboembolic events (event-driven, up to 3.3 years)
- Time to first occurrence of hospitalisation for HF (event-driven, up to 3.3 years)
- Time to first occurrence of thromboembolic events (event-driven, up to 3.3 years)
- Hb change from baseline to week 52
- Percentage of responders, defined as mean Hb within Hb analysis range to week 52
- Number of responders, defined as mean Hb within Hb analysis range to week 52
- Percentage time for which Hb is in analysis range during the efficacy period (week 28 to 52) and during the maintenance period (week 28 to end of trial)
- Change from baseline in SBP, DBP and MAP at week 52 and at end of treatment
- Number of BP exacerbation events/100 patient years (event-driven, up to 3.3 years)
- Number of participants with least one BP exacerbation event during study (event-driven, up to 3.3 years)
- Percentage of participants with least one BP exacerbation event during study (event-driven, up to 3.3 years)
- Time to stopping randomised treatment due to meeting rescue criteria (event-driven, up to 3.3 years)
- Mean change in SF-36 HRQoL scores between baseline and weeks 8, 12, 28, 52, of particular interest are the changes from baseline in the vitality and physical functioning domains at weeks 28 and 52
- Change from baseline in EQ-5D-5L score up to week 52
- Change from baseline in EQ-5D-5L VAS at week 52
- Change from baseline in PGI-S at weeks 8, 12, 28 and 52

Notes

- Funding: GlaxoSmithKline
- Conflicts of interest: "A.K.S. reports consultancy fees from GlaxoSmithKline and stock in Gilead. K.C. reports consultancy fees from GlaxoSmithKline. V.J. reports consultancy fees from GlaxoSmithKline. K.L.J. reports consultancy fees from GlaxoSmithKline. R.D.L. reports grants and personal fees from Bristol-Myers Squibb and Pfizer, personal fees from Boehringer Ingelheim and Bayer AG, and research grants from Amgen Inc., GlaxoSmithKline, Medtronic PLC and Sanofi Aventis. I.C.M.D. reports research grants, consultancy fees and honoraria from GlaxoSmithKline and Vifor Pharma. J.M.M. reports personal fees from Abbott, Hickma, Sun Pharmaceuticals and Servier, and that his employer received fees from Alnylam Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Cardurion, Cytokinetics, Dal-Cor, GlaxoSmithKline, Ionis, Novartis, Pfizer and Theracos. G.T.O. reports personal fees from Roche Mexico, Johnson & Johnson, Vifor and AbbVie. V.P. reports consultancy agreements with AbbVie, Bayer, Boehringer Ingelheim, Chinook, GlaxoSmithKline, Janssen, Pfizer, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pharmalink, Relypsa, Retrophin, Roche, Sanofi, Servier and Vitae; research funding from Pfizer (supplied drug and seed funding for TESTING trial) and GlaxoSmithKline; honoraria from AbbVie, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Pfizer, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Chinook, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi, Tanabe, Mundipharma, Novartis, Novo Nordisk, Pharmalink, Relypsa, Retrophin, Roche, Sanofi, Servier and Vitae; scientific advisor or membership: serving/served on steering committees for trials funded by AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Novartis, Novo Nordisk and Retrophin; other interests/relationships reported include: Board Director: George Clinical, George Institute, Garvan Institute, Mindgardens Network, Childrens Cancer Institute and Victor Chang Cardiac Research Institute. S.S. reports grants and consultancy fees from Alnylam, AstraZeneca, Bayer, Bristol-MyersSquibb, Cytokinetics, Gilead, GlaxoSmithKline, Lilly, MyoKardia, Novartis, Respicardia, Sanofi Pasteur and Theracos grants from Bellerophon, Celladon, Eidos, Ionis, Lone Star Heart, Mesoblast, NIH/NHLBI and Neurotronik, and consultancy fees from Akros, Amgen, Arena, Cardior, Cardurion, Corvia, Daiichi-Sankyo, Ironwood, Merck Sharp Dohme, Roche, Takeda, Quantum Genetics, AoBiome, Janssen, Cardiac Dimensions, Tenaya, Dinaqor, Tremeau, CellProThera and Moderna. C.W. reports consultancy fees from Akebia, Astellas, AstraZeneca, Bayer, Chiesi, FMC Idorsia, Mundipharma, GlaxoSmithKline, Merck Sharp Dohme, Reata, Gilead, Tricida, Vifor, Lilly and Takeda, and grants and consultancy fees from Boehringer Ingelheim, Sanofi Genzyme and Shire. S.S.W. reports personal fees from Public Health Advocacy Institute, CVS, Roth Capital Partners, Kantum Pharma, Mallinckrodt, Wolters Kluewer, GE Health Care, GlaxoSmithKline, Mass Medical International, Barron and Budd (versus Fresenius), JNJ, Venbio, Strataca, Takeda, Cerus, Pfizer, Bunch and James, Harvard Clinical Research Institute (aka Baim), Oxidien, Sironax, Metro Biotechnology, Biomarin and Bain, and grants and personal fees

ASCEND-D 2021 *(Continued)*

from Allena Pharmaceuticals. D.C.W. reports honoraria and/or consultancy fees from AstraZeneca, Amgen, Astellas, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Jansen, Merck Sharp and Dohme, Mundipharma, Napp, Pharmacosmos, Reata, Tricida and Vifor Fresenius. A.W. reports personal fees from Roche, Bayer, Fresenius and Medice. A.R.C., A.B., A.M.M., B.C., L.K. and R.D. are employees of and stockholders in GlaxoSmithKline."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were stratified by dialysis type of HD [including hemodiafiltration (HDF) and hemofiltration (HF)] or PDg, by region, and by participation in the ambulatory blood pressure (BP) monitoring sub-study. Following stratification, patients were randomized 1:1 to receive oral daprodustat or rhEPO control. A central randomisation approach was used to protect against selection bias due to the open-label design." Quote: "Investigators used an interactive voice- or Web-response system to determine treatment assignments."
Allocation concealment (selection bias)	Low risk	Quote: "Investigators used an interactive voice- or Web-response system to determine treatment assignments."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The safety of trial patients was overseen by an independent data monitoring." Not clearly stated if the data monitoring was blinded to the treatment assigned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT population Quote: "Eight patients (5 in the daprodustat group and 3 in the ESA group) were excluded from the safety analyses because they did not receive the randomised treatment"
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	Quote: "The trial drug was stopped prematurely." Quote: "The sponsor conducted the analysis." Similar baseline characteristics, or different non-randomised co-interventions were reported between groups Funder influenced data analysis and study reporting or interpretation. Conflicts of interest were reported

ASCEND-ID 2021

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 52 weeks
Participants	**General information** • Setting: multicentre (number of sites not reported) • Country: international (USA, Argentina, Australia, Austria, Canada, Germany, India, Italy, Korea, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, UK) • Inclusion criteria: aged 18 to 99 years; planning to start chronic dialysis within the next 6 weeks (from the date of the screening visit) OR have started and received dialysis (as specified below) for kidney failure for a maximum of ≤ 90 days immediately prior to randomisation and is not expected to stop dialysis during the duration of the trial: HD ≥ 2 times/week or PD ≥ 4 times/week including incremental schedule; subjects on CAPD and APD; Hb 8 to 10.5 g/dL at screening and 8 to 11.0 g/dL at randomisation; capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol • Exclusion criteria: planned living-related or living-unrelated kidney transplant during the study; ferritin ≤ 100 (ng/mL) at screening or after IV iron supplementation; TSAT ≤ 20% at screening or after IV iron supplementation; vitamin B12 (cobalamin) < LLN at screening or after vitamin B12 supplementation; folate < 2.0 ng/mL at screening; history of bone marrow aplasia or PRCA; untreated pernicious anaemia, thalassaemia major, sickle cell disease, or myelodysplastic syndrome; evidence of actively bleeding gastric, duodenal, or oesophageal ulcer disease or clinically significant GI bleeding ≤ 10 weeks prior to screening through to randomisation (day 1); use of any ESA treatment within 8 weeks prior to screening except for limited use as part of dialysis initiation; MI or acute coronary syndrome: ≤ 10 weeks prior to screening through to randomisation (day 1); stroke or TIA: ≤ 10 weeks prior to screening through to randomisation (day 1); chronic NYHA class IV HF; current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of rHuEPO; QTcB (day 1) > 500 msec, or QTcB >530 msec in subjects with bundle branch block; ALT >2 times ULN (screening only); bilirubin > 1.5 times ULN (screening only); current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis; history of malignancy within the 2 years prior to screening through to randomisation (day 1), or currently receiving treatment for cancer, or complex kidney cyst > 3 cm; use of other investigational agent or device prior to screening through to randomisation (day 1); pregnant, breastfeeding, or does not agree to follow one of the contraceptive options; any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (example intolerance to rHuEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study • Target Hb: 10 to 11 g/dL **Baseline characteristics** • CKD stage: HD and PD • Number (randomised/analysed): treatment group (157/155); control group (155/151) • Mean age (years): treatment group (53.7); control group (55.8) • Sex (M, %): not reported • Time on dialysis: not reported • eGFR: not reported **Comorbidities** • CV disease: not reported • Heart disease: not reported • Hypertension: not reported • Diabetes (number, %): not reported • Prior agents used (number, %)

ASCEND-ID 2021 *(Continued)*

- ESA: treatment group (157/157); control group (155/155)

Interventions	**Treatment group** • Daprodustat (oral): 1, 2, 4, 6, 8, 10, 12, 16, 24 mg/day **Control group** • Darbepoetin alfa (SC or IV) **Co-interventions** • Iron therapy will be administered if ferritin is ≤ 100 ng/mL and/or TSAT is ≤ 20%
Outcomes	**Primary outcome** • Mean change from baseline in Hb during evaluation period to week 52 **Secondary outcomes** • Average monthly IV iron dose mg/subject from baseline to week 52 • Change from baseline in SBP, DBP and MAP to week 52 • Number of BP exacerbation events/100 patient years to week 58 • Number (%) of subjects with at least one BP exacerbation event during study up to week 58 • Change from baseline in Hb up to week 52 • Number (%) of Hb responders week 28 to week 52 • Percentage time for which Hb is in analysis range week 28 to week 52 • Time to rescue up to week 52 • Change in SF-36 HRQoL) scores up to week 52 • Change from baseline in EQ-5D-5L questionnaire score at week 52 • Change from baseline in EQ-5D-5L VAS at week 52 • Change from baseline in the CKD-Anemia Symptoms Questionnaire at week 52 • Change from baseline in patient PGI-S up to week 52 • Summary of pharmacokinetic parameters of plasma daprodustat and three major metabolites in dialysis subjects: predose, 0.5, 1, 2, and 3 hours post dose at week 4, 8 or 12
Notes	• Funding: GlaxoSmithKline • Conflicts of interest: not reported • Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported

ASCEND-ID 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Overall 99% (155/157) pts on Dapro and 97% (151/155) on Darbe completed the study" Loss to follow-up: < 5%
Selective reporting (reporting bias)	High risk	Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Baseline characteristics, or different non-randomised co-interventions were not reported between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were not reported

ASCEND-ND 2021

Study characteristics

Methods	• Study design: parallel RCT • Time frame: December 2016 to December 2020 • Duration of follow-up: 52 weeks
Participants	**General information** • Setting: multicentre (588 sites) • Country: international (USA, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hong-Kong, Hungary, India, Israel, Italy, Korea, Malaysia, Mexico, Netherlands, New Zealand, Philippines, Poland, Portugal, Romania, Russian Federation, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, UK, Vietnam) • Inclusion criteria: 18 to 99 years; KDOQI CKD stages 3, 4, or 5 defined by electronic eGFR using the CKD-EPI formula; no ESA group: no ESA use within the 6 weeks prior to screening and no ESA use between screening and randomisation (day 1), ESA users group; use of any approved ESA for the 6 weeks prior to screening and continuing between screening and randomisation; for ESA group, Hb at week -8 and week 1 should be 8 to 10 g/dL, and for ESA users Hb at week -8 should be 8 to 12 g/dL and at week 1 should be 8 to 11 g/dL; ≥ 80% and ≤ 120% compliance with placebo during run-in period; informed consent (screening only); capable of giving signed informed consent which includes compliance with the requirements and restrictions • Exclusion criteria: on dialysis or clinical evidence of impending need to initiate dialysis within 90 days after study start (day 1); planned living-related or living-unrelated kidney transplant within 52 weeks after study start (day 1); ferritin ≤ 100 ng/mL at screening; (TSAT) (screening only) ≤ 20%; history of bone marrow aplasia or PRCA; untreated pernicious anaemia, thalassaemia major, sickle cell disease or myelodysplastic syndrome; evidence of actively bleeding gastric, duodenal, or oesophageal ulcer disease or clinically significant GI bleeding ≤ 4 weeks prior to screening through to randomisation (day 1); MI or acute coronary syndrome ≤ 4 weeks prior to screening through to randomisation (day 1); stroke or TIA ≤ 4 weeks prior to screening through to randomisation (day 1); chronic NYHA class IV HF, current uncontrolled hypertension as determined by the investigator; QTcB (day 1) > 500 msec, or QTcB > 530 msec in subjects with bundle branch block; ALT > 2 times ULN at screening; bilirubin > 1.5 times ULN at screening; current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis; history of malignancy within the 2 years prior to screening through to randomisation (day 1) or currently receiving treatment for cancer, or complex kidney cyst > 3 cm with the exception of localized squamous cell or basal cell carcinoma of the skin that has been definitively treated ≥ 4 weeks prior to screening; severe allergic reactions or anaphylactic reactions or hypersensitivity to excipients in the investigational product, or darbepoetin alfa; use of strong inhibitors of Cytochrome P4502C8 (e.g. gemfibrozil) or strong inducers of CYP2C8

ASCEND-ND 2021 *(Continued)*

(e.g. rifampin/rifampicin); use of other investigational agent or device prior to screening through to randomisation (day 1); prior treatment with daprodustat for > 30 days; pregnant, breastfeeding, or subject is of reproductive potential and does not agree to follow one of the contraceptive options; any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (e.g. intolerance to darbepoetin alfa) or prevent understanding of the aims or investigational procedures or possible consequences of the study

- Target Hb: 10 to 11 g/dL

Baseline characteristics

- CKD stage: CKD stages 3, 4, or 5
- Number (randomised/analysed): treatment group (1937/1937); control group (1935/1935)
- Mean age ± SD (years): not reported
- Sex (M, %): treatment group (835, 43.3%); control group (864, 44.7%)
- Time on dialysis: not applicable
- eGFR: not reported

Comorbidities

- CVdisease: treatment group (716/1937); control group (716/1935)
- Heart disease: not reported
- Hypertension: treatment group (1828/1937); control group (1829/1935)
- Diabetes: treatment group (1076/1937); control group (1118/1935)
- Prior agents used(number, %)
  - ESA: not reported

Interventions	**Treatment group (medium dose)*** • Daprodustat: once/day; starting dose was between 1 and 4 mg/day, according to the baseline Hb if the patient was not receiving an ESA and according to the ESA dose if the patient was receiving an ESA; stepped changes ranging from 1 to 24 mg were available for dose adjustments **Control group** • Darbepoetin alfa (SC) **Co-interventions** • Participants will receive supplemental iron therapy if ferritin is ≤ 100 ng/mL or TSAT is ≤ 20%. The investigator will choose the route of administration and dose of iron *Note: dose assessed according to Meadowcroft 2019
Outcomes	**Primary outcomes** • Time to the first occurrence of adjudicated MACE up to 4.1 years • Mean change in Hb) between baseline and efficacy period (weeks 28 to 52) **Secondary outcomes** • Time to first occurrence of adjudicated MACE (event-driven, up to 4.1 years) • Time to first occurrence of adjudicated MACE or a thromboembolic event (event-driven, up to 4.1 years) • Time to first occurrence of adjudicated MACE or a hospitalisation for HF (event-driven, up to 4.1 years) • Time to progression of CKD (event-driven, up to 4.1 years) • Time to first occurrence of death (any cause, CV death, fatal or non-fatal MI, fatal or non-fatal stroke (event-driven, up to 4.1 years) • Time to first occurrence of MACE or hospitalisation for heart failure (event-driven, up to 4.1 years) • Time to first occurrence of all-cause hospitalisation (event-driven, up to 4.1 years)

ASCEND-ND 2021 *(Continued)*

- Time to first occurrence of all-cause hospital re-admission within 30 days (event-driven, up to 4.1 years)
- Time to first occurrence of MACE or hospitalisation for HF or thromboembolic events (event-driven, up to 4.1 years)
- Time to first occurrence of hospitalisation for HF (event-driven, up to 4.1 years)
- Time to first occurrence of thromboembolic events (event-driven, up to 4.1 years)
- Time to first occurrence of individual components of CKD progression (event-driven, up to 4.1 years)
- Percentage of responders, defined as mean Hb within the Hb analysis range up to and including week 52
- Number of BP exacerbation events/100 patient-years (event-driven, up to 4.1 years)
- Percentage of participants with least one BP exacerbation event during study (event-driven, up to 4.1 years)
- Number of participants with least one BP exacerbation event during study (event-driven, up to 4.1 years)
- Time to stopping randomised treatment due to meeting rescue criteria (event-driven, up to 4.1 years)
- Change from baseline in EQ-5D-5L score at week 52
- Change from baseline in EQ-5D-5L VAS at week 52
- Time to first occurrence of CV death or non-fatal MI (event-driven, up to 4.1 years)
- Hb change from baseline up to and including week 52
- Number of responders, defined as mean Hb within the Hb analysis range up to and including week 52
- Percentage time for which Hb is in analysis range during the efficacy period (week 28 to 52) and during the maintenance period (week 28 up to 4.1 years)
- Change from baseline in SBP, DBP and MAP at week 52 and at end of treatment
- Mean change in SF-36 HRQoL scores between baseline and weeks 8, 12, 28, 52, of particular interest are the changes from baseline in the vitality and physical functioning domains at weeks 28 and 52
- Change from baseline by domain and overall symptom score on the CKD-Anemia Questionnaire at weeks 8, 12, 28, 52
- Change from baseline in PGI-S at week 8, 12, 28 and 52
- Change from baseline in eGFR at week 52

Notes

- Funding: GlaxoSmithKline
- Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The investigators used an interactive voice-response or Web-response system to determine the treatment assignments. Randomizsation was stratified according to use or nonuse of an ESA, geographic region, and participation or nonparticipation in an ambulatory blood-pressure monitoring substudy."
Allocation concealment (selection bias)	Low risk	Quote: "The investigators used an interactive voice-response or Web-response system to determine the treatment assignments.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label" Quote: "Although the investigators and patients were aware of the treatment assignments, the sponsor and steering committee remained unaware of the aggregate treatment assignments throughout the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded adjudication of cardiovascular outcomes." Quote: "An independent data monitoring committee over- saw the safety of the patients"

ASCEND-ND 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Nineteen patients (<1.0%) in the daprodustat group and 12 patients (<1.0%) in the darbepoetin alfa group had unknown vital status at the end of the trial." ITT analysis
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	Quote: "The sponsor, GlaxoSmithKline, and an academic steering committee designed and oversaw the trial conduct and analysis." Quote: "Daprodustat was discontinued prematurely for reasons other than death in 571 of 1937 patients (29.5%), and darbepoetin alfa was discontinued prematurely for reasons other than death in 560 of 1935 patients (28.9%)." Similar baseline characteristics, or different non-randomised co-interventions were reported between groups Funder influenced data analysis and study reporting or interpretation Conflicts of interest were not reported

ASCEND-NHQ 2021

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 28-week
Participants	**General information** • Setting: multicentre (168 sites) • Country: international (USA, Argentina, Australia, Austria, Brazil, Canada, France, Italy, Korea, Mexico, Poland, Romania, Russian Federation, Spain, UK) • Inclusion criteria: ≥ 18 years; CKD stages 3, 4, or 5 defined by eGFR using the CKD-EPI formula; stable Hb from 8.5 to 10.5 g/dL at screening visit (week -4) and from 8.5 to 10.0 g/dL at randomisation (day 1); may receive up to one IV iron dose within the 8 weeks prior to screening and NO IV iron use between screening visit and randomisation (day 1); males and female; not pregnant, not breastfeeding, not a woman of childbearing potential (WOCBP) OR WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 4 weeks after the last dose of study treatment; capable of giving signed informed consent • Exclusion criteria: on dialysis or clinical evidence of impending need to initiate dialysis within 180 days after randomisation (day 1); planned living-related or living-unrelated kidney transplant within 28 weeks after randomisation (day 1); TSAT < 15% (screening only); ferritin < 50 ng/mL (screening only); history of rHuEPO or rHuEPO analogue use within the 8 weeks prior to screening and rHuEPO use between screening and randomisation (day 1); history of transfusion within the 8 weeks prior to screening and transfusion between screening and randomisation (day 1); history of bone marrow aplasia or PRCA; megaloblastic anaemia (untreated pernicious anaemia and folate deficiency), thalassaemia major, sickle cell disease or myelodysplastic syndrome; evidence of actively bleeding gastric, duodenal, or oesophageal ulcer disease or clinically significant GI bleeding ≤ 8 weeks prior to screening through to randomisation (day 1); history of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product; use of strong inhibitor of CYP2C8 (e.g. gemfibrozil) or strong inducers of CYP2C8 (e.g. rifampin/rifampicin); ferric citrate use within 4 weeks

ASCEND-NHQ 2021 *(Continued)*

prior to randomisation (day 1); use of other investigational agent or device prior to screening through to randomisation (day 1); any prior treatment with daprodustat for a treatment duration of > 30 days; MI or acute coronary syndrome within the 8 weeks prior to screening through to randomisation (day 1); stroke or TIA within the 8 weeks prior to screening through to randomisation (day 1); chronic NYHA class IV HF; QTcB > 500 msec or QTcB > 530 msec in participants with bundle branch block; ALT > 2 times ULN at screening (week -4); bilirubin > 1.5 times ULN at screening (week -4); current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis; history of malignancy within the 2 years prior to screening through to randomisation (day 1), or currently receiving treatment for cancer, or complex kidney cyst > 3 cm; any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study; current uncontrolled hypertension as determined by the investigator

- Target Hb: 11 to 12 g/dL and proportion with ≥ 1 g/dL increase in Hb

Baseline characteristics

- CKD stage: CKD stages 3, 4, or 5
- Number (randomised/analysed): overall (614/not reported); treatment group (not reported); control group (not reported)
- Mean age ± SD (years): not reported
- Sex (M, %): not reported
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %)
  - ESA: treatment group (0); control group (0)

Interventions

Treatment group

- Daprodustat (GSK1278863) (oral): once/day

Control group

- Placebo

Co-interventions

- Iron therapy will be administered if ferritin is < 50 ng/mL and/or TSAT is < 15%

Outcomes

Primary outcome

- Mean change from baseline in Hb up to evaluation period (up to week 28)

Secondary outcomes

- Percentage of participants with Hb increase of ≥ 1.0 g/dL from baseline up to week 28
- Mean change from baseline in SF-36 questionnaire vitality domain score (baseline and week 28)
- Percentage of Hb responders (baseline and up to week 28)
- Percentage time Hb in range (up to week 28)
- Mean change from baseline for additional Hb parameters [(baseline and up to week 28)
- Time to rescue (up to week 28)
- Mean change from baseline in CKD - Anemia Questionnaire score (up to week 28)

ASCEND-NHQ 2021 *(Continued)*

- Change from baseline in Patient Global Impression of Severity (PGI-S) score (baseline and up to week 28)
- Mean change from baseline in SF-36 questionnaire vitality domain score (fatigue) (baseline and up to week 28)
- Mean change from baseline in SF-36 questionnaire physical function domain score (baseline and up to week 28)
- Percentage of participants currently employed on the WPAI, anaemia symptoms, clinical practice version scale (up to week 28)
- Change from baseline in percent mean hours work time missed on the WPAI anaemia symptoms (baseline and up to week 28)
- CPV change from baseline in percent impaired on the WPAI anaemia symptoms, clinical practice version questionnaire (baseline and up to week 28]
- Change from baseline in overall percent work impairment on the WPAI anaemia symptoms, clinical practice version questionnaire (baseline and up to week 28)
- Change from baseline in percent activity impairment on the WPAI anaemia symptoms, clinical practice version questionnaire (baseline and at week 28)
- Change from baseline in EQ-5D-5L score (baseline and up to week 28)
- Change from baseline EQ-VAS score (baseline and up to week 28)
- Change from baseline in SBP, DBP and MAP at week 28 (baseline and at week 28)
- Percentage of participants with at least one BP exacerbation (up to week 28)
- Incidences and severity of adverse events and serious adverse events (up to week 32)

Notes

- Funding: GlaxoSmithKline
- Conflicts of interest: not reported
- Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported in sufficient detail to perform adjudication
Selective reporting (reporting bias)	High risk	Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Baseline characteristics, or different non-randomised co-interventions were not reported between groups Funder was likely to influence data analysis and study reporting or interpretation

ASCEND-NHQ 2021 *(Continued)*

Conflicts of interest were not reported

ASCEND-TD 2021

Study characteristics

Methods

- Study design: parallel RCT
- Time frame: not reported
- Duration of follow-up: 52 weeks

Participants

General information

- Setting: multicentre (91 sites)
- Country: international (USA, Argentina, Australia, Brazil, Canada, France, Italy, Korea, Poland, Romania, Russian Federation, Spain, UK)
- Inclusion criteria: 18 to 99 years; use of any approved rHuEPO or analogue for at least 8 weeks prior to the screening visit and continuing during the screening period until randomisation (day 1); Hb within the following range: week -4 8 to 11.5 g/dL (if Hb is 11.6 to 11.9 g/dL, up to two retests are allowed; the retest value must be between 8 to 11.5 g/dL), day 1: Hb 8 to 11 g/dL and receiving at least the minimum rHuEPO or analogue dose 3; Hb > 11 to 11.5 g/dL and receiving greater than the minimum rHuEPO or analogue dose 3; on HD (including HF or HDF) > 90 days prior to screening and continuing during the screening period; on HD (in-centre) ≥ 3 times/week; male and female subjects are eligible; not pregnant, not breastfeeding, and not a woman of childbearing potential, or a woman of childbearing potential who agrees to follow the contraceptive guidance from at least 28 days prior to first dose of study treatment and for at least 28 days after the last dose of study treatment; capable of giving signed informed consent; In France, a subject will be eligible for inclusion in this study if he or she is either affiliated to or beneficiary of a social security category
- Exclusion criteria: planned living-related or living-unrelated kidney transplant within 52 weeks after randomisation (day 1); ferritin ≤ 100 ng/mL, at screening; TSAT ≤ 20%, at screening; history of bone marrow aplasia or PRCA; conditions, other than anaemia of CKD, which can affect erythropoiesis; MI or acute coronary syndrome within 8 weeks prior to screening through to randomisation (day 1); stroke or TIA within 8 weeks prior to screening through to randomisation (day 1); chronic NYHA class IV HF; current uncontrolled hypertension as determined by the investigator that would contraindicate the use of rHuEPO; QTcB > 500 msec, or QTcB > 530 msec in subjects with bundle branch block; ALT > 2 times ULN; bilirubin > 1.5 times ULN; current unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis; evidence of actively bleeding gastric, duodenal or oesophageal ulcer disease OR clinically significant gastro intestinal bleeding ≤ 8 weeks prior to screening through to randomisation (day 1); history of malignancy within 2 years prior to screening through to randomisation (day 1), currently receiving treatment for cancer, or complex kidney cyst > 3 cm; use of a strong inhibitor of Cytochrome P4502C8 (e.g. gemfibrozil) or a strong inducer of CYP2C8 (e.g. rifampin/rifampicin); history of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (daprodustat) or epoetin alfa; use of another investigational agent within 30 days or within five half-lives of the investigational agent (whichever is longer) or currently participating in a study of an investigational device prior to screening through to randomisation (day 1); any prior treatment with daprodustat for treatment duration of > 30 days; any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (e.g. intolerance to rHuEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study
- Target Hb: 10 to 11 g/dL

Baseline characteristics

- CKD stage: HD
- Number (randomised/analysed): treatment group (270/not reported); control group (137/not reported)

ASCEND-TD 2021 *(Continued)*

- Mean age ± SD (years): not reported
- Sex (M, %): not reported
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %)
  - IV iron: not reported
  - Darbepoetin alfa only: not reported
  - Epoetin only: not reported
  - Methoxy PEG-epoetin beta only: not reported
  - Multiple: not reported

Interventions

Treatment group

- Daprodustat (oral): 2 to 48 mg 3 times/week along with saline by IV route for the 52 weeks treatment period

Control group

- Epoetin alfa (IV): single-dose, preservative-free vials in unit dose strengths of 2000, 3000, 4000 and 10,000 U/mL for the 52 weeks
- Placebo (oral): tablets

Co-interventions

- Not reported

Outcomes

Primary outcome

- Mean change in Hb between baseline and over evaluation period (baseline and up to week 52)

Secondary outcomes

- Mean monthly IV iron dose/subject (up to week 52)
- Number of subjects with adverse events, serious adverse events, adverse event of special interest, and MACE (up to week 52)
- Percentage of time Hb will be in the analysis range (10 to 11.5 g/dL) over evaluation period (weeks 28 to 52)
- Time to stopping study treatment due to meeting rescue criteria (up to week 52)
- Number of responders in the Hb analysis range over evaluation period (weeks 28 to 52)
- Change from baseline in SBP, DBP and MAP at week 52 and at the end of study treatment
- Number of BP exacerbation events/100 subject years (up to week 52)
- Number of subjects with at least one BP exacerbation event during the study (up to week 52]
- Pre-dose trough concentration of daprodustat (pre-dose at any one post-baseline visit between week 8 and 52)
- Pre-dose trough concentration of metabolites M2 (pre-dose at any one post-baseline visit between week 8 and 52)
- Pre-dose trough concentration of metabolites M4 (pre-dose at any one post-baseline visit between week 8 and 52)
- Pre-dose trough concentration of metabolites M3 (pre-dose at any one post-baseline visit between week 8 and 52)

ASCEND-TD 2021 *(Continued)*

- Pre-dose trough concentration of metabolites M5 (pre-dose at any one post-baseline visit between week 8 and 52)
- Pre-dose trough concentration of metabolites M6 (pre-dose at any one post-baseline visit between week 8 and 52)
- Pre-dose trough concentration of metabolites M13 (pre-dose at any one post-baseline visit between week 8 and 52)
- Cmax of daprodustat (pre-dose and 0.5, 1, 2, 3 hours post-dose)
- Cmax of metabolites M2 (pre-dose and 0.5, 1, 2, 3 hours post-dose)
- Cmax of metabolites M3 (pre-dose and 0.5, 1, 2, 3 hours post-dose)
- Cmax of metabolites M4 (pre-dose and 0.5, 1, 2, 3 hours post-dose)
- Cmax of metabolites M5 (pre-dose and 0.5, 1, 2, 3 hours post-dose)
- Cmax of metabolites M6 (pre-dose and 0.5, 1, 2, 3 hours post-dose)
- Cmax of metabolites M13 (pre-dose and 0.5, 1, 2, 3 hours post-dose)
- Change from baseline in PGI-S score (baseline and up to week 52)
- Absolute values over time for composite of haematology parameters as a measure of safety (up to week 52)
- Changes from baseline over time in composite of haematology parameters as a measure of safety (up to week 52)
- Absolute values over time for composite of chemistry parameters as a measure of safety (up to week 52)
- Changes from baseline over time in composite of chemistry parameters as a measure of safety (up to week 52)
- Absolute values of SBP and DBP as a measure of safety (up to week 52)
- Change from baseline in SBP and DBP as a measure of safety (up to week 52)
- Absolute values for heart rate as a measure of safety (up to week 52)
- Change from baseline in heart rate as a measure of safety (up to week 52)

Notes

- Conflicts of interest: not reported
- Funding: GlaxoSmithKline
- Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported in sufficient detail to perform adjudication

ASCEND-TD 2021 *(Continued)*

Selective reporting (reporting bias)	High risk	Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Baseline characteristics, or different non-randomised co-interventions were not reported between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were not reported

Besarab 2015

Study characteristics	
Methods	• Study design: phase 2a, parallel RCT • Time frame: not reported • Duration of follow-up: 16 weeks (4 week treatment + 12 week follow-up)
Participants	**General information** • Setting: multicentre (29 sites) • Country: USA • Inclusion criteria: 18 to 80 years; written informed consent; stage 3, 4 CKD based on eGFR-MDRD (15 to 59 mL/min/1.73 m^2); Hb ≤ 11g/dL (enrolled at 27 treatment sites) or ≤ 13 g/dL (enrolled at 2 pharmacokinetic sites) in Part 1; Hb ≤ 11g/dL in all sites in Part 2 (based on mean of 3 levels within 1 g/dL of each other); TSAT > 8%, ferritin > 25 ng/mL in Part 1 and TSAT > 20% and ferritin > 100 ng/mL in Part 2; B12/folate above LLN; bilirubin < 2 times ULN in Part 1, within normal limits in Part 2; if female, 2 years post menopause, surgically sterile OR not pregnant/breast feeding, agrees to use 2 forms of birth control in study and for 3 months after; if male, medically acceptable form of birth control during study and for 12 weeks after ALP < 2 times ULN, could enter Part 2 if ALP > 2 times ULN if bone specific ALP elevated; no active/chronic bleeding in Part 2; absence of age-related macular degeneration/diabetic retinopathy likely to need treatment during study (Ophthalmologist opinion) • Exclusion criteria: uncontrolled hypertension (DBP > 109 SBP > 170 SBP at screening); positive for HIV, HBsAg, or anti-HCV Ab; history of PCKD; NYHA Class III or IV congestive HF; MI, acute coronary syndrome within 3 months; history of myelodysplastic syndrome, haemolysis. HUS, known marrow fibrosis, haemosiderosis, haemochromatosis; chronic inflammatory disease that could impact response; clinical/laboratory evidence of active infection; significant or uncontrolled medical condition considered a high risk for participation in RCT; thromboembolic event within 4 weeks prior to day 1; androgen therapy within 12 weeks of day 1; ESA within 60 days of day 1; IV iron within 60 days of day 1 or unable to interrupt IV iron during RCT (participants on oral iron allowed but dose must be unchanged); likely to require medications metabolised by CYP2CA isoenzymes during study; likely to require dapsone or acetaminophen (> 2.6 g/day) during treatment or post-treatment period; previous organ transplant; abuse of drugs/alcohol or known excessive alcohol intake; investigational drug or participation in investigational study in 4 weeks before day 1; positive urine toxicology screen • Target Hb: Increase in Hb of ≥ 1g/dL **Baseline characteristics** • CKD stage: stage 3,4 • Number (randomised/analysed): treatment group 1 (23/23); treatment group 2 (21/21); treatment group 3 (21/21); treatment group 4 (23/23); control group (29/28) • Mean age, range (years): all treatment groups (88 participants) (68.5, 47 to 82); control group (68.6, 56 to 79) • Sex (M, %): overall (49, 41.9%); treatment group 1 (12, 52.2%); treatment group 2 (10, 47.6%); treatment group 3 (5, 23.8%); treatment group 4 (6, 26.1%); control group (16, 57.1%)

Besarab 2015 *(Continued)*

- Time on dialysis: not applicable
- Mean eGFR ± SD (mL/min/1.73 m^2): all treatment groups (34.3 ± 12.7); control group (31.4 ± 12.4)

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %)
  - Oral iron supplementation: not reported

Interventions	**Treatment group 1** • Roxadustat (oral): 0.7 mg/kg, 2 or 3 times/week for 4 weeks **Treatment group 2** • Roxadustat (oral): 1 mg/kg, 2 or 3 times/week for 4 weeks **Treatment group 3** • Roxadustat (oral) 1.5 mg/kg, 2 or 3 times/week for 4 weeks **Treatment group 4** • Roxadustat (oral): 2 mg/kg, 2 or 3 times/week for 4 weeks **Control group** • Placebo (oral): 2 or 3 times/week for 4 weeks **Co-interventions** • Not reported
Outcomes	**Primary outcomes** • Increase in Hb from baseline of ≥ 1 g/dL • Increase in Hb from baseline of ≥ 1 g/L and Hb ≥11 g/dL • Number (%) with Hb response between groups **Secondary outcomes** • Time to first Hb response • Median time to response • Number (%) of responders and over shooters stratified by baseline Hb and by baseline Hb + weight • Cumulative number (%) of responders stratified by baseline Hb, ferritin, TSAT • Maximum Hb change from baseline at different time points. Change from Hb baseline slope • Exploratory variables in response to treatment/control were EPO levels, reticulocytes counts, iron levels, ferritin, transferrin or TIBC, TSAT, VEGF, serum/urine hepcidin levels • Incidence/severity of treatment emergent adverse events, finding on physical exam/labs/BP monitoring/ECG • Part 2 ◦ Hepatic monitoring plan: weekly screening of LFTs during study and every 2 weeks after ceasing medication to 12 weeks. Changed to every 4 weeks after ceasing medication at 12 weeks
Notes	• Funding: FibroGen Inc sponsored and designed study • Conflicts of interest: "Amgen, Hoffman la Roche, Akebia, Affymax, Rockwell International; Ownership: Vasc AlertResearch Funding: Abbott, Roche, Fibrogen, Luitpold; Honoraria: Affymax, Amgen, ASN, Ash Access Technology, Bioconnect, FALLON MEDICA, FMC, Genentech, HemoSphere, Hoffman la Roche,

Besarab 2015 *(Continued)*

Hospira, Indiana University, John Hopkins Univ, Luitpold Pharm, Merck and Co, National Kidney Fund, NKF of Michigan, NKF of Georgia, New York Soc of Nephrology, QUINTILES, Renal Advantage, Rockwell Medical, Scientific Consulting Group (NIH) Soc of Nephrology of Puerto Rico, Speedel, St. Michael's Hosp. (Toronto), St. John's Hosp. (Detroit), Takeda, University of Cincinnati, University of Miami, University of Missouri, VascAlert, Walter Kluger (Publisher) Winthrop Univ., Watson Pharma; Scientific Advisor: Amgen, Affymax, Akebia, Rockwell International"

- Note: data on fatigue, diabetic retinopathy, cancer, kidney impairment and hyperkalaemia were reported but not data were reported by different doses. These data were not extracted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were sequentially enrolled into one of four dose cohorts: 1.0, 1.5, 2.0 and 0.7 mg/Kg" Quote: "The first 35 patients at treatment sites were enrolled 7:7:2:2 and at 2:2:1:1 at PK sites to roxadustat BIW, TIW or placebo BIW, TIW. Remaining 82 patients were enrolled 10:10:3:3 at treatment sites only" Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This was a multicenter randomized study (single blind), placebo-controlled, with sequential dose escalation and evaluation of administration"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	According to Figure 1 (Patient disposition), two patients in Roxadustat groups and one in placebo group discontinued treatment because of adverse events (unrelated to medication). One patient in Roxadustat group withdrew consent. Seven patients in Roxadustat group and one in placebo group discontinued dosing by sponsor's decision" 88/88 and 28/29 participants completed the study according to the safety population. 78/88 and 26/28 completed dosing (89.7%). 73/23 (83%) provided efficacy evaluable population. 76/26 (88%) completed study. I could not find reason for sponsor's decisions to withdraw patients All patients were included in the intention-to treat analysis
Selective reporting (reporting bias)	High risk	The planned outcomes (efficacy, safety) on ClincialTrials.gov have been measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported Data on fatigue, diabetic retinopathy, cancer, renal impairment and hyperkalaemia were reported but no data were reported for the different doses
Other bias	High risk	Quote: "All authors except sponsor contributed participants to study."

Besarab 2015 *(Continued)*

	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported. Funders designed study so could influence data analysis and study reporting or interpretation Authors declared conflicts of interest

Brigandi 2016

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 57 days (8 weeks)
Participants	**General information** • Setting: multicentre (22 sites) • Country: multinational (New Zealand, Australia, India, Russia) • Inclusion criteria: males and females; 18 to 85 years; non-dialysis CKD stages 3 to 4 (eGFR 15 to 59 mL/min/1.73 m^2), non-dialysis stage 5 (eGFR 10 to < 15 mL/min/1.73 m^2) based on the KDOQI criteria; ESA-naive with Hb ≤ 11.0 g/dL OR the ESA treatment had been discontinued for a minimum of 7 days or equivalent to the interval between scheduled ESA doses; Hb ≤ 11.5 g/dL at screening with a re-check value of ≤ 11.0 g/dL after appropriate ESA discontinuation) and ferritin was ≥ 40 µg/L or 25 to 39 µg/L with TSAT ≥ 20% along with the absence of microcytic or hypochromic RBC; adequate vitamin B12 and folate levels; no history of IV iron replacement therapy within 30 days before the first dose of study drug until completion of the follow-up visit (ongoing oral iron therapy could be continued, but could not be started, adjusted, or stopped); no history of experimental investigational product taken within 30 days or 5 half-lives or twice the duration of the biological effect (whichever was longer); body weight ≥ 45 kg; Normal QTcB or QTcF interval < 450 msec or QTc interval < 480 msec in subjects with bundle branch block • Exclusion criteria: positive pre-study HBsAg or positive HCV Ab within 3 months prior to screening and one of the following: 1) evidence of autoimmune anaemia, 2) prior anti-viral therapy, 3) evidence of liver damage; positive test for HIV antibody; pre-study drug screen positive due to drug use not associated with a current medication prescription; minimum list of drugs that will be screened for include amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines; AST, ALT, or direct bilirubin > 1.5 times ULN; haemolysis/haemolytic anaemia or active bleeding/blood loss; androgen therapy within 8 weeks prior to first dose of study drug (day 1); RBC transfusion within 90 days prior to first dose of study drug (day 1); iron replacement therapy; history of thrombosis defined as DVT, stroke, pulmonary embolism or other thrombosis related condition within 1 year prior to screening; known active decompensated hyperparathyroidism or history of bone marrow fibrosis; systemic haematologic disease; post-kidney transplantation patients with functioning transplant (failed transplant subjects back on HD are eligible); acute peptic ulcer disease or history of chronic rectal bleeding; history of malignancy tumour within 5 years prior to screening or are receiving medication for cancer; non-melanoma skin cancer within the past 5 years that has been definitively removed is allowed; patients with a pre-existing condition interfering with normal GI anatomy or motility, and/or hepatic function that could interfere with the absorption, metabolism, and/or excretion of the study drugs; active infection or acute inflammatory disease as determined by clinical assessment; class III HF with evidence of recent progression (worsening dyspnoea, hospitalisation within 2-3 months for symptoms, etc), or NYHA class IV HF; uncontrolled hypertension (DBP > 100 mm Hg or SBP >160 mm Hg at screening); MI or acute coronary syndrome within 1 year prior to screening; history of seizure disorder; proliferative choroidal or retinal disease likely to require treatment (intraocular injections or laser photocoagulation) during the study; pregnant or breastfeeding; history of drug abuse or dependence within 6 months prior to screening; unwillingness or inability to follow the procedures, or lifestyle and/or dietary restrictions outlined in the protocol; use of prescription drugs within 7 days prior to first dose of study drug (day 1) until after completion of all study drug doses and Day 29 assessments: which are known to be inhibitors of CYP 2C8 OR which are known to be both CYP2C8 and OATP1B1 substrates OR

Brigandi 2016 *(Continued)*

which rely mainly on OATP1B1/1B3 for hepatic clearance; use of prescription drugs within 14 days prior to first dose of study drug (day 1) until completion of all study drug doses and Day 29 assessments, which are known to be inducers of CYP2C8; use of non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug (day 1) through the follow-up visit (Day 57), unless in the opinion of the Investigator the medication will not interfere with the study procedures or compromise patient safety and GSK Medical Monitor concurs; history of sensitivity to any of the study drugs, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation; history of sensitivity to heparin or heparin-induced thrombocytopenia (if the clinical site uses heparin to maintain intravenous cannula patency); has participated in a clinical trial and has received an experimental investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer); exposure to more than four experimental investigational products within 12 months prior to the first dose of study drug (day 1); patient is mentally or legally incapacitated

- Target Hb: 1.0 and 0.5 g/dL Hb level increase

Baseline characteristics

- Number (randomised/analysed)
  - Non-dialysis participants: treatment group 1 (17/17); treatment group 2 (14/14); treatment group 3 (15/15); treatment group 4 (15/15); control group (9/9)
  - HD participants: treatment group 1 (19/19); treatment group 2 (12/12); control group (6/6)
- Mean age ± SD (years)
  - Non-dialysis participants: treatment group 1 (54.6 ± 14.23); treatment group 2 (57.4 ± 14.29); treatment group 3 (63.6 ± 12.20); treatment group 4 (62.1 ± 12.38); control group (54.7 ± 17.26)
  - HD participants: treatment group 1 (50.2 ± 9.83); treatment group 2 (50.0 ± 12.01); control group (57.2 ± 7.03)
- Sex (M, %): treatment groups (46, 50%); control group (8, 53.3%)
  - Non-dialysis participants: treatment group 1 (5, 29.4%); treatment group 2 (4, 28.6%); treatment group 3 (9, 60%); treatment group 4 (9, 60%); control group (6, 66.7%)
  - HD participants: treatment group 1 (11, 57.9%); treatment group 2 (8, 66.7%); control group (2, 33.3%)
- Time on dialysis
  - CKD participants: not applicable
  - HD participants: not reported
- Mean eGFR ± SD (mL/min/1.73 m^2)
  - Non-dialysis participants: treatment group 1 (25.4 ± 12.96); treatment group 2 (20.7 ± 8.85); treatment group 3 (28.0 ± 9.02); treatment group 4 (19.7 ± 6.41); control group (24.3 ± 10.57)
  - HD participants: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Interventions

Treatment group 1

- Daprodustat (GSK1278863) (oral): 10 mg/day for 4 weeks

Treatment group 2

- Daprodustat (GSK1278863) (oral): 25 mg/day for 4 weeks

Treatment group 3

- Daprodustat (GSK1278863) (oral): 50 mg/day for 4 weeks

Brigandi 2016 *(Continued)*

	Treatment group 4 • Daprodustat (GSK1278863) (oral): 100 mg/day for 4 weeks **Control group** • Placebo (oral) **Co-interventions** • Not reported
Outcomes	**Primary outcomes** • Rate of response in patients achieving the target Hb level • Rate of Hb level increase • Absolute Hb concentrations • Maximum change from baseline • Rate of Hb level decrease following stopping of dosing. Safety endpoints included AEs, clinical safety laboratory tests (haematology, chemistry, and urinalysis, when obtainable), vital signs (BP and heart rate), ECG, and clinical monitoring/observations **Secondary outcomes** • Pharmacokinetic endpoints were population pharmacokinetic parameters estimated from sparse pharmacokinetic samples collected in a subset of individuals on days 1, 15, and 22 • Pharmacodynamic endpoints included change in endogenous EPO concentration, reticulocyte count, HCT, total RBC count, VEGF level, hepcidin level, TIBC, TSAT (percentage), serum iron level, serum ferritin level, and foetal Hb level
Notes	• Funding: GlaxoSmithKline • Conflicts of interest: "Dr Brigandi, Dr Johnson, Mr Russ, and Dr Kumar are employees of GlaxoSmithKline and hold company stocks. Dr Oei was an employee of GlaxoSmithKline during development of the study design and operations and currently holds GlaxoSmithKline stocks. Drs Westerman, Olbina, de Zoysa, Roger, Sahay, Cross, McMahon, Guptha, and Smolyarchuk were study consultants and/or study investigators and were paid for their services by GlaxoSmithKline; however, they were not compensated as authors of the manuscript"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This phase 2A, multicenter (Australia, New Zealand, India, and Russia), single-blind, randomized, placebo-controlled, parallel-group study."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment

Brigandi 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included into the analysis Quote: "Adverse events responsible for withdrawal in 6 non dialysis and 3 dialysis patients. 32/70 withdrawn from CKD group & 11/37 withdrawn from HD group."
Selective reporting (reporting bias)	High risk	Not all the planned outcomes on ClincialTrials.gov have been measured and reported on in the final report. No reasoning provided. No reporting of results of SF36 surveys that were listed as outcome in Clinical Trial Registration Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

Chen 2019

Study characteristics	
Methods	• Study design: 2-arm, parallel RCT • Time frame: December 2015 to June 2016 • Duration of follow-up: 27 weeks (treatment period 26 weeks, follow-up 1 week)
Participants	**General information** • Setting: multicentre (29 sites) • Country: China • Inclusion criteria: aged 18 to 75 years; voluntarily signed and dated an informed consent form, approved by an Ethics Committee, after the nature of the study had been explained and the subject had the opportunity to ask questions; a separate informed consent form was needed for subjects participating in the pharmacokinetic sub-study; CKD with kidney failure on either adequate HD or adequate PD for a minimum of 16 weeks prior to day 1. For subjects undergoing HD, the vascular access must have been set up via native AVF or graft, or permanent, tunnelled catheter; must have been on stable doses of IV or SC injections of epoetin-alfa for at least 6 weeks prior to day 1 (average dose ≤ 15,000 IU/week); mean of the 2 most recent central laboratory Hb values during the screening period, obtained at least 6 days apart, must have been 9.0 to 12.0 g/dL, inclusive, with a difference of ≤ 1.5 g/dL between the highest and the lowest Hb values; ALT and AST lower than 1.5 times ULN, and normal total bilirubin at the screening visit except for subjects with Gilberts syndrome (based on central laboratory results); weight 45 to 100 kg; agreed to not start taking any new TCM for anaemia and not to change dose, schedule, or brand of any prescreening TCM for anaemia from the beginning of the screening period through the end of the follow-up period • Exclusion criteria: any clinically significant infection or evidence of an active underlying infection; positive for any of the following: HIV, HBsAg, or anti-HCV Ab; chronic liver disease; NYHA class III or IV congestive HF; MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event (e.g. deep venous thrombosis or pulmonary embolism) within 52 weeks prior to day 1; uncontrolled hypertension in the opinion of the investigator; diagnosed or suspected renal cell carcinoma as shown on renal ultrasound during the screening period; history of malignancy except for cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, or in situ cancer at any site; chronic inflammatory disease other than GN that could have impacted erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease); clinically significant GI bleeding; known history of myelodysplastic syndrome, multiple myeloma, hereditary hematologic disease

Chen 2019 *(Continued)*

such as thalassaemia, sickle cell anaemia, PRCA, or other known causes for anaemia other than CKD, haemosiderosis, haemochromatosis, known coagulation disorder, or hypercoagulable condition; any prior functioning organ transplant or a scheduled organ transplantation, or anephric; anticipated elective surgery that could have led to significant blood loss during the study period; anticipated use of dapsone or acetaminophen > 2.0 g/day, or > 500 mg/dose repeated every 6 hours for more than 3 days; serum albumin < 2.5 g/dL; androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to day 1; Life expectancy < 12 months; blood transfusion within 12 weeks prior to day 1 or anticipated need for transfusion; IV iron supplement during the screening period and/or unwilling to withhold IV iron; immune suppressive or systemic steroid treatment within 12 weeks prior to day 1; history of alcohol or drug abuse within the past 2 years and inability to avoid consumption of more than > 3 alcoholic beverages/day; prior treatment with FG-4592 or any HIF prolyl hydroxylase inhibitor; use of an investigational medication or treatment, participation in an investigational interventional medication or treatment, or carryover effect of an investigational treatment expected during the study; pregnant or breastfeeding; women of childbearing potential and men with sexual partners of childbearing potential who are not using adequate contraception; any medical condition that, in the opinion of the investigator, posed a safety risk to a subject in this study, confounded efficacy or safety assessments, or interfered with study participation

- Target Hb: the lower boundary of the 95% CI for the treatment difference in the change in Hb level had to be per dL

Baseline characteristics

- CKD stage: dialysis (HD and PD)
  - HD/PD: treatment group (182/22); control group (89/11)
- Number (randomised/analysed): treatment group (204/204); control group (101/100)
- Mean age ± SD (years): treatment group (47.6 ± 11.7); control group (51.0 ± 11.8)
- Sex (M, %): treatment group (126, 61.8%); control group (58, 58%)
- Time on dialysis (years): treatment group (4.5 ± 3.5); control group (4.4 ± 2.9)
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes(number, %): not reported
- Prior agents used(number, %): not reported

Interventions

Treatment group (high dose)*

- Roxadustat: starting dose was either 100 mg (in patients weighing 45 to < 60 kg) or 120 mg (in patients weighing ≥ 60 kg)
- The dose steps were as follows: 20, 40, 50, 70, 100, 120, 150, 200, and 250 mg. Dose adjusted according to change in Hb over last 4 weeks and current Hb. See supplementary Table 2; maximum dose 2.5 mg/kg. Dose adjusted to achieve Hb 10 to 12 g/dL in participants, 3 times/week for 26 weeks

Control group

- EPO alfa (IV): 3 times/week for 26 weeks

Co-interventions

- Overall 67 participants in the intervention group and 43 participants in the control group received oral iron (IV iron was not allowed)

*Note: dose assessed according to NCT01888445

Outcomes

Primary outcomes

- Mean change in the Hb level from baseline to the average level during weeks 23 through 27

Chen 2019 *(Continued)*

Secondary outcomes

- Proportion with a Hb response (defined as a mean Hb level, averaged over weeks 23 through 27, that was no lower than 1.0 g/dL below baseline)
- Proportion with a mean Hb level, averaged over weeks 23 through 27, of at least 10.0 g/dL
- Mean change from baseline in iron biomarker levels at week 27
- First exacerbation of hypertension in a time-to-event analysis
- Mean change from baseline in the MAP measured before the start of a dialysis session, averaged over weeks 23 through 27

Notes

- Funding: FibroGen and FibroGen [China] Medical Technology Development
- Conflicts of interest: Robert Leong, M.D., Chunrong Wang, M.D., Cameron Liu, Ph.D., Thomas Neff, Lynda Szczech, M.D., M.S.C.E., and Kin-Hung P. Yu, M.D. are employees of FibroGen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Randomisation was performed centrally in sequence, stratified according to the dose of epoetin alfa at baseline (<8000 IU or ≥8000 IU per week) and dialysis method (haemodialysis or peritoneal dialysis).” Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This trial (FGCL-4592-806) was a randomized, open-label, active-controlled, phase 3 trial."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “A total of 48 patients (42 in the roxadustat group and 6 in the epoetin alfa group) discontinued the assigned medication. A total of 256 patients (162 in the roxadustat group and 94 in the epoetin alfa group) completed treatment.” 256/304 (84%) participants completed the study according to the safety population. Reason for discontinuations were provided that seemed unrelated with the treatment assigned Lost to follow-up: < 5% 305 patients underwent randomisation (204 patients to the roxadustat group and 101 to the epoetin alfa group). One patient in the epoetin alfa group did not receive treatment, so 304 patients were included in the full analysis set (ITT population) All participants were included in the ITT analysis
Selective reporting (reporting bias)	Low risk	Expected outcomes reported and correlate with the planned outcomes on ClincialTrials.gov.

Chen 2019 *(Continued)*

		Clinically-relevant outcomes that would be expected for this type of intervention were reported (death and CV events).
Other bias	High risk	Quote: "The trial was designed by the first two authors and the sponsor (FibroGen). The sponsor provided financial support and was responsible for data collection and analysis." There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

Chen 2019a

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: December 2015 to September 2016 • Duration of follow-up: 9 weeks
Participants	**General information** • Setting: multicentre (29 sites) • Country: China • Inclusion criteria: aged 18 to 75 years; voluntarily signed and dated an informed consent form; diagnosis of CKD KDOQI Stage 3, 4, or 5, not receiving dialysis; with an eGFR < 60 mL/min/1.73 m^2 estimated using the MDRD equation; no use of an ESA for at least 5 weeks before randomisation; mean of the 2 most recent Hb values during the screening period, obtained at least 6 days apart, must have been ≥ 7.0 g/dL and < 10.0 g/dL; ALT and AST ≤ 1.5 times ULN, and normal total bilirubin at screening visits (based on central laboratory results); weight 40 to 100 kg; agreed not to start taking any new TCM for anaemia and not to change dose, schedule, or brand of any prescreening TCM for anaemia from beginning of screening period through end of follow-up period without approval of the FibroGen China Medical Monitor • Exclusion criteria: any clinically significant infection or evidence of an active underlying infection; positive for any of the following: HIV, HBsAg, or anti-HCV Ab; chronic liver disease; NYHA class III or IV congestive heart failure; MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event (e.g. deep venous thrombosis or pulmonary embolism) within 52 weeks prior to day 1; uncontrolled hypertension in the opinion of the investigator; diagnosed or suspected renal cell carcinoma as shown on renal ultrasound during the screening period; history of malignancy except for cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, or in situ cancer at any site; chronic inflammatory disease other than GN that could have impacted erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease); clinically significant GI bleeding; known history of myelodysplastic syndrome, multiple myeloma, hereditary hematologic disease such as thalassaemia, sickle cell anaemia, PRCA, or other known causes for anaemia other than CKD, haemosiderosis, haemochromatosis, known coagulation disorder, or hypercoagulable condition; any prior functioning organ transplant or a scheduled organ transplantation, or anephric; anticipated elective surgery that could have led to significant blood loss during the study period; anticipated use of dapsone or acetaminophen > 2.0 g/day, or > 500 mg/dose repeated every 6 hours for more than 3 days; serum albumin < 2.5 g/dL; androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to day 1; Life expectancy < 12 months; blood transfusion within 12 weeks prior to day 1 or anticipated need for transfusion; IV iron supplement during the screening period and/or unwilling to withhold IV iron; immune suppressive or systemic steroid treatment within 12 weeks prior to day 1; history of alcohol or drug abuse within the past 2 years and inability to avoid consumption of more than > 3 alcoholic beverages/day; prior treatment with FG-4592 or any HIF prolyl hydroxylase inhibitor; use of an investigational medication or treatment, participation in an investigational inter-

Chen 2019a *(Continued)*

ventional medication or treatment, or carryover effect of an investigational treatment expected during the study; pregnant or breastfeeding; women of childbearing potential and men with sexual partners of childbearing potential who are not using adequate contraception; any medical condition that, in the opinion of the investigator, posed a safety risk to a subject in this study, confounded efficacy or safety assessments, or interfered with study participation

- Target Hb: 10.0 g/dL, the second definition was increase from baseline of at least 1.0 g/dL in patients with a baseline Hb level ≥ 8.0 g/dL or an increase of at least 2.0 g/dL in patients with a baseline Hb level < 8.0 g/dL. However, in this review we have considered only the first definition

Baseline characteristics

- CKD stage: stage 3, 4, or 5, not receiving dialysis; with an eGFR < 60 mL/min/1.73 m^2
- Number (randomised/analysed): treatment group (102/101); control group (52/51)
- Mean age ± SD (years): treatment group (54.7 ± 13.3); control group (53.2 ± 13,1)
- Sex (M, %): overall (56, 36%); treatment group (36, 36%); control group (20, 39%)
- Time on dialysis: not applicable
- MeaneGFR±SD (mL/min/1.73 m^2): treatment group (16.5 ± 8); control group (14.5 ± 7.6)

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension(number, %): treatment group (89, 88%); control group (41, 80%)
- Diabetes(number, %): treatment group (22, 22%); control group (16, 31%)
- Prior agents used(number, %)
  - Oral iron supplementation: treatment group (40, 40%); control group (24, 47%)

Interventions

Treatment group (high dose)*

- Roxadustat (oral): titrated between 20 to 250 mg, 3 times/day for 8 weeks

Control group

- Placebo for 8 weeks

Co-interventions

- Not reported

*Note: dose assessed according to NCT01888445

Outcomes

Primary outcome

- Change in Hb from baseline to the average level to weeks 7 to 9

Secondary outcomes

- Proportion who achieve a confirmed Hb response (up to and including week 9)
- Proportion with mean Hb ≥10.0 g/dL (weeks 7 to 9)
- Mean change from baseline in LDL cholesterol averaged (weeks 7 to 9)
- Effect on iron metabolism: measurement of serum iron (week 9)
- SF-36 physical functioning sub score measured in week 9 in the FAS subjects with baseline physical functioning sub score below 35 (week 9)
- Mean change from baseline in SF-36 vitality sub score measured in week 9 in FAS subjects with baseline vitality sub score below 50 (week 9)
- Mean change from baseline in MAP (weeks 7 to 9)
- Proportion who received rescue therapy (composite of blood transfusion, ESA use, and IV iron) (up to week 9)
- Percent with treatment-emergent adverse events or serious adverse events (week 1 up to week 53)
- Number with treatment-emergent adverse events or serious adverse events (week 1 up to week 53)

Chen 2019a *(Continued)*

- Changes from baseline in vital signs (week 1 up to week 53)
- Changes from baseline in ECG findings (week 1 up to week 53)
- Changes from baseline in clinical laboratory values (week 1 up to week 53)
- Proportion on rescue therapy (week 1 up to week 53)
- Time to rescue therapy from date of first dose (week 1 up to week 53)

Notes	• Funding: FibroGen and FibroGen [China] Medical Technology Development • Conflicts of interest: "X. Peng, H. Lin, A. Yin, Y. Tao, X. Liang, Z. Liu, L. Zuo, and Y. Liao report receiving lecture fees from FibroGen; R. Leong, C. Wang, and B.-C. Liu, being employed by FibroGen; T. Neff, L. Szczech, and K.-H. Yu, being employed by and having an equity interest in FibroGen; and T. Neff, holding a patent (8,614,204) on “Enhanced erythropoiesis and iron metabolism,” owned by FibroGen. No other potential conflict of interest relevant to this article was reported"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomly assigned in a 2:1 ratio to receive roxadustat or placebo. Randomization was performed centrally and was stratified according to the use or nonuse of an erythropoiesis-stimulating agent within 12 weeks before randomisation and according to the estimated glomerular filtration rate (GFR) (<20 ml or ≥20 ml per minute per 1.73 m2 of body-surface area)." Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind phase" Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. However, since interventions were different, it was possible that investigators and/or participants were aware of treatment allocation. In the treatment groups were reported side effects that participants and/or investigators could know to be specific for one of the interventions. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient in each group discontinued participation in the trial because of hyperkalaemia." "2 [participants] did not receive a trial regimen. One patient in the safety population took one dose of placebo and was lost to follow-up" 151/154 participants completed the study according to the intention-to-treat population and 152/154 participants completed the study according to the safety population Loss to follow-up: < 5%, without differences between groups Reason for discontinuations were provided that seemed unrelated with the treatment assigned

Chen 2019a *(Continued)*

Selective reporting (reporting bias)	High risk	Not all of the planned outcomes on ClincialTrials.gov have been measured and reported on in the final report. No reasoning provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Quote: "The first two authors designed the trial in collaboration with representatives of the sponsor, FibroGen; company representatives were responsible for the collection and analysis of the data." There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

Chen DD 2017

Study characteristics

Methods	• Study design: parallel RCT • Time frame: September 2011 to June 2012 • Duration of follow-up: 8 weeks
Participants	**General information** • Setting: multicentre (9 sites) • Country: China • Inclusion criteria: voluntarily signed and dated an informed consent form; aged 18 to 75 years; kidney failure receiving maintenance HD 3 time/week for ≥ 4 months prior to day 1; Hb values in 4 screening visits and the mean Hb must be between 9.0 and 12.0 g/dL (inclusive), and the difference between them must be ≤ 1.5 g/dL; stable doses of IV or SC injection of epoetin alfa, defined as follows: 1) Epoetin alfa dose range for 6 weeks prior to day -7: 2) 3000 to 20,000 IU/week; 3) stable doses of epoetin alfa (i.e. the maximum epoetin alfa dose does not exceed 130% of the lowest dose of epoetin alfa taken in this period); complete blood count, haematology, liver function blood tests within acceptable limits; serum folate and vitamin B12 levels above the LLN; body weight 40 to 100 kg (dry weight); BMI 16 to 38 kg/m^2 inclusive; for HD subjects dialysis vascular access via native AVF or synthetic graft (not via catheter) • Exclusion criteria: anticipated change in HD prescription or access during the screening or dosing period of the study; any clinically significant infection or evidence of an underlying infection such as a WBC > ULN during screening on 2 separate occasions; positive for HIV, HBsAg, anti-HCV Ab; history of chronic liver disease; NYHA Class III or IV congestive heart failure; chronic inflammatory disease other than GN that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; active or chronic GI bleeding, or a known coagulation disorder; haemoglobinopathy (e.g. homozygous sickle-cell disease, thalassaemia of all types); haematological disorders, including myelodysplastic syndrome, multiple myeloma, or PRCA; history of haemosiderosis, haemochromatosis, PCKD, or anephric; active haemolysis or diagnosis of HUS; known bone marrow fibrosis; uncontrolled or symptomatic secondary hyperparathyroidism (PTH > 600 ng/L); any prior organ transplantation; drug-treated gastroparesis, short-bowel syndrome, or any other GI condition that may lead to reduced absorption of study drug; history of alcohol or drug abuse; positive drug screen for a substance that has not been prescribed for the subject; prior treatment with FG-4592; use of TCM during the screening visit to day 1 or plans to use TCM during the study unless approved in advance by the Medical Monitor • Target Hb: ≥ 1 g/dL

Chen DD 2017 *(Continued)*

Baseline characteristics

- CKD stage: eGFR of 10 to < 60 mL/min/1.73 m² (patients undergoing dialysis were not included)
- Number (randomised/analysed): treatment group 1 (22/22); treatment group 2 (21/18); treatment group 3 (22/20); control group (22/22)
- Mean age ± SD (years): treatment group 1 (49.9 ± 14.7); treatment group 2 (50.2 ± 69.3); treatment group 3 (49.8 ± 13.5); control group (53.8 ± 10.0)
- Sex (M, %): treatment group 1 (14, 64%); treatment group 2 (12, 58.3%); treatment group 3 (13, 60%); control group (13, 59.1%)
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes(number, %): not reported
- Prior agents used(number, %): not reported

Interventions	**Treatment group 1 (low dose)*** • Roxadustat (FG-4592): 1.1 to 1.8 mg/kg 3 times/week, using weight-tiered dosing (40 to 60 kg, > 60 to 80 kg or > 80 to 100 kg) for 8 weeks **Treatment group 2 (medium dose)** • Roxadustat (FG-4592): 1.5 to 2.3 mg/kg 3 times/week, using weight-tiered dosing (40 to 60 kg, > 60 to 80 kg or > 80 to 100 kg) for 8 weeks **Treatment group 3 (high dose)** • Roxadustat (FG-4592): 1.7 to 2.3 mg/kg 3 times/week, using weight-tiered dosing (40 to 60 kg, > 60 to 80 kg or > 80 to 100 kg) for 8 weeks **Control group** • EPO alfa **Co-interventions** • Oral iron supplementation was allowed *Note: dose assessed according to NCT01888445
Outcomes	**Primary outcomes** • The percentage of subjects with successful dose conversion defined as a Hb level maintained at no less than 0.5 g/dL below mean baseline value (baseline was mean of 3 measurements on day 1 and two previous) during the last 2 weeks of the 6-week dosing period in the EE population • Mean change from baseline in Hb after 6 weeks due to HIF **Secondary outcomes** • Laboratory parameters assessed at baseline and end of treatment
Notes	• Funding: FibroGen • Conflicts of interest: "S.H. served as lead medical writer and illustrator of this manuscript.D.N., C.L., S.H., L.S., A.B., T.B.N., K.P.Y. and F.H.V. are employees of FibroGen and hold stock and/or stock options in FibroGen. T.B.N. and K.P.Y. have patents regarding FG4592 and HIF-PHIs. N.C., J.Q., C.M., C.H. and L.Z. received honoraria and non financial support from FibroGen for speaking engagements and advisory board participation related to physician education. Institutions of N.C., J.Q., J.C., X.Y., C.M., H.L., C.H.,

Chen DD 2017 *(Continued)*

G.J., L.Z., X.Z. and X.L. received funding from FibroGen to conduct the clinical study covered by the work herein"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The open-label DD study."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of 65 subjects, 5 that were randomized to FG-4592 withdrew from the study within 2 weeks, including a subject who incorrectly received a single dose of epoetin-alfa and a subject who developed a Grade 1rash. The other three early terminations withdrew consent. Therefore, the pre-specified EE population" 22/22 participants in treatment group 1, 18/22 participants in treatment group 2, 20/22 participants in treatment group 3, 22/22 participants in control group were included into the analysis (< 5% lost to follow-up, with differences between groups) Reasons for discontinuations were reported as follows: "Withdrawn due to having had one dose of epoetin alfa (prohibited medication) administered in error, brash (hypersensitivity)."
Selective reporting (reporting bias)	High risk	All of the planned outcomes on ClincialTrials.gov have been measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups FibroGen Inc. was the study sponsor that designed the study in consultation with the Principal Investigators (N.C. and J.Q.) FibroGen was responsible for data collection and analysis Authors declared conflicts of interest

Chen NDD 2017

Study characteristics

Chen NDD 2017 *(Continued)*

Methods	• Study design: parallel RCT • Time frame: December 2011 to August 2012 • Duration of follow-up: 8 weeks

Participants	**General information**
	• Setting: multicentre (11 sites)
	• Country: China
	• Inclusion criteria: aged 18 to 80 years; voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study had been explained and the subject had the opportunity to ask questions; CKD with eGFR 10 to < 60mL/min/1.73 m^2 not requiring dialysis; Hb value in 4 screening visits and mean Hb < 10.0 g/dL during the screening period, with only one Hb value exception in the 4 screening visits; ALT and AST ≤ ULN during the screening period; ALP ≤ 2 times ULN; total bilirubin ≤ ULN during the screening period; serum folate and vitamin B12 levels > LLN; weight 40 to 100 kg; BMI: 16 to 38 kg/m^2; subjects taking TCM agreed not to change dose, schedule or brand from beginning of screening through end of follow-up without prior approval by the Medical Monitor
	• Exclusion criteria: received any ESA within 12 weeks prior to day 1; any clinically significant infection or evidence of an active underlying infection such as a WBC count > ULN during screening on 2 separate occasions; positive for any of the following: HIV, HBsAg, or Anti-HCV Ab; history of chronic liver disease; serum albumin < 11 g/dL; NYHA class III or IV congestive heart failure; MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event (e.g. deep venous thrombosis or pulmonary embolism) within 12 weeks prior to day 1); uncontrolled hypertension (SBP > 170 mm Hg or DBP >110 mm Hg) noted during screening on 2 separate occasions; history of malignancy (except cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ); chronic inflammatory disease other than GN that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it was in remission; active or chronic GI bleeding, or a known coagulation disorder; haemoglobinopathy (e.g. homozygous sickle-cell disease, thalassaemia of all types); haematological disorders, including myelodysplastic syndrome, multiple myeloma, or PRCA; history of haemosiderosis, haemochromatosis or PCKD; active haemolysis or diagnosis of haemolytic syndrome; known bone marrow fibrosis; uncontrolled or symptomatic secondary hyperparathyroidism (PTH > 600 ng/L); seizure disorder or having received anti-epilepsy medication for seizure disorder in the 6 months prior to screening; any prior or anticipated (during study period) organ transplantation; anticipated elective surgery during the study period; life expectancy < 12 months; drug-treated gastroparesis, short-bowel syndrome, or any other GI condition that could lead to reduced absorption of study drug; anticipated use of dapsone or acetaminophen > 2.0 g/day, or > 500 mg/dose repeated every 6 hours, during the screening visit and the treatment or follow-up periods of the study; androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to day 1; RBC transfusion within 12 weeks prior to day 1 or anticipated need for transfusion during the dosing period; IV iron supplement during the screening visit and /or unwilling to withhold IV iron during the dosing period; immune suppressive or steroid treatment within 12 weeks prior to day 1; history of alcohol or drug abuse within the past year and inability to avoid consumption of more than 3 alcoholic beverages/day during the dosing period; or a positive drug screen for a substance that has not been prescribed for the subject; prior treatment with FG-4592; use of an investigational medication or treatment, participation in an investigational interventional study, or carryover effect of an investigational treatment expected, during the screening visit, treatment and follow-up period; pregnant or breastfeeding; females of childbearing potential and males with sexual partners of child bearing potential, unless they were using contraception as detailed in the protocol (Section 4.5.3); any medical condition that in the opinion of the investigator or could pose a safety risk to a subject in this study or which could interfere with study participation
	• Target Hb
	  ○ Hb ≥ 11 g/dL
	  ○ ≥1 g/dL (data were reported considering this definition)
	Baseline characteristics
	• CKD stage: CKD, eGFR of 10 to < 60 (patients undergoing dialysis were not included)
	• Number (randomised/analysed): treatment group 1 (30/30); treatment group 2 (31/31); control group (30/30)

Chen NDD 2017 *(Continued)*

- Mean age ± SD (years): treatment group 1 (48.1 ± 13); treatment group 2 (49.6 ± 13.8); control group (51.4 ± 11.9)
- Sex (M, %): treatment group 1 (8, 26.7%); treatment group 2 (10, 32.3%); control group (8, 26.7%)
- Time on dialysis: not applicable
- Mean eGFR ± SD (mL/min/1.73 m^2): treatment group 1 (21.1 ± 10.2); treatment group 2 (17.7 ± 8.6); control group (23.0 ± 13.4)

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %)
  - Oral iron supplementation: not reported

Interventions	**Treatment group 1 (low dose)*** • Roxadustat (FG-4592): 1.1 to 1.75 mg/kg 3 times/week, using weight tiered dosing (40 to 60 kg, > 60 to 80 kg or > 80 to 100 kg) for 8 weeks **Treatment group 2 (high dose)** • Roxadustat (FG-4592): 1.50 to 2.25 mg/kg 3 times/week, using weight tiered dosing (40 to 60 kg, > 60 to 80 kg or > 80 to 100 kg), for 8 weeks **Control group** • Placebo (oral): 3 times/week for 8 weeks **Co-interventions** • Oral iron supplementation was allowed *Note: dose assessed according to NCT01888445
Outcomes	**Primary outcomes** • The percentage of subjects with successful dose conversion defined as a Hb level maintained at no less than 0.5 g/dL below mean baseline value (baseline was mean of 3 measurements on day 1 and 2 previous) during the last 2 weeks of the 6-week dosing period in the EE population • Mean change from baseline in Hb after 6 weeks due to HIF **Secondary outcomes** • Laboratory parameters assessed at baseline and end or treatment
Notes	• Funding: FibroGen • Conflicts of interest: "S.H. served as lead medical writer and illustrator of this manuscript.D.N., C.L., S.H., L.S., A.B., T.B.N., K.P.Y. and F.H.V. are employees of FibroGen and hold stock and/or stock options in FibroGen. T.B.N. and K.P.Y. have patents regarding FG4592 and HIF-PHIs. N.C., J.Q., C.M., C.H. and L.Z. received honoraria and non financial support from FibroGen for speaking engagements and advisory board participation related to physician education. Institutions of N.C., J.Q., J.C., X.Y., C.M., H.L., C.H., G.J., L.Z., X.Z. and X.L. received funding from FibroGen to conduct the clinical study covered by the work herein"

Risk of bias

Bias	Authors' judgement	Support for judgement

Chen NDD 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: “Qualified subjects were randomized 2:1 to FG-4592 or placebo orally thrice weekly (TIW) sequentially into first low- (1.1–1.75 mg/kg) and then high-dose (1.50–2.25 mg/kg) FG-4592 cohorts using weight tiered dosing (40–60 kg, >60 to 80 kg or >80 to 100 kg), and were treated for 8 weeks.” Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: “The double-blinded NDD study.” Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. However, since interventions were different, it was possible that investigators and/or participants were aware of treatment allocation. In the treatment groups were reported side effects that participants and/or investigators could know to be specific for one of the interventions. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. Reporting of some outcomes (adverse effects) were unlikely to be biased because outcome assessors were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “The intent-to-treat (ITT) populations included all randomized subjects in each study. The safety populations in both studies included all subjects that had received at least one dose of study drug (FG-4592, placebo or active comparator)”. Quote: "Two adverse events in the low dose FG-4592 arm were urinary tract infection and worsening chronic renal failure. The one placebo subject was discontinued for adverse event of worsening anaemia (and received rescue therapy)." Quote: “91 subjects were randomized from December 2011 to August 2012 to receive either FG-4592 (n = 61) or placebo (n = 30) at 11 study sites in China (Figure 1A), constituting both ITT and safety populations” All ITT populations analysed in groups to which they were allocated. 4/2/3 discontinued treatment but all included in the analyses
Selective reporting (reporting bias)	High risk	All of the planned outcomes on ClincialTrials.gov have been measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups FibroGen Inc. was the study sponsor that designed the study in consultation with the Principal Investigators (N.C. and J.Q.). FibroGen was responsible for data collection and analysis Authors declared conflicts of interest

DIALOGUE 1 2019

Study characteristics	
Methods	• Study design: phase 2b parallel RCT • Time frame: not reported • Duration of follow-up: 17 weeks (16 weeks treatment)
Participants	**General information** • Setting: multicentre (56 sites) • Country: multinational (Bulgaria, France, Germany, Hungary, Italy, Israel, Poland, Romania, Spain, Turkey, UK, South Korea, Australia, and Japan) • Inclusion criteria: women without childbearing potential; male or female subjects ≥ 18 years with anaemia of CKD at screening; eGFR of < 60 mL/min/1.73 m^2 (MDRD or the formula according to Matsuo, et al); not on dialysis and not expected to begin dialysis during the treatment period of the study (at least 16 weeks from randomisation); not treated with any ESA within 8 weeks before randomisation; mean screening Hb concentration ≤ 10.5 g/dL; weight of 45 kg to 125 kg at screening • Exclusion criteria: subjects with significant acute or chronic bleeding, such as overt GI bleeding; chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; previous or concurrent cancer except cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis, and T1) or any cancer curatively treated > 3 years prior to randomisation; subjects treated with any ESA within the 8 weeks before randomisation; RBC containing transfusion within the 8 weeks before randomisation; history of cardio-(cerebro-) vascular events (e.g. unstable angina, MI, stroke, TIA, DVT, pulmonary embolism) within the last 6 months from initial screening visit; severe rhythm or conduction disorders (e.g. heart rate < 50 or > 110 bpm, atrial flutter, prolonged QT > 500 msec, third degree atrioventricular block); NYHA class III or IV congestive heart failure; severe hepatic insufficiency (ALT or AST > 3 times ULN, total bilirubin > 2 mg/dL, or Child-Pugh B and C) or active hepatitis, in the investigator's opinion • Target Hb: not reported **Baseline characteristics** • CKD stage: CKD who were not receiving dialysis treatment • Number (randomised/analysed): treatment group 1 (19/19); treatment group 2 (21/21); treatment group 3 (22/22); treatment group 4 (19/19); treatment group 5 (20/20); control group (20/20) - ITT and FAS • Mean age ± SD (years): treatment group 1 (69 ± 12); treatment group 2 (68 ± 13); treatment group 3 (71 ± 10; treatment group 4 (70 ± 12); treatment group 5 (65 ± 13); control group (67.1 ± 15.9) • Sex (M, %): treatment group 1 (14, 74%); treatment group 2 (9, 43%); treatment group 3 (13, 59%); treatment group 4 (10, 53%); treatment group 5 (10, 50%); control group (9, 45%) • Time on dialysis: not applicable • MeaneGFR ± SD (mL/min/1.73 m^2): treatment group 1 (25 ± 14); treatment group 2 (23 ± 11); treatment group 3 (24 ± 10); treatment group 4 (25 ± 12); treatment group 5 (21 ± 14); control group (23.0 ± 11.6) **Comorbidities** • CVdisease: not reported • Heart disease: not reported • Hypertension: not reported • Diabetes (number, %): not reported • Prior agents used (number, %): not reported
Interventions	**Treatment group 1 (low dose)*** • Molidustat (BAY85-3934) 25 mg once/day **Treatment group 2 (medium dose)** • Molidustat (BAY85-3934) 50 mg once/day

DIALOGUE 1 2019 *(Continued)*

Treatment group 3 (high dose)

- Molidustat (BAY85-3934) 75 mg once/day

Treatment group 4 (medium dose)

- Molidustat (BAY85-3934) 25 mg twice/day (50 mg in total)

Treatment group 5 (high dose)

- Molidustat (BAY85-3934) 50 mg twice/day (100 mg in total)

Control group

- Placebo

Co-interventions

- Iron supplementation was left at the discretion of the investigator

*Note: this study was considered as a reference for HIF dosage

Outcomes	**Primary outcomes** • Change in local laboratory Hb from baseline to the average during the last 4 weeks treatment period (baseline and week 12 to 16) **Secondary outcomes** • Change in local laboratory Hb baseline up to 12 weeks • Speed of change in Hb/unit time (up to 16 weeks • Duration of treatment exposure (up to 16 weeks) • Number with serious adverse events as a measure of safety and tolerability (up to 16 weeks) • Pharmacodynamics characterised by EPO concentration (several time points up to 16 weeks) • Pharmacodynamics characterised by reticulocyte count (several time points up to 16 weeks) • ECG and vital signs were measured during the study period
Notes	• Funding: Bayer AG • Conflicts of interest: "T.A.: has received consulting fees from Astellas, Bayer Yakuhin Ltd., GlaxoSmithKline, J.T. Pharmaceuticals, Kissei Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, Nipro Corporation, Fuso Pharmaceutical Industries Ltd., and Ono Pharmaceutical Co. Ltd., and lecture fees from Bayer Yakuhin Ltd., Chugai Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, and Torii Pharmaceutical Co. Ltd. I.C.M. has received research funding for the DIALOGUE studies, honoraria for steering committee activities, and speaker fees from Bayer Pharma AG; and has received research support and speakers' honoraria from Akebia, Astellas, FibroGen, and GlaxoSmith- Kline. J.S.B. has served on the executive committees for the DIALOGUE studies and for an Amgen-sponsored darbepoetin clinical trial. M.T. and K.I. are employees of Bayer Yakuhin Ltd. T.B. is an employee of Bayer AG"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Macdougall 2019 quote: "At the randomizations visit, the investigator had to check the patient's eligibility and stratification factor levels; an interactive response system subsequently randomly assigned the treatment group according to computer generated randomisation lists." No imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Low risk	Macdougall 2019 quote: "At the randomizations visit, the investigator had to check the patient's eligibility and stratification factor levels; an interactive response system subsequently randomly assigned the treatment group accord-

DIALOGUE 1 2019 *(Continued)*

		ing to computer generated randomisation lists." No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind." Macdougall 2019 quote: "Both, patients and physicians were blinded to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Macdougall 2019 quote: "An independent adjudication committee assessed all deaths and any serious AEs of severe arrhythmias, thromboembolic events, syncope or symptomatic hypotension, or heart failure." It was not reported if the independent adjudication committee was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Akizawa 2019 (Nephron) quote: "Of 121 patients randomized in D1, all (101 molidustat, 20 placebo) were included in the FAS and ITT population, and 60 patients (59.5%) receiving molidustat and 2 patients (10.0%) receiving placebo discontinued the study. Of those who discontinued molidustat, the majority discontinued by the last 4 weeks and had a blood Hb concentration above the upper limit of 13 g/dL or an increase in blood Hb concentration of > 1.0 g/dL in 2 weeks." All participants were included in FAS and ITT analyses
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

DIALOGUE 2 2019

Study characteristics	
Methods	• Study design: phase 2b parallel RCT • Time frame: not reported • Duration of follow-up: 17 weeks (16 weeks treatment)
Participants	**General information** • Setting: multicentre (51 sites) • Country: multinational (Bulgaria, France, Germany, Hungary, Italy, Israel, Poland, Romania, Spain, Turkey, UK, South Korea, Australia, and Japan) • Inclusion criteria: Males or females ≥ 18 years with anaemia of CKD at screening; eGFR < 60 mL/min/1.73 m^2; not on dialysis and not expected to begin dialysis during the treatment period of the study (at least 16 weeks from randomisation); treated with darbepoetin via (IV or SC route with a weekly, bi-weekly, or monthly dose, having had no more than 1 dose change within 8 weeks prior to randomisation; at least one kidney; mean screening Hb of 10.0 to 12.0 g/dL; men who agree to use adequate contraception when sexually active or women without childbearing potential

DIALOGUE 2 2019 *(Continued)*

- Exclusion criteria: subjects with significant acute or chronic bleeding, such as overt GI bleeding; active haemolysis or diagnosis of haemolytic syndrome; history of myelodysplastic syndrome, multiple myeloma, marrow fibrosis, or PRCA; history of haemosiderosis or haemochromatosis; hereditary haemoglobinopathies (such as sickle cell disease and thalassaemia major); aplastic anaemia; chronic lymphoproliferative diseases; proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy that is likely to require invasive treatment (intraocular injections or laser photocoagulation) during the study; chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; known hypersensitivity to the study drugs (active substances or excipients of the preparations); uncontrolled and symptomatic hyperparathyroidism; uncontrolled active infection; previous or concurrent cancer except cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumours (Ta, Tis, and T1) or any cancer curatively treated > 3 years prior to randomisation; any allograft (including kidney allograft) in place and on immunosuppressive therapy or a scheduled kidney transplant within the next 16 weeks (being on a waiting list does not exclude the subject)
- Target Hb: 10.0 to 12.0 g/dL

Baseline characteristics

- CKD stage: CKD who were not receiving dialysis treatment
- Number (randomised/analysed): treatment group 1 (30/30); treatment group 2 (30/30); treatment group 3 (32/32); control group (32/32) - ITT and FAS
- Mean age ± SD (years): treatment group 1 (66 ± 9); treatment group 2 (65 ± 10); treatment group 3 (73 ± 11); control group (68.8 ± 8.7)
- Sex (M, %): treatment group 1 (12, 40%); treatment group 2 (17, 57%); treatment group 3 (16, 50%); control group (18, 56.2%)
- Time on dialysis: not applicable
- MeaneGFR ± SD (mL/min/1.73 m^2): treatment group 1 (20 ± 10); treatment group 2 (18 ± 9); treatment group 3 (23 ± 14); control group (21.9 ± 12.1)

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): all participants used ESA before randomisation

Interventions

Treatment group 1 (low dose)*

- Molidustat (BAY85-3934): 25 mg once/day
- Dose regimens were adapted every 4 (± 1) weeks for each patient based on changes in blood Hb concentrations at the previous dose to achieve or maintain Hb levels of 10.0 to 12.0 g/dL

Treatment group 2 (medium dose)

- Molidustat (BAY85-3934): 50 mg once/day
- Dose regimens were adapted every 4 (± 1) weeks for each patient based on changes in blood Hb concentrations at the previous dose to achieve or maintain Hb levels of 10.0 to 12.0 g/dL

Treatment group 3 (high dose)

- Molidustat (BAY85-3934) 75 mg once/day
- Dose regimens were adapted every 4 (± 1) weeks for each patient based on changes in blood Hb concentrations at the previous dose to achieve or maintain Hb levels of 10.0 to 12.0 g/dL

Control group

- Darbepoetin alfa
- Darbepoetin was dosed according to prescribing information and the site's standard practice

DIALOGUE 2 2019 *(Continued)*

Co-interventions

- Iron supplementation was left to the discretion of the investigator

*Note: dose assessed according to DIALOGUE 1 2019

Outcomes

Primary outcomes

- Change in local laboratory Hb from baseline to the average during the last 4 weeks treatment period (baseline and week 12 to 16)

Secondary outcomes

- Maintenance in Hb target range (10.0 to 12.0 g/dL) (up to 16 weeks)
- Change in Hb (baseline up to 16 weeks)
- Number of patients with Hb outside the target range (week 12 to 16)
- Dose level in the evaluation period (week 12 to 16)
- Duration of exposure on each dose level (up to 16 weeks)
- Number of subjects requiring titration of dose (up to 16 weeks)
- Number of participants with serious adverse events as a measure of safety and tolerability (up to 16 weeks)
- ECG at vital signs were measured during the study period

Notes

- Funding: Bayer AG
- Conflicts of interest: "T.A.: has received consulting fees from Astellas, Bayer Yakuhin Ltd., GlaxoSmithKline, J.T. Pharmaceuticals, Kissei Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, Nipro Corporation, Fuso Pharmaceutical Industries Ltd., and Ono Pharmaceutical Co. Ltd., and lecture fees from Bayer Yakuhin Ltd., Chugai Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, and Torii Pharmaceutical Co. Ltd. I.C.M. has received research funding for the DIALOGUE studies, honoraria for steering committee activities, and speaker fees from Bayer Pharma AG; and has received research support and speakers' honoraria from Akebia, Astellas, FibroGen, and GlaxoSmith- Kline. J.S.B. has served on the executive committees for the DIALOGUE studies and for an Amgen-sponsored darbepoetin clinical trial. M.T. and K.I. are employees of Bayer Yakuhin Ltd. T.B. is an employee of Bayer AG"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Macdougall 2019 quote: "At the randomizations visit, the investigator had to check the patient's eligibility and stratification factor levels; an interactive response system subsequently randomly assigned the treatment group according to computer generated randomisation lists." No imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Low risk	Macdougall 2019 quote: "At the randomizations visit, the investigator had to check the patient's eligibility and stratification factor levels; an interactive response system subsequently randomly assigned the treatment group according to computer generated randomisation lists." No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Macdougall 2019 quote: "An independent adjudication committee assessed all deaths and any serious AEs of severe arrhythmias, thromboembolic events, syncope or symptomatic hypotension, or heart failure."

DIALOGUE 2 2019 *(Continued)*

		It was not reported if the independent adjudication committee was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Akizawa 2019 (Nephron) quote: "In D2, all of the 124 randomized patients (92 molidustat, 32 darbepoetin) were included in the FAS and ITT population, and 20 patients (21.7%) receiving molidustat and 5 patients (15.6%) receiving darbepoetin discontinued the study." All participants were included in FAS and ITT analyses
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

DIALOGUE 4 2019

Study characteristics	
Methods	• Study design: phase 2b parallel RCT • Time frame: not reported • Duration of follow-up: 17 weeks (16 weeks treatment)
Participants	**General information** • Setting: multicentre (number of sites not reported) • Country: multinational (USA and Japan) • Inclusion criteria: male or female subject ≥ 18 years with anaemia of CKD at screening; women without childbearing potential; on dialysis, defined as regular long-term HD, with the same modality of dialysis for ≥ 3 months before randomisation; dialysis vascular access via native AVF, synthetic graft, long-term catheters, or long-term tunnelled catheters; treated with epoetin alfa (USA or Japan) or epoetin beta (Japan) via IV or SC route, on stable dosing defined as < 50% change from the maximum prescribed weekly dose with no change in the prescribed frequency during the last 8 weeks prior to randomisation; at least one kidney; mean screening Hb concentration 9.0 to 11.5 g/dL inclusive (mean of all local laboratory Hb measurements (at least 2 measurements must be taken ≥ 2 days apart) during the 4 week screening period, AND none of the measurements can be < 9.0 g/dL or > 12.0 g /dL; serum ferritin ≥ 100 µg/L OR TSAT ≥ 20% at screening; iron substitution is allowed; folate and vitamin B12 levels above the LLN; supplementation is allowed • Exclusion criteria: significant acute or chronic bleeding, such as overt GI bleeding; hereditary haemoglobinopathies (including, but not limited to, sickle cell disease, beta thalassaemia, and thalassaemia major) which may be the primary cause of anaemia; chronic lymphoproliferative diseases; any allograft (including kidney allograft) in place and on immunosuppressive therapy, or a scheduled kidney transplant within the next 16 weeks (being on a waiting list does not exclude the subject); chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease); subjects treated with immuno- or myelosuppressive therapy within 8 weeks prior to randomisation (e.g. everolimus, sirolimus, rituximab, AZA, mycophenolate mofetil, mycophenolic acid, cyclosporine, methotrexate, tacrolimus, chemotherapeutic agents and other anticancer agents, and systemic steroids (except inhaled steroids) for 7 days); RBC-containing transfusion within 8 weeks before randomisation; history of cardio- (cerebro-) vascular events (e.g. unstable angina, MI, stroke, TIA, DVT, pulmonary embolism) within the last 6 months from the initial screening visit; sustained, poorly

DIALOGUE 4 2019 *(Continued)*

controlled arterial hypertension or hypotension at screening, defined as a mean BP ≥ 180/110 mm Hg or SBP < 95 mm Hg, respectively; severe rhythm or conduction disorder (e.g. heart rate < 50 or > 110 bpm, atrial flutter, prolonged QT > 500 msec, second or third degree atrioventricular block if not treated with a pacemaker) NYHA class III or IV congestive heart failure; severe hepatic insufficiency (defined as ALT, aspartate AST, or gamma-glutamyl transferase > 3 times ULN, total bilirubin > 2 mg/dL, or Child-Pugh B or C) or active hepatitis in the investigator's opinion; scheduled surgery that may be expected to lead to significant blood loss

- Target Hb: 10.0 to 11.0 g/dL

Baseline characteristics

- CKD stage: HD
- Number (randomised/analysed): treatment group 1 (44/44); treatment group 2 (40/40); treatment group 3 (44/44); treatment group 4 (29/29); control group (42/42) - ITT and FAS
- Mean age ± SD (years): treatment group 1 (63 ± 11); treatment group 2 (59 ± 13); treatment group 3 (58 ± 13); treatment group 4 (58 ± 14); control group (58.9 ± 9.1)
- Sex (M, %): treatment group 1 (26, 59%); treatment group 2 (23, 57%); treatment group 3 (24, 55%); treatment group 4 (18, 62%); control group (29, 69%)
- Time on dialysis (years): treatment group 1 (6 ± 5.9); treatment group 2 (5 ± 5.6); treatment group 3 (4 ± 3.6); treatment group 4 (5 ± 5.3); control group (5.3 ± 4.0)
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): all participants used ESA before randomisation

Interventions

Treatment group 1 (low dose)*

- Molidustat (BAY85-3934): 25 mg
- Dose regimens were adapted every 4 (±1) weeks for each patient based on changes in blood Hb concentrations at the previous dose to achieve or maintain Hb levels of 10.0 to 11.0 g/dL

Treatment group 2 (medium dose)

- Molidustat (BAY85-3934): 50 mg
- Dose regimens were adapted every 4 (±1) weeks for each patient based on changes in blood Hb concentrations at the previous dose to achieve or maintain Hb levels of 10.0 to 11.0 g/dL

Treatment group 3 (high dose)

- Molidustat (BAY85-3934): 75 mg
- Dose regimens were adapted every 4 (±1) weeks for each patient based on changes in blood Hb concentrations at the previous dose to achieve or maintain Hb levels of 10.0 to 11.0 g/dL

Treatment group 4 (high dose)

- Molidustat (BAY85-3934): 150 mg
- Dose regimens were adapted every 4 (±1) weeks for each patient based on changes in blood Hb concentrations at the previous dose to achieve or maintain Hb levels of 10.0 to 11.0 g/dL

Control group

- Epoetin alfa or beta
- Epoetin was dosed according to prescribing information and the site's standard practice

Co-interventions

DIALOGUE 4 2019 *(Continued)*

- Iron supplementation was left at the discretion of the investigator

*Note: dose assessed according to DIALOGUE 1 2019

Outcomes	**Primary outcomes** • Change in local laboratory Hb from baseline to the average during the last 4 weeks treatment period (baseline and weeks 14 to 17) **Secondary outcomes** • Mean of the Hb levels in the target range (10.0 to 11.0 g/dL) (weeks 14 to 17) • Mean of the Hb in the target range (9.5 to 11.5 g/dL) (weeks 14 to 17) • Change from baseline in Hb during active treatment (baseline and weeks 14 to 17) • Number of patients with Hb outside the target range (weeks 14 to 17) • Dose level in the evaluation period (up to 16 weeks) • Duration of exposure on each dose level (up to 16 weeks) • Number of subjects requiring titration of dose (up to 16 weeks) • Number of participants with serious adverse events as a measure of safety and tolerability (up to 16 weeks) • ECG at vital signs were measured during the study period
Notes	• Funding: Bayer AG • Conflicts of interest: "T.A.: has received consulting fees from Astellas, Bayer Yakuhin Ltd., GlaxoSmithKline, J.T. Pharmaceuticals, Kissei Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, Nipro Corporation, Fuso Pharmaceutical Industries Ltd., and Ono Pharmaceutical Co. Ltd., and lecture fees from Bayer Yakuhin Ltd., Chugai Pharmaceutical Co. Ltd., Kyowa Hakko Kirin, and Torii Pharmaceutical Co. Ltd. I.C.M. has received research funding for the DIALOGUE studies, honoraria for steering committee activities, and speaker fees from Bayer Pharma AG; and has received research support and speakers' honoraria from Akebia, Astellas, FibroGen, and GlaxoSmith- Kline. J.S.B. has served on the executive committees for the DIALOGUE studies and for an Amgen-sponsored darbepoetin clinical trial. M.T. and K.I. are employees of Bayer Yakuhin Ltd. T.B. is an employee of Bayer AG"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Macdougall 2019 quote: "At the randomizations visit, the investigator had to check the patient's eligibility and stratification factor levels; an interactive response system subsequently randomly assigned the treatment group according to computer generated randomisation lists." No imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Low risk	Macdougall 2019 quote: "At the randomizations visit, the investigator had to check the patient's eligibility and stratification factor levels; an interactive response system subsequently randomly assigned the treatment group according to computer generated randomisation lists." No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Macdougall 2019 quote: "An independent adjudication committee assessed all deaths and any serious AEs of severe arrhythmias, thromboembolic events, syncope or symptomatic hypotension, or heart failure."

DIALOGUE 4 2019 *(Continued)*

		It was not reported if the independent adjudication committee was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Akizawa 2019 (Nephron) quote: "All of the 199 patients randomized in D4 (157 molidustat, 42 epoetin) were included in the FAS and ITT population, and 53 patients (33.8%) receiving molidustat and 3 patients (7.1%) receiving epoetin discontinued the study." All participants were included in FAS and ITT analyses
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interest

DOLOMITES 2021

Study characteristics	
Methods	• Study design: phase 3, parallel RCT • Time frame: March 2014 to June 2018 • Duration of follow-up: 2 years
Participants	**General information** • Setting: multicentre (156 sites) • Country: international (Austria, Belarus, Bulgaria, Croatia, Czech Republic, Finland, France, Georgia, Germany, Hungary, Ireland, Israel, Latvia, Montenegro, Netherlands, North Macedonia, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Ukraine, UK) • Inclusion criteria: diagnosis of CKD KDOQI Stage 3, 4 or 5, not on dialysis; eGFR < 60 mL/min/1.73 m^2 estimated using MDRD equation; mean Hb ≤ 10.5 g/dL, with a difference of ≤ 1.0 g/dL; deemed suitable for treatment with ESA using the criteria specified in the KDIGO 2012 recommendation considering the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anaemia; serum folate ≥ LLN at screening; serum vitamin B12 ≥ LLN at screening; ALT and AST ≤ 3 times ULN, and total bilirubin ≤ 1.5 times ULN; weight 45.0 kg to 160.0 kg; males must not donate sperm starting from screening, throughout the study period and up to 12 weeks after final study drug administration • Exclusion criteria: received any ESA treatment within 12 weeks prior to randomisation; received any dose of IV iron within 6 weeks prior to randomisation; received a RBC transfusion within 8 weeks prior to randomisation; subject has a known history of myelodysplastic syndrome or multiple myeloma; known hereditary haematologic disease such as thalassaemia or sickle cell anaemia, PRCA, or other known causes for anaemia other than CKD; known haemosiderosis, haemochromatosis, coagulation disorder, or hypercoagulable condition; known chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; anticipated to undergo elective surgery that is expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization; active or chronic GI bleeding; received any prior treatment with roxadustat or a HIF-PHI; treated with iron-chelating agents within 4 weeks prior to randomisation; history of chronic liver disease (e.g. cirrhosis or fibrosis of the liver); known NYHA class III or IV congestive heart failure; MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (e.g. DVT or pulmonary embolism) within 12 weeks prior to randomisation;

DOLOMITES 2021 *(Continued)*

one or more contraindications for treatment with darbepoetin alfa; uncontrolled hypertension, or 2 or more SBP ≥160 mm Hg or DBP ≥ 95 mm Hg within 2 weeks prior to randomisation; known hypersensitivity to darbepoetin alfa, rHuEPO, or any of the excipients; subject has a diagnosis or suspicion (e.g. complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma as shown on renal ultrasound within 12 weeks prior to randomisation; history of malignancy, except cancers determined to be cured or in remission ≥ 5 years, curatively basal cell or squamous cell skin cancers, cervical cancer in situ, or colonic polyps; positive for HIV, HBsAg or Anti-HCV Ab; active clinically significant infection that is manifested by WBC > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection within 1 week prior to randomisation; known untreated proliferative diabetic retinopathy, diabetic macular oedema, macular degeneration or retinal vein occlusion; subject has had any prior organ transplant (that has not been explanted), subject is scheduled for organ transplantation, or subject is likely to initiate KRT including dialysis within the first year of the study; has received investigational therapy within 30 days or 5 half-lives or limit set by national law, whichever is longer, prior to initiation of screening, condition which makes the subject unsuitable for study participation; an anticipated use of dapsone in any dose amount or chronic use of acetaminophen/paracetamol >2.0 g/day during the treatment or follow-up period of the study; subject has a history of alcohol or drug abuse within 2 years prior to randomisation

- Target Hb: 10 to 12 g/dL

Baseline characteristics

- CKD stage: CKD stages 3, 4, or 5
- Number (randomised/analysed): treatment group (323/215); control group (293/209) - ITT analysis
- Mean age ± SD (years): treatment group (66.8 ± 13.6); control group (65.7 ± 14.4)
- Sex (M, %): treatment group (145, 44.9%); control group (129, 44%)
- Time on dialysis (years): not applicable
- Mean eGFR ± SD (mL/min/1.73 m^2): treatment group (20.31 ± 11.49); control group (20.34 ± 10.73)

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %)
  - ESA: treatment group (22/323); control group (17/293)
  - IV iron: treatment group (47/323); control group (39/293)
  - Oral iron: treatment group (142/323); control group (155/293)

Interventions

Treatment group (high dose)*

- Roxadustat (ASP1517): 3 times/week
- Initial roxadustat dose from 70, 100 and 150 mg to 70 and 100mg; (maximum dose from 3.5 to 3.0 mg/kg and maximum absolute dose from 400 to 300 mg
- The mean SD weekly dose consumed was 223.20 (127.43) mg

Control group

- Darbepoetin alfa (Aranesp): 3 times/week

Co-interventions

- Not reported

*Note: dose assessed according to NCT01888445

Outcomes

Primary outcomes

- Hb response to treatment with roxadustat without the use of rescue therapy (up to week 24)

DOLOMITES 2021 *(Continued)*

Secondary outcomes

- Hb change from baseline to the average Hb, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period (baseline and weeks 28 to 36)
- Change from baseline in LDL cholesterol to the average LDL cholesterol (baseline and weeks 12 to 28)
- Mean monthly IV iron (mg) use/subject (up to week 36)
- Change from baseline in SF-36 Physical Functioning sub-score to the average Physical functioning sub-score (baseline and weeks 12 to 28)
- Change from in SF-36 Vitality sub-score to the average Vitality sub-score (baseline and weeks 12 to 28)
- Change from baseline in MAP to the average MAP value (baseline and weeks 20 to 28)
- Occurrence of hypertension (up to week 36)
- Time to occurrence of hypertension (up to week 36)
- Hb change from baseline to the average Hb value regardless of rescue therapy (baseline and weeks 28 to 52)
- Time (weeks) to achieve the first Hb response as defined by primary endpoint
- Hb response (up to week 24)
- Hb averaged over weeks 28 to 36, 44 to 52, 72 to 80, 96 to 104, without use of rescue therapy within 6 weeks prior to and during this evaluation period (up to week 104)
- Hb value to each post-dosing time point to end of study (up to week 108)
- Hb change from baseline to each post-dosing time point to end of study (up to week 108)]
- Hb change from baseline to the average Hb value regardless of the use of rescue therapy (weeks 28 to 36, weeks 44 to 52, weeks 72 to 80, weeks 96 to 104)
- Proportion of Hb values within 10.0 to 12.0 g/dL in weeks 28 to 36, 44 to 52, 72 to 80, 96 to 104, without use of rescue therapy within 6 weeks prior to and during the 8-week evaluation period (up to week 104)
- Occurrence (number) of hospitalisation(s) (up to week 104)
- Number of days of hospitalisation (up to week 104)
- Number having received rescue therapy (composite of RBC transfusions (all subjects) and darbepoetin alfa use (roxadustat treated subjects only) (up to week 104)
- Number having received RBC transfusions (up to week 104)
- Number of RBC packs/subject (up to week 104)
- Volume of RBC transfused/subject (up to week 104)
- Change from baseline to each scheduled measurement in total cholesterol (baseline up to up to week 108)
- Change from baseline to each scheduled measurement in LDL/HDL ratio (baseline up to week 108)
- Change from baseline to each scheduled measurement in non-HDL cholesterol (baseline up to week 108)
- Change from baseline to each scheduled measurement in Apo A1 (baseline up to week 108)
- Change from baseline to each scheduled measurement in ApoB (baseline up to week 108)
- Change from baseline to each scheduled measurement in ApoB/ApoA1 ratio (baseline (up to week 108)
- Occurrence of mean LDL cholesterol < 100 mg/dL (mean LDL calculated over weeks 12 to 28, and weeks 36 to 52 of treatment) (up to week 52)
- Occurrence of achieved anti-hypertensive treatment goal (SBP < 130 mm Hg and DBP < 80 mm Hg) based on the mean SBP and mean DBP calculated over weeks 12 to 28 and 36 to 52 of treatment with study drug (up to week 52)
- Change from baseline to the average value in Physical Component Score of SF-36 (baseline, weeks 12 to 28 and weeks 36 to 52)
- Change from baseline to the average value in Anemia Subscale ("Additional Concerns") of FACT-Anaemia Score (baseline, weeks 12 to 28 and weeks 36 to 52)
- Change from baseline to the average value in Total FACT-Anaemia score (baseline, weeks 12 to 28 and weeks 36 to 52)
- Change from baseline to the average value in EQ-5D-5L VAS score (baseline, weeks 12 to 28 and weeks 36 to 52)
- Change from baseline to the average value in WPAI-Anemic Symptoms score (baseline, weeks 12 to 28 and weeks 36 to 52)

DOLOMITES 2021 *(Continued)*

- PGIC (up to week 104)
- Change from baseline to each scheduled measurement serum ferritin (baseline up to week 108)
- Change from baseline to each scheduled measurement in TSAT (baseline up to week 108)
- Change from baseline to each scheduled measurement in HbA1c (baseline up to week 108)
- Change from baseline to each scheduled measurement in fasting blood glucose (baseline up to week 108)
- Change from baseline to each scheduled measurement in eGFR, including eGFR slope over time (baseline up to week 108)
- Change from baseline to each scheduled measurement in UACR (baseline up to week 108)
- Time to first of occurrence of SCr having doubled during study in comparison with baseline (baseline up to week 108)
- Occurrence of kidney failure (baseline up to week 108)
- Safety assessed by nature, frequency, and severity of treatment emergent adverse events (baseline up to week 108)
- Number of participants with laboratory value abnormalities and/or adverse events related to treatment (baseline up to week 108)
- Number of participants with vital signs abnormalities and/or adverse events related to treatment (baseline up to week 108)
- Safety assessed by 12- lead ECG (baseline up to week 108)
- Occurrence of prespecified adjudicated CV events (baseline up to week 108)
- Occurrence of prespecified adjudicated cerebrovascular events (baseline up to week 108)

Notes

- Funding: Astellas Pharma Europe B.V., FibroGen
- Conflicts of interest: not reported
- Authors were contacted and extra information have been added to this review. Additional information are available at
  - https://clinicaltrials.gov/ct2/show/results/NCT02021318?term=1517-CL-0610&draw=2&rank=1
  - https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-000951-42/results
  - https://www.clinicaltrials.astellas.com/study/?pid=1517-CL-0610

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An Independent Review Committee was established to adjudicate cardiovascular events in a blinded manner."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of 616 randomized pts (roxadustat, 323; DA, 293), 424 completed 2 years of treatment (roxadustat, 215; DA, 209)." Quote: "A total of 424 [roxadustat group, n= 215 (66.6%); DA group, n= 209 (71.3%)] patients completed 2 years of treatment, whereas 33.4and 28.7% of patients discontinued treatment in the roxadustat and DA groups, respective-

DOLOMITES 2021 *(Continued)*

		ly. Primary reasons for discontinuation in the roxadustat and DA groups were death [n= 27 (8.4%) versus n= 30 (10.2%)], withdrawal by patient [n= 32 (9.9%) versus n= 20 (6.8%)], progressive disease [n= 8 (2.5%) versus n= 15 ([5.1%)] and AEs [n= 21 (6.5%) versus n= 8] (2.7%)." ITT on 322 participants in the intervention group and 292 participants in the control group
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	Baseline characteristics, or different non-randomised co-interventions were not reported between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were not reported

HIMALAYAS 2021

Study characteristics

Methods

- Study design: parallel RCT
- Time frame: February 2014 and September 2018
- Duration of follow-up: 52 weeks

Participants

General information

- Setting: multicentre (number of sites not reported)
- Country: multinational (17 countries)
- Inclusion criteria: ESA-naive or limited prior use; Incident dialysis patients; ≥18 years
- Exclusion criteria: not reported
- Target Hb:
  - 11 g/dL and an increase of 1 g/dL if baseline Hb was > 8 g/dL
  - 11 g/dL and an increase of 2 g/dL if baseline Hb was < 8 g/dL

Baseline characteristics

- CKD stage: dialysis (HD and PD)
  - HD: treatment group (469/522); control group (462/521)
  - PD: treatment group (53/522); control group (58/521)
- Number (randomised/analysed): treatment group (522/522); control group (521/521)
- Mean age ± SD (years): treatment group (53.8 ± 14.7); control group (54.3 ± 14.6)
- Sex (M, %): treatment group (309, 59.2%); control group (307, 58.9%)
- Time on dialysis: treatment group (10.1 ± 3.9); control group (10.2 ± 3.6)
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: treatment group (505/522); control group (504/521)
- Diabetes: treatment group (205/522); control group (204/521)

HIMALAYAS 2021 *(Continued)*

- Prior agents used(number, %): not reported

Interventions	**Treatment group (medium dose)*** • Roxadustat (FG-4592): 70 to 100 mg, 3 times/week (minimum value was 85 mg) • The initial roxadustat dose was weight-based • An algorithm determined the doses **Control group** • Epoetin alfa • EPO was prescribed according to the country-specific product labelling **Co-interventions**: • Oral iron was allowed • Parenteral iron was restricted *Note: dose assessed as high according to NCT01888445
Outcomes	**Primary outcomes** • USAFDA: mean Hb change from baseline to weeks 28 to 52 • EU EMA: % of patients achieving a Hb response through week 1 to 24 **Secondary outcomes** • Adverse events measured during the study period • Vital signs measured during the study period • ECG findings measured during the study period • Clinical laboratory values measured during the study period
Notes	• Funding: Fibrogen Inc • Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Provenzano 2021 quote: "The randomisation code for patients was generated by a third party vendor in a blinded fashion based a permuted block design in a 1:1 ratio (oral roxadustat: parenteral epoetin alfa), stratified by the randomisation stratification factors specified in the protocol (mean qualifying screening haemoglobin (≤8.0 vs. >8.0 g/dL), history of cardiovascular (CV), cerebrovascular, or thromboembolic disease (yes/no), and geographical region (US vs. Ex-US). Then the randomisation code was uploaded into an Interactive Response Technology (IRT) system accessible by all eligible sites. Each site would screen patients and log onto the secured IRT system to randomised eligible patients and get the treatment assignment. Eligible patients were randomized by sites sequentially across all sites according to the randomisation code in the IRT system. The randomisation code was concealed in the IRT system managed by the third party vendor."
Allocation concealment (selection bias)	Low risk	Provenzano 2021 quote: "The randomisation code for patients was generated by a third party vendor in a blinded fashion based a permuted block design in a 1:1 ratio (oral roxadustat: parenteral epoetin alfa), stratified by the randomisation stratification factors specified in the protocol (mean qualifying screening haemoglobin (≤8.0 vs. >8.0 g/dL), history of cardiovascular (CV), cerebrovascular, or thromboembolic disease (yes/no), and geographical region (US vs. Ex-US). Then the randomisation code was uploaded into an Inter-

HIMALAYAS 2021 *(Continued)*

		active Response Technology (IRT) system accessible by all eligible sites. Each site would screen patients and log onto the secured IRT system to randomised eligible patients and get the treatment assignment. Eligible patients were randomized by sites sequentially across all sites according to the randomisation code in the IRT system. The randomisation code was concealed in the IRT system managed by the third party vendor.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-Label."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT population Provenzano 2021: 304/522 in the intervention group and 306/521 completed the study
Selective reporting (reporting bias)	High risk	ClincialTrials.gov information was not reported. Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Authors' disclosure was not reported

Holdstock 2019

Study characteristics	
Methods	• Study design: phase 2B, parallel RCT (after screening there were two different randomisation Holdstock 2019 and Holdstock 2019a) • Time frame: December 2013 to June 2015 • Duration of follow-up: 28 weeks (24 weeks treatment phase + 4 weeks follow-up)
Participants	**General information** • Setting: multicentre (84 sites) • Country: multinational (15 countries) • Inclusion criteria: ≥ 18 years; female and male subjects; if of childbearing potential, must agree to use one of the approved contraception methods, from screening until completion of the follow-up visit OR of non-childbearing potential defined as pre-menopausal females with a documented tubal ligation, hysterectomy, or oophorectomy; or postmenopausal defined as 12 months of spontaneous amenorrhoea; females on HRT whose menopausal status is in doubt will be required to use one of the approved contraception methods if they wish to continue their HRT during the study, otherwise they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment; QTcB < 470 msec or QTcB < 480 msec in subjects with bundle branch block; KDOQI CKD stages 3/4/5 defined by electronic eGFR using the CKD-EPI formula; if on oral iron, then doses must not be changed

Holdstock 2019 *(Continued)*

for the 4 weeks prior to week -4, during the screening phase, and through the first 4 weeks after randomisation
  - Group 1 (rHuEPO naive): baseline Hb of 8.0 to 11.0 g/dL (USA sites only: 8.0 to 10.0 g/dL); group 2 (rHuEPO users): baseline Hb of 9.0 to 11.5 g/dL (USA sites only: 9.0 to 10.5 g/dL)
  - Group 2 subjects must be using the same rHuEPO (epoetins or their biosimilars, or darbepoetin) with total weekly doses that varied by no more than 50% during the 4 weeks prior to week -4. At day 1 (randomisation), confirm that total weekly doses varied by no more than 50% during the screening period
- Exclusion criteria: on dialysis or planning to initiate dialysis during the study; pre-emptive or scheduled kidney transplant; epoetin dose of ≥ 360 IU/kg/week IV or ≥ 250 IU/kg/week SC or darbepoetin dose of ≥ 1.8 µg/kg/week IV or SC within the prior 8 weeks through day 1; use of methoxy polyethylene glycol epoetin beta within the prior 8 weeks through day ; use of IV iron for 4 weeks prior to screening week -4, during the screening phase, and through the first 4 weeks after randomisation; vitamin B12 below the lower limit of the reference range (may rescreen in a minimum of 8 weeks); folate < 2.0 ng/mL (may rescreen in a minimum of 4 weeks); ferritin < 40 ng/mL; TSAT below the lower limit of the reference range; MI or acute coronary syndrome within the 8 weeks prior to screening through day 1; stroke or TIA within the 8 weeks prior to week -4 screening through day 1; NYHA class III/IV heart failure diagnosed prior to week -4 screening through day 1; symptomatic right heart failure diagnosed prior to week -4 screening through day 1; uncontrolled hypertension(DBP > 100 mm Hg or SBP > 170 mm Hg at week -4 and reconfirmed at day 1; history of thrombotic disease (e.g. venous thrombosis such as DVT or pulmonary embolism, or arterial thrombosis such as new onset or worsening limb ischaemia requiring intervention), except vascular access thrombosis within the 8 weeks prior to week -4 screening through day 1; any ophthalmologic-related exclusion criteria determined at the screening ophthalmology exam; active chronic inflammatory disease that could impact erythropoiesis (e.g. scleroderma, SLE, rheumatoid arthritis, coeliac disease) diagnosed prior to week -4 screening through day 1; any hematological disease including those affecting platelets, WBC or RBC (e.g. sickle cell anaemia, myelodysplastic syndromes, hematological malignancy, myeloma, haemolytic anaemia and thalassaemia), coagulation disorders (e.g. antiphospholipid syndrome, protein C or S deficiency), or any other cause of anaemia other than kidney disease diagnosed prior to week -4 screening through day 1; current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) or evidence at screening of abnormal liver function tests ALT or AST > 2.0 times ULN (ULN) or total bilirubin >1.5 times ULN; other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participation in the study; major surgery (excluding vascular access surgery) within the prior 8 weeks, during the week -4 screening phase or planned during the study; blood transfusion within the prior 8 weeks, during the week -4 screening phase or an anticipated need for blood transfusion during the study; evidence of actively bleeding peptic, duodenal, or oesophageal ulcer disease OR clinically significant GI bleeding within the 8 weeks prior to week -4 screening through day 1; clinical evidence of acute infection or history of infection requiring IV antibiotic therapy within the 8 weeks prior to week -4 screening through day 1; history of malignancy within the prior 5 years, who receiving treatment for cancer, or who have a strong family history of cancer (e.g. familial cancer disorders); with the exception of squamous cell or basal cell carcinoma of the skin that has been definitively treated prior to week -4 screening through day 1; history of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (see GSK1278863 IB for list of excipients and rHuEPO (refer to local product labelling for details); use of any prescription or non-prescription drugs or dietary supplements that are prohibited from week -4 screening until the follow-up visit; has participated in a clinical trial and has received an experimental investigational product within the prior 30 days from week -4 screening through day 1; any other condition, clinical or laboratory abnormality, or examination finding that the Investigator considers would put the subject at unacceptable risk; unwillingness or inability of the subject to follow the procedures or lifestyle or dietary restrictions outlined in the protocol; pregnant OR women who are lactating at week -4 screening or during the trial
- Target Hb (rHuEPO-naive participants): 9 to 10.5 g/L

Baseline characteristics

- CKD stage: stages 3–5 CKD not receiving dialysis
- Number (randomised/analysed): treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (45/41) - ITT, however, considering both Holdstock 2019 and Holdstock 2019a, 252 participants were randomised, 250 were included in the safety population, 235 ITT

Holdstock 2019 *(Continued)*

- Mean age ± SD (years): treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (64.3 ± 14.22 - data referred to 43 participants)
- Sex (M, %): overall (82, 45.6% - data referred to 166 participants); treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (20, 47% - data referred to 43 participants)
- Time on dialysis: not applicable
- eGFR (mL/min/1.73 m^2): treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (19.4 ± 10.9)

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (0, 0% - data referred to 45 participants)
- Diabetes (number, %): treatment group 1 (0, 0% - overall data referred to 134 participants); treatment group 2 (0, 0% - overall data referred to 134 participants); treatment group 3 (0, 0% - overall data referred to 134 participants); control group (0, 0% - data referred to 45 participants)
- Prior agents used (number, %): not reported

Interventions

Treatment group 1 (rHuEPO-naive participants) (low dose)*

- Daprodustat (GSK1278863): 1 mg
- Study medication was titrated to maintain Hb 9 to 10.5 g/dL (Cohort 1)

Treatment group 2 (rHuEPO-naive participants) (low dose)

- Daprodustat (GSK1278863): 2 mg
- Study medication was titrated to maintain Hb 9 to 10.5 g/dL (Cohort 1)

Treatment group 3 (rHuEPO-naive participants) (low dose)

- Daprodustat (GSK1278863): 4 mg
- Study medication was titrated to maintain Hb 9 to 10.5 g/dL (Cohort 1)

Control group (rHuEPO-naive participants)

- rHuEPO per standard of care
- rHuEPO dose could be administered in 3 different ways: epoetin IV, epoetin SC, or darbepoetin (IV or SC)
- For participants randomised to control, the Principal Investigator decided whether a participant required rHuEPO, selected the type of rHuEPO (if needed), and chose the rHuEPO dose to achieve and maintain Hb within the target range, with the historical rHuEPO dose and the current Hb value being considered

Co-interventions

- Not reported

*Note: dose assessed as low according to Akizawa 2017

Outcomes

Primary outcomes

- Summary of Hb concentration at week 24

Secondary outcomes

- Echocardiology and ophthalmology examinations were assessed during the study period
- Number with Hb in the target range at week 24
- Number reaching pre-defined Hb stopping criteria over a period of 24 weeks
- Percent change from baseline in hepcidin concentration at week 24

Holdstock 2019 *(Continued)*

- Maximum observed change from baseline in serum EPO to week 24
- Maximum observed percent change from baseline in VEGF to week 24
- Percentage of time within, below, and above Hb target range between weeks 12 and 24
- Change from baseline in ferritin concentration at week 24
- Change from baseline in transferrin concentration at week 24
- Percent change from baseline in TSAT at week 24
- Change from baseline in total iron at week 24
- Change from baseline in TIBC at week 24
- Change from baseline in CHr at week 24
- Change from baseline in HCT at week 24
- Change from baseline in RBC count at week 24
- Change from baseline in reticulocyte cell count at week 24
- Mean number of dose adjustments from week 4 up to 24 weeks
- Number with dose adjustments up to 24 weeks, as a measure of dose adjustment frequency from week 4 up to 24 weeks
- Timing of dose adjustments at weeks 4, 8, 12, 16, and 20
- Mean total cumulative dose of GSK1278863 up to 24 weeks
- Mean final dose of GSK1278863 up to 24 weeks
- Number of Hb excursions up to 24 weeks
- Number of (Hb cycles up to 24 weeks
- Number of dose cycles up to 24 weeks
- Number with at least 1 Hb excursion up to 24 weeks
- Number with at least 1 dose cycle up to 24 weeks
- Number receiving additional therapies of blood transfusions, IV iron or rHuEPO at any time post-baseline up to week 28
- Number of weeks dose withheld because Hb exceeded the upper limit from week 4 up to week 24

Notes

- Funding: GlaxoSmithKline
- Conflicts of interest: "B.C., A.M.M., N.B., D.J., J.J.L. and A.R.C. are employees of, and hold stock in, GlaxoSmithKline (GSK). D.J., J.J.L. and A.R.C. also own stock options in GSK. L.H. and B.M.J. are former employees of GSK, and hold stock options in GSK. S.G.K. is an employee of Hallym University, and receives research funding from C.J. Healthcare and Fibrogen. S.Z. has no conflicts to declare"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Separate randomisation lists were generated for the two groups (rhEPO naive and rhEPO users) using the GlaxoSmithKline randomisation system RandAll."
Allocation concealment (selection bias)	Low risk	Quote: "Separate randomisation lists were generated for the two groups (rhEPO naive and rhEPO users) by a GlaxoSmithKline statistician using the GlaxoSmithKline randomisation system RandAll." Quote: "Participants were assigned a randomisation number by an interactive voice/web response system."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An internal GlaxoSmithKline Safety Review Team reviewed blinded safety data instream and an independent data monitoring committee periodically reviewed the same safety data, but it was unblinded."

Holdstock 2019 *(Continued)*

		Quote: "Other adverse events of interest, based on the mechanism of action or pharmacological activity of hypoxia-inducible factor-prolyl hydroxylase inhibitors, were monitored and evaluated by blinded review based on individual case details during the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Two hundred fifty-two participants were randomized to either daprodustat (n=172) or control (n=80). Of those randomized, 250 (>99%) were included in the safety population and 235 (93%) in the ITT population, with 222 (88%) completing the study (i.e. participants who completed the Week 24 visit regardless of whether they remained on study treatment) [148 (86%) in the daprodustat group and 74 (93%) in the control group]. The most common reasons for premature withdrawal were an AE in the daprodustat group (5%) and withdrawal by participant in the control group (3%). Similar proportions of participants (20% randomized to daprodustat;18% randomized to control) discontinued study treatment prematurely. The most common reasons for treatment discontinuation were an AE in the daprodustat group (10%) and reaching the protocol-defined stopping criteria in the control group (8%) [included renal transplant, increased systolic pulmonary artery pressure (sPAP) of 20mmHg, drop of left ventricular ejection fraction (LVEF) 10% from baseline and <50% and blood transfusion]." Only 235/252 performed ITT > 5% lost to follow-up with discrepancies between group
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were reported (death and CV events)
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

Holdstock 2019a

Study characteristics	
Methods	• Study design: phase 2B, parallel RCT (after the screening there were 2 different randomisation Holdstock 2019 and Holdstock 2019a) • Time frame: December 2013 to June 2015 • Duration of follow-up: 28 weeks (24 weeks treatment phase + 4 weeks follow-up)
Participants	**General information** • Setting: multicentre (84 sites) • Country: multinational (15 countries) • Inclusion criteria: ≥ 18 years; female and male subjects; if of childbearing potential, must agree to use one of the approved contraception methods, from screening until completion of the follow-up visit OR of non-childbearing potential defined as pre-menopausal females with a documented tubal ligation, hysterectomy, or oophorectomy; or postmenopausal defined as 12 months of spontaneous amenorrhoea; females on HRT whose menopausal status is in doubt will be required to use one of the approved contraception methods if they wish to continue their HRT during the study, otherwise

Holdstock 2019a *(Continued)*

they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment; QTcB < 470 msec or QTcB < 480 msec in subjects with bundle branch block; KDOQI CKD stages 3/4/5 defined by electronic eGFR using the CKD-EPI formula; if on oral iron, then doses must not be changed for the 4 weeks prior to week -4, during the screening phase, and through the first 4 weeks after randomisation

  - Group 1 (rHuEPO naive): baseline Hb of 8.0 to 11.0 g/dL (USA sites only: 8.0 to 10.0 g/dL); group 2 (rHuEPO users): baseline Hb of 9.0 to 11.5 g/dL (USA sites only: 9.0 to 10.5 g/dL)
  - Group 2 subjects must be using the same rHuEPO (epoetins or their biosimilars, or darbepoetin) with total weekly doses that varied by no more than 50% during the 4 weeks prior to week -4. At day 1 (randomisation), confirm that total weekly doses varied by no more than 50% during the screening period

- Exclusion criteria: on dialysis or planning to initiate dialysis during the study; pre-emptive or scheduled kidney transplant; epoetin dose of ≥ 360 IU/kg/week IV or ≥ 250 IU/kg/week SC or darbepoetin dose of ≥ 1.8 µg/kg/week IV or SC within the prior 8 weeks through day 1; use of methoxy polyethylene glycol epoetin beta within the prior 8 weeks through day ; use of IV iron for 4 weeks prior to screening week -4, during the screening phase, and through the first 4 weeks after randomisation; vitamin B12 below the lower limit of the reference range (may rescreen in a minimum of 8 weeks); folate < 2.0 ng/mL (may rescreen in a minimum of 4 weeks); ferritin < 40 ng/mL; TSAT below the lower limit of the reference range; MI or acute coronary syndrome within the 8 weeks prior to screening through day 1; stroke or TIA within the 8 weeks prior to week -4 screening through day 1; NYHA class III/IV heart failure diagnosed prior to week -4 screening through day 1; symptomatic right heart failure diagnosed prior to week -4 screening through day 1; uncontrolled hypertension(DBP > 100 mm Hg or SBP > 170 mm Hg at week -4 and reconfirmed at day 1; history of thrombotic disease (e.g. venous thrombosis such as DVT or pulmonary embolism, or arterial thrombosis such as new onset or worsening limb ischaemia requiring intervention), except vascular access thrombosis within the 8 weeks prior to week -4 screening through day 1; any ophthalmologic-related exclusion criteria determined at the screening ophthalmology exam; active chronic inflammatory disease that could impact erythropoiesis (e.g. scleroderma, SLE, rheumatoid arthritis, coeliac disease) diagnosed prior to week -4 screening through day 1; any hematological disease including those affecting platelets, WBC or RBC (e.g. sickle cell anaemia, myelodysplastic syndromes, hematological malignancy, myeloma, haemolytic anaemia and thalassaemia), coagulation disorders (e.g. antiphospholipid syndrome, protein C or S deficiency), or any other cause of anaemia other than kidney disease diagnosed prior to week -4 screening through day 1; current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) or evidence at screening of abnormal liver function tests ALT or AST > 2.0 times ULN (ULN) or total bilirubin >1.5 times ULN; other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participation in the study; major surgery (excluding vascular access surgery) within the prior 8 weeks, during the week -4 screening phase or planned during the study; blood transfusion within the prior 8 weeks, during the week -4 screening phase or an anticipated need for blood transfusion during the study; evidence of actively bleeding peptic, duodenal, or oesophageal ulcer disease OR clinically significant GI bleeding within the 8 weeks prior to week -4 screening through day 1; clinical evidence of acute infection or history of infection requiring IV antibiotic therapy within the 8 weeks prior to week -4 screening through day 1; history of malignancy within the prior 5 years, who receiving treatment for cancer, or who have a strong family history of cancer (e.g. familial cancer disorders); with the exception of squamous cell or basal cell carcinoma of the skin that has been definitively treated prior to week -4 screening through day 1; history of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product (see GSK1278863 IB for list of excipients and rHuEPO (refer to local product labelling for details); use of any prescription or non-prescription drugs or dietary supplements that are prohibited from week -4 screening until the follow-up visit; has participated in a clinical trial and has received an experimental investigational product within the prior 30 days from week -4 screening through day 1; any other condition, clinical or laboratory abnormality, or examination finding that the Investigator considers would put the subject at unacceptable risk; unwillingness or inability of the subject to follow the procedures or lifestyle or dietary restrictions outlined in the protocol; pregnant OR women who are lactating at week -4 screening or during the trial
- Target Hb (rHuEPO-users participants): 10 to 11.5 g/dL

Baseline characteristics

- CKD stage: stages 3–5 CKD not receiving dialysis

Holdstock 2019a *(Continued)*

- Number (randomised/analysed): treatment group (36/32); control group (36/33) - ITT, however, considering both Holdstock 2019 and Holdstock 2019a, 252 participants were randomised, 250 were included in the safety population, 235 ITT
- Mean age ± SD (years): treatment group (62.0 ± 14.06); control group (66.7 ± 12.89)
- Sex (M, %): treatment group (16, 48%); control group (13, 36%)
- Time on dialysis: not applicable
- Mean eGFR ± SD (mL/min/1.73 m^2): treatment group (17.9 ± 9.17); control group (18.8 ± 11.97)

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: treatment group (1, 3% - data referred to 36 participants); control group (0, 0% - data referred to 35 participants)
- Diabetes (number, %): treatment group (2, 6% - data referred to 36 participants); control group (0, 0% - data referred to 35 participants)
- Prior agents used (number, %): not reported

Interventions

Treatment group (rHuEPO-users participants) (low dose)*

- Daprodustat (GSK1278863): 2 mg
- Study medication was titrated to maintain Hb 10 to 11.5 g/dL (Cohort 2)

Control group (rHuEPO-users participants)

- rHuEPO per standard of care
- rHuEPO dose could be administered in 3 different ways: epoetin IV, epoetin SC, or darbepoetin (IV or SC)
- For participants randomised to control, the Principal Investigator decided whether a participant required rHuEPO, selected the type of rHuEPO (if needed), and chose the RhuEPO dose to achieve and maintain Hb within the target range, with the historical rHuEPO dose and the current Hb value being considered

Co-interventions

- Not reported

*Note: dose assessed as low according to Akizawa 2017

Outcomes

Primary outcome

- Summary of Hb concentration at week 24

Secondary outcomes

- Echocardiology and ophthalmology examinations were assessed during the study period
- Number with Hb in the target range at week 24
- Number reaching pre-defined Hb stopping criteria over a period of 24 weeks
- Percent change from baseline in hepcidin concentration at week 24
- Maximum observed change from baseline in serum EPO to week 24
- Maximum observed percent change from baseline in VEGF up to week 24
- Percentage of time within, below, and above Hb target range between weeks 12 and 24
- Change from baseline in ferritin concentration at week 24
- Change from baseline in transferrin concentration at week 24
- Percent change from baseline in TSAT at week 24
- Change from baseline in total iron at week 24
- Change from baseline in TIBC at week 24
- Change from baseline in CHr at week 24

Holdstock 2019a *(Continued)*

- Change from baseline in HCT at week 24
- Change from baseline in RBC count at week 24
- Change from baseline in reticulocyte cell count at week 24
- Mean number of dose adjustments from week 4 up to 24 weeks
- Number with dose adjustments from week 4 up to 24 weeks, as a measure of dose adjustment frequency
- Timing of dose adjustments at weeks 4, 8, 12, 16, and 20
- Mean total cumulative dose of GSK1278863 up to 24 weeks
- Mean final dose of GSK1278863 up to 24 weeks
- Number of Hb excursions up to 24 weeks
- Number of Hb cycles up to 24 weeks
- Number of dose cycles up to 24 weeks
- Number with at least 1 Hb excursion up to 24 weeks
- Number with at least 1 dose cycle up to 24 weeks
- Number receiving additional therapies of blood transfusions, IV iron or rHuEPO at any time post-baseline up to week 28
- Number of weeks dose withheld because Hb exceeded the upper limit from week 4 up to week 24

Notes

- Funding: GlaxoSmithKline
- Conflicts of interest: "B.C., A.M.M., N.B., D.J., J.J.L. and A.R.C. are employees of, and hold stock in, GlaxoSmithKline (GSK). D.J., J.J.L. and A.R.C. also own stock options in GSK. L.H. and B.M.J. are former employees of GSK, and hold stock options in GSK. S.G.K. is an employee of Hallym University, and receives research funding from C.J. Healthcare and Fibrogen. S.Z. has no conflicts to declare"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Separate randomisation lists were generated for the two groups (rhEPO naive and rhEPO users) using the GlaxoSmithKline randomisation system RandAll."
Allocation concealment (selection bias)	Low risk	Quote: "Separate randomisation lists were generated for the two groups (rhEPO naive and rhEPO users) by a GlaxoSmithKline statistician using the GlaxoSmithKline randomisation system RandAll." Quote: "Participants were assigned a randomisation number by an interactive voice/web response system."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An internal GlaxoSmithKline Safety Review Team reviewed blinded safety data instream and an independent data monitoring committee periodically reviewed the same safety data, but it was unblinded." Quote: "Other adverse events of interest, based on the mechanism of action or pharmacological activity of hypoxia-inducible factor-prolyl hydroxylase inhibitors, were monitored and evaluated by blinded review based on individual case details during the study."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Two hundred fifty-two participants were randomized to either daprodustat (n=172) or control (n=80). Of those randomized, 250 (>99%) were included in the safety population and 235 (93%) in the ITT population, with 222 (88%) completing the study (i.e. participants who completed the Week 24 vis-

Holdstock 2019a *(Continued)*

		it regardless of whether they remained on study treatment) [148 (86%) in the daprodustat group and 74 (93%) in the control group]. The most common reasons for premature withdrawal were an AE in the daprodustat group (5%) and withdrawal by participant in the control group (3%). Similar proportions of participants (20% randomized to daprodustat;18% randomized to control) discontinued study treatment prematurely. The most common reasons for treatment discontinuation were an AE in the daprodustat group (10%) and reaching the protocol-defined stopping criteria in the control group (8%) [included renal transplant, increased systolic pulmonary artery pressure (sPAP) of 20mmHg, drop of left ventricular ejection fraction (LVEF) 10% from baseline and <50% and blood transfusion]." Only 235/252 performed ITT > 5% lost to follow-up with discrepancies between group
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were reported (death and CV events)
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

Hou 2021

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: September 2019 to 15 June 2020 • Duration of follow-up: 26 weeks (24 weeks treatment + 2 weeks follow-up)
Participants	**General information** • Setting: single centre • Country: China • Inclusion criteria: diagnosed with CKD and renal anaemia receiving PD; Hb values during screening period < 12 g/dL; ESA-converted group prior to enrolment must be discontinued for 7 days; agree not to start taking any new TCM for anaemia and not to change dose, schedule, or brand of any prescreening TCM for anaemia from beginning of screening period through end of follow-up period • Exclusion criteria: undergoing HD; intend to change dialysis modality; any other anaemia caused by a disease other than CKD, such as thalassaemia; history of severe drug allergies or are known to be allergic to the active ingredient or excipient of roxadustat; severe liver damage; ALT or AST ≥ 3 times ULN during screening visit; total bilirubin ≥2 times ULN during screening visit; pregnant or breastfeeding; doctor judged a patient with a serious illness (such as malignancy, functional grade III or IV congestive heart failure) • Target Hb: 10 to 12 g/dL **Baseline characteristics** • CKD stage: PD • Number (randomised/analysed): treatment group (86/86); control group (43/43)

Hou 2021 *(Continued)*

- Mean age ± SD (years): treatment group (48 ± 12); control group (48.3 ± 13)
- Sex (M, %): treatment group (47, 54.7%); control group (25, 58.1%)
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Interventions	**Treatment group (high dose)*** • Roxadustat: he initial dose of roxadustat was given according to weight - 100 mg for patients weighing 45 to < 60 kg and 120 mg for patients weighing at least 60 kg according to a previous study **Control group** • ESA **Co-interventions** • Phosphate binders were given at least 1 hour before or after roxadustat • The use of oral iron therapy was allowed; IV iron therapy was prohibited except as rescue therapy *Note: dose assessed as low according to NCT01888445
Outcomes	**Primary outcomes** • Mean Hb at week 24 • Change in average Hb from baseline to week 24 • Cumulative response rate throughout the treatment period **Secondary outcomes** • Changes in hepcidin and iron indices and serum lipid levels throughout the treatment period • Adverse events throughout the treatment period
Notes	• Funding: Ethics Committee of Harbin Medical University • Conflicts of interest: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. However, it was likely that participants and/or investigators could be aware of treatment assigned

Hou 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of those randomized, 129 patients were enrolled in the ITT population (86 in the roxadustat group and 43 in the ESAs group) and the safety population (86 in the roxadustat group and 43 in the ESAs group). In total, 74 patients in the roxadustat group and 38 patients in the ESAs group completed treatment" ITT analyses
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were reported (death and CV events)
Other bias	Low risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups There was nothing to declare in the disclosure Funder was unlikely to influence data analysis and study reporting or interpretation

INNO2VATE 2020

Study characteristics	
Methods	• Study design: parallel RCT (Incident DD-CKD trial) • Time frame: not reported • Duration of follow-up: 52 weeks of treatment, form week 53 to end of treatment it was the long-term treatment + 4 week follow-up
Participants	**General information** • Setting: multicentre (118 sites) • Country: international (USA, Argentina, Brazil, Germany, Italy, Korea, Mexico, Poland, Russian Federation, Ukraine) • Inclusion criteria: ≥18 years; initiated chronic maintenance dialysis (either peritoneal or HD) for kidney failure within 16 weeks prior to screening; mean screening Hb between 8.0 and < 11.0 g/dL • Exclusion criteria: meeting the criteria of ESA resistance within 8 weeks prior to or during screening defined as follows: 1) epoetin: > 7700 units/dose 3 times/week or > 23,000 units/ week, 2) darbepoetin alfa: > 100 µg/week, 3) methoxy polyethylene glycol-epoetin beta: > 100 µg every other week or > 200 µg/month; anaemia due to a cause other than CKD or subjects with active bleeding or recent blood loss; anticipated to recover adequate kidney function to no longer require dialysis; uncontrolled hypertension; severe heart failure at screening (NYHA class IV); acute coronary syndrome (hospitalisation for unstable angina, MI); surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity); surgical or percutaneous valvular replacement or repair; sustained ventricular tachycardia; hospitalisation for CHF; or stroke within 12 weeks prior to or during screening; hypersensitivity to vadadustat, darbepoetin alfa or any of their excipients • Target Hb: 8 to 11 g/dL **Baseline characteristics**

INNO2VATE 2020 *(Continued)*

- CKD stage: HD (325); PD (35)
- Number (randomised/analysed): treatment group (181/179); control group (188/186)
- Mean age ± SD (years): treatment group (56.5 ± 14.8); control group (55.6 ± 14.6)
- Sex (M, %): treatment group (107, 59.1%); control group (113, 60.1%)
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CV disease: treatment group (69/181); control group (73/188)
- Heart disease: not reported
- Hypertension: not reported
- Diabetes: treatment group (105/181); control group (73/188)
- Prior agents used (number, %)
  - Oral iron: not reported
  - IV iron: not reported

Interventions

Treatment group (medium dose)*

- Vadadustat (AKB-6548) (oral): 150 to 450 mg/day, starting dose 300 mg, to a maximum of 600 mg/day

Control group

- Darbepoetin alfa (Aranesp) (SC/IV): titrated to achieve target Hb concentrations (USA: 10 to 11 g/dL; non-USA: 10 to 12 g/dL)

Co-interventions

- Not reported

*Note: dose assessed as medium according to NDD-CKD 2020

Outcomes

Primary outcomes

- Mean change in Hb between baseline and week 36
- MACE from baseline visit to end of study (event-driven, minimum 1 year)

Secondary outcomes

- Mean change in Hb value between baseline and week 52
- Proportion with Hb values within the target range during the primary evaluation period (week 36)
- Adverse and serious adverse events to end of study (event-driven, minimum 1 year)
- Proportion of time with Hb values within the target range during the primary evaluation period (week 36)
- Proportion of time with Hb values within the target range during the secondary evaluation period (week 52)
- Proportion with Hb values within the target range during the secondary evaluation period (week 52)
- Proportion with Hb increase of > 1.0 g/dL from baseline to end of study (event-driven, minimum 36 weeks)
- Time to achieve Hb increase of > 1.0 g/dL from baseline to end of study (event-driven, minimum 36 weeks)
- Mean change in Hb between baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from weeks 24 to 36 stratified by pre-baseline ESA exposure (baseline visit, week 36)
- Proportion receiving IV iron therapy by week 52
- Mean monthly dose of IV elemental iron administered in subjects who have received IV iron (week 52)
- Proportion receiving RBC transfusion(s) (week 52)

Notes

- Funding: Akebia Therapeutics

INNO2VATE 2020 *(Continued)*

- Conflicts of interest: "K.U.E. has received fees from Akebia and Bayer and grants from Amgen, Bayer, Fresenius, Genzyme, Shire and Vifor. R.A. is a consultant for and on the scientific advisory board of Akebia; has received consulting fees from Bayer, Boehringer Ingelheim, Takeda, Daiichi Sankyo, Eli Lilly, Rlypsa, Reata, Opko, ZS Pharma and Merck; is on the data safety monitoring committee for AstraZeneca, Amgen (past) and Celgene (past) and attended advisory board meetings for AbbVie, Johnson & Johnson, Boehringer Ingelheim and Relypsa. A.G.J.: none. M.J.K. is a member of the Executive Steering Committee for Akebia; a consultant for FibroGen and is on the Data and Safety Management Committee for Micelle BioPharma. K.M. is a consultant for Akebia, Kyowa Kirin, Healthy.io and Fukuda Denshi and has received grants from Kyowa Kirin, Fukuda Denshi and the National Institutes of Health. P.A.M. is a consultant for Akebia. P.P. is on the Executive Steering Committee for Akebia. M.J.S. is a consultant for Cardurian and is on the Advisory Board for Bayer and the Steering Committee for Akebia. W.C.W. is on the Executive Steering Committee for Akebia and is a consultant for AstraZeneca, Bayer, Janssen, Merck, Relypsa and Vifor Fresenius Medical Care Renal Pharma. Y.M.K.F., Z.K., W.L., G.R. and D.V. are employees of Akebia. G.M.C. has received grants from the National Institute of Diabetes and Digestive and Kidney Diseases and Amgen; personal fees from Akebia during the study; personal fees and other from Ardelyx; personal fees from AstraZeneca, Baxter, Cricket, DiaMedica, Gilead, Reata, Sanifit, Vertex, Satellite Healthcare, Angion, Bayer and ReCor and other fees from CloudCath, Durect and Outset"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ecardt 2021: cumulative data were reported for INNO2VATE 2020 and INNO2VATE 2020a: overall 3902/3923 participants were included into the analyses
Selective reporting (reporting bias)	High risk	Not all of the planned outcomes on ClincialTrials.gov have been measured and reported on in the final report. No reasoning provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

INNO2VATE 2020a

Study characteristics	
Methods	• Study design: parallel RCT (prevalent DD-CKD trial) • Time frame: not reported • Duration of follow-up: 52 weeks of treatment, form week 53 to end off treatment it was the long-term treatment + 4 week follow-up

Participants	**General information**
	• Setting: multicentre (278 sites)
	• Country: international (Argentina, Australia, Brazil, Bulgaria, Canada, France, Germany, Israel, Italy, Korea, Mexico, Poland, Russian Federation, Serbia, Ukraine, UK; USA)
	• Inclusion criteria: ≥ 18 years; receiving chronic maintenance dialysis (either peritoneal or HD) for kidney failure for at least 12 weeks prior to screening; currently maintained on ESA therapy, with a dose received within 6 weeks prior to or during screening; mean screening Hb between 8.0 and 11.0 g/dL (USA) and between 9.0 and 12.0 g/dL (outside the USA)
	• Exclusion criteria: anaemia due to a cause other than CKD or subjects with active bleeding or recent blood loss; uncontrolled hypertension; severe heart failure at screening (NYHA class IV); acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for heart failure, or stroke within 12 weeks prior to or during screening; hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients
	• Target Hb
	  ◦ USA: 10 to 11 g/dL
	  ◦ non-USA: 10 to 12 g/dL
	Baseline characteristics
	• CKD stage: HD (3279); PD (272)
	• Number (randomised/analysed): treatment group (1777/1768); control group (1777/1769)
	• Mean age ± SD (years): treatment group (57.9 ± 13.9); control group (58.4 ± 13.8)
	• Sex (M, %): treatment group (990, 55.7%); control group (1004, 56.5%)
	• Time on dialysis: not reported
	• eGFR: not reported
	Comorbidities
	• CV disease: treatment group (868/1777); control group (932/1777)
	• Heart disease: not reported
	• Hypertension: not reported
	• Diabetes: treatment group (971/1777); control group (998/1777)
	• Prior agents used (number, %)
	  ◦ Oral iron: not reported
	  ◦ IV iron: not reported

Interventions	**Treatment group (medium dose)*** • Vadadustat (AKB-6548) (oral): 150 to 450 mg//day, starting dose 300 mg, to a maximum of 600 mg/day **Control group** • Darbepoetin alfa (Aranesp) (SC/I): titrated to achieve target Hb concentrations (USA: 10 to 11 g/dL; non-USA: 10 to 12 g/dL) **Co-interventions**:

INNO2VATE 2020a *(Continued)*

- Not reported

*Note: dose was considered medium according to NDD-CKD 2020

Outcomes	**Primary outcomes** • Mean change in Hb between baseline and week 24 and 36 • MACE from baseline visit to end of study (event-driven, minimum 1 year) **Secondary outcomes** • Mean change in Hb value between baseline and week 52 • Proportion with Hb values within the target range during the primary evaluation period (week 36) • Adverse and serious adverse events to end of study (event-driven, minimum 1 year) • Proportion of time with Hb values within the target range during the primary evaluation period (week 36) • Proportion of time with Hb values within the target range during the secondary evaluation period (week 52) • Proportion with Hb values within the target range during the secondary evaluation period (week 52) • Proportion with Hb increase of > 1.0 g/dL from baseline to end of study (event-driven, minimum 36 weeks) • Time to achieve Hb increase of > 1.0 g/dL from baseline to end of study (event-driven, minimum 36 weeks) • Mean change in Hb between baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from weeks 24 to 36 stratified by pre-baseline ESA exposure (baseline visit, week 36) • Proportion receiving IV iron therapy by week 52 • Mean monthly dose of IV elemental iron administered in subjects who have received IV iron (week 52) • Proportion receiving RBC transfusion(s) (week 52)
Notes	• Funding: Akebia Therapeutics • Conflicts of interest: "K.U.E. has received fees from Akebia and Bayer and grants from Amgen, Bayer, Fresenius, Genzyme, Shire and Vifor. R.A. is a consultant for and on the scientific advisory board of Akebia; has received consulting fees from Bayer, Boehringer Ingelheim, Takeda, Daiichi Sankyo, Eli Lilly, Rlypsa, Reata, Opko, ZS Pharma and Merck; is on the data safety monitoring committee for AstraZeneca, Amgen (past) and Celgene (past) and attended advisory board meetings for AbbVie, Johnson & Johnson, Boehringer Ingelheim and Relypsa. A.G.J.: none. M.J.K. is a member of the Executive Steering Committee for Akebia; a consultant for FibroGen and is on the Data and Safety Management Committee for Micelle BioPharma. K.M. is a consultant for Akebia, Kyowa Kirin, Healthy.io and Fukuda Denshi and has received grants from Kyowa Kirin, Fukuda Denshi and the National Institutes of Health. P.A.M. is a consultant for Akebia. P.P. is on the Executive Steering Committee for Akebia. M.J.S. is a consultant for Cardurian and is on the Advisory Board for Bayer and the Steering Committee for Akebia. W.C.W. is on the Executive Steering Committee for Akebia and is a consultant for AstraZeneca, Bayer, Janssen, Merck, Relypsa and Vifor Fresenius Medical Care Renal Pharma. Y.M.K.F., Z.K., W.L., G.R. and D.V. are employees of Akebia. G.M.C. has received grants from the National Institute of Diabetes and Digestive and Kidney Diseases and Amgen; personal fees from Akebia during the study; personal fees and other from Ardelyx; personal fees from AstraZeneca, Baxter, Cricket, DiaMedica, Gilead, Reata, Sanifit, Vertex, Satellite Healthcare, Angion, Bayer and ReCor and other fees from CloudCath, Durect and Outset"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups

INNO2VATE 2020a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ecardt 2021: cumulative data were reported for INNO2VATE 2020 and INNO2VATE 2020a: overall 3902/3923 participants were included into the analyses
Selective reporting (reporting bias)	High risk	Not all of the planned outcomes on ClincialTrials.gov have been measured and reported on in the final report. No reasoning provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

Meadowcroft 2019

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: November 2013 to March 2015 • Duration of follow-up: 28 weeks (4 weeks treatment comparing HIF versus placebo, 20 weeks comparing HIF versus control (placebo group assumed EPO, as needed) plus 4 weeks follow-up)
Participants	**General information** • Setting: multicentre (67 sites, dialysis centres and hospitals) • Country: 16 countries including Australia, Canada, Czech Republic, Denmark, France, Germany, Hungary, Japan, Korea, Norway, Poland, Russian Federation, Spain, Sweden, UK, USA • Inclusion criteria: ≥ 18 years (week -4 verification only); females and males subjects (week -4 verification only); females: if of childbearing potential, must agree to use one of the approved contraception methods, from screening until completion of the follow-up visit OR of non-childbearing potential defined as pre-menopausal females with a documented tubal ligation, hysterectomy, or oophorectomy; or postmenopausal defined as 12 months of spontaneous amenorrhoea; females on HRT whose menopausal status is in doubt will be required to use one of the approved contraception methods if they wish to continue their HRT during the study. otherwise they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment; for most forms of HRT, at least 2 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT, following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method; QTcB < 470 msec or QTcB < 480 msec

Meadowcroft 2019 *(Continued)*

in subjects with bundle branch block; CKD-related criteria; HD 3 to 5 times/week for at least 4 weeks prior to week -4 screening through week 4. NOTE: Combination methods including HF or UF with HD are allowed however, the type of dialysis (HD, HDF or UF) should not change during the study; a Kt/V urea ≥ 1.2 based on a historical value obtained within the prior month in order to ensure the adequacy of dialysis. If Kt/V urea is not available, then an average of the last 2 URR values of at least 65% at week -4; baseline Hb of 9.0 to 11.5 g/dL (may rescreen in a minimum of 2 weeks); using the same rHuEPO (epoetin or their biosimilars, or darbepoetin) with total weekly doses varying by no more than 50% during the 4 weeks prior to week -4, at day 1 (randomisation), confirm that total weekly doses varied by no more than 50% during the screening period; may be on stable maintenance oral or IV (≤ 100 mg/week) iron supplementation. If subjects are on oral or IV iron, then doses must be stable for the 4 weeks prior to week -4, during the screening phase, and through the first 4 weeks after randomisation

- Exclusion criteria: planned change from HD to PD within the study time period; pre-emptive or scheduled kidney transplant; epoetin dose of ≥ 360 IU/Kg/week IV or ≥ 250 IU/kg/week SC or darbepoetin dose of ≥ 1.8 µg/kg/week IV or SC within the prior 8 weeks through day 1; use of methoxy polyethylene glycol epoetin beta within the prior 8 weeks through day 1; vitamin B12 ≤ LLN; folate < 2.0 ng/mL; ferritin < 100 ng/mL; TSAT outside of the reference range; MI or acute coronary syndrome within the 8 weeks prior to screening through day 1; stroke or TIA within the 8 weeks prior to week -4 screening through day 1; NYHA class III/IV heart failure diagnosed prior to week -4 screening through day 1; symptomatic right heart failure diagnosed prior to week -4 screening through day 1; hypertension (week -4, day 1) DBP) > 100 mm Hg) or SBP > 170 mm Hg; history of thrombotic disease within the 8 weeks prior to week -4 screening through day 1; meeting any ophthalmologic-related exclusion criteria determined at the screening ophthalmology exam; active chronic inflammatory disease that could impact erythropoiesis (e.g. scleroderma, SLE, rheumatoid arthritis, coeliac disease) diagnosed prior to week -4 screening through day 1; any haematological disease including those affecting platelets, white or RBCs (e.g. sickle cell anaemia, myelodysplastic syndromes, haematological malignancy, myeloma, haemolytic anaemia and thalassaemia), coagulation disorders (e.g. antiphospholipid syndrome, protein C or S deficiency), or any other cause of anaemia other than kidney disease diagnosed prior to week -4 screening through day 1; current liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) or evidence at screening of abnormal liver function tests ALT or AST > 2.0 times ULN or total bilirubin > 1.5 times ULN; or other hepatic abnormalities that in the opinion of the investigator would preclude the subject from participation in the study. NOTE: Those with Hepatitis B or Hepatitis C are eligible provided these exclusions are not met; Major surgery (excluding vascular access surgery) within the prior 8 weeks, during the week -4 screening phase or planned during the study; blood transfusion within the prior 8 weeks, during the week -4 screening phase or an anticipated need for blood transfusion during the study; evidence of actively bleeding peptic, duodenal, or oesophageal ulcer disease OR clinically significant GI bleeding within the 8 weeks prior to week -4 screening through day 1; clinical evidence of acute infection or history of infection requiring IV antibiotic therapy within the 8 weeks prior to week -4 screening through day 1 NOTE: IV antibiotics as prophylaxis are allowed; history of malignancy within the prior 5 years, who receiving treatment for cancer, or who have a strong family history of cancer (e.g. familial cancer disorders); with the exception of squamous cell or basal cell carcinoma of the skin that has been definitively treated prior to week -4 screening through day 1; history of severe allergic or anaphylactic reactions or hypersensitivity to excipients in the investigational product; use of any prescription or non-prescription drugs or dietary supplements that are prohibited from week -4 screening until the follow-up visit; has participated in a clinical trial and has received an experimental investigational product within the prior 30 days from week -4 screening through day 1; any other condition, clinical or laboratory abnormality, or examination finding that the Investigator considers would put the subject at unacceptable risk; pregnancy; an individual subject may not be rescreened more than twice; there is no predetermined amount of time that the investigator needs to wait to rescreen a previously ineligible subject, except those excluded for Hb or folate who may only rescreen in 2 and 4 weeks, respectively, and those excluded for Vitamin B12 who may rescreen in 8 weeks
- Target Hb: 10.0 to 11.50 g/dL

Baseline characteristics

- CKD stage: 5D (HD)
- Number (randomised/analysed): treatment group (177/171); control group (39/39)
- Mean age ± SD (years): treatment group (59.6 ± 13.3); control group (59.7 ± 18.7)
- Sex (M, %): overall (134, 62%); treatment group (108, 63%); control group (26, 67%)
- Time on dialysis: not reported

Meadowcroft 2019 *(Continued)*

- eGFR: not reported

Comorbidities

- CVdisease: treatment group (166, 94%); control group (38, 97%)
- Heart disease: not reported
- Hypertension: treatment group (160, 90%); control group (37, 95%)
- Diabetes (number, %): treatment group (62, 35%); control group (18, 46%)
- Prior agents used (number, %): not reported

Interventions	**Treatment group** • Daprodustat (oral tablets): starting doses from 4, 6, 8, 10, or 12 mg • Time: 4 weeks (the rest of the study was conducted changing the control group) • Titrated at week 4 to achieve and maintain Hb 10 to 11.5 g/dL **Control group** • Placebo for GSK1278863 (oral tablets) from week 1. Patients were randomised to placebo for 4 weeks then open-label rHuEPO, as required **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Hb change from baseline at week 4 **Secondary outcomes** • Hb concentration at week 24 • Percentage of time within, below and above Hb target range between weeks 20 to 24 • Number (%) with Hb in the target range at week 24 • Number (%) reaching predefined Hb stopping criteria • Change from baseline in hepcidin, ferritin, transferrin, TSAT, total iron, TIBC, and CHr at week 24 • Change from baseline in HCT, RBC count, and reticulocyte number at week 24 • Maximum observed change from baseline in EPO • Maximum observed change from baseline in VEGF • Incidence and severity of adverse and serious adverse events • Reasons for discontinuation of study medication • Discontinuation for safety-related reasons (prespecified stopping criteria or adverse events) until the end of follow-up period • Absolute values and changes from baseline in laboratory parameters, sPAP, left ventricular ejection fraction, ophthalmology assessments and vital signs • Preliminary assessment of MACE and other CV events
Notes	• Funding: GlaxoSmithKline • Conflicts of interest: "A.M.M., B.C., N.B., D.J., J.J.L. and A.R.C. are employees of and hold stock in GlaxoSmithKline (GSK). L.H. and B.M.J. are former employees of GSK and hold stock options in GSK. A.K.N. received research grants from GSK and research sponsorship from Affymax. M.A. has no potential conflicts of interest to report. This manuscript is not under consideration for publication elsewhere. The results presented in this article have not been published previously in whole or part, except in abstract form. Some of the data included in the present article were presented at the American Society of Nephrology meeting in Chicago, IL, USA, 15–20 November 2016."

Risk of bias

Meadowcroft 2019 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were assigned to study treatment in accordance with a randomisation schedule that utilized central randomisation. The randomisation schedule was computer generated using the randomisation system RandAll" Quote: "Eligible participants were stratified by region (Japan versus non-Japan) and prior rhEPO dose and then randomized 2:2:2:2:1:2."
Allocation concealment (selection bias)	Low risk	Quote: "Participants randomized to daprodustat had automatic dose adjustments through an interactive voice/web response system based on a prespecified dose-adjustment algorithm," Quote: "The response system managed by Perceptive, Nottingham, UK"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "For the first 4 weeks, treatment was fully blinded to treatment group with control participants receiving placebo QD. Thereafter, only the dose of daprodustat was blinded, with control participants receiving standard-of-care open-label rhEPO (epoetin or their biosimilars, or darbepoetin alfa) as required for the remaining 20 weeks to achieve haemoglobin within the target range (10–11.5 g/dL)." For the scope of this review, we considered only the first 4 weeks, where the comparison was clearly HIF vs placebo. The first 4 weeks were conducted in double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An internal GlaxoSmithKline Safety Review Team reviewed blinded safety data in stream and an independent data monitoring committee periodically reviewed the same safety data but unblinded."
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported in sufficient detail to perform adjudication in the first 4 weeks of the treatment. Overall, ITT performed on 171/177 participants in the intervention group. and 39/39 participants in the control group. Imbalance between the two groups
Selective reporting (reporting bias)	High risk	All pre-specified outcomes were not reported, for the end of the 4th week where the intervention were compared only with placebo Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Stopped early due to some data-dependent process (including a formal-stopping rule) Funder was likely to influence data analysis and study reporting or interpretation Authors declared conflicts of interests

MIYABI HD-M 2019

Study characteristics	
Methods	• Study design: phase III, parallel RCT • Time frame: not reported • Duration of follow-up: 52 weeks + 4 weeks follow-up

MIYABI HD-M 2019 *(Continued)*

Participants	**General information** • Setting: multicentre (61 sites) • Country: Japan • Inclusion criteria: males and females ≥ 18 years with kidney failure on regular dialysis (including, HDF, HF, HD, and other modalities except for PD) weekly or more than weekly for at least 12 weeks prior to randomisation; weight (after dialysis) > 40 and ≤ 160 kg at screening; at least one kidney; treated with weekly or bi-weekly dose of darbepoetin alfa, monthly or bi-weekly dose of EBP, OR weekly, twice or 3 times/week dose of epoetin alfa/beta, and having had no more than one dose change within 8 weeks prior to randomisation; mean screening Hb level ≥ 9.5 and < 12.0 g/dL during the screening period, AND all Hb level must be measured by the central laboratory, AND the difference between the lowest level and highest level is < 1.2 g/dL, with the last screening Hb level measurement within 14 days prior to randomisation; ferritin ≥ 100 ng/mL or TSAT ≥ 20% at screening; serum folate and serum vitamin B12 > LLN at screening • Exclusion criteria: NYHA Class III or IV congestive HF; history of cardio- (cerebro-) vascular events (e.g. unstable angina, MI, stroke, pulmonary thromboembolism, and acute limb ischaemia) within 6 months prior to randomisation; sustained, poorly controlled arterial hypertension (defined as SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg) or hypotension (SBP < 90 mm Hg) at randomisation; proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy requiring invasive treatment (e.g. intraocular injections or laser photocoagulation) at screening • Target Hb: 10 to 12 g/dL **Baseline characteristics** • CKD stage: 5D (HD) • Number (randomised/analysed): treatment group (153/115); control group (76/65) - ITT • Mean age ± SD (years): treatment group (66.2 ± 10.3); control group (64.8 ± 10.6) • Sex (M, %): treatment group (91, 59.5%); control group (49, 64.5%) • Time on dialysis: not reported • eGFR: not reported **Comorbidities** • CV disease: not reported • Heart disease: not reported • Hypertension: not reported • Diabetes (number, %): not reported • Prior agents used (number, %) ○ ESA: treatment group (153/153); control group (76/76)
Interventions	**Treatment group (high dose)*** • Molidustat: (starting dose 75 mg/day): planned doses for titration are 5, 12.5, 25, 50, 70, 100, 150 and 200 mg once/day; Hb target range ≥ 100 to < 120 g/L • Darbepoetin alfa placebo • The maintenance dose of molidustat/molidustat placebo (at least 200 mg) or darbepoetin/darbepoetin placebo (at least 180 mg) **Control group** • Molidustat placebo + darbepoetin alfa • The maintenance dose of molidustat/molidustat placebo (at least 200 mg) or darbepoetin/darbepoetin placebo (at least 180 mg) **Co-interventions**

MIYABI HD-M 2019 *(Continued)*

- Iron, vitamin B12 and folate supplementation is permitted if required and will be administered according to Japanese guideline recommendations. Iron supplementation will be administered to reach a target serum ferritin level of at least 100 ng/mL or TSAT of at least 20%

*Note: dose assessed as high according to DIALOGUE 1 2019

Outcomes	**Primary outcomes** • The mean Hb level during the evaluation period (week 33 to 36) • The change in mean Hb level during the evaluation period from baseline (week 33 to 36) **Secondary outcomes** • Responder rate: proportion of responders among the subjects (week 33 to 36) • Proportion of subjects who meet each component of the response (week 33 to 36) • Hb level (to 52 weeks) • Change in Hb level (up to 52 weeks) • Proportion whose mean Hb is in the target range (week 33 to 36) • Proportion whose mean Hb is above the target range (week 33 to 36) • Proportion whose mean Hb is below the target range (week 33 to 36) • Proportion with Hb in the target range (up to 52 weeks) • Proportion with Hb above the target range (up to 52 weeks) • Proportion with Hb below the target range (up to 52 weeks) • Proportion whose maximum rise in Hb between each consecutive visits is above 0.5 g/dL/week (up to 52 weeks) • Number with serious adverse events (up to 52 weeks) • Cmax at baseline, week 8, 24 and 52 • AUC at baseline, week 8, 24 and 52 • EPO concentration week 8, 24 and 52 • HRQoL using the EQ-5D-5L
Notes	• Funding: Bayer Yakuhin Ltd. The sponsor will have access to the full trial data set • Conflicts of interest: some authors reported conflicts of interest including consulting, manuscript and lecture fees • Authors were contacted to request extra information but they did not reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment allocation was conducted via an interactive voice/web response system (IxRS), and the computer-prepared randomisation list was provided to the IxRS supplier by the sponsor."
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was conducted via an interactive voice/web response system (IxRS), and the computer-prepared randomisation list was provided to the IxRS supplier by the sponsor."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind" Quote: "Investigators and patients were blinded to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported

MIYABI HD-M 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of 229 patients randomized to molidustat (n=153) or darbepoetin alfa (n=76), 180 completed 52 weeks of treatment (n=115 and 65)." 151/153 participants in the intervention group and 74/76 participants in the control group completed the follow-up period, as reported in Figure 1 Some analyses were performed on the ITT population
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions were reported between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

MIYABI ND-C 2019

Study characteristics	
Methods	• Study design: phase 3, parallel RCT • Time frame: not reported • Duration of follow-up: 52 weeks + 4 weeks follow-up
Participants	**General information** • Setting: multicentre (61 sites) • Country: Japan • Inclusion criteria: eGFR < 60 mL/min/1.73 m^2 (CKD stages 3 to 5); weight > 40 and ≤ 160 kg at screening; males and females ≥ 20 years at screening; not on dialysis and not expected to start dialysis during the study period; not treated with ESAs and/or HIF-PH inhibitors within 8 weeks prior to randomisation; mean of the last 2 central laboratory Hb levels during the screening period must be ≥ 8.0 and < 11.0 g/dL and the last measurements must be taken within 14 days prior to randomisation; ferritin ≥ 50 ng/mL at screening • Exclusion criteria: NYHA class III or IV congestive HF; history of cardio- (cerebro-) vascular events (e.g. unstable angina, MI, stroke, pulmonary thromboembolism, and acute limb ischaemia) within 6 months prior to randomisation; sustained and poorly controlled arterial hypertension (SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg) or hypotension (SBP < 90 mm Hg) at randomisation; proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy requiring invasive treatment (e.g. intraocular injections or laser photocoagulation) • Target Hb: 11 to 13 g/dL **Baseline characteristics** • CKD stage: stages 3 to 5 • Number (randomised/analysed): treatment group (82/82); control group (80/79) • Mean age ± SD (years): treatment group (72.1 ± 9.3); control group (71.2 ± 10.1) • Sex (M/F): treatment group (50/82); control group (50/80) • Time on dialysis: not applicable • MeaneGFR±SD (mL/min/1.73 m^2): treatment group (19 ± 8.5); control group (22.1 ± 12)

MIYABI ND-C 2019 *(Continued)*

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes(number, %): not reported
- Prior agents used(number, %): not reported

Interventions

Treatment group (medium dose)*

- Molidustat (BAY85-3934): once/day, starting dose of 25 mg
- Doses for the titration of molidustat were 5, 12.5, 25, 50, 75, 100, 150 and 200 mg once/day, actual dosages were 46.30 ± 30.64 mg/day and median 40.1 (range 3.9 to 143.6) mg/day

Control group

- Darbepoetin alfa: once every 2 weeks, starting dose of 30 µg
- Doses for the titration of darbepoetin alfa were 15, 30, 60, 90, 120 and 180 µg every 2 to 4 weeks

Co-interventions

- Iron, vitamin B12, and folate supplementation was permitted

*Note: assessed as medium-dose according to DIALOGUE 1 2019

Outcomes

Primary outcomes

- Mean Hb (week 30 to 36)
- Change in Hb from baseline to the average during the evaluation period (week 30 to 36)

Secondary outcomes

- Responder rate: proportion of responders among the subjects (week 30 to 36)
- Rate of rise in Hb (g/dL/week) (up to 8 weeks)
- Rate of rise in Hb (g/dL/week) (up to 4 weeks)
- Proportion who meet each component of the response (week 30 to 36)
- Cumulative proportion who achieved the lower limit of the target Hb range at least once (up to 52 weeks)
- Change in Hb (up to 52 weeks)
- Hb (up to 52 weeks)
- Proportion whose mean Hb is in the target range (week 30 to 36)
- Proportion whose mean Hb is above the target range (week 30 to 36)
- Proportion whose mean Hb is below the target range (week 30 to 36)
- Proportion with Hb in the target range (up to 52 weeks)
- Proportion with Hb above the target range (up to 52 weeks)
- Proportion with Hb below the target range (up to 52 weeks)
- Proportion whose maximum rise in Hb between each consecutive visits is above 0.5 g/dL/week (up to 52 weeks)
- Number with serious adverse events (up to 52 weeks)
- Cmax)(baseline, week 12, 24 and 52)
- AUC (baseline, week 12, 24 and 52)
- EPO concentration (baseline, week 12, 24 and 52)

Notes

- Funding: Bayer. The sponsor will have access to the full trial dataset
- Conflicts of interest: some authors reported conflicts of interest including consulting, manuscript and lecture fees
- Authors were contacted to request extra information but they did not reply

MIYABI ND-C 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were then randomized 1:1 using an interactive voice/web response system to receive either molidustat or darbepoetin treatment for 52 weeks."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were then randomized 1:1 using an interactive voice/web response system to receive either molidustat or darbepoetin treatment for 52 weeks."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Following screening, 162 patients were randomized to receive molidustat (n = 82) or darbepoetin (n = 80) (online suppl. Fig. 2). All randomized patients received the assigned study drug except for 1 in the darbepoetin group. In total, 135 patients completed treatment up to week 36 (63 [76.8%] for molidustat and 72 [90.0%] for darbepoetin), and 118 patients completed treatment up to week 52 (53 [64.6%] for molidustat and 65 [81.3%] for darbepoetin)." Some analyses were performed on the ITT population
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions were reported between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

MIYABI ND-M 2019

Study characteristics	
Methods	• Study design: phase 3, parallel RCT • Time frame: not reported • Duration of follow-up: 56 weeks (52 weeks treatment period + 4 weeks follow-up)
Participants	**General information** • Setting: multicentre (59 sites) • Country: Japan

MIYABI ND-M 2019 *(Continued)*

- Inclusion criteria: eGFR < 60 mL/min/1.73 m² (CKD stages 3 to 5); used the same ESA for 8 weeks prior to screening; treated with darbepoetin alfa with bi-weekly or monthly dose, EBP with monthly, OR epoetin alfa/beta weekly or bi-weekly, and having had no more than one dose change within 8 weeks prior to randomisation; weight > 40 and ≤ 160 kg at screening; males or females ≥ 20 years of age at screening; not on dialysis and not expected to start dialysis during the study period; mean screening Hb level ≥ 10.0 and < 13.0 g/dL during the 8-week screening period, AND all Hb level must be measured by the central laboratory, AND the difference between the lowest level and highest level is < 1.2 g/dL, with the last screening Hb level measurement within 14 days prior to randomisation; ferritin ≥ 100 ng/mL or TSAT ≥ 20%
- Exclusion criteria: NYHA class III or IV congestive HF; history of cardio- (cerebro-) vascular events (e.g. unstable angina, MI, stroke, pulmonary thromboembolism, and acute limb ischaemia) within 6 months prior to randomisation; sustained and poorly controlled arterial hypertension (defined as SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg) or hypotension (SBP < 90 mm Hg) at randomisation; proliferative choroidal or retinal disease, such as neovascular age-related macular degeneration or proliferative diabetic retinopathy requiring invasive treatment (e.g. intraocular injections or laser photocoagulation)
- Target Hb: 11 to 13 g/dL

Baseline characteristics

- CKD stage: stages 3 to 5
- Number (randomised/analysed): treatment group (82/57); control group (82/62)
- Mean age ± SD (years): treatment group (69 ± 10.3); control group (72.4 ± 10.3)
- Sex (M, %): treatment group (45, 54.9%); control group (54, 65.9%)
- Time on dialysis: not applicable
- Mean eGFR ± SD (mL/min/1.73 m²): treatment group (18.7 ± 10.7); control group (17.5 ± 9)

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Interventions

Treatment group (medium dose)*

- Molidustat (BAY85-3934): starting dose of 25 mg or 50 mg molidustat once/day will be titrated based on the subject's Hb response
  - Up to week 52, mean dosages were mean 51.21 ± 32.35 mg/day in the molidustat group
- Doses for the titration of molidustat are 5, 12.5, 25, 50, 75, 100, 150 and 200 mg once/day

Control group

- Darbepoetin alfa, starting dose and frequency of darbepoetin alfa are based on previous ESA
- Doses for the titration of darbepoetin alfa are 15, 30, 60, 90, 120 and 180 µg every 2 to 4 weeks

Co-interventions

- Iron, vitamin B12 and folate supplementation is permitted

*Note: dose assessed as medium-dose according to DIALOGUE 1 2019

Outcomes

Primary outcomes

- Mean Hb level (week 30 to 36)
- Change in Hb from baseline to the average during the evaluation period (week 30 to 36)

Secondary outcomes

- Responder rate: proportion of responders among the subjects (week 30 to 36)

MIYABI ND-M 2019 *(Continued)*

- Proportion of subjects who meet each component of the response (week 30 to 36)
- Hb level (up to 52 weeks)
- Change in Hb level (up to 52 weeks)
- Proportion whose mean Hb are in the target range during the evaluation period (week 30 to 36)
- Proportion whose mean Hb are above the target range during the evaluation period (week 30 to 36)
- Proportion whose mean Hb are below the target range during the evaluation period (week 30 to 36)
- Proportion whose Hb are in the target range (up to 52 weeks)
- Proportion whose Hb are above the target range (up to 52 weeks)
- Proportion whose Hb are below the target range (up to 52 weeks)
- Proportion whose maximum rise in Hb between each consecutive visits is above 0.5 g/dL/week (up to 52 weeks)
- Number with serious adverse events (up to 52 weeks)
- Cmax of molidustat (baseline, week 12, 24 and 52)
- AUC of molidustat (baseline, week 12, 24 and 52)
- EPO concentration (baseline, week 12, 24 and 52)

Notes

- Funding: Bayer. The sponsor will have access to the full trial dataset
- Conflicts of interest: some authors reported conflicts of interest including consulting, manuscript and lecture fees

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Interactive voice/web response system"
Allocation concealment (selection bias)	Low risk	Quote: "Interactive voice/web response system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "In total, 164 patients were randomized to molidustat (n = 82) or darbepoetin (n = 82). Of these, 133 patients completed treatment up to week 36 (65 [79.3%] in the molidustat group and 68 [82.9%] in the darbepoetin group) and 120 patients completed treatment up to week 52 (57 [69.5%] in the molidustat group and 63 [76.8%] in the darbepoetin group)." ITT analyses
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions were reported between groups

MIYABI ND-M 2019 *(Continued)*

	Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

Nangaku 2021

Study characteristics	
Methods	• Study design: RCT, 2-arm, parallel, phase III • Time frame: not reported • Duration of follow-up: 52 weeks - data were reported at 24 weeks (preliminary analysis)
Participants	**General information** • Setting: multicentre (number of sites not reported) • Country: Japan • Inclusion criteria: CKD receiving HD or HDF 3 times/week for more than 12 weeks prior to the screening period, excluding receiving home dialysis or combination of PD; treated with ESAs for the recent 8 weeks prior to the screening period; mean of the two screening Hb levels closest in time to the baseline visit is ≥ 9.5 g/dL and ≤ 12.0 g/dL; fluctuation between the 2 Hb levels closest in time to the baseline visit during the screening period < 1.5 g/dL; serum ferritin ≥ 100 ng/mL, or TSAT ≥ 20% during the screening period; folate and vitamin B12 ≥ LLN during the screening period • Exclusion criteria: anaemia due to a main cause other than CKD: sickle cell disease, myelodysplastic syndrome, bone marrow fibrosis, haematologic malignancy, haemolytic anaemia, thalassaemia, or PRCA; active bleeding or recent blood loss within 8 weeks prior to the screening period; RBC transfusion within 8 weeks prior to the screening period; received testosterone enanthate or mepitiostane within 8 weeks prior to the screening period; AST, ALT, or total bilirubin >2.5 times ULN during the screening period; uncontrolled hypertension (DBP > 110 mm Hg or SBP >180 mm Hg) at the first day of the screening period and day 1; ophthalmic examinations during the screening period correspond to either of the following criteria; 1) no available fundal findings, 2) findings indicating the presence of active fundal disease; severe heart failure (NYHA class IV); cerebrovascular disorder or acute coronary syndrome (hospitalisation due to unstable angina or MI), requiring hospitalisation due to urgent percutaneous intervention for coronary or heart failure within 12 weeks prior to the screening period; current or history of malignancy; history of malignancy with no recurrence for the recent 5 years is not an exclusion criterion; new onset or recurrent event of DVT or pulmonary embolism within 12 weeks prior to the screening period; current or history of haemosiderosis or haemochromatosis; history of prior organ transplantation or scheduled organ transplant, or prior transplantation of hematopoietic stem cell or bone marrow; males and females of childbearing potential who are unwilling to use an acceptable method of contraception during the designated period (males: during the study and 90 days after the last dose; females: during study and 30 days after the last dose); pregnant or breast feeding, or are predicted to be pregnant • Target Hb: 10 to 12 g/dL **Baseline characteristics** • CKD stage: HD • Number (randomised/analysed): treatment group (162/120); control group (161/135) • Mean age ± SD (years): treatment group (66.0 ± 11.3); control group (64.9 ± 11.7) • Sex (M, %): treatment group (104, 64.2%); control group (109, 67.7%) • Time on dialysis (years): treatment group (7.4 ± 6.7); control group (7.6 ± 7.6) • eGFR: not reported **Comorbidities** • CV disease: not reported • Heart disease: not reported

Nangaku 2021 *(Continued)*

- Hypertension: treatment group (152/162); control group (147/161)
- Diabetes (number, %): treatment group (35/162); control group (49/161)
- Prior agents used (number, %)
  - Epoetin: treatment group (49/162); control group (53/161)
  - Darbepoetin alfa: treatment group (97/162); control group (90/161)
  - EBP: treatment group (16/162); control group (18/161)

Interventions	**Treatment group (medium dose)*** • Vadadustat (MT-6548), initial dose 300 mg daily, orally, then doses were adjusted to achieve a Hb target within 150–600 mg (mean dose 375 mg) **Control group** • Darbepoetin alfa, intravenous administration **Co-interventions** • Not reported *Note: assessed as medium dose according to NDD-CKD 2020
Outcomes	**Primary outcomes** • Average Hb at weeks 20 and 24 **Secondary outcomes** • Iron parameters were measured during the study period • Safety was assessed up to 24 weeks • Mean Hb weeks 48 and 52 • Hb level at each assessment time point (up to week 52) • Proportion with Hb level at each assessment time point within the target range (up to week 52)
Notes	• Funding: Mitsubishi Tanabe Pharma Corporation • Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind phase" Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. However, since interventions were different, it was possible that investigators and/or participants were aware of treatment allocation. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias)	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors

Nangaku 2021 *(Continued)*

All outcomes		occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the 323 randomized patients, 120 and 135 completed the 52-week treatment period in the vadadustat and darbepoetin alfa groups, respectively." Reasons for discontinuation were provided and some of them were related to the intervention ITT analyses were performed for some outcomes
Selective reporting (reporting bias)	High risk	Not all of the planned outcomes on ClincialTrials.gov have been measured and reported on in the final report. No reasoning provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions were reported between groups Funding was reported and authors' disclosure were not reported Funder was likely to influence data analysis and study reporting or interpretation

Nangaku 2021a

Study characteristics	
Methods	• Study design: phase 3, parallel RCT • Time frame: October 2017 to August 2019 • Duration of follow-up: 54 weeks (52-week treatment period + 2 weeks follow-up)
Participants	**General information** • Setting: multicentre (86 sites) • Country: Japan • Inclusion criteria: anaemia; aged at least 20 years with CKD who were not on dialysis and had an eGFR of < 60 mL/min/1.73 m^2; both “ESA users” and “ESA non-users”; serum ferritin ≥100 ng/mL or TSAT ≥ 20% • Exclusion criteria: anaemia attributable to causes other than CKD; active bleeding or blood loss less than 8 weeks before screening; received RBC transfusion less than 8 weeks before screening; active fundus disease or ocular fundus observations not available; uncontrolled hypertension; malignancy in the last 5 years; severe heart failure; cerebrovascular disorder or acute coronary syndrome within 12 weeks of screening • Target Hb: 11 to 13 g/dL **Baseline characteristics** • CKD stage: non-dialysis dependent CKD • Number (randomised/analysed): treatment group (151/111); control group (153/123) • Mean age ± SD (years): treatment group (71.7 ± 10.3); control group (72.2 ± 9.5) • Sex (M, %): treatment group (75, 49.7%); control group (73, 47.7%) • Time on dialysis: not applicable • Mean eGFR ± SD (mL/min/1.73 m^2): treatment group (21.28 ± 11.66); control group (22.6 ± 11.6)

Nangaku 2021a *(Continued)*

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: treatment group (147/151); control group (145/153)
- Diabetes (number, %): treatment group (57/151); control group (62/153)
- Prior agents used (number, %)
  - Epoetin: treatment group (0/151); control group (0/153)
  - Darbo alfa: treatment group (47/151); control group (45/153)
  - EPO beta pegol: treatment group (33/151); control group (37/153)

Interventions	**Treatment group (medium dose)***

- Vadadustat (MT-6548): initial dose of 300 mg/day, doses were adjusted within 150 to 600 mg to achieve and maintain target Hb 11 to 13 g/dL (mean dose 375 mg)

Control group

- Darbepoetin alfa: initial dose was set in accordance with previous ESAs in ESA users and was 30 µg once every 2 weeks in ESA non–users. Doses were adjusted between 15 and 180µg once every 4 weeks, every 2 weeks, or weekly to maintain Hb levels within the target range

Co-interventions

- Iron supplements were administered during the screening and treatment periods to maintain serum ferritin levels ≥ 100 ng/mL or TSAT ≥ 20%
- Patients receiving an iron-containing phosphate binder at screening continued its use at the same dose during the treatment period
- Oral iron or iron-containing phosphate binders were not to be taken within 2 hours of vadadustat dosing to avoid a decline in the bioavailability of vadadustat
- Administration of ESAs, RBC transfusion, or phlebotomy was permitted as rescue therapy at the investigators' discretion

*Note: dose assessed as medium according to NDD-CKD 2020

Outcomes	**Primary outcome**

- Average Hb at weeks 20 and 24

Secondary outcomes

- Iron parameters were measured during the study period (dose of iron supplementation, iron-related parameters (TIBC, TSAT, serum ferritin, and serum hepcidin), and RBC indices (mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, and RBC distribution width
- Safety was assessed up to 24 weeks, including CV events/cardiac failure, thromboembolism, pulmonary hypertension, malignancy, retinal disorders, and hyperkalaemia
- Laboratory tests including plasma VEGF, vital signs, and ophthalmoscopy over 52 weeks
- Mean Hb at each time point and the proportion of patients with mean Hb within the target range of 11.0–13.0 g/dL
- proportions of patients with a confirmed Hb at least 13.0 g/dL or at least 14.0 g/dL and with a rapid Hb rise >2.0 g/dL over 4 weeks

Notes	

- Funding: Mitsubishi Tanabe Pharma Corporation
- Conflicts of interest:"M. Nangaku reports receiving grants or honoraria from Akebia, Alexion, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, GlaxoSmithKline (GSK), Japan Tobacco (JT), Kyowa Kirin, Mitsubishi Tanabe, Ono, Taisho, Takeda, and Torii; reports being a scientific advisor or member of Akebia, Astellas, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, GSK, JT, Kyowa-Kirin, and Mitsubishi-Tanabe. Y. Komatsu reports receiving honoraria from AstraZeneca, Baxter, Chugai, and Kyowa Kirin; and reports consultancy agreements with Mitsubishi Tanabe. G. Kaneko, K.

Nangaku 2021a *(Continued)*

Kondo, K. Ueta, T. Tandai, Y. Kawaguchi, and Y. Kokado are employees of Mitsubishi Tanabe Pharma Corporation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were enrolled by the investigator and randomized 1:1 (using a web-based system) to oral vadadustat (Akebia Therapeutics Inc., Cambridge, MA) or subcutaneous darbepoetin alfa (Kyowa Kirin Co., Ltd, Tokyo, Japan)."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the 432 patients who gave informed consent, 304 were randomized to vadadustat (151 patients) or darbepoetin alfa (153 patients) (Figure 2).Of these, 271 patients (130 in the vadadustat group, 141 in the darbepoetin alfa group) completed the 24-week treatment period and 234 patients (111 in the vadadustat group, 123 in the darbepoetin alfa group) completed the 52-week treatment period. The most common reason for withdrawal from both groups was initiation of kidney replacement therapy, including chronic haemodialysis/peritoneal dialysis or kidney transplant." Data were reported on the ITT population
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

Nangaku 2021b

Study characteristics

Methods	• Study design: parallel RCT • Time frame: June 2016 to October 2018 • Duration of follow-up: 56 weeks (52 weeks of treatment + 4 weeks follow-up)
Participants	**General information**

Nangaku 2021b *(Continued)*

- Setting: multicentre (number of sites not reported)
- Country: Japan
- Inclusion criteria: non-dialysis (cohort 1 and 3) and PD (cohort 2) patients with renal anaemia*; ≥ 20 years; CKD stages 3, 4, and 5 defined by eGFR using the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives formula; ESA 1) ESA non-users: have not used ESAs for at least 8 weeks prior to screening, 2) ESA users: have used the same ESA for at least 8 weeks prior to screening. However, in the ND patients, the dose of darbepoetin alfa or EBP must be stable (administered once every 4 weeks and up to one-step dose change during at least 8 weeks prior to screening); Hb 1) ESA non-users: ≥ 8.0 g/dL and < 11.0 g/dL, 2) ESA users: ≥ 9.0 g/dL and ≤ 13.0 g/dL; ferritin > 100 ng/mL or TSAT > 20% (screening verification only); females: not pregnant not breast-feeding, of non-childbearing potential or postmenopausal; females on HRT whose menopausal status is in doubt will be required to use one of the most effective contraception methods if they wish to continue their HRT during the study; females of childbearing potential must agree to comply with one of the contraception methods listed as requirements from at least 28 days prior to the first dose of study medication until the completion of the follow-up visit (for subjects randomised to the GSK1278863 group) or 7 weeks after the last dose of study treatment (for subjects randomised to the EBP group); informed consent
- Exclusion criteria: dialysis or kidney transplant; aplasia, other causes of anaemia, GI bleeding; MI, acute coronary syndrome, stroke, or TIA diagnosed within 8 weeks prior to screening or during a period from screening to day 1; NYHA class IV heart failure; QTc > 500 msec or QTc > 530 msec in subjects with bundle branch block; liver disease; malignancy; planned use of IV iron during the screening phase or during a period from day 1to week 4; severe allergic reactions; use or planned use of any prescription or non-prescription drugs or dietary supplements that are prohibited during the study period (prohibited medications: strong inducers and inhibitor of CYP2C8); use of an investigational agent within 30 days or 5 half-lives of the investigational agent (whichever is longer); any prior treatment with GSK1278863 for a treatment duration of > 30 days; any other condition, clinical or laboratory abnormality, or examination finding that the investigator (or sub investigator) considers would put the subject at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study
- Target Hb: 11.0 to 13.0 g/dL

Baseline characteristics

- CKD stage: non-dialysis-dependent CKD (from the protocol: CKD (cohort 1 AND 3) and PD (cohort 2); no publications reported data on PD
- Number (randomised/analysed): treatment group (149/111); control group (150/113) - ITT
- Mean age ± SD (years): treatment group (68 ± 12); control group (70 ± 9)
- Sex (M, %): overall (188, 63%); treatment group (96, 64%); control group (92, 61%)
- Time on dialysis: not applicable
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: treatment group (141/149); control group (145/150)
- Diabetes: treatment group (65/149); control group (69/150)
- Prior agents used:
  - Epoetin: treatment group (0/149); control group (0/150)
  - Darbo alfa: treatment group (33/149); control group (38/150)
  - EPO beta pegol: treatment group (25/149); control group (21/150)

*Note: in this review we have reported data only on CKD patients because no other publications were identified

Interventions	**Treatment group (cohort 1) (low dose)** • Daprodustat (GSK1278863): starting dose 2 to 4 mg for 52 weeks orally administered once/day; median dose 4.0 (2.3 to 6.0) mg/day in ESA-naïve and 5.3 (3.3 to 7.3) mg/day in ESA users

Nangaku 2021b *(Continued)*

- After week 4, dose adjustments will be made within the dose range of 1 to 24 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hb within the target range (11.0 to 13 0 g/dL)
- ESA non-users: SC treatment with EBP will be started at a dose of 25 mg once every 2 weeks on day 1. Subsequently, dose adjustments will be made within the dose range of 25 to 150 mg every 4 weeks according to the prespecified initial dose adjustment criteria to achieve the lower limit of the Hb target (11.0 g/dL). Once Hb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm. After it is confirmed that all of the criteria for dosing interval change are met, dosing frequency will be changed to once every 4 weeks, and dose adjustments will be made within the dose range of 25 to 250 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hb within the target Hb range (11.0 to 13.0 g/dL).

Control group (cohort 1)

- EBP (Mircera) (SC): administered once every 2 or 4 weeks
  - ESA users: prior ESA therapy will be replaced with SC treatment with EBP at the equivalent dose once every 4 weeks according to prespecified dose conversion. Subsequently, dose adjustments will be made within the dose range of 25 to 250 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hb within the target range (11.0 to 13.0 g/dL) for 52 weeks

Treatment group (cohort 3) (low dose)*

- GSK1278863 (oral): starting dose was 4 mg once/day for 52 weeks; median dose 4.0 (2.3 to 6.0) mg/day in ESA-naïve and 5.3 (3.3 to 7.3) mg/day in ESA users
  - For ESA non-user with baseline Hb ≥ 8.0 and < 9.0 g/dL, treatment with GSK1278863 was started at a dose of 4 mg once/day on day 1
  - For ESA non-user with baseline Hb ≥ 9.0 and < 11.0 g/dL, treatment with GSK1278863 was started at a dose of 2 mg once/day on day 1
- After week 4, dose adjustments made within the dose range of 1 to 24 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hb within the target range (11.0-13 0 g/dL)
  - ESA non-users: SC treatment with EBP will be started at a dose of 25 mg once every 2 weeks on day 1. Subsequently, dose adjustments will be made within the dose range of 25 to 150 mg every 4 weeks according to the prespecified initial dose adjustment criteria to achieve the lower limit of the Hb target (11.0 g/dL). Once Hb increases to 11.0 g/dL or more, dose adjustments will be made according to the prespecified dose adjustment algorithm. After it is confirmed that all of the criteria for dosing interval change are met, dosing frequency will be changed to once every 4 weeks, and dose adjustments will be made within the dose range of 25 to 250 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hb within the target Hb range (11.0 to13.0 g/dL)

Control group (cohort 3)

- EBP (Mircera) (SC): administered once every 2 or 4 weeks
  - ESA users: prior ESA therapy will be replaced with SC treatment with EBP at the equivalent dose once every 4 weeks according to prespecified dose conversion. Subsequently, dose adjustments will be made within the dose range of 25 to 250 mg every 4 weeks according to the prespecified dose adjustment algorithm to achieve and/or maintain Hb within the target range (11.0 to 13.0 g/dL) for 52 weeks

Co-interventions

- Supplemental iron therapy

*Note: assessed as low dose according to Meadowcroft 2019

Outcomes

Primary outcomes

- Mean Hb during the primary efficacy evaluation period (weeks 40 to 52)

Nangaku 2021b *(Continued)*

Secondary outcomes

- Number (%) with mean Hb in the target range (11.0 to 13.0 g/dL) during the primary efficacy evaluation period (weeks 40 to 52)
- Change from baseline in Hb at week 4 (Hb increase rate)
- Number (%) by Hb change from baseline category at week 4
- Distribution of the dose level
- Duration of treatment interruption due to Hb > 13 g/dL
- Frequency of dose adjustments
- Hb and change from baseline at each assessment visit
- Number (%) with Hb within the target range (11.0 to 13.0 g/dL) at each assessment visit
- Time (%) in Hb target range (11.0-13.0 g/dL) during the primary efficacy evaluation period(weeks 40 to 52)
- Time (in days) to reach the lower Hb target (11.0 g/dL)
- Number (%) who have an Hb level < 7.5 g/dL
- Number (%) who have an Hb increase > 2 g/dL over any 4 weeks
- Number (%) who have an Hb level > 13.0 g/dL and number of episodes
- Dose of oral iron during the study period and the primary efficacy evaluation period (weeks 40 to 52)
- Number (%) who use oral iron during the study period and the primary efficacy evaluation period (weeks 40 to 52)
- Change from baseline in ferritin
- Change from baseline in TSAT
- Changes from baseline in hepcidin, serum iron, and TIBC
- AUC and Cmax of plasma GSK1278863
- eGFR and change from baseline
- SCr and change from baseline
- Urine creatinine and urine albumin, and changes from baseline
- UACR and change from baseline
- Changes from baseline in SF-36 HR-QoL scores (Physical Component Summary, Mental Component Summary, and 8 subscales)
- Change from baseline in EQ-5D-5L score
- Change from baseline in EQ-5D-5L VAS
- Incidence and severity of adverse and serious adverse events, including adverse events of special interest
- Reasons for discontinuation of study medication
- Laboratory tests, ECG, vital signs, and ophthalmology assessments

Notes

- Funding: GlaxoSmithKline
- Conflicts of interest: "M.N. has received grants and personal fees from Astellas Pharma Inc. (Astellas), Chugai Pharmaceutical Co. Ltd. (Chugai), Daiichi Sankyo Co. Ltd., GlaxoSmithKline (GSK), Kyowa Kirin Co. Ltd. (KKC), Mitsubishi Tanabe Pharma, and Torii Pharmaceutical Co. Ltd. (Torii); grants from Bayer Yakuhin Ltd. (Bayer), Ono Pharmaceutical Co. Ltd. (Ono), and Takeda Pharmaceutical Co. Ltd. (Takeda); and personal fees from AstraZeneca and JT Pharmaceuticals. T.H. has received grants and personal fees from Asahi Kasei Pharma Corporation, Bayer, Chugai, Kissei Pharmaceutical Co. Ltd. (Kissei), Otsuka Pharmaceutical Co. Ltd. (Otsuka), and Torii; grants, person- al fees, and other from KKC, and Ono; personal fees and other from Astellas; grants from Eisai Co. Ltd., Fuso Pharmaceutical Industries Ltd. (Fuso), Takeda, and Terumo Corporation; and other from GSK. T.A. has received personal fees from Astellas, Bayer, Chugai, Fuso, GSK, JT Pharmaceuticals, KKC, Kissei, Nipro Corporation, Ono, Ostuka, Torii, and Sanwa Chemical Industrial Co. Ltd. Y.T. has received personal fees from Chugai, GSK, KKC, and Torii. R.N. is an employee of GSK. N.O., K.K., T.N., N.P.J., Y.E., and A.R.C. are employees of and hold equity stock in GSK."
- Note: the study reported a cohort 2: 50 PD patients - GSK1278863 group (starting dose: 4 mg) (data were not reported in this review) for 52 weeks

Risk of bias

Nangaku 2021b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A biostatistician generated the randomisation codes using a company-validated system. A random permutation of treatment assignments within blocks (block size was set to 4) stratified by current ESA use/nonuse and the haemoglobin level (ESA-naïve: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) was used for the randomisation sequence. Investigators accessed the Inter- active Web Response System to obtain the assigned interventions."
Allocation concealment (selection bias)	Low risk	Quote: "A biostatistician generated the randomisation codes using a company-validated system. A random permutation of treatment assignments within blocks (block size was set to 4) stratified by current ESA use/nonuse and the haemoglobin level (ESA-naïve: ≤9.5 g/dL, >9.5 g/dL, ESA users: <11.0 g/dL, ≥11.0 g/dL) was used for the randomisation sequence. Investigators accessed the Inter- active Web Response System to obtain the assigned interventions."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Team blinded to treatment assignment conducted periodic case reviews to evaluate which events constituted AEs of special interest."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	111/149 participants in the intervention group and 113/150 participant in the control group completed the study ITT analyses was performed
Selective reporting (reporting bias)	High risk	Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were not reported
Other bias	High risk	Similar baseline characteristics, or different non-randomised co-interventions between groups Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

NCT01888445

Study characteristics	
Methods	• Study design: 4-arm parallel RCT • Time frame: not reported • Duration of follow-up: 28 weeks (24 weeks treatment and 5 weeks follow-up)
Participants	**General information** • Setting: multicentre (28 sites) • Country: Japan • Inclusion criteria: CKD on stable maintenance HD and renal anaemia receiving ESA with Hb level before dialysis of ≥ 10.0 g/dL; 20 to < 75 years; weight after the end of dialysis of ≥ 40.0 kg and < 80.0 kg

NCT01888445 *(Continued)*

- Exclusion criteria: proliferative retinopathy, age-related macular degeneration, retinal vein occlusion and/or macular oedema that is considered to require treatment; immunological disease with severe inflammation as assessed by the Investigator; even if the inflammation is in remission, the subject is excluded (e.g. SLE, rheumatoid arthritis, Sjogren's syndrome, coeliac disease); history of gastric/intestinal resection considered influential on the absorption of the drug in the GI tract or active gastroparesis; uncontrollable hypertension (SBP ≥160 mm Hg and DBP ≥110 mm Hg, before dialysis, at screening test); NYHA class III congestive heart failure; history of hospitalisation for stroke, MI or lung infarction within 24 weeks before 1st registration; positive for HIV, HBsAg, or Anti-HCV Ab; anaemia other than anaemia due to low/absent renal production of EPO (e.g. iron deficiency anaemia, haemolytic anaemia, pancytopenia); PRCA; using anabolic androgenic steroid, testosterone enanthate or mepitiostane within 6 weeks before 1st registration
- Target Hb: 10 to12 g/dL

Baseline characteristics

- CKD stage: HD
- Number (randomised/analysed): treatment group 1 (33/32); treatment group 2 (32/32); treatment group 3 (33/31); control group (32/32)
- Mean age ± SD (years): treatment group 1 (62.3 ± 8.7); treatment group 2 (62.4 ± 9.7); treatment group 3 (61.7 ± 9.8); control group (60.0 ± 7.9)
- Sex (M, %): treatment group 1 (22, 68.8%); treatment group 2 (24, 75%); treatment group 3 (25, 80.6%); control group (22, 68.8%)
- Time on dialysis (months): treatment group 1 (83.47± 71.95); treatment group 2 (76.41 ± 61.01); treatment group 3 (88.16 ± 80.02); control group (133.41 ± 108.50)
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %)
  - Prior iron therapy: treatment group 1 (9, 28.1%); treatment group 2 (9, 28.1%); treatment group 3 (7, 22.6%; control group (11, 34.4%)
  - Prior statin use, prior phosphate binders use were also reported

Interventions

Treatment group 1

- Roxadustat (ASP1517) (oral): initial dose of 50 mg 3 times/week to ESA washout patients, administered maximum for 24 weeks

Treatment group 2

- Roxadustat (ASP1517) (oral): initial dose of 70 mg 3 times/day to ESA washout patients, administered maximum for 24 weeks

Treatment group 3

- Roxadustat (ASP1517) (oral) initial dose of 100 mg 5 time/week to ESA washout patients, administered maximum for 24 weeks

Control group

- Darbepoetin alfa (IV): initial dose of 20 µg once/week to ESA washout patients, administered maximum for 24 weeks

Co-interventions

- Not reported

NCT01888445 *(Continued)*

Outcomes	**Primary outcome** • Rate of rise in Hb (g/dL/week) from baseline to the final assessment in the fixed dose period (week 6, time of discontinuation, or time of dose adjustment) **Secondary outcomes** • Cumulative response rate during the period from the start of the titration period to the end of treatment (responder: Hb ≥ 10.0 g/dL and achieve an increase in Hb ≥ 1.0 g/dL from baseline) • Percentage of measurement time points at which each patient maintains the target Hb level (10.0 to 12.0 g/dL) after achieving Hb of ≥ 10.0 g/dL • Rate of patients who achieve the target Hb level (10.0 to 12.0 g/dL) at each week • The number and percentage who achieve Hb ≥ 10.0 g/dL, and time to first achieving the lower limit of the target Hb level (10.0 g/dL) • Change in Hb from baseline at each week • Cumulative response rate during the overall treatment period (responder: Hb ≥ 10.0 g/dL and who achieve an increase in Hb of ≥ 1.0 g/dL from baseline) • Average Hb of weeks 18 to 24 • Hb change from baseline to the average Hb of weeks 18 to 24 • Maintenance rate (Hb response: average Hb during weeks 18 to 24 within the target range of 10.0 to 12.0 g/dL) • Maintenance rate (Hb response: all Hb during weeks 18 to 24 within the target range of 10.0 to 12.0 g/dL) • Average dose-response relationship in weeks 18 to 24 • Time course of Hb by prior and concomitant iron therapy • Time course of Hb in weeks 18 to 24 by average ferritin and TSAT category • Time course of Hb by prior and concomitant phosphate binder use • Plasma concentration of unchanged ASP1517 • Adverse events • Laboratory data • Vital signs (BP, pulse rate) • Standard 12-lead ECG (including QT assessment at baseline and at week 24 or the time of discontinuation) • X-ray (cardiothoracic ratio) • Ophthalmological examination (fluorescein fundus angiography, fundus photography, optical coherence tomography, and visual acuity test) • Death • Withdrawn • SF-36 Physical Functioning, vitality, physical, mental sub scores
Notes	• Funding: Astellas Pharma Inc • Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Web registration system."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent.
Blinding of participants and personnel (performance bias)	High risk	Quote: "The investigator(s) prescribed ASP1517, under double-blind conditions to patients assigned to Treatment Arms 1, 2 and 3 based on the drug number that was randomly assigned to Treatment Arms 1 to 4 and notified by

NCT01888445 *(Continued)*

All outcomes		the web registration system at the time of second registration. The investigator(s) administered darbepoetin alfa to patients assigned to Treatment Arm 4 under open-label conditions."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 130 randomized patients, 129 (99.2%) were included in the safety analysis set (SAF), 127 (97.7%) were included in the full analysis set (FAS) and pharmacokinetic analysis set (PKAS) and 86 (66.2%) were included in the per protocol set (PPS)." Quote: "A total of 130 patients were randomized. Of these, 129 patients were treated with the study treatment and 1 patient in the ASP1517 100 mg group discontinued before the first dose of study treatment due to the withdrawal of consent. A total of 80 (61.5%) patients completed the study and 50 (38.5%) patients discontinued. A total of30 (23.1%) patients discontinued during the fixed dose period and most of them (27 patients) discontinued within first 1 week in the fixed dose period. The frequency of study discontinuation during the fixed dose period was higher in the pooled ASP1517 group (27.6%) compared with the darbepoetin alfa group (9.4%). The frequency of study discontinuation during the titration period was similar between the pooled ASP1517(14.3%) and darbepoetin alfa (15.6%) groups. The most common reason for the study discontinuation was the discontinuation criterion of Hb being < 8.0 g/dL (31 patients, 23.8%) and most of them (27 patients) were reported during the fixed dose period. A total of 6 (4.6%) patients discontinued due to AEs and all of them were reported in the ASP1517 groups. Most of study discontinuation due to AEs (5 patients) were reported in the titration period." 127/130 participants completed the full analysis (>5% lost to follow-up), with differences between groups. Reasons were provided
Selective reporting (reporting bias)	Low risk	All of the planned outcomes on ClincialTrials.gov were measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were reported (death and CV events)
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding was reported and authors' disclosure were not reported Funder was likely to influence data analysis and study reporting or interpretation

NDD-CKD 2020

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 18 weeks (16 weeks of treatment + 2 weeks follow-up)
Participants	**General information**

NDD-CKD 2020 *(Continued)*

- Setting: multicentre (30 sites)
- Country: Japan
- Inclusion criteria: males and females aged ≥ 20 years; diagnosis of CKD based on an eGFR ≤ 60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Hb ≤ 10.5 g/dL during screening; not currently being treated with dialysis and not expected to start dialysis within 3 months of screening; serum ferritin ≥ 50 ng/mL during screening; TSAT ≥ 20% during screening; folate and vitamin B12 ≥ LLN during screening; for participants who were receiving oral and/or IV iron supplementation, the dose of iron supplementation had to be stable for at least 28 days prior to the screening period; for participants who were not receiving oral or IV iron supplementation, no iron supplementation was to have been administered for at least 28 days prior to the screening period; understood the procedures and requirements of the study and provided written informed consent and authorization for protected health information disclosure
- Exclusion criteria: anaemia due to a cause other than CKD or presence of active bleeding or recent blood loss; sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, haematologic malignancy, myeloma, haemolytic anaemia, thalassaemia, or PRCA; RBC transfusion within 4 weeks prior to or during screening; IV iron within 4 weeks prior to or during screening; any ESA use within 6 weeks prior to or during screening (e.g. rHuEPO, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta); AST/SGOT, ALT/SGPT, or total bilirubin >2.0 times ULN during screening; uncontrolled hypertension (confirmed DBP > 110 mm Hg or SBP > 180 mm Hg)during screening; BMI > 42.0 kg/m^2; severe heart failure during screening (NYHA class III or IV); history of untreated proliferative diabetic retinopathy, diabetic macular oedema, age-related macular degeneration, central retinal vein occlusion, active retinal haemorrhage, or ongoing ocular treatment with laser photocoagulation or anti-VEGF therapies; acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for heart failure, or stroke within 12 weeks prior to or during screening; history of active malignancy within 2 years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, cervical carcinoma in situ, or resected benign colonic polyps; history of DVT or pulmonary embolism requiring active treatment within 8 weeks prior to or during screening[1]; history of haemosiderosis or haemochromatosis; history of prior organ transplantation or scheduled organ transplant, or prior haematopoietic stem cell or bone marrow transplant[2]; use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever was longer), prior to screening; previous participation in a study with HIF-PHI, other than vadadustat, within 90 days prior to screening; hypersensitivity to vadadustat, or to any of its excipients; pregnant or breast feeding; females of childbearing potential who were unable or unwilling to use an acceptable method of contraception; non-vasectomized males who were unable or unwilling to use an acceptable method of contraception; any other reason that in the opinion of the investigator made the participant unsuitable for participation in the study
- Target Hb: 10 to 12 g/dL

Baseline characteristics

- CKD stage: eGFR ≤ 60 mL/min/1.73 m^2; only one participant was Stage 3a (150 mg vadadustat group), with the remaining participants in Stage 3b–5
- Number (randomised/analysed): treatment group 1 (12/12); treatment group 2 (12/12); treatment group 3 (13/13); control group (14/14)
- Mean age ± SD (years): treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (71.4 ± 11.6)
- Sex (M, %): overall (29, 57%); treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (4, 29%)
- Time on dialysis: not applicable
- Mean eGFR ± SD (mL/min/1.73 m^2): treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (22.0 ± 9.8)

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported

NDD-CKD 2020 *(Continued)*

- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Note 1 from DD study: active treatment indicated treatment with an anticoagulant (blood thinner), such as heparin, enoxaparin, warfarin, rivaroxaban, apixaban, edoxaban, argatroban, and fondaparinux. Aspirin was not considered active treatment for DVT or pulmonary embolism

Note 2: subjects on kidney transplant wait list, or with a history of failed kidney transplant, corneal transplants, or stem cell therapy for knee arthritis were not excluded

Interventions	**Treatment group 1** • Vadadustat 150 mg (oral): once/day for 16 weeks **Treatment group 2** • Vadadustat (oral): 300 mg, once/day for 16 weeks **Treatment group 3** • Vadadustat 600 mg (oral), once/day for 16 weeks **Control group** • Placebo for 16 weeks **Co-interventions** • Not reported
Outcomes	**Primary outcomes** • Mean change in Hb from pretreatment to week 6 **Secondary outcomes** • Mean change in Hb between pre-treatment and the end of the dose adjustment and maintenance period (week 6) • Mean Hb levels at week 6 and 16 • Proportion who achieve Hb target at week 16 • Mean change from baseline to week 6 and 16 in iron indices, TSAT, TIBC • Proportion requiring rescue with RBC transfusion or ESAs at week 6 and 16 • Changes in HCT, RBC count and reticulocytes count from baseline at week 6 and 16 • Number of dose adjustments from baseline to week 6 and 16 • Adverse events • Serious adverse events • Vital signs • Laboratory evaluation
Notes	• Funding: Akebia Therapeutics • Conflicts of interest: "M.N. has received honorarium, an advisory fee and research grant from Mitsubishi-Tanabe and an advisory fee from Akebia Y.M.K.F., W.L., D.V. and Z.K. are employees of Akebia and Ed.G. was an employee of Akebia at the time of manuscript development"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups

NDD-CKD 2020 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind" Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. However, since interventions were different, it was possible that investigators and/or participants were aware of treatment allocation. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All participants were included in the safety and ITT populations."
Selective reporting (reporting bias)	High risk	All planned outcomes on ClincialTrials.gov have been measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

NDD-CKD 2020a

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 18 weeks (16 weeks of treatment + 2 weeks follow-up)
Participants	**General information** • Setting: multicentre (31 sites) • Country: Japan • Inclusion criteria: • Male and female Japanese participants aged ≥ 20 years; receiving chronic maintenance HD for kidney failure for at least 8 weeks prior to screening; for participants not being treated with ESAs: Hb < 10.0 g/dL, average of 2 measurements obtained during screening; for participants being treated with ESAs: Hb < 10.0 g/dL, average of 2 measurements obtained during screening after the protocol defined ESA washout period; serum ferritin ≥ 50 ng/mL during screening; TSAT ≥ 20% during screening; folate and vitamin B12 ≥ LLN during screening; for participants receiving oral and/or IV iron supplementation, the dose of iron supplementation had to be stable for at least 28 days prior to the screening period; for participants not receiving oral or IV iron supplementation, no iron supplementation was to have been administered for at least 28 days prior to the screening period; understood the procedures and

NDD-CKD 2020a *(Continued)*

requirements of the study and provided written informed consent and authorization for protected health information disclosure

- Exclusion criteria: anaemia due to a cause other than CKD or presence of active bleeding or recent blood loss; sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, haemolytic anaemia, thalassaemia, or PRCA; RBC transfusion within 4 weeks prior to or during screening; anticipated to recover adequate kidney function such that HD was no longer required during study participation; on PD or expected to change dialysis modality during study participation; hypo-responsiveness to ESA defined as any of the following ESA treatments within 8 weeks prior to screening: (i) IV epoetin dose ≥ 3,000 units/dose 3 times/week, (ii) IV darbepoetin alfa dose ≥ 60 µg once/week, or (iii) EBP ≥ 200 µg once/month or ≥ 100 µg once every 2 weeks; AST/SGOT, ALT/SGPT, or total bilirubin > 2.0 times ULN during screening; uncontrolled hypertension (DBP > 110 mm Hg or SBP > 190 mm Hg) during screening; BMI > 42.0 kg/m^2; severe heart failure during screening (NYHA class III or IV); history of untreated proliferative diabetic retinopathy, diabetic macular oedema, age-related macular degeneration, central retinal vein occlusion, active retinal haemorrhage, or ongoing ocular treatment with laser photocoagulation or anti-VEGF therapies; acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for heart failure, or stroke within 12 weeks prior to or during screening; history of active malignancy within 2 years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, cervical carcinoma in situ, or resected benign colonic polyps; history of DVT or pulmonary embolism requiring active treatment within 8 weeks prior to or during screening[1]; history of haemosiderosis or haemochromatosis; history of prior organ transplantation or scheduled organ transplant, or prior haematopoietic stem cell or bone marrow transplant[2]; use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever was longer), prior to screening; previous participation in a study with HIF-PHI, other than vadadustat, within 90 days prior to screening; hypersensitivity to vadadustat, or to any of its excipients; pregnant or breast feeding; females of childbearing potential who were unable or unwilling to use an acceptable method of contraception; non-vasectomized males who were unable or unwilling to use an acceptable method of contraception; any other reason that in the opinion of the investigator made the participant unsuitable for participation in the study
- Target Hb: 10 to 12 g/dL

Baseline characteristics

- CKD stage: HD
- Number (randomised/analysed): treatment group 1 (15/15); treatment group 2 (15/15); treatment group 3 (15/14);control group (15/14)
- Mean age ± SD (years): treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (65.7 ± 11.6)
- Sex (M, %): overall (40, 69%); treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (6, 43%)
- Time on dialysis (years): treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); control group (7.6 ± 9.9)
- eGFR: not reported

Comorbidities (DD patients)

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Note 1 from DD study: active treatment indicated treatment with an anticoagulant (blood thinner), such as heparin, enoxaparin, warfarin, rivaroxaban, apixaban, edoxaban, argatroban, and fondaparinux. Aspirin was not considered active treatment for DVT or pulmonary embolism

NDD-CKD 2020a *(Continued)*

	Note 2: subjects on kidney transplant wait list, or with a history of failed kidney transplant, corneal transplants, or stem cell therapy for knee arthritis were not excluded
Interventions	**Treatment group 1** • Vadadustat 150 mg (oral): once/day for 16 weeks **Treatment group 2** • Vadadustat 300 mg (oral): once/day for 16 weeks **Treatment group 3** • Vadadustat 600 mg (oral), once/day for 16 weeks **Control group** • Placebo for 16 weeks **Co-interventions** • Not reported
Outcomes	**Primary outcomes** • Mean change in Hb from pretreatment to week 6 **Secondary outcomes** • Mean change in Hb between pre-treatment and the end of the dose adjustment and maintenance period (week 6) • Mean Hb levels at week 6 and 16 • Proportion who achieve Hb target at week 16 • Mean change from baseline to week 6 and 16 in iron indices, TSAT, TIBC • Proportion requiring rescue with RBC transfusion or ESAs at week 6 and 16 • Changes in HCT, RBC count and reticulocytes count from baseline at week 6 and 16 • Number of dose adjustments from baseline to week 6 and 16 • Adverse events • Serious adverse events • Vital signs • Laboratory evaluation
Notes	• Funding: Akebia Therapeutics • Conflicts of interest: "M.N. has received honorarium, an advisory fee and research grant from Mitsubishi-Tanabe and an advisory fee from Akebia Y.M.K.F., W.L., D.V. and Z.K. are employees of Akebia and Ed.G. was an employee of Akebia at the time of manuscript development"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "Double-blind"

NDD-CKD 2020a *(Continued)*

All outcomes		Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. However, since interventions were different, it was possible that investigators and/or participants were aware of treatment allocation. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "All participants were included in the safety population and 58 were included in the ITT population." 58/68 participants completed the full analysis (>5% lost to follow-up), with differences between groups. Reasons were provided
Selective reporting (reporting bias)	High risk	All planned outcomes on ClincialTrials.gov have been measured and reported on in the final report Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

OLYMPUS 2021

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: June 2014 to May 2017 • Duration of follow-up: 56 weeks (52 weeks of treatment + 4 weeks follow-up)
Participants	**General information** • Setting: multicentre (385 sites) • Country: multinational (25 countries) • Inclusion criteria: anaemia (Hb <m10.0 g/dL); informed consent prior to any study specific procedures; ≥ 18 years; eGFR < 60 mL/min/1.73 m^2; mean of 2 most recent Hb values during the screening period, obtained at least 7 days apart, must be < 10.0 g/dL; ferritin ≥ 50 ng/mL; TSAT ≥ 15 %; serum folate ≥ LLN; serum vitamin B12 level ≥ LLN; ALT and AST ≤ 3 times ULN and total bilirubin ≤ 1.5 times ULN; weight 45 to 160 kg • Exclusion criteria: involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site); previous randomisation in the present study; any EPO analogue treatment within 6 weeks of randomisation; NYHA class III or IV congestive heart failure at enrolment; MI, acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event (e.g. DVT or pulmonary embolism) within 12 weeks prior to randomisation; history of chronic liver disease (e.g. chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver); known hereditary haematologic disease such as thalassaemia, sickle cell anaemia, a history of PRCA or other known causes for anaemia other than CKD; known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis); diagnosis

OLYMPUS 2021 *(Continued)*

	or suspicion of renal cell carcinoma on renal ultrasound (or other imaging procedure) conducted at screening or within 12 weeks prior to randomisation; SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg within 2 weeks prior to randomisation 9(patients may be rescreened once BP controlled); history of prostate cancer, breast cancer or any other malignancy, except cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps; positive for HIV, HBsAg or Anti-HCV Ab; chronic inflammatory diseases such as rheumatoid arthritis, SLE, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease that is determined to be the principal cause of anaemia; known haemosiderosis, haemochromatosis or hypercoagulable condition; any prior organ transplant or a scheduled organ transplantation date; any RBC transfusion during the screening period; any current condition leading to active significant blood loss; any treatment with roxadustat or a HIF-PHI; received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within at least 1 month of the first administration of IP in this study; history of alcohol or drug abuse within 2 years prior to randomisation; females of childbearing potential, unless using contraception as detailed in the protocol or sexual abstinence; pregnant or breast-feeding; known allergy to the investigational product or any of its ingredients; any medical condition, including active, clinically significant infection, that in the opinion of the investigator or Sponsor may pose a safety risk to a patient in this study, which may confound efficacy or safety assessment or may interfere with study participation • Target Hb: 10 to 12 g/dL **Baseline characteristics** • CKD stage: 3 to 5 • Number (randomised/analysed): treatment group (1393/1384); control group (1388/1376) • Mean age ± SD (years): overall (61.7, SD not reported) • Sex (M, %): overall (number was not reported, 42%) • Time on dialysis: not applicable • eGFR: not reported **Comorbidities** • CV disease: not reported • Heart disease: not reported • Hypertension: not reported • Diabetes (number, %): not reported • Prior agents used (number, %): not reported
Interventions	**Treatment group (medium dose)*** • Roxadustat (oral): 70 mg 3 times/week • The dose was subsequently adjusted to achieve and maintain Hb 11 ± 1 g/dL. Study drug doses must be administered at least 2 days apart and no more than 4 days apart, except in subjects who require dose hold or dose reduction to 20 mg once weekly **Control group** • Placebo **Co-interventions** • Not reported *Note: dose assessed as medium according to NCT01888445
Outcomes	**Primary outcomes** • Mean change from baseline Hb to average Hb over weeks 28 to 52 (USA FDA submission) • Proportion with Hb response at 2 consecutive visits during the first 24 weeks of treatment without anaemia rescue therapy

OLYMPUS 2021 *(Continued)*

Secondary outcomes

- RBC transfusion
- Rescue therapy
- Adverse events
- Serious adverse events (including death and CV disease)
- Changes in vital signs
- ECG
- Laboratory values
- Proportion of total time of Hb ≥ 10 g/dL from week 28 to week 52
- Proportion of total time of Hb within the interval of 10 to 12 g/dL from week 28 to week 52
- Mean change in Hb from baseline to mean level between week 28 to week 52 in subjects with baseline high-sensitivity C-reactive protein> ULN
- Mean change in LDL cholesterol from baseline to week 24
- Time-to-first (and proportion of subjects receiving) instance of receiving IV iron, RBC transfusions, or EPO analogue as rescue therapy
- Time to first (and proportion of subjects receiving) instance of receiving RBC transfusions as rescue therapy
- Changes in generic HRQoL as measured by the SF-36 (Vital Status and Physical Functioning)
- Annual rate of eGFR change in log scale, calculated as the linear slope of log (eGFR values) to prior to initiation of dialysis/kidney transplant
- Short Form 36 (SF-36)
- FACT-anaemia
- Patients' Global Impression of Change
- EQ-5D-5L
- Hospitalisations

Notes

- Funding: AstraZeneca
- Conflicts of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A total of approximately 2600 patients will be randomized at 1:1 ratio to roxadustat or placebo via an Interactive Web Response System (IWRS)/ Interactive Voice Response System (IVRS)."
Allocation concealment (selection bias)	Low risk	Quote: "A total of approximately 2600 patients will be randomized at 1:1 ratio to roxadustat or placebo via an Interactive Web Response System (IWRS)/ Interactive Voice Response System (IVRS)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "This is a double blind, placebo-controlled study. The investigator, study site staff and the patient, are blinded to study treatment, but not to the dose or dosing frequency. The Sponsor and designees except the personnel analysing the pharmacokinetic (PK) samples are blinded to study treatment, dose and dosing frequency. Sponsor study team members responsible for IWRS system are blinded to study treatment and can in special cases be unblinded to dose and dosing frequency."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment

OLYMPUS 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote Fishbane 2021: "2781 patients were randomized to roxadustat (1393) or placebo (1388). Twenty patients were excluded due to incorrect randomisation (4) or significant GCP violations (16) in obtaining or recording the data that might affect the validity of the data; therefore, the ITT population comprised 1384 and 1377 patients receiving roxadustat and placebo, respectively. The FAS included 2728 patients (roxadustat 1371; placebo 1357) and the OT +28 population included 2760 patients (roxadustat 1384; placebo 1376)." ITT population was not reported for all patients but loss was < 5%
Selective reporting (reporting bias)	High risk	All planned outcomes reported in the study protocol were not reported on in the final report. Reasons were not provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	It was not possible to assess if there was imbalance between intervention groups Funding was reported and authors' disclosure were not reported Funder was likely to influence data analysis and study reporting or interpretation

Pergola 2016

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 20 weeks
Participants	**General information** • Setting: multicentre (61 sites) • Country: USA • Inclusion criteria: non-dialysis-dependent CKD patients with anaemia; aged 18 to 82 years; GFR ≥ 10 and ≤ 65 mL/min/1.73 m^2; screening Hb as per protocol; iron replete with ferritin and TSAT levels as defined per protocol • Exclusion criteria: anaemia due to haemolysis or blood loss, recent or anticipated RBC transfusion; recent androgen or IV iron therapy; previous receipt of vadadustat or another HIF-PHI in a clinical trial; chronic liver disease, prolonged QT interval, uncontrolled hypertension, NYHA class III or IV congestive heart failure, recent MI, acute coronary syndrome, stroke, TIA or venous thromboembolism, or BMI > 50.0 kg/m^2; males and females with childbearing potential not using contraception; infection or liver disease; participation in investigational study, or treatment for malignancy; history of active malignancy, myelodysplastic syndrome, bone marrow fibrosis, SLE, haemosiderosis, schedule for organ, stem cell or bone marrow transplantation; macular/retinal disease likely to require treatment during the study • Target Hb: at least 11.0 g/dL or an increase in Hb of at least 1.2 g/dL over the predose average (average of the 2 Hb values obtained before dosing at screening and baseline) (data were reported using the first definition) **Baseline characteristics** • CKD stage: 3 to 5 • Number (randomised/analysed): treatment group (138/136); control group (72/72) • Mean age ± SD (years): treatment group (66.6 ± 9.97); control group (65.9 ± 12.33)

Pergola 2016 *(Continued)*

- Sex (M, %): treatment group (57, 41.3%); control group (38, 52.8%)
- Time on dialysis: not applicable
- MeaneGFR ± SD (mL/min/1.73 m^2): treatment group (25.2 ± 10.41); control group (25.0 ± 11.72)

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): treatment group (106, 76.8%); control group (57, 79.2%)
- Prior agents used (number, %): not reported

Interventions

Treatment group (medium dose)*

- Vadadustat (AKB-6548) (oral): 450 mg, once/day, titrated by 1 tablet (150 mg) according to Hb response (maximum of 600 mg and minimum of 150 mg)

Control group

- Placebo

Co-interventions

- Oral iron supplementation was permitted throughout the study to maintain ferritin levels between 50 and 300 ng/mL

*Note: assessed as medium dose according to NDD-CKD 2020

Outcomes

Primary outcomes

- Percentage who, during the last 2 weeks of treatment, achieved or maintained either a mean Hb ≥11.0 g/dL or a mean increase in Hb ≥1.2 g/dL over the predose average (20 weeks)

Secondary outcomes

- Analysis/reanalysis of the primary endpoint with regard to Hb control, need for rescue, baseline Hb, and protocol-defined study groups (20 weeks)
- Haematologic response to include actual values and change from baseline in haematologic parameters (20 weeks)
- Need for transfusion and/or ESA rescue (20 weeks)
- Safety and tolerability measures to include assessments of adverse events, vital signs, ECGs, and laboratory assay results (20 weeks of therapy, 4-week follow-up)
- Iron metabolism to include actual values and change from baseline in iron indices (20 weeks)
- Iron utilization (both oral and intravenous) (20 weeks)
- Concentration measurements of AKB-6548 and metabolites (weeks 12 and 20 visits)
- Neurocognitive and patient reported outcome measures (20 weeks)

Notes

- Funding: Akebia Therapeutics
- Conflicts of interest:"PEP is supported by honoraria and lecture fees from Akebia Therapeutics, Keryx, Relypsa, Vifor/Fresenius Pharma, and ZS Pharma. BS is supported by honoraria and lecture fees from Akebia Therapeutics, Hospira, Vifor/Fresenius Pharma, and ZS Pharma. CSH was employed by Akebia Therapeutics. BM is employed by Akebia Therapeutics. VHH is supported by the Krick-Brooks chair in Nephrology and serves on the scientific advisory board of Akebia Therapeutics"

Risk of bias

Bias	Authors' judgement	Support for judgement

Pergola 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double-blind" Although author reported that the study used a double-blind design, information about blinding of participants and investigators were not clearly stated. However, since interventions were different, it was possible that investigators and/or participants were aware of treatment allocation. Possible deviations from the intended intervention that arose from the trial context were not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The intent-to-treat population included 210 patients who received the study drug (vadadustat, n= 138; placebo, n= 72) and were included in the safety analyses. The modified intent-to-treat population, used for all efficacy analyses, comprised 208 patients who had a baseline and at least 1 post baseline Hb and red blood cell measurement (vadadustat, n= 136; placebo, n= 72)." In the modified ITT analysis 208/210 participants were included into the analysis (< 5% lost to follow-up, slight imbalance between the two groups) Quote: "There were 160 patients who qualified for the per-protocol population."
Selective reporting (reporting bias)	High risk	All planned outcomes on ClincialTrials.gov were not measured and reported on in the final report. Reasons were not provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

PRO2TECT-CONVERSION 2021

Study characteristics	
Methods	• Study design: phase III, parallel RCT • Time frame: not reported • Duration of follow-up: 53 weeks + 4 weeks of follow-up
Participants	**General information** • Setting: multicentre (503 sites)

PRO2TECT-CONVERSION 2021 *(Continued)*

- Country: multinational (Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, France, Germany, Hungary, Israel, Italy, Korea, Malaysia, Mexico, New Zealand, Poland, Puerto Rico, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Turkey, Ukraine, UK; USA)
- Inclusion criteria: ≥ 18 years; diagnosis of CKD with an eGFR ≤ 60 mL/min/1.73 m^2 at screening and not expected to start dialysis within 6 months of screening; currently maintained on ESA therapy, with a dose received within 6 weeks prior to or during screening; mean screening Hb between 8.0 and 11.0 g/dL in the USA and between 9.0 and 12.0 g/dL outside of the USA
- Exclusion criteria: uncontrolled hypertension; severe heart failure at screening (NYHA class IV); acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for heart failure, or stroke within 12 weeks prior to or during screening; hypersensitivity to darbepoetin or vadadustat or to any of their excipients
- Target Hb:
  - USA: 10 to 11 g/dL
  - non-USA: 10 to 12 g/dL

Baseline characteristics

- CKD stage: CKD stages 3 to 5
- Number (randomised/analysed): treatment group (862/811); control group (863/811)
- Mean age ± SD (years): treatment group (67.3 ± 13.1); control group (66.5 ± 13.5)
- Sex (M, %): treatment group (394, 45.7%); control group (375, 43.6)
- Time on dialysis: not applicable
- Mean eGFR ± SD (mL/min/1.73 m^2): treatment group (22.6 ± 11.6); control group (22.8 ± 12.0)

Comorbidities

- CV disease: treatment group (375/862); control group (402/863)
- Heart disease: not reported
- Hypertension: treatment group (462/862); control group (466/863)
- Diabetes: treatment group (517/862); control group (518/863)
- Prior agents used (number, %)
  - IV iron: treatment group (43/862); control group (49/863)
  - ESA: treatment group (833/862); control group (843/863)

Interventions

Treatment group (medium dose)*

- Vadadustat (AKB-6548) (oral): dose staring with 300 mg once/day, with flexible titration 150 to 600 mg/day based on Hb level (maximum 600 mg)

Control group

- Darbepoetin alfa (Aranesp) (SC)

Co-interventions

- Not reported

*Note: assessed as medium dose according to NDD-CKD 2020

Outcomes

Primary outcomes

- Mean change in Hb between baseline and the primary evaluation period (week 36)
- MACE from baseline visit to end of study (event-driven, minimum 1 year)

Secondary outcomes

- Mean change in Hb value between baseline and the secondary evaluation period (week 52)
- Proportion with Hb values within the target range during the primary evaluation period (week 36)

PRO2TECT-CONVERSION 2021 *(Continued)*

- Adverse events and serious adverse events to end of study (event-driven, minimum 1 year)
- Proportion of time with Hb values within the target range during the primary evaluation period (week 36)
- Proportion of time with Hb values within the target range during the secondary evaluation period (week 52)
- Proportion with Hb values within the target range during the secondary evaluation period (week 52)
- Proportion with Hb increase of > 1.0 g/dL from baseline to end of study (event-driven, minimum 36 weeks)
- Time to achieve Hb increase of 1.0 g/dL from baseline visit to end of study (event-driven, minimum 36 weeks)
- Mean change in Hb between baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from weeks 24 to 36) stratified pre-baseline ESA exposure (week 36)
- Proportion receiving IV iron therapy (week 52)
- Mean monthly dose of IV elemental iron administered in subjects who have received IV iron (week 52)
- Proportion of subjects receiving RBC transfusion(s) (week 52)

Notes

- Funding: Akebia Therapeutics
- Conflicts of interest: "GMC reports grants from NIDDK and Amgen and personal fees from Akebia Therapeutics, Inc., Satellite Healthcare, Ardelyx, AstraZeneca, Baxter, Cricket, DiaMedica, Gilead, Reata, Sanifit, Vertex, Angion, Bayer, and ReCor. PEP reports personal fees from Akebia Therapeutics, Inc., Astra-Zeneca, Bayer, Reata, Gilead, Corvidia, FibroGen, Tricida, and Ardelyx. PEP's institution, Renal Associates (PA), has received support from multiple pharmaceutical companies, including Akebia Therapeutics, Inc. RA reports personal fees from Akebia Therapeutics, Inc., Relypsa Inc., a Vifor Pharma Group Company, AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Sandoz, ZS Pharma, Takeda, Sanofi, Reata, Iron-wood Pharmaceuticals, Otsuka, OPKO Health, and Bird Rock Bio. RA has also served as associate editor of the American Journal of Nephrology and Nephrology, Dialysis, Transplantation and has received research grants from the USA Veterans Administration and the National Institutes of Health. GAB reports grants, personal fees, and non financial support from Akebia Therapeutics, Inc., Keryx Biopharmaceuticals, Inc., Astra-Zeneca, Kirin, and Ardelyx, Inc., as well as personal fees from U.S. Renal Care. YMKF reports personal fees and other from Akebia Therapeutics, Inc. AGJ has nothing to disclose. MJK reports personal fees from Akebia Therapeutics, Inc., FibroGen, Inc., and Micelle BioPharma, Inc. WL was an employee of Akebia Therapeutics, Inc., during the conduct of this study. ZK was an employee of Akebia Therapeutics, Inc., during the conduct of this study. EFL reports grants from Akebia Therapeutics, Inc. KM reports grants from NIH and personal fees from Akebia Therapeutics, Inc.; KM also reports grants and personal fees from Kyowa Kirin and Fukuda Denshi. PAM reports personal fees from Akebia Therapeutics, Inc. PSP reports personal fees from Akebia Therapeutics, Inc.; PSP was also a member of an advisory committee for Vifor Pharma and was a member of the data monitoring committee for the CREDANCE trial for Janssen. JW and KAW are employees of Statistics Collaborative, Inc., which received fees from Akebia Therapeutics, Inc. for conduction of study analyses. CT and TL are employees of Firma Clinical Research, which received fees from Akebia Therapeutics, Inc. for data analyses. MJS was a member of the steering committee for Akebia Therapeutics, Inc.; MJS also reports personal fees from Bayer and Carurian. DLV is an employee of Akebia Therapeutics, Inc. WCW reports personal fees from Akebia Therapeutics, Inc., Amgen, and Relypsa. and personal fees and non financial support from AstraZeneca, Bayer, Daiichi-Sankyo, Janssen, Merck, and Vifor Fresenius Medical Care Renal Pharma. KUE reports grants from Amgen, Astra Zeneca, Bayer, Fresenius, Genzyme, and Vifor and personal fees from Akebia Therapeutics, Inc., Bayer, and Boehringer Ingelheim."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups

PRO2TECT-CONVERSION 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent clinical end-points committee, whose members were unaware of the treatment assignments, adjudicated MACE."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the pooled data from NCT02648347 + NCT02680574 3471/3476 participants were included in the analyses Some outcomes were reported in 821/879 participants in the intervention groups and 811/872 participants in the control group
Selective reporting (reporting bias)	Low risk	All planned outcomes on ClincialTrials.gov were measured and reported Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

PRO2TECT-CORRECTION 2021

Study characteristics	
Methods	• Study design: phase III, parallel RCT • Time frame: not reported • Duration of follow-up: 53 weeks + 4 weeks follow-up

Participants	**General information**
	
	• Setting: multicentre (439)
	• Country: multinational (Argentina, Australia, Brazil, Bulgaria, France, Hungary, Israel, Italy, Korea, Malaysia, Mexico, New Zealand, Poland, Puerto Rico, Russia, South Africa, Spain, Ukraine, UK, USA)
	• Inclusion criteria: ≥18 years; diagnosis of CKD with an eGFR ≤ 60 mL/min/1.73 m^2 at screening and not expected to start dialysis within 6 months of screening; mean screening Hb < 10.0 g/dL
	• Exclusion criteria: anaemia due to a cause other than CKD or subjects with active bleeding or recent blood loss; any ESA within 8 weeks prior to randomisation; uncontrolled hypertension; severe heart failure at screening (NYHA class IV); acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular, or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for heart failure, or stroke within 12 weeks prior to or during screening; hypersensitivity to darbepoetin or vadadustat or to any of their excipients
	• Target Hb
	  ◦ USA: 10 to 11 g/dL
	  ◦ non-USA: 10 to 12 g/dL
	
	Baseline characteristics
	
	• CKD stage: CKD stages 3 to 5

PRO2TECT-CORRECTION 2021 *(Continued)*

- Number (randomised/analysed): treatment group (879/821); control group (872/811)
- Mean age ± SD (years): treatment group (65.2 ± 14.3); control group (64.9 ± 13.7)
- Sex (M, %): treatment group (404, 46%); control group (366, 42%)
- Time on dialysis: not applicable
- Mean eGFR ± SD (mL/min/1.73 m^2): treatment group (21.2 ± 12.0); control group (21.9 ± 12.6)

Comorbidities

- CV disease: treatment group (406/879); control group (412/872)
- Heart disease: not reported
- Hypertension: treatment group (512/879); control group (485/872)
- Diabetes: treatment group (581/879); control group (599/872)
- Prior agents used (number, %)
  - IV iron: treatment group (22/879); control group (20/872)
  - ESA: treatment group (none); control group (none)

Interventions	**Treatment group (medium dose)*** • Vadadustat (AKB-6548) (oral): dose staring with 300 mg once/day, with flexible titration 150 to 600 mg/day based on Hb level (maximum 600 mg) **Control group** • Darbepoetin alfa (Aranesp) (SC) **Co-interventions** • Not reported *Note: assessed as medium dose according to NDD-CKD 2020
Outcomes	**Primary outcomes** • Mean change in Hb between baseline and the primary evaluation period (week 36) • MACE from baseline visit to end of study (event-driven, minimum 1 year) **Secondary outcomes** • Mean change in Hb value between baseline and the secondary evaluation period (week 52) • Proportion with Hb values within the target range during the primary evaluation period (week 36) • Adverse events and serious adverse events to end of study (event-driven, minimum 1 year) • Proportion of time with Hb values within the target range during the primary evaluation period (week 36) • Proportion of time with Hb values within the target range during the secondary evaluation period (week 52) • Proportion with Hb values within the target range during the secondary evaluation period (week 52) • Proportion with Hb increase of > 1.0 g/dL from baseline to end of study (event-driven, minimum 36 weeks) • Time to achieve Hb increase of 1.0 g/dL from baseline visit to end of study (event-driven, minimum 36 weeks) • Mean change in Hb between baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from weeks 24 to 36) stratified pre-baseline ESA exposure (week 36) • Proportion receiving IV iron therapy (week 52) • Mean monthly dose of IV elemental iron administered in subjects who have received IV iron (week 52) • Proportion of subjects receiving RBC transfusion(s) (week 52)
Notes	• Funding: Akebia Therapeutics • Conflicts of interest: "GMC reports grants from NIDDK and Amgen and personal fees from Akebia Therapeutics, Inc., Satellite Healthcare, Ardelyx, AstraZeneca, Baxter, Cricket, DiaMedica, Gilead, Reata,

PRO2TECT-CORRECTION 2021 *(Continued)*

Sanifit, Vertex, Angion, Bayer, and ReCor. PEP reports personal fees from Akebia Therapeutics, Inc., Astra-Zeneca, Bayer, Reata, Gilead, Corvidia, FibroGen, Tricida, and Ardelyx. PEP's institution, Renal Associates (PA), has received support from multiple pharmaceutical companies, including Akebia Therapeutics, Inc. RA reports personal fees from Akebia Therapeutics, Inc., Relypsa Inc., a Vifor Pharma Group Company, AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Sandoz, ZS Pharma, Takeda, Sanofi, Reata, Iron-wood Pharmaceuticals, Otsuka, OPKO Health, and Bird Rock Bio. RA has also served as associate editor of the American Journal of Nephrology and Nephrology, Dialysis, Transplantation and has received research grants from the US Veterans Administration and the National Institutes of Health. GAB reports grants, personal fees, and non financial support from Akebia Therapeutics, Inc., Keryx Biopharmaceuticals, Inc., Astra-Zeneca, Kirin, and Ardelyx, Inc., as well as personal fees from U.S. Renal Care. YMKF reports personal fees and other from Akebia Therapeutics, Inc. AGJ has nothing to disclose. MJK reports personal fees from Akebia Therapeutics, Inc., FibroGen, Inc., and Micelle BioPharma, Inc. WL was an employee of Akebia Therapeutics, Inc., during the conduct of this study. ZK was an employee of Akebia Therapeutics, Inc., during the conduct of this study. EFL reports grants from Akebia Therapeutics, Inc. KM reports grants from NIH and personal fees from Akebia Therapeutics, Inc.; KM also reports grants and personal fees from Kyowa Kirin and Fukuda Denshi. PAM reports personal fees from Akebia Therapeutics, Inc. PSP reports personal fees from Akebia Therapeutics, Inc.; PSP was also a member of an advisory committee for Vifor Pharma and was a member of the data monitoring committee for the CREDANCE trial for Janssen. JW and KAW are employees of Statistics Collaborative, Inc., which received fees from Akebia Therapeutics, Inc. for conduction of study analyses. CT and TL are employees of Firma Clinical Research, which received fees from Akebia Therapeutics, Inc. for data analyses. MJS was a member of the steering committee for Akebia Therapeutics, Inc.; MJS also reports personal fees from Bayer and Carurian. DLV is an employee of Akebia Therapeutics, Inc. WCW reports personal fees from Akebia Therapeutics, Inc., Amgen, and Relypsa. and personal fees and non financial support from AstraZeneca, Bayer, Daiichi-Sankyo, Janssen, Merck, and Vifor Fresenius Medical Care Renal Pharma. KUE reports grants from Amgen, Astra Zeneca, Bayer, Fresenius, Genzyme, and Vifor and personal fees from Akebia Therapeutics, Inc., Bayer, and Boehringer Ingelheim."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent clinical end-points committee, whose members were unaware of the treatment assignments, adjudicated MACE."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the pooled data from NCT02648347 + NCT02680574 3471/3476 participants were included in the analyses Some outcomes were reported in 821/879 participants in the intervention groups and 811/872 participants in the control group
Selective reporting (reporting bias)	Low risk	All planned outcomes on ClincialTrials.gov were measured and reported Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported

PRO2TECT-CORRECTION 2021 *(Continued)*

Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported. Funder was likely to influence data analysis and study reporting or interpretation

Provenzano 2008

Study characteristics

Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 15 weeks
Participants	**General information** • Setting: not reported • Country: USA • Inclusion criteria: non-dialysis CKD; ESA-naive; Hb < 10.8 g/dL • Exclusion criteria: not reported • Target Hb: 1 g/L increase **Baseline characteristics** • CKD stage: 3 to 4 • Number (randomised/analysed): overall (142/96); treatment group 1 (26/not reported); treatment group 2 (52/not reported); treatment group 3 (50/not reported); control group (14/not reported) • Mean age ± SD (years): not reported • Sex (M, %): not reported • Time on dialysis: not applicable • eGFR: not reported **Comorbidities** • CV disease: not reported • Heart disease: not reported • Hypertension: not reported • Diabetes (number, %): not reported • Prior agents used (number, %): not reported
Interventions	**Treatment group 1** • FG2216: initial dose 375 mg, twice/week for 15 weeks; after 4 weeks the dose was titrated to achieve target Hb **Treatment group 2** • FG2216: initial dose 625 mg, twice/week for 15 weeks; after 4 weeks the dose was titrated to achieve target Hb **Treatment group 3** • FG2216: initial dose 1250 mg, twice/week for 15 weeks; after 4 weeks the dose was titrated to achieve target Hb **Control group**

Provenzano 2008 *(Continued)*

	• Placebo: twice/week for 15 weeks **Co-interventions** • Not reported
Outcomes	**Primary outcomes** • Percentage participants achieving Hb target **Secondary outcomes** • Laboratory parameters • Serious adverse events (including death)
Notes	• Funding: the study had a sponsor but the name was not reported • Conflicts of interest: not reported • Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	96/142 participants completed the study
Selective reporting (reporting bias)	High risk	Protocol was not reported Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	It was not possible to assess if there was imbalance between intervention groups Funding was reported and authors' disclosure were not reported Funder was likely to influence data analysis and study reporting or interpretation

Provenzano 2016

Study characteristics

Methods	• Study design: parallel RCT • Time frame: May 2010 to October 2012 • Duration of follow-up: 14 weeks (6 weeks treatment period and 8 weeks follow-up)
Participants	**General information** • Setting: multicentre (number of sites not reported) • Country: USA • Inclusion criteria: 18 to 75 years in good health, older than 75 years of age may be permitted on a case-by-case basis, at the discretion of the sponsor medical monitor; kidney failure receiving maintenance HD 3 times/week for ≥ 4 months prior to day 1; 2 most recent Hb values obtained during the screening period must be 1) in the 8 weeks prior to randomisation to be within 9.0 to 13.5 g/dL with no more than one value outside of this range. 2) mean Hb value of the two screening Hb (obtained prior to Day -3, approximately 1 week apart) range between 9.0 and 13.0 g/dL, and the difference between the two screening Hb values must be ≤ 1.0 g/dL; stable dose of IV epoetin-alfa: 1) Cohorts A-1 to A-4: current and previous (past 4 weeks) epoetin-alfa dose range: 25 to 85 IU/kg/dose, 3 times/week; weekly dose between 75 and 255 IU/kg/week; 2) Cohort A-5 and Cohort A-9: current and previous (past 4 weeks) epoetin-alfa dose range: ≥ 85 to 115 for Cohort A-5 and ≥ 85 to 150 IU/kg/dose for Cohort A-9, 3 times/week (NOTE: must also meet baseline Hb and dose stability criteria for normo-responders); total weekly dose between 255 and 450 IU/kg/week, 3) Cohorts A-6 to A-8: current and previous (past 4 weeks) epoetin-alfa dose range: 25 to 115 IU/kg/dose, 2 or 3 times/week; total weekly dose between 75 and 345 IU/kg/week; 4) Cohorts A-10 to A-12: Optional cohorts TBD, dosing frequency and dose range to be determined by sponsor, 5) Stable doses of ESA dose at baseline, Cohorts A-1 to A-12*: IV epoetin-alfa (i.e., no more than a 30% fluctuation in the weekly dose) during the 4 weeks prior to study Day -3, and not to exceed 450 IU/kg/week in Cohorts A-9 to 1-12*, and up to 345 IU/kg/week in Cohorts A-5 to A-8 (255 IU/kg/week for Cohorts A-1 to A-4); ALT and AST must be ≤ 2 times ULN at both screening visits; ALP ≤ 2 times ULN (subjects with serum ALP values between 1 and 2 times ULN may be included only if bone-specific ALP (BSAP) is also elevated above the ULN); total bilirubin ≤ ULN; most recently delivered Kt/V urea ≥1.2 within 30 days prior to Day -5; serum folate and vitamin B12 above LLN; absence of active or chronic GI bleeding; CRP < 60 mg/L for cohorts A-8 through A-12 enrolled; weight 40 to 140 kg (dry weight); BMI 18 to 45 kg/m^2; dialysis vascular access via native AVF or synthetic graft, or permanent (tunnelled) catheter (not via temporary catheter), permanent and temporary catheters are prohibited in Cohort A-5 • Exclusion criteria: anticipated change in HD prescription or access during the screening or dosing period of the study; received any ESA therapy other than IV epoetin-alfa within 12 weeks prior to day 1; received IV epoetin-alfa within 3 days prior to day 1; any clinically significant infection or evidence of an underlying infection such as a WBC > ULN; positive for HIV, HBsAg, or Anti-HCV Ab; history of chronic liver disease; NYHA class III or IV congestive heart failure; MI or acute coronary syndrome within 3 months prior to day 1; thromboembolic event within 12 weeks preceding day 1; inadequately controlled hypertension noted during screening (pre- and post-HD SBP > 170 mm Hg and/or DBP > 110 mm Hg) (for any single BP values above the 170/110 thresholds, the FibroGen medical monitor has discretion to allow study entry on a selected basis; in such cases, please communicate BP values to the medical monitor before proceeding with the screening); history of malignancy, except the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps; chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; haemoglobinopathy (e.g. homozygous sickle-cell disease, thalassaemia of all types); history of myelodysplastic syndrome; history of haemosiderosis, haemochromatosis, PCKD, or anephric; active haemolysis or diagnosis of haemolytic syndrome; known bone marrow fibrosis; uncontrolled or symptomatic secondary hyperparathyroidism; epileptic seizure in the 6 months prior to screening; any prior organ transplantation (subjects with explanted allografts will be allowed into the study); anticipated elective surgery that is expected to lead to significant blood loss during the study period, including kidney transplantation; life expectancy < 12 months; drug-treated gastroparesis or short-bowel syndrome; serum albumin < 3 g/dL. anticipated use of dapsone or acetaminophen > 2.0 g/day, or > 500 mg/dose repeated every 6 hours, during the treatment or follow-up periods; androgen therapy within 12 weeks prior to day 1; RBC transfusion within 12 weeks prior to day 1, or anticipated need for RBC transfusion during the dosing period; IV iron supplement within 2 weeks prior to day 1

Provenzano 2016 *(Continued)*

and/or unwilling to withhold IV iron during the dosing/treatment period' history of alcohol or drug abuse; or a positive drug screen for a substance that has not been prescribed for the subject; prior treatment with FG-4592 or with any other HIF-PHI; use of an investigational medication or treatment, or carryover of effect of such investigational treatment expected, within 4 weeks prior to day 1; Pregnant or breastfeeding; females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless male agrees to use of contraception; any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study or which may interfere with study participation; diagnosis or suspicion (e.g. complex kidney cyst of Bosniak Category II or higher) of renal cell carcinoma on renal ultrasound within 3 months prior to randomisation

- Target Hb: 11 to 13 g/dL

Baseline characteristics

- CKD stage: HD
- Number (randomised/analysed): overall (54/not reported); treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); treatment group 4 (not reported); control group (13/not reported)
- Mean age ± SD (years): not reported
- Sex (M, %): not reported
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Interventions

Treatment group 1

- Roxadustat (FG4592) (oral): 1 mg 3 times/week

Treatment group 2

- Roxadustat (FG4592) (oral): 1.5 mg 3 times/week

Treatment group 3

- Roxadustat (FG4592) (oral): 1.8 mg 3 times/week

Treatment group 4

- Roxadustat (FG4592) (oral): 2 mg 3 times/week

Control group

- EPO alpha (IV): 3 times/week

Co-interventions

- Treatment with androgens was prohibited
- IV iron use and RBC transfusions were guided by rescue criteria
- Oral iron supplementation was permitted but not required

Outcomes

Primary outcome

- Proportion whose Hb levels did not decrease by > 0.5 g/dL from baseline (defined as the mean of the last 3 Hb values obtained prior to the first dose of study treatment)

Provenzano 2016 *(Continued)*

Secondary outcomes

- Laboratory parameters
- Adverse events through the study period (including CV events)
- Severe adverse events through the study period (including death and CV death)
- Plasma endogenous EPO levels
- Blood transfusion

Notes

- Funding: FibroGen
- Conflicts of interest: "Drs Besarab, Saikali, Poole, Soha, Hemmerich, Szczech, Yu, and Neff are employees of FibroGen and hold stock and/or stock options in FibroGen. At the time the study was performed, Dr Besarab was affiliated with the Henry Ford Health System and Wayne State University School of Medicine, and Dr Provenzano was affiliated with St. Clairs Specialty Physicians, LLC, and Wayne State University School of Medicine. Dr Provenzano is currently an employee of and holds stock in DaVita Healthcare Partners. The other authors declare that they have no other relevant financial interests."
- Note: death, adverse events and number of patients who reached target Hb were reported for phase 1 and phase 2 but no data were extractable for each treatment dose, as requested from the study protocol. These data were not included in this review
- Note: study included part 1 and part 2 with 2 different populations with same intervention but different follow-up period - the study was split into Provenzano 2016 and Provenzano 2016a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Independent data monitoring committee." Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment It was not reported if the Independent data monitoring committee was blind to the treatments assigned
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Reasons for discontinuation from the study were lack of efficacy (10), withdrawal of consent (4), AE/serious AE (6; including 3 deaths), 3 protocol violations, and 3 others (leaving canter, prolonged hospitalisation, and kidney transplantation)." Not reported in sufficient detail to perform adjudication for part 1 and 2 separately
Selective reporting (reporting bias)	High risk	All planned outcomes on ClincialTrials.gov were not measured and reported on in the final report. Reasons were not provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported

Provenzano 2016 *(Continued)*

Other bias	High risk	Quote: "FibroGen was the study sponsor and designed the study in consultation with the principal investigators." There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

Provenzano 2016a

Study characteristics

Methods	• Study design: parallel RCT • Time frame: May 2010 to October 2012 • Duration of follow-up: 23 weeks (19 weeks treatment period and 4 weeks follow-up)
Participants	**General information** • Setting: multicentre (number of sites not reported) • Country: USA • Inclusion criteria: 18 to 75 years in good health, older than 75 years of age may be permitted on a case-by-case basis, at the discretion of the sponsor medical monitor; kidney failure receiving maintenance HD 3 times/week for ≥ 4 months prior to day 1; 2 most recent Hb values obtained during the screening period must be 1) in the 8 weeks prior to randomisation to be within 9.0 to 13.5 g/dL with no more than one value outside of this range. 2) mean Hb value of the two screening Hb (obtained prior to Day -3, approximately 1 week apart) range between 9.0 and 13.0 g/dL, and the difference between the two screening Hb values must be ≤ 1.0 g/dL; stable dose of IV epoetin-alfa: 1) Cohorts A-1 to A-4: current and previous (past 4 weeks) epoetin-alfa dose range: 25 to 85 IU/kg/dose, 3 times/week; weekly dose between 75 and 255 IU/kg/week; 2) Cohort A-5 and Cohort A-9: current and previous (past 4 weeks) epoetin-alfa dose range: ≥ 85 to 115 for Cohort A-5 and ≥ 85 to 150 IU/kg/dose for Cohort A-9, 3 times/week (NOTE: must also meet baseline Hb and dose stability criteria for normo-responders); total weekly dose between 255 and 450 IU/kg/week, 3) Cohorts A-6 to A-8: current and previous (past 4 weeks) epoetin-alfa dose range: 25 to 115 IU/kg/dose, 2 or 3 times/week; total weekly dose between 75 and 345 IU/kg/week; 4) Cohorts A-10 to A-12: Optional cohorts TBD, dosing frequency and dose range to be determined by sponsor, 5) Stable doses of ESA dose at baseline, Cohorts A-1 to A-12*: IV epoetin-alfa (i.e., no more than a 30% fluctuation in the weekly dose) during the 4 weeks prior to study Day -3, and not to exceed 450 IU/kg/week in Cohorts A-9 to 1-12*, and up to 345 IU/kg/week in Cohorts A-5 to A-8 (255 IU/kg/week for Cohorts A-1 to A-4); ALT and AST must be ≤ 2 times ULN at both screening visits; ALP ≤ 2 times ULN (subjects with serum ALP values between 1 and 2 times ULN may be included only if bone-specific ALP (BSAP) is also elevated above the ULN); total bilirubin ≤ ULN; most recently delivered Kt/V urea ≥1.2 within 30 days prior to Day -5; serum folate and vitamin B12 above LLN; absence of active or chronic GI bleeding; CRP < 60 mg/L for cohorts A-8 through A-12 enrolled; weight 40 to 140 kg (dry weight); BMI 18 to 45 kg/m^2; dialysis vascular access via native AVF or synthetic graft, or permanent (tunnelled) catheter (not via temporary catheter), permanent and temporary catheters are prohibited in Cohort A-5 • Exclusion criteria: anticipated change in HD prescription or access during the screening or dosing period of the study; received any ESA therapy other than IV epoetin-alfa within 12 weeks prior to day 1; received IV epoetin-alfa within 3 days prior to day 1; any clinically significant infection or evidence of an underlying infection such as a WBC > ULN; positive for HIV, HBsAg, or Anti-HCV Ab; history of chronic liver disease; NYHA class III or IV congestive heart failure; MI or acute coronary syndrome within 3 months prior to day 1; thromboembolic event within 12 weeks preceding day 1; inadequately controlled hypertension noted during screening (pre- and post-HD SBP > 170 mm Hg and/or DBP > 110 mm Hg) (for any single BP values above the 170/110 thresholds, the FibroGen medical monitor has discretion to allow study entry on a selected basis; in such cases, please communicate BP values

Provenzano 2016a *(Continued)*

to the medical monitor before proceeding with the screening); history of malignancy, except the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps; chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; haemoglobinopathy (e.g. homozygous sickle-cell disease, thalassaemia of all types); history of myelodysplastic syndrome; history of haemosiderosis, haemochromatosis, PCKD, or anephric; active haemolysis or diagnosis of haemolytic syndrome; known bone marrow fibrosis; uncontrolled or symptomatic secondary hyperparathyroidism; epileptic seizure in the 6 months prior to screening; any prior organ transplantation (subjects with explanted allografts will be allowed into the study); anticipated elective surgery that is expected to lead to significant blood loss during the study period, including kidney transplantation; life expectancy < 12 months; drug-treated gastroparesis or short-bowel syndrome; serum albumin < 3 g/dL; anticipated use of dapsone or acetaminophen > 2.0 g/day, or > 500 mg/dose repeated every 6 hours, during the treatment or follow-up periods; androgen therapy within 12 weeks prior to day 1; RBC transfusion within 12 weeks prior to day 1, or anticipated need for RBC transfusion during the dosing period; IV iron supplement within 2 weeks prior to day 1 and/or unwilling to withhold IV iron during the dosing/treatment period' history of alcohol or drug abuse; or a positive drug screen for a substance that has not been prescribed for the subject; prior treatment with FG-4592 or with any other HIF-PHI; use of an investigational medication or treatment, or carryover of effect of such investigational treatment expected, within 4 weeks prior to day 1; pregnant or breastfeeding; females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless male agrees to use of contraception; any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study or which may interfere with study participation; diagnosis or suspicion (e.g. complex kidney cyst of Bosniak Category II or higher) of renal cell carcinoma on renal ultrasound within 3 months prior to randomisation

- Target Hb: 11 to 13 g/dL

Baseline characteristics

- CKD stage: HD
- Number (randomised/analysed): overall (90/not reported); treatment group 1 (not reported); treatment group 2 (not reported); treatment group 3 (not reported); treatment group 4 (not reported); treatment group 5 (not reported); treatment group 6 (not reported); control group (22/not reported)
- Mean age ± SD (years): not reported
- Sex (M, %): not reported
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Interventions

Treatment group 1

- Roxadustat (FG4592) (oral): 1.3 mg 3 times/week

Treatment group 2

- Roxadustat (FG4592) (oral): 1.8 mg 3 times/week

Treatment group 3

- Roxadustat (FG4592) (oral): 2 mg 3 times/week

Treatment group 4

- Roxadustat (FG4592) (oral) weight tiered: 70-100-150 mg 3 times/week

Provenzano 2016a *(Continued)*

	Treatment group 5 • Roxadustat (FG4592) (oral) weight tiered: 70-120-200 mg 3 times/week **Treatment group 6** • Roxadustat (FG4592) (oral) weight tiered: 70-120-200 mg 3 times/week **Control group** • EPO alpha (IV): 3 times/week **Co-interventions** • Treatment with androgens was prohibited • IV iron use and RBC transfusions were guided by rescue criteria • Oral iron supplementation was permitted but not required
Outcomes	**Primary outcome** • Proportion whose mean Hb level was ≥ 11 g/dL averaged over the last 4 weeks (weeks 16 through 19) **Secondary outcomes** • Laboratory parameters • Adverse events through the study period (including CV events) • Severe adverse events through the study period (including death and CV death) • Plasma endogenous EPO levels • Blood transfusion
Notes	• Funding: FibroGen • Conflicts of interest: "Drs Besarab, Saikali, Poole, Soha, Hemmerich, Szczech, Yu, and Neff are employees of FibroGen and hold stock and/or stock options in FibroGen. At the time the study was performed, Dr Besarab was affiliated with the Henry Ford Health System and Wayne State University School of Medicine, and Dr Provenzano was affiliated with St. Clairs Specialty Physicians, LLC, and Wayne State University School of Medicine. Dr Provenzano is currently an employee of and holds stock in DaVita Healthcare Partners. The other authors declare that they have no other relevant financial interests." • Note: death, adverse events and number of patients who reached target Hb were reported for phase 1 and phase 2 but no data were extractable for each treatment dose, as requested from the study protocol. These data were not included in this review • Note: study included part 1 and part 2 with 2 different populations with same intervention but different follow-up period - the study was split into Provenzano 2016 and Provenzano 2016a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label."
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Independent data monitoring committee."

Provenzano 2016a *(Continued)*

All outcomes		Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment It was not reported if the Independent data monitoring committee was blind to the treatments assigned
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Reasons for discontinuation from the study were lack of efficacy (10), withdrawal of consent (4), AE/serious AE (6; including 3 deaths), 3 protocol violations, and 3 others (leaving canter, prolonged hospitalisation, and kidney transplantation)." Not reported in sufficient detail to perform adjudication for part 1 and 2 separately
Selective reporting (reporting bias)	High risk	All planned outcomes on ClincialTrials.gov were not measured and reported on in the final report. Reasons were not provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	Quote: "FibroGen was the study sponsor and designed the study in consultation with the principal investigators." There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding and authors' disclosure were reported Funder was likely to influence data analysis and study reporting or interpretation

PYRENEES 2021

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: November 2014 to July 2018 • Duration of follow-up: 108 weeks (treatment period (minimum of 52 weeks, maximum of 104 weeks) and a post-treatment follow-up period of 4 weeks
Participants	**General information** • Setting: multicentre (150 sites) • Country: 17 countries including Belgium, Bulgaria, Croatia, Czech Republic, France, Georgia, Germany, Hungary, Italy, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Spain, and UK • Inclusion criteria: males or females aged ≥ 18 years who were on stable HD, HDF or PD for anaemia; received the same mode of dialysis for ≥ 4 months prior to randomisation; received treatment with IV or SC epoetin or darbepoetin alfa treatment for ≥ 8 weeks prior to randomisation, with stable weekly doses during 4 weeks prior to randomisation; mean of 3 most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart, were to 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 • Exclusion criteria: received a RBC transfusion within 8 weeks prior to randomisation; known hereditary haematologic disease such as thalassaemia or sickle cell anaemia, PRCA, or other known causes for anaemia other than CKD; MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thrombo-embolic event (e.g. DVT or pulmonary embolism) within 12 weeks prior to randomisation; uncontrolled hypertension, in the opinion of the investigator, within 2 weeks prior to randomisation; history

PYRENEES 2021 *(Continued)*

of malignancy, except for the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps; any prior organ transplant (that has not been explanted), or participant is scheduled for organ transplantation

- Target Hb: 10 to 12 g/dL

Baseline characteristics

- CKD stage:
  - HD: treatment group (379/414); control group (405/420)
  - PD: treatment group (35/414); control group (15/420)
- Number (randomised/analysed): treatment group (415/249); control group (423/309)
- Mean age ± SD (years): treatment group (61.0 ± 13.8); control group (61.8 ± 13.4)
- Sex (M, %): treatment group (245, 59.2%); control group (235, 56.0%)
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes: treatment group (104/414); control group (133/420)
- Prior agents used (number, %)
  - ESA: treatment group (256/414); control group (257/420)
  - Darbo alfa: treatment group (158/414); control group (163/420)

Interventions

Treatment group (high dose)*

- Roxadustat (oral): 20 to 400 mg 3 times/week

Control group

- EPO alpha (EPREX) (IV):1000 to 8000 IU
- Darbo alpha (ARANESP)

Co-interventions

- Oral iron treatment was recommended for supplementation to support erythropoiesis and as first-line treatment for iron deficiency, unless participant was intolerant to this treatment. For participants receiving roxadustat the recommended daily dose was 200 mg of elemental iron. Participants were advised to take roxadustat at least 1 hour before or 1 hour after oral iron. IV iron supplementation for participants receiving roxadustat was allowed if all of the following criteria were met: Hb level had not responded adequately to roxadustat following two consecutive dose increases or reached the maximum dose limit, and ferritin was < 100 ng/mL (< 220 pmol/L) or TSAT < 20%, or they were intolerant of oral iron therapy. For participants treated with epoetin alfa or darbepoetin alfa, IV iron supplementation was given according to standard of care

*Note: dose assessed as high (mean dose 210 mg) according to NCT01888445

Outcomes

Primary outcomes

- Change in Hb from baseline to the average level during the evaluation period (defined as week 28 until week 36), without having received rescue therapy (i.e., RBC transfusion for all patients or ESA for patients treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period
- The USA (FDA) primary efficacy endpoint was change in Hb from baseline to the average level during the evaluation period (defined as week 28 until week 52), regardless of rescue therapy

Secondary outcomes

PYRENEES 2021 *(Continued)*

- Hb response, defined as mean Hb during weeks 28 to 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
- Change from baseline in LDL cholesterol to the average LDL cholesterol of weeks 12 to 28
- Mean monthly IV iron use (mg) during day 1 to week 36 (monthly defined as a period of 4 weeks)
- Change from baseline in the SF-36 Physical Functioning sub score to the average Physical Functioning sub score of weeks 12 to 28
- Change from baseline in SF-36 Vitality sub score to the average Vitality sub score of weeks 12 to 28
- Change in MAP from baseline to the average MAP of weeks 20 to 28 and time to an increase in BP during weeks 1 to 36
- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug), and pre-specified adjudicated CV and cerebrovascular events (reported separately)
- Vital signs: SBP and DBP, heart rate, and respiratory rate
- Clinical laboratory variables: haematology, biochemistry including liver enzymes and total bilirubin, and urinalysis
- Physical examination
- 12-lead ECG
- Vascular access thrombosis
- Hospitalisation
- SF-36

Notes

- Funding: Astellas Pharma
- Conflicts of interest: "U. Valluri is an employee of Astellas Pharma, Inc. M. Reusch is an employee of Astellas Pharma Europe B.V. J. Barratt, B. Csiky, C. Esposito, M. Schomig, and W. Sulowicz have nothing to disclose"
- Authors were contacted to request extra information but they did not reply

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. There were no imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-Label."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "All data from site (2 patients randomized to the ESA treatment group) are excluded due to Good Clinical Practice (GCP) violations; therefore a total of 836 patients were considered randomized for analysis: 415 to the roxadustat treatment group and 421 to ESA." Quote: "A total of 558 (66.7%) patients completed the study up to 2 years of treatment, 249 (60.0%)in the roxadustat treatment group and 309 (73.4%) in the ESA treatment group. Overall, 40.0% of patients in the roxadustat treatment group and 26.6% of patients in the ESA treatment group discontinued treatment up to 2 years. A total of 13.0% of patients withdrew due to death

PYRENEES 2021 *(Continued)*

		(14.9% roxadustat vs 11.2% ESA) and 9.1% withdrew by patient(12.0% vs 6.2%)." Analyses were performed on different number of participants (> 5% lost to follow-up with imbalance between the two groups)
Selective reporting (reporting bias)	High risk	All planned outcomes on ClincialTrials.gov were not measured and reported on in the final report. Reasons were not provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding was reported and authors' disclosure were not reported Funder was likely to influence data analysis and study reporting or interpretation Conflicts of interest were reported

ROCKIES 2019

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 52 weeks
Participants	**General information** • Setting: multicentre (250 sites were planned) • Country: multinational (countries not reported) • Inclusion criteria: anaemic dialysis-dependent patients ≥ 18 years with baseline Hb of < 12 g/dL if treated with an EPO analogue or < 10 g/dL; provision of informed consent; ≥ 18 years; patients are considered not currently treated if they have not received either Mircera for at least 8 weeks or any other EPO analogue for at least4 weeks prior to visit 1; ferritin ≥ 100 ng/mL; TSAT ≥ 20%; serum folate level ≥ LLN; serum vitamin B12 level ≥ LLN; ALT and AST ≤ 3 times ULN; total bilirubin ≤1.5 times ULN; weight 45 to 160 kg (prescribed dry weight) • Exclusion criteria:**i**nvolvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site); previous randomisation in the present study; NYHA class III or IV congestive heart failure; MI, acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event (e.g. DVT or pulmonary embolism) within 12 weeks prior to randomisation; history of chronic liver disease (e.g. chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver); known hereditary haematologic disease such as thalassaemia, sickle cell anaemia, a history of PRCA or other known causes for anaemia other than CKD; known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis); diagnosis or suspicion (e.g. complex kidney cyst of Bosniak Category IIF, III or IV) of renal cell carcinoma on renal ultrasound (or other imaging procedure e.g. CT scan or MRI) conducted at screening or within 12 weeks prior to randomisation; uncontrolled hypertension at the time of randomisation (defined as SBP ≥ 180 mm Hg or DBP ≥ 100 mm Hg on repeated measurement post-dialysis in HD patients or at any time in PD patients), contraindication to epoetin alfa treatment (e.g. PRCA, hypersensitivity or know inability to tolerate epoetin alfa); history of prostate cancer, breast cancer or any other malignancy, except the following: cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ or resected colonic polyps; positive for HIV, HBsAg or Anti-HCV Ab; chronic inflammatory diseases such as rheumatoid arthritis, SLE, ankylosing spondylitis, psoriatic arthritis or inflammatory bowel disease

ROCKIES 2019 *(Continued)*

that is determined to be the principal cause of anaemia; known haemosiderosis, haemochromatosis or hypercoagulable condition; any prior organ transplant with the exception of an autologous kidney transplant or a kidney transplant that was subsequently removed ("explanted") or scheduled organ transplantation date; any RBC transfusion during the screening period; any current condition leading to active significant blood loss; any prior treatment with roxadustat or a HIF-PHI; received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within the month preceding the first administration of IP in this study; history of alcohol or drug abuse within 2 years prior to randomisation; females of childbearing potential, unless using contraception as detailed in the protocol or sexual abstinence; pregnant or breastfeeding; known allergy to the investigational product or any of its ingredients; any medical condition, including active, clinically significant infection, that in the opinion of the investigator or Sponsor may pose a safety risk to a patient in this study, which may confound efficacy or safety assessment, or may interfere with study participation

- Target Hb: 10 to 12 g/dL

Baseline characteristics

- CKD stage: dialysis (HD/PD)
- Number (randomised/analysed): treatment group (1068/not reported); control group (1065/not reported)
- Mean age ± SD (years): overall (54, SD was not reported)
- Sex (M, %): 59%
- Time on dialysis: not reported
- eGFR: not reported

Comorbidities

- CV disease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): not reported

Interventions

Treatment group

- Roxadustat: 20 to400 mg 3 times/week, to maximum 3 mg/kg
  - Dose adjustments are permitted starting at week 4 and at intervals of every 4 weeks thereafter in order to achieve an Hb level of 11 g/dL and maintain an Hb of 11 ± 1 g/dL

Control group

- EPO alpha: initial dosing for patients not currently receiving any EPO at study entry will be 50 IU/kg 3 times/week with subsequent dose adjustments to achieve an Hb level of 11 g/dL

Co-interventions

- Oral iron was allowed; IV iron was used as standard-of-care in EPO arm and with evidence of iron deficiency in roxadustat arm

Outcomes

Primary outcomes

- Mean Hb change from baseline to Hb averaged over weeks 28 to 52
- Adjudicated CV safety data

Secondary outcomes

- Laboratory parameters
- Proportion of total time of Hb ≥ 10 g/dL from week 28 to 52
- Proportion of total time of Hb within the interval of 10 to 12 g/dL from week 28 to 52
- Mean change from baseline in LDL cholesterol from baseline to week 24

ROCKIES 2019 *(Continued)*

- Mean change in Hb from baseline to the subjects mean level between week 28 to 52 in subjects with baseline high-sensitivity CRP > ULN
- Average monthly IV iron use
- Time-to-first (and proportion of subjects receiving) administration of RBC transfusion as rescue therapy
- Adverse events
- Serious adverse events
- Changes in vital signs, ECG
- EQ-5D-5L
- Hospitalisation

Notes

- Funding: AstraZeneca
- Conflicts of interest: not reported
- Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. It was not possible to assess if there was imbalance between intervention groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Not reported in sufficient detail to perform adjudication
Selective reporting (reporting bias)	High risk	All planned outcomes on ClincialTrials.gov were not measured and reported on in the final report. Reasons were not provided Clinically-relevant outcomes that would be expected for this type of intervention were not reported
Other bias	High risk	It was not possible to assess if there was imbalance between intervention groups Funding was reported and authors' disclosure were not reported Funder was likely to influence data analysis and study reporting or interpretation

SIERRAS 2021

Study characteristics

Methods

- Study design: phase III, parallel RCT
- Time frame: January 2015 and September 2018
- Duration of follow-up: 52 weeks

Participants

General information

- Setting: multicentre (76 sites)
- Country: multinational (USA, Puerto Rico)
- Inclusion criteria: ≥ 18 years; receiving adequate dialysis using the same modality of dialysis for kidney failure for ≥ 3 months prior to and during screening (Amendment 1 only: incident dialysis subjects receiving dialysis for native kidney failure for ≥ 2 weeks but ≤ 4 months at the time of randomisation); receiving IV or SC ESA for ≥ 8 weeks prior to screening and on a stable ESA (≤ 30% change) dose during 4 weeks (8 weeks if on Mircera) prior to randomisation (Amendment 1 Only: incident dialysis subjects must be on ESA for ≥ 4 weeks prior to screening, mean of subject's 3 most recent Hb values must be ≥ 9.0 g/dL and ≤ 12.0 g/dL; with an absolute difference of ≤ 1.3 g/dL between the highest and the lowest value; Amendment 1 only: for incident dialysis subjects, mean of the 3 most recent central lab Hb values during the screening period must be ≥ 8.5 g/dL and ≤12.0 g/dL); ferritin ≥ 100 ng/mL; TSAT ≥ 20%; serum folate ≥ LLN, Vitamin B12 level ≥ LLN; ALT and AST ≤ 3 times ULN, total bilirubin ≤ 1.5 times ULN; weight 45 kg to 160 kg
- Exclusion criteria: received an RBC transfusion within 8 weeks prior to randomisation; known history of myelodysplastic syndrome or multiple myeloma; known inherited disease such as thalassaemia or sickle cell anaemia or other known causes for anaemia other than CKD; known haemosiderosis, haemochromatosis, coagulation disorder, or hypercoagulable condition; known chronic inflammatory disease that could cause anaemia; anticipated surgery that is expected to cause blood loss; known GI bleeding; history of chronic liver disease (e.g. chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver); congestive heart failure (NYHA Class III or IV); had a heart attack, stroke, seizure, or a thrombotic/thromboembolic event (e.g. DVT or pulmonary embolism) within 12 weeks prior to participating in the study; uncontrolled high BP within 2 weeks prior to participating in the study; history of malignancy, except for cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps; positive for HIV, HBsAG, or anti-HCV Ab; has had any prior organ transplant (that has not been explanted); known untreated conditions (proliferative diabetic retinopathy, diabetic macular oedema, macular degeneration or retinal vein occlusion)
- Target Hb: 10 to 12 g/dL, also at least 10 g/dL (both targets were evaluated) - the analyses reported here were related to the target at least 10 g/dL

Baseline characteristics

- CKD stage: HD and PD
  - HD: treatment group (354/370); control group (16/371)
  - PD: treatment group (354/370); control group (17/371)
- Number (randomised/analysed): treatment group (370/334 ITT); control group (371/337 ITT)
- Mean age ± SD (years): treatment group (57.6 ± 13.6); control group (58.4 ± 13.3)
- Sex (M, %): treatment group (187, 50.5%); control group (215, 58%)
- Time on dialysis (years): treatment group (4 ± 3.5); control group (3.9 ± 3.8)
- eGFR: not reported

Comorbidities

- CVdisease: not reported
- Heart disease: data on MI, stroke and congestive heart failure reported
- Hypertension: treatment group (366/370); control group (367/371)
- Diabetes: treatment group (250/370); control group (254/371)
- Prior agents used (number, %):
  - EPO alfa: treatment group (290/370); control group (293/371)
  - Darbepoetin alfa: treatment group (65/370); control group (65/371)

SIERRAS 2021 *(Continued)*

- Mircera: treatment group (14/370); control group (8/371)
- Other: treatment group (1/370); control group (4/371)

Interventions	**Treatment group (high dose)*** • Roxadustat (FG-4592) (oral): starting doses were 70, 100, 150, or 200 mg 3 times/week based on the patient's prescribed pre-study ESA dose **Control group** • Epoetin alfa (IV): 3 times/week **Co-interventions** • Not reported *Note: dose assessed as high according to NCT01888445
Outcomes	**Primary outcome** • The primary efficacy endpoint for USA is defined as each subject's Hb change from baseline to the average level during the evaluation period, defined as weeks 28 to 52 **Secondary outcomes** • USA (FDA) submission: the proportion of subjects with a mean Hb level ≥ 10.0 g/dL during the evaluation period (day 1 to week 52) • Ex-USA submissions: Hb response (mean 10.0 to 12.0 g/dL), during weeks 28 to 36 without having received rescue therapy • Average monthly IV Iron use per subject (weeks 1 to 36) • Change from baseline in LDL (weeks 12 to 28) • Change from baseline in SF-36 Physical Functioning sub-score (weeks 20 to 28) • Change from baseline in SF-36 Vitality sub-score (weeks 20 to 28) • Effect on predialysis BP (weeks 1 to 36)
Notes	• Funding: FibroGen, Astellas Pharma Europe B.V., AstraZeneca • Conflicts of interest: "CC serves on Advisory Boards for AstraZeneca and FibroGen and received research support for Akebia, AstraZeneca, FibroGen, and GlaxoSmithKline. RMK owns FibroGen stock. MB received grants from FibroGen during the conduct of the study. GS, CB, ME, RL, KGS, CL, LS, and KHPY are employees of FibroGen and hold stock and/or stock options in FibroGen. EM, DS, SLD, and MM have no conflicts of interest to disclose. Roxadustat is in clinical development for the treatment of anaemia of CKD in collaboration with Astellas Pharma and AstraZeneca."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Automated randomisation and treatment assignments were performed using an Interactive Web Response System."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation code was concealed in the IRT system managed by the third party vendor. In this setting, the sponsor, a site or a patient would not know the treatment assignment beforehand and could not predict the treatment assignment for the next patient in line." Quote: "Automated randomisation and treatment assignments were performed using an Interactive Web Response System."

SIERRAS 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Objective and subjective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT population 334/370 participants in the intervention group and 337/371 participants in the control group The number of participants included in the safety population, full analysis set and per protocol set varied
Selective reporting (reporting bias)	Low risk	All planned outcomes on ClincialTrials.gov were measured and reported Clinically-relevant outcomes that would be expected for this type of intervention (death and CV events) were reported
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Funding influenced data analysis and study reporting or interpretation Conflicts of interest were reported.

SYMPHONY HD 2021

Study characteristics	
Methods	• Study design: parallel RCT • Time frame: not reported • Duration of follow-up: 26 weeks (treatment phase 24 weeks + 2 weeks follow-up)
Participants	**General information** • Setting: not reported • Country: Japan • Inclusion criteria: ≥ 20 years; received HD 3 times/week including HDF for at least 12 weeks before screening visit 1; TSAT > 20% or ferritin > 75 ng/mL; received rHuEPO (epoetin alfa, beta, or kappa) in the range of 750 to 9,000 IU/week or darbepoetin in the range of 10 to 40 µg/week; Hb levels 9.5 to 12.0 g/dL during the screening period with an absolute difference of ≤ 1.0 g/dL between visits 1 and 2 • Exclusion criteria: poorly controlled hypertension; severe hepatobiliary disease; congestive heart failure (NYHA class III or more severe); severe hyperparathyroidism; suspected to have anaemia caused by non-infectious inflammatory disease • Target Hb: 10 to 12 g/dL **Baseline characteristics** • CKD stage: HD • Number (randomised/analysed): treatment group 1 (87/87); control group (86/86) • Mean age ± SD (years): treatment group (63.2 ± 10.8); control group (64.8 ± 10.3) • Sex (M, %): treatment group (61, 70.9%); control group (61, 70.9%) • Time on dialysis (years): treatment group (8.56 ± 7.45); control group (7.56 ± 6.91) • eGFR: not reported

SYMPHONY HD 2021 *(Continued)*

Comorbidities

- CVdisease: not reported
- Heart disease: not reported
- Hypertension: not reported
- Diabetes (number, %): not reported
- Prior agents used (number, %): all participants used EPO
  - Oral iron: treatment group (39, 45.3%); control group (29, 33.7%)
  - rHuEPO: treatment group (45, 52.3%); control group (40, 46.5%)
  - Darbepoetin: treatment group (41, 47.7%); control group (46, 53.5)

Interventions

Treatment group (medium dose)*

- Enarodustat (JTZ-951) (oral): once/day for 24 weeks, initial doses were 4 mg/day up to 8 mg

Control group

- Darbepoetin alfa (SC): every 2 or 4 weeks for 24 weeks, 10 to 40 µg/week as the initial dose

Co-interventions

- IV iron preparations were prohibited
- Stable oral iron preparations were permitted if they have been used before the screening period

*Note: dose assessed as medium according to SYMPHONY ND 2021

Outcomes

Primary outcomes

- Difference in the mean Hb level between arms during the evaluation period defined as weeks 20 to 24

Secondary outcomes

- Adverse events during the study period
- Time course of Hb levels, proportion of subjects who maintained Hb levels within the target range, mean prescribed dose, and number of dose adjustment during the study period
- Laboratory tests during the study period
- Vital signs during the study period
- Achievement of an Hb level within the range of week 0 ± 1.0 g/dL at week 4, achievement of an Hb level within a target range defined as ≥10.0 and <12.0 g/dL during the end of treatment period

Notes

- Funding: Japan Tobacco Inc.
- Conflicts of interest: "T.A. reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Astellas, Bayer Yakuhin Ltd., Kyowa Kirin Co. Ltd., Kissei Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Fuso Pharmaceutical Industries Ltd., Torii Pharmaceutical Co. Ltd., GlaxoSmithKline, Nipro Corporation, Otsuka Pharmaceutical, Sanwa Chemical, Chugai Pharmaceutical Co. Ltd., and Mitsubishi Tanabe Pharma Corporation outside of the submitted work. M.N. is an Editorial Board Member of the journal Kidney Diseases and reports grants and personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Kyowa Kirin Co. Ltd., Astellas, Astra Zeneca, GlaxoSmithKline, Mitsubishi Tanabe Pharma Corporation, Akebia Therapeutics Inc., Bayer Yakuhin Ltd., and Torii Pharmaceutical Co. Ltd. and grants from Kyowa Kirin Co. Ltd., Astellas, Mitsubishi Tanabe Pharma Corporation, Bayer Yakuhin Ltd., and Torii Pharmaceutical Co. Ltd outside of the submitted work. T.Y. reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Ono Pharmaceutical Co. Ltd., Kowa, Chugai Pharmaceutical Co. Ltd., TSUMURA & Co., CAC Croit Corporation, Kyowa Kirin Co. Ltd., Daiichi Sankyo, ASAHI INTECC, Asahi Kasei Corporation, Kaken Pharmaceutical, 3H Clinical Trial Co. Ltd., Welby, 3H Medi Solution, and Nipro Corporation and grants from Ono Pharmaceutical Co. Ltd., CAC Croit Corporation, Kyowa Kirin Co. Ltd., Daiichi Sankyo, 3H Clinical Trial Co. Ltd., AC Medical, A2 Healthcare, Facet Biotech, Japan Media Corporation, Luminary Medical, Medidata Solutions Inc., Senju Pharmaceutical, Otsuka Pharmaceutical, Eisai, FMD K&L Japan, Intellim, Welby, 3H Medi Solution, Nipro Corporation, Hemp Kitchen, NOBORI, Puravida Technologies LLC., and Medrio Inc. outside of the submitted work. H.H.

SYMPHONY HD 2021 *(Continued)*

reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Kyowa Kirin Co. Ltd., Chugai Pharmaceutical Co. Ltd., and Torii Pharmaceutical Co. Ltd. outside of the submitted work. R.K., K.M., and Y.M. are employees of Japan Tobacco Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Interactive Web Response System was contacted by the site and randomly assigned the eligible subject with permutated block at a 1:1 ratio to receive once-daily oral enarodustat tablet."
Allocation concealment (selection bias)	Low risk	Quote: "Interactive Web Response System was contacted by the site and randomly assigned the eligible subject with permutated block at a 1:1 ratio to receive once-daily oral enarodustat tablet."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blind"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "In total, 173 subjects were randomized into the study and administered the study drug (87 subjects in the enarodustat arm and 86 subjects in the DA arm). All subjects were included in the SAF. Overall, 172 subjects were included in the FAS because 1 subject in the enarodustat arm had <2 efficacy measurements. In the enarodustat arm, 79 subjects completed the treatment period, and 78 subjects were included in the PPS because 1 subject experienced protocol deviation. In the DA arm, 80 subjects completed the treatment period, and all were included in the PPS." ITT analyses
Selective reporting (reporting bias)	High risk	Clinically-relevant outcomes that would be expected for this type of intervention were not reported (death and CV events)
Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Conflict of interest were reported Funder was likely to influence data analysis and study reporting or interpretation Kyowa Kirin Co administered DA

SYMPHONY ND 2021

Study characteristics

Methods	• Study design: parallel RCT • Time frame: February 2018 to June 2019 • Duration of follow-up: 26 weeks (treatment phase 24 weeks + 2 weeks follow-up)

SYMPHONY ND 2021 *(Continued)*

Participants	**General information**
	• Setting: not reported
	• Country: Japan
	• Inclusion criteria: ≥ 20 years with CKD not requiring dialysis (eGFR < 60 mL/min/1.73 m^2) who were unlikely to receive KRT; predefined Hb level for each subpopulation (ESA-naïve and ESA-treated patients); TSAT >20% or ferritin >50 ng/mL
	• Exclusion criteria: received RBC transfusion within 12 weeks before screening visit 1; suspected to have anaemia caused by non-infectious chronic inflammatory disease; intact PTH ≥ 500 pg/mL
	• Target Hb: 10 to 12 g/dL
	Baseline characteristics
	• CKD stage: CKD
	• Number (randomised/analysed): treatment group 1 (107/97); control group (109/96)
	• Mean age ± SD (years): treatment group (70.4 ± 9.1); control group (68.9 ± 9.1)
	• Sex (M, %): treatment group (61, 62.9%); control group (47, 49%)
	• Time on dialysis: not reported
	• Mean eGFR ± SD (mL/min/1.73 m^2): treatment group (18.6 ± 10.1); control group (17.3 ± 8.3)
	Comorbidities
	• CV disease: not reported
	• Heart disease: not reported
	• Hypertension: not reported
	• Diabetes (number, %): not reported
	• Prior agents used (number, %)
	  ◦ Oral iron: treatment group (15, 15.5%); control group (16, 16.7%)
	  ◦ rHuEPO: treatment group (0/57 who used ESA); control group (1/55 who used ESA)
	  ◦ Darbepoetin: treatment group (27/57, 47.4% who used ESA); control group (34/55, 61.8% who used ESA)
	  ◦ EBP: treatment group (30/57, 52.6% who used ESA); control group (20/55, 36.4% who used ESA)

Interventions	**Treatment group (low dose)** • Enarodustat (JTZ-951) (oral): once/day for 24 weeks, 2 mg/day as the initial dose, the dose was adjusted every 4 weeks within the range of 1 to 8 mg/day in the enarodustat arm; mean prescribed dose of enarodustat was 2.68 mg/day **Control group** • Darbepoetin alfa (SC) every 2 or 4 weeks for 24 weeks, 30 mg/2 weeks as the initial dose **Co-interventions** • IV iron preparations were prohibited • Stable oral iron preparations were permitted if they have been used before the screening period
Outcomes	**Primary outcomes** • Difference in the mean Hb level between arms during the evaluation period defined as weeks 20 to 24 **Secondary outcomes** • Adverse events during the study period • Time course of Hb levels, proportion of subjects who maintained Hb levels within the target range, mean prescribed dose, and number of dose adjustment during the study period • Laboratory tests during the study period

SYMPHONY ND 2021 *(Continued)*

- Vital signs during the study period

Notes

- Funding: not reported
- Conflicts of interest: "T.A. reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Astellas, Bayer Yakuhin, Kyowa Kirin, Kissei Pharmaceutical, Ono Pharmaceutical, Fuso Pharmaceutical Industries, Torii Pharmaceutical, GlaxoSmithKline, Nipro Corporation, Otsuka Pharmaceutical, Sanwa Chemical, and Chugai Pharmaceutical outside of the submitted work. M.N. reports grants and personal fees from Japan Tobacco Inc. during the conduct of the study and grants and/or personal fees from Kyowa Kirin, Astellas, Astra Zeneca, GlaxoSmithKline, Mitsubishi Tanabe Pharma Corporation, Akebia Therapeutics, Bayer Yakuhin, and Torii Pharmaceutical outside of the submitted work. T.Y. reports personal fees from Japan Tobacco Inc. during the conduct of the study and grants and/or personal fees from Ono Pharmaceutical, Kowa, Chugai Pharmaceutical, TSUMURA & Co., CAC Croit Corporation, Kyowa Kirin, Daiichi Sankyo, ASAHI INTECC, Asahi Kasei, Kaken Pharmaceutical, 3H Clinical Trial, AC Medical, A2 Healthcare, Facet Biotech, Japan Media Corporation, Luminary Medical, Medidata Solutions, Senju Pharmaceutical, Otsuka Pharmaceutical, Eisai, FMD K&L Japan, Intellim, Welby, 3H Medi Solution, Nipro Corporation, Hemp Kitchen, NOBORI, Puravida Technologies and Medrio outside of the submitted work. H.H. reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Kyowa Kirin, Chugai Pharmaceutical, and Torii Pharmaceutical outside of the submitted work. R.K., K.M., and Y.M. are employees of Japan Tobacco Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation methods were not reported in sufficient detail to permit judgement. However, no imbalance between intervention groups was apparent
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported in sufficient detail to permit judgement. No imbalance between intervention groups was apparent
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were principally laboratory measures and were at low risk of detection bias regardless of whether blinding of investigators or outcome assessors occurred. However, some outcomes (adverse events) could be influenced by knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "In total, 216 subjects (102 ESA-naïve and 114 ESA- treated subjects) were randomly assigned to the enarodustat arm (n ¼ 107; 50 ESA-naïve and 57 ESA-treated subjects) or DA arm (n ¼ 109; 52 ESA-naïve and 57 ESA-treated subjects) and 195 subjects completed the study. The PPS included 193 subjects after the exclusion of 23 subjects (10 in the enarodustat arm and 13 in the DA arm) with <3 Hb measurements during the evaluation period. Overall, 212 subjects were included in the full analysis set after the exclusion of four subjects (2 in the enarodustat arm and 2 in the DA arm) with <2efficacy measurements from week 4 onward." All 216 subjects (107 in the enarodustat arm and 109 in the DA arm) were included the safety population
Selective reporting (reporting bias)	High risk	Clinically-relevant outcomes that would be expected for this type of intervention were not reported (death and CV events)

SYMPHONY ND 2021 *(Continued)*

Other bias	High risk	There was no evidence of different baseline characteristics, or different non-randomised co-interventions between groups Conflict of interest were reported Funder was not reported

ALP - alkaline phosphatase; ALT - alanine aminotransferase; APD - automated peritoneal dialysis; Apo - apolipoproteins; AST - aspartate aminotransferase; AVF - arteriovenous fistula; AUC - area under the curve; AZA - azathioprine; BMI - body mass index; BP - blood pressure; CAPD - continuous ambulatory peritoneal dialysis; CFB - change from baseline; CHF - chronic heart failure; CHr - reticulocyte haemoglobin; CKD - chronic kidney disease; CKD-EPI - CKD Epidemiology Collaboration; Cmax - maximum concentration; CRP - C-reactive protein; CV - cardiovascular; DBP - diastolic blood pressure; DVT - deep vein thrombosis; EBP - epoetin beta pegol; ECG - electrocardiogram; eGFR - estimated glomerular filtration rate; EPO - erythropoietin; EQ-5D-5L - EuroQol 5 Dimension 5 Level Health Utility Index; ESA - erythropoietin-stimulating agent; FACT - Functional Assessment of Cancer Therapy; FAS - full analysis set; GI - gastrointestinal; GN - glomerulonephritis; Hb - haemoglobin; HCT - haematocrit; HbA1c - haemoglobin A1c (glycated); HBsAg - hepatitis B surface antigen; HCV Ab - hepatitis C virus antibody; HD - haemodialysis; HF - haemofiltration; HDF - haemodiafiltration; HDL - high-density lipoprotein; HIF - hypoxia-inducible factor; HIF-PHI - Hypoxia-inducible factor prolyl hydroxylase inhibitor; HIV - human immunodeficiency virus; HRQoL - heath-related quality of life; HRT - hormone replacement therapy; HUS - haemolytic uraemic syndrome; ITT - intention to treat; IU - international units; IV - intravenous; KDOQI - Kidney Disease Outcomes Quality Initiative; KRT - kidney replacement therapy; LDL - low-dose lipoprotein; LFT - liver function test/s; LLN - lower limit of normal; MACE - major adverse cardiovascular event (composite of death (any cause), non-fatal MI, and non-fatal stroke); MAP - mean arterial pressure; MI - myocardial infarction; NYHA - New York Heart Association; PCKD - polycystic kidney disease; PD - peritoneal dialysis; PGI-S - Patient Global Impression of Severity Scale; PPS - per protocol set; PRCA - pure red cell aplasia; PTH - parathyroid hormone; QtcB - Bazett's corrected QT interval; RBC - red blood cell; RCT - randomised controlled trial; rHuEPO - recombinant human EPO; SAS - safety analysis set; SBP - systolic blood pressure; SCr - serum creatinine; SGOT - serum glutamic oxaloacetic transaminase; SGPT - serum glutamic pyruvic transaminase; SLE - systemic lupus erythematosus; SC - subcutaneously; sPAP - systolic pulmonary artery pressure; TCM - traditional Chinese medicine; TIA - transient ischaemic attack; TIBC - total iron-binding capacity; TSAT - transferrin saturation; UACR - urinary albumin:creatinine ratio; UF - ultrafiltration; UIBC - unbound iron binding capacity; ULN - upper limit of normal; URR - urea reduction ratio; VAS - Visual Analogue Scale; VEGF - vascular endothelial growth factor; WBC - white blood cell; WPAI - Work Productivity and Activity Impairment

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akizawa 2015a	Wrong intervention/control: different dosing regimens of JTZ-951
Akizawa 2019a	Duration of follow-up < 8 weeks Phase 1: patients randomised to different doses of enarodustat versus placebo for 6 weeks Phase 2: all participants, including those in the placebo group, took enarodustat until the end of the follow-up period. It was not clearly stated if the second phase was randomised
Akizawa 2019b	Duration of follow-up < 8 weeks Phase 1: patients randomised to different doses of enarodustat versus placebo for 6 weeks Phase 2: all participants, including those in the placebo group, took enarodustat until the end of the follow-up period. It was not clearly stated if the second phase was randomised
Akizawa 2020	Wrong intervention: patients not previously receiving ESA were randomised to roxadustat at a starting dose of 50 or 70 mg 3 times/week; patients previously receiving ESA switched from ESA to roxadustat 70 or 100 mg 3 times/week depending on the prior ESA dose
Akizawa 2020b	Wrong intervention/control: different dosing regimens of roxadustat

Study	Reason for exclusion
Akizawa 2020g	Wrong intervention: patients not previously receiving ESA were randomised to roxadustat at a starting dose of 50 or 70 mg 3 times weekly; patients previously receiving ESA switched from ESA to roxadustat 70 or 100 mg three times weekly depending on the prior ESA dose
ASCEND:Fe 2018	Duration of follow-up < 8 weeks: protocol reporting that at day 28 participants will be crossed over
ASCEND-BP 2017	Duration of follow-up < 8 weeks: protocol reporting that at day 28 participants will be crossed over
Bailey 2019	Duration of follow-up < 8 weeks
Besarab 2016	Wrong intervention/control: roxadustat + no iron, roxadustat + oral iron, roxadustat + IV iron
Buch 2014	Duration of follow-up < 8 weeks
DD-CKD 2020	Duration of follow-up < 8 weeks: 2 RCTs were included, with dialysis or CKD participants. In both studies in the first 6 weeks patients were randomised to vadadustat 150, 300 or 600 mg versus placebo. For the following 10 weeks vadadustat dose adjustments to achieve target Hb level of 10.0 to 12.0 g/dL, and placebo patients switched to vadadustat 150, 300 or 600 mg. It was not clearly stated if the second phase was randomised for a second time
EudraCT2012-004049-34	Duration of follow-up < 8 weeks
EudraCT2012-004050-29	Duration of follow-up < 8 weeks
EudraCT2015-004790-32	Duration of follow-up < 8 weeks
Frohna 2007	Duration of follow-up < 8 weeks
Haase 2016	Wrong intervention/control: different dosing regimens of vadadustat
Hartman 2014	Duration of follow-up < 8 weeks
Holdstock CKD 2016	Duration of follow-up < 8 weeks
Holdstock HD 2016	Duration of follow-up < 8 weeks
Martin 2017	Duration of follow-up < 8 weeks
NCT01679587	Wrong intervention/control: different dosing regimens of molidustat
NCT01971164	Duration of follow-up < 8 weeks
NCT03992066	Duration of follow-up < 8 weeks
NCT04059913	Wrong intervention/control: different dosing regimens of roxadustat
Pai 2015	Duration of follow-up < 8 weeks
Parmar 2019	Duration of follow-up < 8 weeks
Provenzano 2011	Duration of follow-up < 8 weeks
Provenzano 2011a	Duration of follow-up < 8 weeks
Provenzano 2016b	Wrong intervention/control: different dosing regimens of roxadustat

Study	Reason for exclusion
Wiecek 2005	Duration of follow-up < 8 weeks

CKD - chronic kidney disease; ESA - erythropoietin-stimulating agent; Hb - haemoglobin; IV - intravenous; RCT - randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

FO2RWARD-2 2019

Methods	• Study design: parallel RCT • Expected duration of follow-up: 28 weeks
Participants	**General information** • Setting: multicentre (41 sites) • Country: USA • Inclusion criteria: ≥18 years providing informed consent; receiving chronic outpatient in-centre HD (3 times/week) for kidney failure for at least 12 weeks prior to screening; maintained on IV epoetin alfa therapy for 8 weeks prior to and including screening through screening visit 2; eligibility in the main study and ESA hypo-responder parallel study is based on the following mean weekly epoetin alfa doses: 1) Main study: mean weekly epoetin alfa dose < 300 U/kg/week for 8 weeks prior to screening visit 2; 2) ESA hypo-responder parallel study: mean weekly epoetin alfa dose ≥ 300 U/kg/week for 8 weeks prior to screening visit 2; 2 Hb values measured at least 4 days apart between screening visit 1 and screening visit 2 as indicated: 1) Main study: 2 Hb values between 8.5 and 11.0 g/dL; and 2) ESA hypo-responder parallel study: 2 Hb values between 8.0 and 10.0 g/dL; serum ferritin ≥ 100 ng/mL and TSAT ≥ 20% during screening; folate and vitamin B12 measurements ≥ LLN during screening; HD adequacy as indicated by single-pool Kt/V urea ≥ 1.2 using the most recent historical measurement within 8 weeks prior to or during screening; understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure • Exclusion criteria: anaemia due to a cause other than CKD (e.g. sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, haematologic malignancy, myeloma, haemolytic anaemia, thalassaemia, or PRCA); active bleeding or recent blood loss within 8 weeks prior to randomisation; RBC transfusion within 8 weeks prior to randomisation; anticipated to discontinue HD during the study; judged by the Investigator that the participant is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrolment in the study; history of chronic liver disease (e.g. chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver); AST/SGOT, ALT/SGPT, or total bilirubin > 1.5 times ULN during screening; current uncontrolled hypertension as determined by the investigator that would contraindicate the use of epoetin alfa; acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for heart failure or NYHA class IV heart failure, or stroke within 12 weeks prior to or during screening; history of new or recurrent malignancy within 2 years prior to and during screening or currently receiving treatment or suppressive therapy for cancer; history of DVT or pulmonary embolism within 12 weeks prior to or during screening; history of haemosiderosis or haemochromatosis; history of prior organ transplantation (failed kidney transplant or corneal transplants are not excluded); scheduled organ transplant from a living donor and participants on the kidney transplant wait-list who are expected to receive a transplant within 6 months; history of a prior haematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded); known hypersensitivity to vadadustat, epoetin alfa, or any of their excipients; any prior use of a HIF-PHI or any use of an investigational medication within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to randomisation; female participants of non-childbearing potential: 1) inability to confirm surgical sterility (e.g. hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to screening; 2) not considered post-menopausal; for female participants of childbearing potential: 1) lack of confirmation of the use of acceptable forms of contraception for a minimum of one complete menstrual cycle prior to screening; 2) positive serum pregnancy test at screening visit 2; 3) unwilling to use two acceptable

FO2RWARD-2 2019 *(Continued)*

	forms of contraception (at least one of which must be a barrier method) starting baseline/day 1, throughout the treatment period and for 30 days after the final study drug administration; breast-feeding during screening or throughout the treatment period and for 30 days after the final study drug administration; donation of ova starting at screening, throughout the treatment period, and for 30 days after the final study drug administration; male participants who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat; bilateral native nephrectomy; any other reason, which in the opinion of the investigator, would make the participant not suitable for participation in the study; acceptable forms of contraception include: 1) established use of oral, injected or implanted hormonal methods of contraception; 2) placement of an intrauterine device or intrauterine system; 3) barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository • Target Hb: 10.0 to 11.0 g/dL • CKD stage: 175 patients undergoing HD
Interventions	**Treatment group 1** • Vadadustat (AKB-6548): 300, 450, or 600 mg **Treatment group 2** • Vadadustat (oral): 3 times/week **Control group** • Epoetin alfa (Procrit, Epogen) **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Mean change in Hb between baseline (average pretreatment Hb) and the primary evaluation period (weeks 10 to 12) **Secondary outcomes** • Proportion with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (weeks 10 to 12) • For participants who transitioned to 3 times/week vadadustat dosing, mean change in Hb from weeks 10 to 12 to the secondary evaluation period (weeks 18 to 20) • Mean change in Hb between baseline and the secondary evaluation period (weeks 18 to 20) • Proportion with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (weeks 18 to 20) • For who transitioned to 3 times/week vadadustat dosing, proportion of participants with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (weeks 18 to 20) • Proportion with a mean increase in Hb from baseline to the primary evaluation period ≥ 0.5 g/dL (weeks 10 to 12) • Proportion with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (weeks 10 to 12) • Proportion with a mean increase in Hb from baseline to the secondary evaluation period ≥ 0.5 g/dL (weeks 18 to 20) • Proportion with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (weeks 18 to 20) • Number requiring IV iron supplementation (up to 28 weeks) • Number requiring ESA rescue (up to 28 weeks) • Number requiring RBC transfusion (up to 28 weeks)

FO2RWARD-2 2019 *(Continued)*

Notes	• Study completion status: completed • Funding: Akebia Therapeutics

ALP - alkaline phosphatase; AST - aspartate aminotransferase; CKD - chronic kidney disease; DVT - deep vein thrombosis; ESA - erythropoietin-stimulating agent; Hb - haemoglobin; HD - haemodialysis; HIF-PHI - Hypoxia-inducible factor prolyl hydroxylase inhibitor; IV - intravenous; LLN - lower limit of normal; MI - myocardial infarction; NYHA - New York Heart Association; PRCA - pure red cell hyperplasia; RBC - red blood cell; RCT - randomised control trial; SGOT - serum glutamic oxaloacetic transaminase; SGPT - serum glutamic pyruvic transaminase; TSAT - transferrin saturation; ULL - upper limit of normal

Characteristics of ongoing studies *[ordered by study ID]*

ASCEND-FBF 2018

Study name	Anemia study in chronic kidney disease (CKD): erythropoiesis via a novel prolyl hydroxylase inhibitor (PHI) daprodustat -forearm blood flow (ASCEND-FBF)
Methods	• Study design: parallel RCT • Expected duration of follow-up: 8 weeks (6 weeks treatment period, and a follow-up visit up to 14 days later)
Participants	**General information** • Setting: multicentre • Country: UK • Inclusion criteria: males and females ≥ 18 years at the time of signing the informed consent; stage 3, 4 or 5 CKD defined by eGFR using the CKD Epidemiology Collaboration (CKD-EPI) formula; Hb ≤ 11.0 g/dL; palpable brachial artery as assessed at screening; may be on stable maintenance oral iron supplementation (< 50% change in overall dose and compliance of 80% of prescribed doses in the 4 weeks prior to and including the screening period); not pregnant or breastfeeding, not a woman of childbearing potential or who has been on an approved form of contraceptive for the 4 weeks prior to day 1 and agrees to follow the contraceptive guidance until the follow-up visit; capable of giving signed informed consent • Exclusion criteria: on dialysis or clinical evidence of impending need to initiate dialysis within 12 weeks of day 1; planned kidney transplant within 12 weeks of day 1; presence of AVF; rHuEPO use within the 12 weeks prior to the screening visit and through day 1; history of severe allergic or anaphylactic reactions or hypersensitivity to the study treatment or challenge agents, or excipients in the study treatments or challenge agents; planned use of any prescription or non-prescription drugs or dietary supplements that are prohibited from screening until all assessments on day 42 have been successfully completed; at or below the LLN of the reference range at screening for vitamin B12 (may re-screen in a minimum of 8 weeks); ferritin ≤ 50 mg/mL; TSAT ≤ 15%; folate < 2.0 ng/mL (may re-screen in a minimum of 8 weeks) at screening; High sensitivity CRP ≥ 50 µg/mL at screening; MI or acute coronary syndrome ≤ 12 weeks prior to screening and through day 1; hospitalisation for greater than 24 hours ≤ 12 weeks prior to screening and through day 1; stroke or TIA ≤ 12 weeks prior to screening and through day 1; NYHA class 4 heart failure; resting SBP > 180 mm Hg or DBP > 110 mm Hg at screening visit or current uncontrolled hypertension as determined by the investigator; QTcB > 500 msec, or QTcB >530 msec in participants with bundle branch block; active chronic inflammatory disease that could impact erythropoiesis; history of bone marrow aplasia or PRCA; conditions, other than anaemia of CKD, which can affect erythropoiesis; evidence of actively bleeding gastric, duodenal, or oesophageal ulcer disease or clinically significant GI bleeding from ≤ 8 weeks prior to screening and through day 1; ALT >2 times ULN (screening only); bilirubin >1.5 times ULN (screening only); isolated bilirubin >1.5 times ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%; current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); major surgery within the 12 weeks prior to screening and through day 1, or planned during the study; anticipated or planned vascular access surgery (e.g. AVF) within the 12 weeks prior to screening and through the day 42 assessments; received a tissue heart valve replacement or repair within the 6 months prior to screening or has received a mechanical heart valve replacement; blood transfusion within 6 weeks prior to screening and through day 1, or an

ASCEND-FBF 2018 *(Continued)*

	anticipated need for blood transfusion during the study; clinical evidence of an acute infection, or history of infection requiring IV antibiotic therapy from 8 weeks prior to screening and through day 1; history of malignancy within the 2 years prior to screening and through day 1 or currently receiving treatment for cancer, with the exception of localized squamous cell or basal cell carcinoma of the skin definitively treated 12 weeks prior to day 1; platelet count < 50,000/µL (history of a bleeding disorder (e.g. haemophilia); any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study • Target Hb: not reported • CKD stage: 50 patients with CKD stage 3, 4 or 5
Interventions	**Treatment group** • Daprodustat (oral): 2 mg once/day for 41 days **Control group** • Darbepoetin alfa (SC): once every 2 weeks (days 1, 14 and 28) **Co-interventions** • Acetylcholine will be used as a challenge agent and will be infused at 7.5, 15 and 30 µg/min each for 6 min/infusion into the brachial artery of the test arm • Sodium nitroprusside will be used as a challenge agent and will be infused at 3 and 10 µg/min each for 6 min/infusion into the brachial artery of the test arm • L-N-monomethyl arginine acetate will be used as a challenge agent and will be infused at a dose of 2 and 8 µmol/min for 6 minutes into the brachial artery of the test arm
Outcomes	**Primary outcome** • Change in FBF ratio from day 1 to day 42 in response to acetylcholine **Secondary outcomes** • Change in the absolute FBF from day 1 to day 42 in response to acetylcholine • Change in FBF ratio from day 1 to 42 in response to sodium nitroprusside • Change in the absolute FBF from day 1 to day 42 in response to sodium nitroprusside • Change in FBF ratio from day 1 to day 42 in response to L-N-monomethyl arginine acetate • Change in the absolute FBF from day 1 to day 42 in response to L-N-monomethyl arginine acetate • Change in FBF ratio in response to challenge agent at day 42 versus day 1 in participants treated with daprodustat • Change in the absolute FBF in response to challenge agent at day 42 versus day 1 in participants treated with daprodustat • Change in FBF ratio in response to challenge agent at day 42 versus day 1 in participants treated with darbepoetin alfa • Change in the absolute FBF in response to challenge agent at day 42 versus day 1 in participants treated with darbepoetin alfa • Change in augmentation index from day 1 to 42 • Change in pulse wave velocity from day 1 to day 42 • Number with any adverse events up to 59 days • Number with any adverse events by severity up to 59 days • Number with any serious adverse events up to 59 days • Number with any adverse events of special interest up to 59 days • Number discontinuing the randomised study treatment up to day 42 • Absolute values of SBP and DBP up to 59 days • Change from baseline in SBP and DBP up to day 59 • Absolute values of heart rate up to 59 days

ASCEND-FBF 2018 *(Continued)*

- Change from baseline in heart rate up to day 59
- Absolute values of ECG parameters - PR interval, QRS interval, and QT (uncorrected) interval and QTcB(up to 59 days
- Change from baseline in ECG parameters - PR interval, QRS duration, and QT (uncorrected) interval and QTcB up to day 59
- Absolute values in platelet count, WBC count (absolute), basophils, eosinophils, lymphocytes, monocytes and neutrophils up to 59 days
- Change from baseline in platelet count, WBC count (absolute), basophils, eosinophils, lymphocytes, monocytes and neutrophils up to day 59
- Absolute values of RBC count and reticulocyte count up to 59 days
- Change from baseline in RBC count and reticulocyte count up to day 59
- Absolute values of Hb and mean corpuscle Hb concentration up to 59 days
- Change from baseline of Hb and mean corpuscle Hb concentration up to day 59
- Absolute values of HCT up to 59 days
- Absolute values of HCT up to 59 days
- Absolute values of RBC distribution width up to 59 days
- Change from baseline in RBC distribution width up to day 59
- Absolute values of mean corpuscular Hb up to 59 days
- Change from baseline in mean corpuscular Hb up to day 59
- Absolute values of mean corpuscular volume up to 59 days
- Change from baseline of mean corpuscular volume up to day 59
- Absolute values of sodium, potassium, carbon-dioxide (total), chloride, glucose and urea Up to 59 days
- Change from baseline in sodium, potassium, carbon-dioxide (total), chloride, glucose and urea up to day 59
- Absolute values of creatinine and bilirubin (direct/indirect and total) up to 59 days
- Change from baseline of creatinine and bilirubin (direct/indirect and total) up to day 59
- Absolute values ALT, ALP and AST up to 59 days
- Change from baseline in ALT, ALP and AST up to day 59
- Absolute values of albumin up to 59 days
- Change from baseline of albumin up to day 59

Starting date	January 2019
Contact information	GSKClinicalSupportHD@gsk.com [mailto:GSKClinicalSupportHD%40gsk.com?subject=NCT03446612, 205767, Anemia Study in Chronic Kidney Disease (CKD) : Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat -Forearm Blood Flow (ASCEND-FBF)]
Notes	• Study completion status: recruiting • Funding: GlaxoSmithKline

CTRI/2019/06/019635

Study name	Desidustat in the treatment of anaemia in chronic kidney disease (CKD)
Methods	• Study design: parallel RCT • Expected duration of follow-up: 24 weeks
Participants	**General information** • Setting: multicentre • Country: international

CTRI/2019/06/019635 *(Continued)*

- Inclusion criteria: current clinical diagnosis of anaemia due to CKD, baseline Hb concentrations must be 7.0 to 10.0 g/dL (both inclusive) before the enrolment; ability to understand and give informed consent for participation; male or female patients diagnosed with CKD (stage III to V, not receiving dialysis) defined by eGFR using the CKD Epidemiology Collaboration (CKD-EPI) formula; aged 18 to 80 years; body weight > 40 kg; not on dialysis and not expected to start dialysis during the study period; not be treated with ESA therapy within 6 weeks prior to enrolment; eGFR < 10 mL/min/1.73 m^2, serum ferritin <100 ng/mL and/or TSAT > 20%, no iron, folate or vitamin B12 deficiency; females of childbearing potential, must agree to use one of the approved contraception methods, from screening until completion of the follow-up visit
- Exclusion criteria: prior chronic HD or chronic PD treatment; IV iron within 14 days prior to enrolment; prior exposure of RhuEPO analogues less than 4 weeks; RBC transfusion within 8 weeks prior to enrolment; history of previous or concurrent cancer; serologic status reflecting active hepatitis B or C infection or HIV infection; active infection prior to enrolment; history of kidney transplant; major surgery within 90 days of the first day of study drug dosing, and minor surgery within 30 days of the first day of study drug dosing; unable to swallow tablets or disease significantly affecting GI function and/or inhibiting small intestine absorption such as malabsorption syndrome, resection of the small bowel or poorly controlled inflammatory bowel disease affecting the small intestine
- History of uncontrolled autoimmune haemolytic anaemia, ITP or thalassaemia
- Target Hb: not reported
- CKD stage: 588 patients with CKD stages 3, 4, or 5

Interventions	**Treatment group** • Desidustat (oral): 100 mg 3 times/week **Control group** • Darbepoetin (IV or SC): 0.75 µg/kg once every 2 weeks **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Change in Hb levels at week 16 and 24 **Secondary outcomes** • Percentage of time spent in target Hb range up to week 24 • Change in hepcidin • Change in QoL by SF-36 at week 12 and 24
Starting date	June 2019
Contact information	kevinkumar.kansagra@zyduscadila.com
Notes	• Study completion status: approved • Funding: Cadila Healthcare Ltd

DREAM-D 2019

Study name	Desidustat in the treatment of anaemia in CKD
Methods	• Study design: parallel RCT • Expected duration of follow-up: 24 weeks

DREAM-D 2019 *(Continued)*

Participants	**General information** • Setting: multicentre • Country: international • Inclusion criteria: ability to understand and give informed consent for participation; male or female patients diagnosed with CKD, stage V-D (dialysis) and ≥18 years at screening visit; Hb values during the screening period must be 8 to 11 g/dL; patients will be considered not treated with EPO analogue (epoetin and darbepoetin) if they have not received EPO analogue for at least 4 weeks and Mircera for at least 8 weeks prior to screening visit OR patients who are on ESA therapy must be on stable dose for 4 weeks prior to enrolment (30% of dose change); patients on HD (at least 2 times/week) for at least 12 weeks prior to screening visit and have access consisting of an AVF, AV graft, or catheter (permanent/temporary); patients with no planned change in dialysis modality and with no planned kidney transplant during study period; left ventricular ejection fraction 40% by ECG prior to randomisation; adequate serum ferritin ≥ 200 ng/mL and/or TSAT > 20%; no iron, folate or Vitamin B12 deficiency; females of childbearing potential, must agree to use one of the approved contraception methods, from screening until completion of the follow-up visit • Exclusion criteria: RBC transfusion within 8 weeks prior to participating in the study; history of previous or concurrent cancer; serologic status reflecting active hepatitis B or C infection or HIV infection; active infection at initiation of study; history of kidney transplant; uncontrolled hypertension (defined as SBP > 180 mm Hg or DBP > 100 mm Hg) at screening visit (before dialysis); on high rHuEPO dose at screening visit; major surgery within 90 days of the first day of study drug dosing, and minor surgery within 30 days of the first day of study drug dosing; unable to swallow tablets or disease significantly affecting GI function and/or inhibiting small intestine absorption such as malabsorption syndrome, resection of the small bowel or poorly controlled inflammatory bowel disease affecting the small intestine; history of uncontrolled autoimmune haemolytic anaemia, ITP or thalassaemia; presence or a history of bleeding disorders or clinical conditions (e.g. GI bleeding or constitutional disorders) that may increase risk of life-threatening bleeding; history of stroke or intracranial haemorrhage within 6 months prior to enrolment; history of allergic reactions attributed to compounds of similar chemical or biologic composition to desidustat or epoetin alfa or to any erythropoiesis-stimulating agent; pregnant and breastfeeding women • Target Hb: not reported • CKD stage: stage 5D
Interventions	**Treatment group** • Desidustat (oral): 100 mg as a starting dose 3 times/week for 24 weeks **Control group** • Epoetin alfa (SC): 50 IU/Kg as a starting dose, 2 or 3 times/week for 24 weeks **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Change in Hb levels at weeks 12 and 24 **Secondary outcomes** • No Hb responders at weeks 12 and 24 • Percentage of time spent in target Hb range at weeks 12 and 24 • Time to achieve target range Hb level at weeks 12 and 24
Starting date	December 2019
Contact information	kevinkumarkansagra@zyduscadila.com
Notes	• Study completion status: open to recruitment

DREAM-D 2019 *(Continued)*

- Funding: Cadila Healthcare Ltd

NCT04027517

Study name	A study to evaluate efficacy and safety of JTZ-951 compared to darbepoetin alfa in Korean renal anemia patients receiving hemodialysis
Methods	• Study design: parallel RCT • Expected duration of follow-up: 30 weeks
Participants	**General information** • Setting: not reported • Country: Korea • Inclusion criteria: Korean patients aged ≥ 19 years at the time of consent; receiving HD (including HDF) consistently 3 times/week for at least 12 weeks before screening visit 1; TSAT > 20% or ferritin > 75 ng/mL; being treated with ESAs for at least 4 weeks before visit 1; receiving ESAs at protocol specified dose regimen (i.e. frequency and dose); have received the same ESA received in most recent week before visit 1 as during the period between visit 1 and the day before week 0 at the same total dose and dosing frequency 4 times/week; pre-dialysis Hb levels measured after the maximum interdialytic interval at visit 1 and visit 2 (2 weeks after visit 1) of ≥ 9.5 g/dL and < 12.0 g/dL and a difference (in absolute value) between the 2 visits of ≤1.0 g/dL • Exclusion criteria: poorly controlled hypertension; severe hepatobiliary disease; congestive heart failure NYHA Class III or more or unstable angina; developed MI, cerebral infarction (excluding asymptomatic cerebral infarction), or venous thromboembolism (pulmonary embolism or DVT) during the period between 24 weeks before visit 1 and week 0; will undergo an ophthalmological procedure (photocoagulation therapy or vitreous surgery) for the treatment of diabetic retinopathy, diabetic macular oedema, or age-related macular degeneration during the period between visit 1 and the end of the study; undergone RBC transfusion during the period between 12 weeks before visit 1 and week 0; received protein anabolic hormones, testosterone enanthate, or mepitiostane during the period between 12 weeks before visit 1 and week 0; severe hyperparathyroidism; severe infection, systemic blood disorder (e.g. myelodysplastic syndrome, aplastic anaemia, abnormal Hb disease), or haemolytic anaemia, or patients with anaemia caused by obvious bleeding lesions (e.g. GI haemorrhage); suspected to have anaemia caused by non-infectious chronic inflammatory disease (e.g. connective tissue disease); malignancy (including haematological malignancy) or previous history of malignancy during the period between 5 years before visit 1 and week 0; previous history of a serious drug allergy such as anaphylactic shock or a hypersensitivity to darbepoetin alfa; current or previous history of drug dependence or alcohol dependence; received another investigational product or have received treatment with an investigational device, or have participated in clinical research involving intervention (medical action beyond the scope of ordinary medical practice intended for research purposes) and received treatment within 12 weeks before visit 1; previously participated in a clinical study of JTZ-951 and received the investigational product; pregnant, lactating, or may be pregnant; female patients of childbearing potential who have not agreed to use appropriate contraception methods (medically accepted contraceptive methods: surgical sterilization, intrauterine device, condom, diaphragm, etc.) from the time of signing of informed consent to the end of the study, or male patients who have not agreed to use appropriate contraception methods from the start of study treatment to the end of the study; other patients who, in the judgment of the PI or the SI, are ineligible for the study • Target Hb: not reported • CKD stage: HD
Interventions	**Treatment group** • Enarodustat (JTZ-951) (oral): dose adjustments as maintenance dose is allowed according to the result of Hb level

NCT04027517 *(Continued)*

	Control group • Darbepoetin alfa (IV): dose adjustments as maintenance dose is allowed according to the result of Hb level **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Difference in mean Hb level change during the evaluation period from baseline between study arm and control arm (weeks 20 to 24) **Secondary outcomes** • Difference in mean Hb level between study arm and control arm during the evaluation period (baseline and weeks 20 to 24) • Proportion with Hb level within the range of baseline ± 1.0 g/dL at week 4 • Proportion with mean Hb level of ≥ 10.0 g/dL and < 12.0 g/dL during the evaluation period (weeks 20, 22, 24) • Hb level at each visit (weeks 2, 4, 8, 12, 16, 20, 22, 24) • Change from baseline in Hb level at each visit (weeks 0, 2, 4, 8, 12, 16, 20, 22, 24)
Starting date	January 2019
Contact information	cslimjy@gmail.com [mailto:cslimjy%40gmail.com?subject=NCT04027517, JWP-JTZ-301, A Study to Evaluate Efficacy and Safety of JTZ-951 Compared to Darbepoetin Alfa in Korean Renal Anemia Patients Receiving Hemodialysis.]
Notes	• Study completion status: recruiting • Funding: JW Pharmaceutical

NCT04134026

Study name	Evaluate the efficacy and safety of roxadustat for the treatment of anemia and risks of cardiovascular and cerebrovascular events in ESRD newly initiated dialysis patients
Methods	• Study design: parallel RCT • Expected duration of follow-up: minimum of 52 weeks and a maximum of approximately up to 3 years
Participants	**General information** • Setting: multicentre • Country: China • Inclusion criteria: patient or his/her legal guardian signs the informed consent; ≥18 years; weight 45 to 100 kg; kidney failure receiving HD treatment ≤ 4 weeks, dialysis frequency was stable, Kt/V urea ≥ 1.2, and planned to continue dialysis treatment during the study period; no iron deficiency; no folate or vitamin B12 deficiency; no abnormal liver tests; during the screening period, value of Hb is < 10.0 g/dL • Exclusion criteria: evidence of any clinically significant infection or active potential infection; active hepatitis or any of the following abnormalities (ALT ≥ 2 times ULN value, AST ≥ 2 times ULN value, direct bilirubin ≥ 2 times ULN); severe CV disease have had MI, coronary artery bypass or percutaneous coronary intervention operation within 3 months prior to participating in the study; have experienced severe cerebrovascular diseases within 3 months prior to participating in the study (stroke; obvious neurological dysfunction after stroke); active GI bleeding occurred

NCT04134026 *(Continued)*

	within 3 months prior to participating in the study; poor control of hypertension determined by the researchers; previous or current malignancies (except for excised non-melanoma skin cancer and carcinoma in situ); known to have blood system diseases (including congenital and postnatal diseases, such as thalassaemia, Fanconi anaemia, aplastic anaemia, myelodysplastic syndrome, haemolytic anaemia, coagulation dysfunction) or other causes of anaemia (e.g. faecal occult blood positive GI haemorrhage or hookworm disease); known autoimmune diseases (e.g. rheumatoid arthritis, SLE, anti-neutrophil cytoplasmic antibody associated vasculitis); any previous functional organ transplant or scheduled organ transplant or no kidney; elective surgery that is expected to result in significant blood loss during the study period; serum albumin < 25 g/L; treated with androgen, deferoxamine, deferrone or deferestrol within 8 weeks before administration on the first day; life expectancy < 12 months; transfusion within 4 weeks before administration on day 1, or is expected; IV iron supplementation and/or unwillingness to stop IV iron injection during the screening period; drug abuse or addiction; received any test drug within 4 weeks before inclusion or plan to receive other drug tests during the trial; women who can become pregnant must use contraception; men with sexual partners who can become pregnant must use birth control, unless the man agrees to use contraception; any medical condition, that in the opinion of the study doctor, may pose a safety risk to the patient, may confound efficacy or safety assessment, or may interfere with study participation • Target Hb: not reported • CKD stage: HD
Interventions	**Treatment group** • Roxadustat (FG-4592) (oral): 3 times/week **Control group** • Epoetin alfa **Co-interventions** • Not reported
Outcomes	**Primary outcomes** • Mean Hb change from baseline to average levels from week 28 to week 52 • Proportion who achieve a Hb response during the first 24 weeks of treatment • The incidence of CV and cerebrovascular events within 52 weeks **Secondary outcomes** • Death (any cause) from week 52 up to 3 years after last subject is randomised • BP effect 1: the proportion of subjects with increased hypertension to week 27 • BP effect 2: the proportion of subjects with increased hypertension from week 28 to week 52 • Change of left ventricular structure (weeks 12, 36, 52) • Change of left ventricular systolic function (weeks 12, 36, 52) • Change of right ventricular systolic function (weeks 12, 36, 52) • Systolic lateral tricuspid annulus velocity (S') was measured by tissue Doppler • Change of diastolic function (weeks 12, 36, 52) • Serum lipid parameters (weeks 25 to 27) • Inflammatory evaluation 1 (weeks 25 to 27) • Inflammatory evaluation 2 (weeks 25 to 27) • Inflammatory evaluation 3 (weeks 25 to 27) • Inflammatory evaluation 4 (weeks 25 to 27) • Serum iron level (weeks 0 to 27)
Starting date	October 2019

NCT04134026 *(Continued)*

Contact information	liuh0618@163.com [mailto:liuh0618%40163.com?subject=NCT04134026, CSU-SXH-CT-2019-015, Evaluate the Efficacy and Safety of Roxadustat for the Treatment of Anemia and Risks of Cardiovascular and Cerebrovascular Events in ESRD Newly Initiated Dialysis Patients]
Notes	• Study completion status: recruiting • Funding: Second Xiangya Hospital of Central South University

NCT04313153

Study name	Trial evaluating the efficacy and safety of oral vadadustat once daily (QD) and three times weekly (TIW) for the maintenance treatment of anemia in hemodialysis subjects converting from erythropoiesis-stimulating agents (ESAs)
Methods	• Study design: parallel RCT • Expected duration of follow-up: 64 weeks
Participants	**General information** • Setting: multicentre (76 sites) • Country: multinational (Belgium, Czech Republic, Hungary, Italy, Poland, Spain, USA) • Inclusion criteria: Receiving chronic, outpatient 3 times/week in-centre HD for kidney failure for at least 12 weeks prior to screening; HD adequacy as indicated by single-pool Kt/V urea ≥ 1.2 using the most recent historical measurement within 8 weeks prior to or during screening; use of any approved ESA for at least the 8 weeks prior to screening visit 2; 2 Hb values, at least 4 days apart, within the following prespecified ranges: 1) Hb values between 8.0 and 11.0 g/dL (inclusive) in the USA; 2)Hb values between 9.0 and 12.0 g/dL (inclusive) in Europe; serum ferritin ≥ 100 ng/mL and TSAT ≥ 20% during screening; folate and vitamin B12 measurements ≥ LLN during screening • Exclusion criteria: women of childbearing potential who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of investigational medicinal product, if employing birth control, 2 of the following precautions must be used: vasectomy of partner, tubal ligation, vaginal diaphragm, intrauterine device, or birth control; male participants who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat; women who are breast feeding and/or who have a positive pregnancy test result; contraindication to required trial assessment; in opinion of the investigator or medical monitor, have a medical history or medical findings inconsistent with safety or trial compliance; anaemia due to a cause other than CKD (e.g. sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, haematologic malignancy, myeloma, haemolytic anaemia, thalassaemia, or PRCA); meeting cut-off of the following equivalent mean weekly doses calculated over 8 weeks prior to screening visit 2' methoxy polyethylene glycol-epoetin beta > 50 µg/week; darbepoetin alfa > 100 µg/week; epoetin analogues > 23,000 IU/week; active bleeding or recent blood loss within 8 weeks prior to randomisation; RBC transfusion within 8 weeks prior to randomisation; anticipated to discontinue HD during the trial; judged by the investigator that the participant is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrolment in the trial; history of chronic liver disease (e.g. chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver); AST/(SGOT), ALT/SGPT, or total bilirubin > 1.5 times ULN during screening; current uncontrolled hypertension as determined by the investigator that would contraindicate the use of an ESA; acute coronary syndrome (hospitalisation for unstable angina or MI), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalisation for heart failure or NYHA class IV heart failure, or stroke within 12 weeks prior to or during screening; history of new or recurrent malignancy within 2 years prior to and during screening or currently receiving treatment or suppressive therapy for cancer (treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded); history of a new or recurrent episode of DVT or pulmonary embolism within 12 weeks prior to or during screening; history of haemosiderosis or haemochro-

NCT04313153 *(Continued)*

	matosis; history of prior organ transplantation (participants with a history of failed kidney transplant or corneal transplants are not excluded); scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months; history of a prior haematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded); known hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients; use of an investigational medication within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to screening or during screening and any prior use of a HIF-PHI; may participate in another concurrent trial only if that trial is a non-interventional, observational investigation; bilateral native nephrectomy; treated with probenecid within the 28-day screening period prior to randomisation or during the study treatment duration; any other reason, which in the opinion of the investigator, would make the participant not suitable for participation in the trial • Target Hb: not reported • CKD stage: HD
Interventions	**Treatment group 1** • Vadadustat (oral): once/day **Treatment group 2** • Vadadustat (oral): 3 times/week **Control group** • Darbepoetin alfa (IV or SC) **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Change in Hb between baseline and the primary evaluation period (weeks 20 to 26) **Secondary outcome** • Change in Hb value between baseline and the secondary evaluation period (weeks 46 to 52)
Starting date	May 2020
Contact information	trials@akebia.com
Notes	• Study completion status: recruiting • Funding: Akebia Therapeutics, Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)

PER-038-14

Study name	A phase 3, multicenter, randomized, open-label active-controlled study of the efficacy and safety of FG-4592 in the treatment of anaemia in incident-dialysis patients
Methods	• Study design: parallel RCT • Expected duration of follow-up: 48 months
Participants	**General information** • Setting: multicentre

PER-038-14 *(Continued)*

- Country: multinational (South Korea, Thailand, Bulgaria, Poland, Ukraine, Chile, Philippines, Taiwan, Estonia, Romania, Australia; Colombia, Malaysia, Belarus, Latvia, Russia, Argentina, Mexico)
- Inclusion criteria: ≥ 18 years; been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines; receiving HD or PD for native kidney failure for a minimum of 2 weeks and a maximum of 4 months, prior to randomisation; HD access consisting of an AVF, AV graft, or tunnelled (permanent) catheter, or PD catheter in use; mean of the 3 most recent Hb values during the screening period, obtained at least 4 days apart, must be ≤ 10.0 g/dL, with a difference of ≤ 1.3 g/dL between the highest and the lowest values, the last Hb value must be drawn within 10 days prior to randomisation; ferritin ≥ 50 ng/mL; TSAT ≥ 10%; serum folate level, performed within 8 weeks prior to randomisation ≥ LLN; serum vitamin B12 level, performed within 8 weeks prior to randomisation ≥ LLN; ALT or AST ≤ 3 times ULN, and total bilirubin < 1.5 times ULN; body weight 45 to 160 kg (dry weight)
- Exclusion criteria: any ESA treatment within 12 weeks prior to randomisation; more than one dose of IV iron within 4 weeks prior to randomisation; RBC transfusion within 8 weeks prior to randomisation; active, clinically significant infection that could be manifested by WBC count > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection; history of chronic liver disease (e.g. chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver); NYHA class III or IV congestive heart failure; MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event (e.g. DVT or pulmonary embolism) within 12 weeks prior to randomisation; uncontrolled hypertension, in the opinion of the investigator, (e.g. that requires change in anti-hypertensive medication) within 2 weeks prior to randomisation; kidney ultrasound performed within 12 weeks prior to randomisation indicative of a diagnosis or suspicion of renal cell carcinoma; history of malignancy, except for cancers determined to be cured or in remission for ≥ 5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps; positive for HIV, HBsAg, or Anti-HCV Ab; chronic inflammatory disease that could impact erythropoiesis (e.g. SLE, rheumatoid arthritis, coeliac disease) even if it is currently in remission; known, untreated proliferatives diabetic retinopathy, diabetic macular oedema, macular degeneration, or retinal vein occlusion; known history of myelodysplastic syndrome or multiple myeloma; known hereditary haematologic disease such as thalassaemia or sickle cell anaemia, PRCA, or other known causes for anaemia other than CKD; known haemosiderosis, haemochromatosis, coagulation disorder, or a hypercoagulable condition; any prior organ transplant (that has not been explanted), or a scheduled organ transplantation; anticipated elective surgery, except for vascular access surgery or dialysis catheter placement, that is expected to lead to significant blood loss, or anticipated elective coronary revascularization; known, active or chronic GI bleeding; any prior treatment with FG-4592 or a HIF-PHI; use of iron-chelating agents within 4 weeks prior to randomisation; known hypersensitivity reaction to any ESA; use of an investigational drug or treatment, participation in an investigational study, or presence of an expected carryover effect of an investigational treatment, within 4 weeks prior to randomisation; anticipated use of dapsone in any dose amount or chronic use of acetaminophen or paracetamol > 2.0 g/day during the treatment or follow-up periods of the study; history of alcohol or drug abuse within 2 years prior to randomisation; females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception; pregnant or breastfeeding females; any medical condition, that in the opinion of the investigator, may pose a safety risk to a subject in this study, may confound efficacy or safety assessment, or may interfere with study participation
- Target Hb: not reported
- CKD stage: HD and PD

Interventions

Treatment group 1

- Vadadustat (FG-4592) (oral): 20 mg; initial doses subjects will receive tiered, weight-based initial doses

Treatment group 2

- Vadadustat (FG-4592) (oral): 50 to 100 mg; initial doses subjects will receive tiered, weight-based initial doses

Treatment group 3

PER-038-14 *(Continued)*

	• Vadadustat (FG-4592) (oral): 100 mg initial doses subjects will receive tiered, weight-based initial doses **Control group** • Epoetin alfa **Co-interventions** • Not reported
Outcomes	**Primary outcomes** • Abnormal liver function test result **Secondary outcomes** • Liver function test • Repeat liver function test 2-3 times/week, then weekly or less until abnormalities stabilize or return to within normal limits. Liver function test should include the usual (ALT, AST, total bilirubin and ALP). If close monitoring for liver function test in a subject is not possible, study drug should be discontinued
Starting date	December 2014
Contact information	angela.flores@iconplc.com
Notes	• Study completion status: not reported • Funding: FibroGen

SLCTR-2019-032

Study name	A phase 3, multicenter, multi-country, open-label, randomized, active-controlled clinical trial to evaluate the efficacy and safety of desidustat versus darbepoetin for the treatment of anemia in patients with chronic kidney disease (CKD) who are not on dialysis
Methods	• Study design: parallel RCT • Expected duration of follow-up: up to 30 weeks (treatment period 24 weeks)
Participants	**General information** • Setting: multicentre • Country: multinational • Inclusion criteria: current clinical diagnosis of anaemia due to CKD with baseline Hb concentrations between 7.0 to 10.0 g/dL (both inclusive) before the enrolment; ability to understand and give informed consent for participation; male or female patients diagnosed with CKD (stage III to V, not receiving dialysis) defined by eGFR using the CKD-EPI formula; male or female, 18 to 80 years of age; body weight > 40 kg; not on dialysis and not expected to start dialysis during the study period; must not be treated with ESA therapy within 6 weeks prior to enrolment; eGFR > 10 mL/min/1.73 m^2; serum ferritin > 100 ng/mL and/or TSAT > 20%; no iron, folate or Vitamin B12 deficiency; females of childbearing potential, must agree to use one of the approved contraception methods, from screening until completion of the follow-up visit • Exclusion criteria: prior chronic HD or chronic PD treatment; intravenous iron within 14 days prior to enrolment; prior exposure of rHuEPO analogues less than 4 weeks; RBC transfusion within 8 weeks prior to enrolment; history of previous or concurrent cancer; serologic status reflecting active hepatitis B or C infection or HIV infection; active infection prior to enrolment; history of kidney transplant; major surgery within 90 days of the first day of study drug dosing, and minor surgery within 30 days of the first day of study drug dosing; unable to swallow tablets or dis-

SLCTR-2019-032 *(Continued)*

	ease significantly affecting GI function and/or inhibiting small intestine absorption such as; malabsorption syndrome, resection of the small bowel or poorly controlled inflammatory bowel disease affecting the small intestine; history of uncontrolled autoimmune haemolytic anaemia, ITP or thalassemias; presence or a history of bleeding disorders or clinical conditions (e.g. GI bleeding or constitutional disorders) that may increase risk of life-threatening bleeding; history of stroke or intracranial haemorrhage within 6 months prior to enrolment; history of severe allergic or hypersensitivity to investigational products and its excipients; requires or is receiving anticoagulation with warfarin or equivalent vitamin K antagonists or other medications within 28 days of the first dose of study drug that in the investigator's opinion, could compromise patient safety; pregnant and breastfeeding women; current life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety; other laboratory abnormalities that, in the opinion of the investigator, would compromise the patient's safety or interfere with data interpretation; presence of other systemic disorders or diseases (e.g. respiratory, GI, endocrine, immunological, dermatological, neurological, psychiatric disease or any other body system involvement) which, in the investigator's opinion, could compromise the patient's safety; history of significant alcoholism or drug abuse within the past 1 year; history or presence of significant smoking (> 10 cigarettes/day) or consumption of tobacco/nicotine products (> 10 times/day); history of difficulty with donating blood; history or presence of any clinically significant ECG abnormalities during screening; have participated in any drug research study other than the present trial within past 3 months; have donated one unit (350 mL) of blood in the past 3 months or history of whole blood transfusion in last 120 days prior to enrolment; history of chronic inflammatory disease (rheumatoid arthritis, coeliac disease, ulcerated colitis, Crohn's disease, SLE.); in DM patients HbA1c > 9%; in hypertensive patients, SBP and DBP is > 160 and 100 mm Hg respectively or uncontrolled BP; females with following criteria will not be eligible: 1) history of pregnancy or lactation in the past 3 months. 2) fertile females not protected against pregnancy by adequate long-term anti-fertility measures, 3) history of less than 1 year of menopause and not using adequate long-term anti fertility measures, 4) oral HRT, 5) positive serum hCG level at the screening visit; currently active clinically significant CV disease such as uncontrolled arrhythmia, congestive heart failure, any NYHA class 3 or 4 cardiac disease; history of MI in the past 6 months; WBC count < 3 x 10^3/µL; platelets count < 100 x 10^3/µL; bilirubin > 2.0 mg/dL; ALT and/or AST > 2.5 times ULN • Target Hb: not reported • CKD stage: CKD not on dialysis
Interventions	**Treatment group** • Desidustat (oral): 100 mg 3 times/week **Control group** • Darbepoetin alfa: initial dose 0.75 µg/kg **Co-interventions** • Not reported
Outcomes	**Primary outcome** • Mean change Hb at 24 weeks **Secondary outcomes** • Hb responders at 24 weeks • Time to achieve target range Hb level at 24 weeks • Serum hepcidin level at 24 weeks • Serum potassium at 24 weeks • QoL SF-36 at 24 weeks • Need to rescue therapy at 24 weeks • VEGF at 24 weeks • Lipids and lipoprotein at 24 weeks

SLCTR-2019-032 *(Continued)*	
Starting date	August 2018
Contact information	ercmed@kln.ac.lk
Notes	• Study completion status: Recruiting • Funding: Cadila Healthcare Ltd

ALP - alkaline phosphatase; ALT - alanine aminotransferase; AST - aspartate aminotransferase; AVF - arteriovenous fistula; BP - blood pressure; CKD - chronic kidney disease; CKD-EPI - CKD Epidemiology Collaboration; CRP - C-reactive protein; CV - cardiovascular; DBP - diastolic blood pressure; DVT - deep vein thrombosis; ECG - electrocardiogram; eGFR - estimated glomerular filtration rate; EPO - erythropoietin; ESA - erythropoietin-stimulating agent; FBF - forearm blood flow; GI - gastrointestinal; Hb - haemoglobin; HCT - hematocrit; HbA1c - haemoglobin A1c (glycated); HBsAg - hepatitis B surface antigen; HCV Ab - hepatitis C virus antibody; HD - haemodialysis; HDF - haemodiafiltration; HIF-PHI - Hypoxia-inducible factor prolyl hydroxylase inhibitor; HIV - human immunodeficiency virus; HRT - hormone replacement therapy; ITP - idiopathic thrombocytopenic purpura; IU - international units; IV - intravenous; KRT - kidney replacement therapy; LDL - low-dose lipoprotein; LLN - lower limit of normal; MI - myocardial infarction; NYHA - New York Heart Association; PD - peritoneal dialysis; PRCA - pure red cell aplasia; QoL - quality of life; QtcB - Bazett's corrected QT interval; RBC - red blood cell; RCT - randomised controlled trial; rHuEPO - recombinant human EPO; SBP - systolic blood pressure; SCr - serum creatinine; SGOT - serum glutamic oxaloacetic transaminase; SGPT - serum glutamic pyruvic transaminase; SLE - systemic lupus erythematosus; SC - subcutaneously; TCM - traditional Chinese medicine; TIA - transient Ischaemic attack; TSAT - transferrin saturation; ULN - upper limit of normal; VEGF - vascular endothelial growth factor; WBC - white blood cell

DATA AND ANALYSES

Comparison 1. Hypoxia-inducible factor (HIF) stabiliser versus placebo

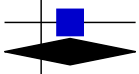
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cardiovascular death	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 Low-dose HIF	8	349	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.1.2 Medium-dose HIF	8	563	Risk Ratio (M-H, Random, 95% CI)	3.68 [0.19, 70.21]
1.1.3 High-dose HIF	9	508	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.1.4 Overall dose HIF	10	1114	Risk Ratio (M-H, Random, 95% CI)	3.68 [0.19, 70.21]
1.2 Death (any cause)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 Low-dose HIF	8	349	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2.2 Medium-dose HIF	10	3918	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.97, 1.30]
1.2.3 High-dose HIF	9	508	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2.4 Overall dose HIF	12	4469	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.97, 1.30]
1.3 Nonfatal myocardial infarction	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 Low-dose HIF	2	93	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3.2 Medium-dose HIF	3	707	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.32, 7.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.3 High-dose HIF	2	116	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.06, 34.46]
1.3.4 Overall dose HIF	3	822	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.31, 5.36]
1.4 Fatal or nonfatal myocardial infarction (overall)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Low-dose HIF	2	93	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4.2 Medium-dose HIF	5	4384	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.60, 1.96]
1.4.3 High-dose HIF	2	116	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.06, 34.46]
1.4.4 Overall dose HIF	5	4499	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.59, 1.90]
1.5 Nonfatal stroke	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 Low-dose HIF	2	93	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5.2 Medium-dose HIF	2	113	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5.3 High-dose HIF	2	116	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5.4 Overall dose HIF	2	228	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6 Fatal or nonfatal stroke (overall)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Low-dose HIF	2	93	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6.2 Medium-dose HIF	3	707	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.23, 18.46]
1.6.3 High-dose HIF	2	116	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6.4 Overall dose HIF	3	822	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.23, 18.46]
1.7 Peripheral arterial events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 Low-dose HIF	1	39	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.02, 8.10]
1.7.2 Medium-dose HIF	1	60	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.03, 7.59]
1.7.3 High-dose HIF	1	62	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 3.83]
1.7.4 Overall dose HIF	1	121	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.04]
1.8 Transfusion	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 Low-dose HIF	5	205	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.23, 2.79]
1.8.2 Medium-dose HIF	7	4077	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.38, 0.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.3 High-dose HIF	5	229	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.15, 2.21]
1.8.4 Overall dose HIF	8	4329	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.44, 0.60]
1.9 Proportion reaching target haemoglobin	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 Low-dose HIF	4	197	Risk Ratio (M-H, Random, 95% CI)	4.16 [2.28, 7.59]
1.9.2 Medium-dose HIF	8	4698	Risk Ratio (M-H, Random, 95% CI)	9.36 [8.06, 10.86]
1.9.3 High-dose HIF	5	351	Risk Ratio (M-H, Random, 95% CI)	7.16 [3.62, 14.14]
1.9.4 Overall dose HIF	10	5102	Risk Ratio (M-H, Random, 95% CI)	8.36 [6.42, 10.89]
1.10 Kidney failure	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 Low-dose HIF	4	191	Risk Ratio (M-H, Random, 95% CI)	2.12 [0.46, 9.82]
1.10.2 Medium-dose HIF	6	1855	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.94, 1.62]
1.10.3 High-dose HIF	5	324	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.43, 6.24]
1.10.4 Overall dose HIF	8	2228	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.98, 1.51]
1.11 Thrombosis	3	3452	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.19, 4.66]
1.11.1 Medium-dose HIF	3	3452	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.19, 4.66]
1.12 Loss of unassisted patency (stenosis)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.12.1 Low-dose HIF	1	30	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.12.2 Medium-dose HIF	2	127	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.16, 14.05]
1.12.3 High-dose HIF	1	30	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.26]
1.12.4 Overall dose HIF	2	157	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.13, 10.31]
1.13 Hyperkalaemia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.13.1 Low-dose HIF	2	99	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.21, 3.42]
1.13.2 Medium-dose HIF	5	4541	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.04, 1.56]
1.13.3 High-dose HIF	3	275	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.26, 3.84]
1.13.4 Overall dose HIF	7	4845	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.01, 1.64]

Analysis 1.1. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 1: Cardiovascular death

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Low-dose HIF						
NDD-CKD 2020	0	12	0	14		Not estimable
NDD-CKD 2020a	0	15	0	15		Not estimable
Besarab 2015	0	23	0	28		Not estimable
Brigandi 2016	0	36	0	15		Not estimable
Chen NDD 2017	0	30	0	30		Not estimable
DIALOGUE 1 2019	0	19	0	20		Not estimable
Akizawa 2017	0	19	0	19		Not estimable
Akizawa 2019	0	27	0	27		Not estimable
Subtotal (95% CI)		**181**		**168**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.2 Medium-dose HIF						
Akizawa 2019	0	26	0	27		Not estimable
NDD-CKD 2020	0	12	0	14		Not estimable
NDD-CKD 2020a	0	15	0	15		Not estimable
Akizawa 2017	0	39	0	19		Not estimable
Besarab 2015	0	42	0	28		Not estimable
Brigandi 2016	0	41	0	15		Not estimable
DIALOGUE 1 2019	0	40	0	20		Not estimable
Pergola 2016	3	138	0	72	100.0%	3.68 [0.19 , 70.21]
Subtotal (95% CI)		**353**		**210**	**100.0%**	**3.68 [0.19 , 70.21]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
1.1.3 High-dose HIF						
NDD-CKD 2020a	0	15	0	15		Not estimable
Akizawa 2017	0	20	0	19		Not estimable
Akizawa 2019	0	27	0	27		Not estimable
Besarab 2015	0	23	0	28		Not estimable
Chen NDD 2017	0	31	0	30		Not estimable
DIALOGUE 1 2019	0	42	0	20		Not estimable
Brigandi 2016	0	15	0	15		Not estimable
Chen 2019a	0	102	0	52		Not estimable
NDD-CKD 2020	0	13	0	14		Not estimable
Subtotal (95% CI)		**288**		**220**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.4 Overall dose HIF						
Akizawa 2017	0	78	0	19		Not estimable
NDD-CKD 2020	0	37	0	14		Not estimable
Chen 2019a	0	102	0	52		Not estimable
NDD-CKD 2020a	0	45	0	15		Not estimable
Akizawa 2019	0	80	0	27		Not estimable
Besarab 2015	0	88	0	28		Not estimable
Brigandi 2016	0	92	0	15		Not estimable
Chen NDD 2017	0	61	0	30		Not estimable
DIALOGUE 1 2019	0	101	0	20		Not estimable



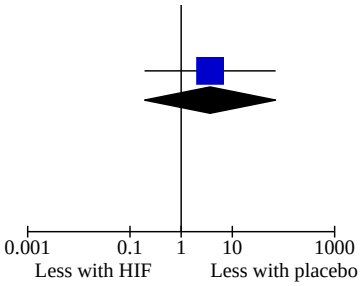
Analysis 1.1. (Continued)

Chen NDD 2017	0	61	0	30		Not estimable
DIALOGUE 1 2019	0	101	0	20		Not estimable
Pergola 2016	3	138	0	72	100.0%	3.68 [0.19 , 70.21]
Subtotal (95% CI)		**822**		**292**	**100.0%**	**3.68 [0.19 , 70.21]**
Total events:	3		0			

Heterogeneity: Not applicable

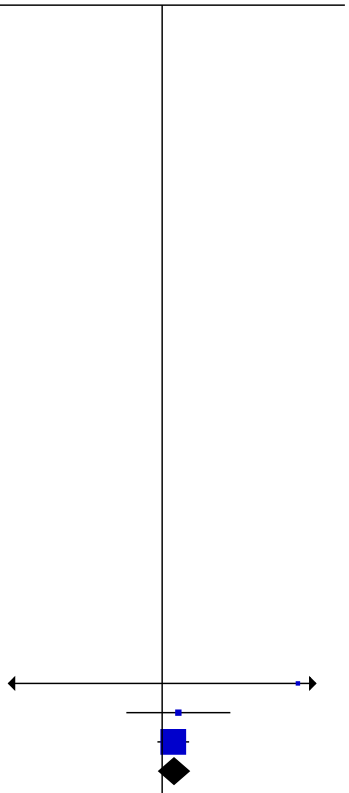
Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 1.00), $I^2 = 0\%$



Analysis 1.2. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 2: Death (any cause)

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Low-dose HIF						
NDD-CKD 2020	0	12	0	14		Not estimable
NDD-CKD 2020a	0	15	0	15		Not estimable
Besarab 2015	0	23	0	28		Not estimable
Brigandi 2016	0	36	0	15		Not estimable
Chen NDD 2017	0	30	0	30		Not estimable
DIALOGUE 1 2019	0	19	0	20		Not estimable
Akizawa 2017	0	19	0	19		Not estimable
Akizawa 2019	0	27	0	27		Not estimable
Subtotal (95% CI)		**181**		**168**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.2 Medium-dose HIF						
DIALOGUE 1 2019	0	40	0	20		Not estimable
Akizawa 2017	0	39	0	19		Not estimable
NDD-CKD 2020	0	12	0	14		Not estimable
NDD-CKD 2020a	0	15	0	15		Not estimable
Besarab 2015	0	42	0	28		Not estimable
Brigandi 2016	0	41	0	15		Not estimable
Akizawa 2019	0	26	0	27		Not estimable
Pergola 2016	3	138	0	72	0.2%	3.68 [0.19 , 70.21]
ALPS 2021	45	391	20	203	8.5%	1.17 [0.71 , 1.92]
OLYMPUS 2021	284	1384	254	1377	91.3%	1.11 [0.96 , 1.29]
Subtotal (95% CI)		**2128**		**1790**	**100.0%**	**1.12 [0.97 , 1.30]**
Total events:	332		274			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.66$, df = 2 (P = 0.72); $I^2 = 0\%$						
Test for overall effect: Z = 1.53 (P = 0.13)						
1.2.3 High-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
NDD-CKD 2020	0	13	0	14		Not estimable
NDD-CKD 2020a	0	15	0	15		Not estimable
Besarab 2015	0	23	0	28		Not estimable
Brigandi 2016	0	15	0	15		Not estimable
Chen NDD 2017	0	31	0	30		Not estimable
DIALOGUE 1 2019	0	42	0	20		Not estimable
Chen 2019a	0	102	0	52		Not estimable
Akizawa 2017	0	20	0	19		Not estimable
Subtotal (95% CI)		**288**		**220**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.4 Overall dose HIF						
Chen NDD 2017	0	61	0	30		Not estimable
Akizawa 2019	0	80	0	27		Not estimable
DIALOGUE 1 2019	0	101	0	20		Not estimable
Chen 2019a	0	102	0	52		Not estimable
NDD-CKD 2020	0	37	0	14		Not estimable
NDD-CKD 2020a	0	45	0	15		Not estimable
Besarab 2015	0	88	0	28		Not estimable



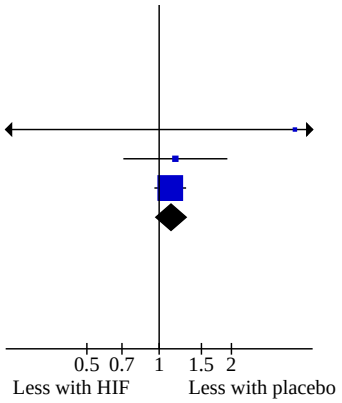
Analysis 1.2. (Continued)

NDD-CKD 2020a	0	45	0	15		Not estimable
Besarab 2015	0	88	0	28		Not estimable
Akizawa 2017	0	78	0	19		Not estimable
Brigandi 2016	0	92	0	15		Not estimable
Pergola 2016	3	138	0	72	0.2%	3.68 [0.19 , 70.21]
ALPS 2021	45	391	20	203	8.5%	1.17 [0.71 , 1.92]
OLYMPUS 2021	284	1384	254	1377	91.3%	1.11 [0.96 , 1.29]
Subtotal (95% CI)		**2597**		**1872**	**100.0%**	**1.12 [0.97 , 1.30]**
Total events:	332		274			

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%

Test for overall effect: Z = 1.53 (P = 0.13)

Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%



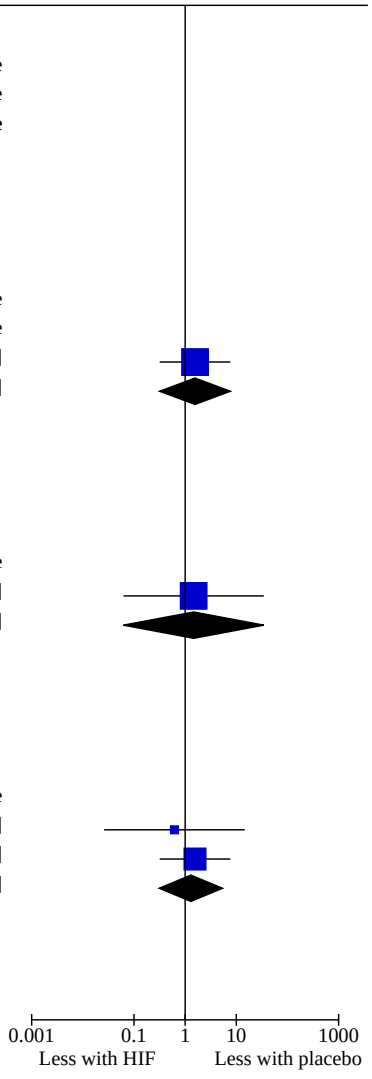
Analysis 1.3. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 3: Nonfatal myocardial infarction

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Low-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
DIALOGUE 1 2019	0	19	0	20		Not estimable
Subtotal (95% CI)		**46**		**47**		**Not estimable**
Total events:	0		0			
1.3.2 Medium-dose HIF						
Akizawa 2019	0	26	0	27		Not estimable
DIALOGUE 1 2019	0	40	0	20		Not estimable
ALPS 2021	6	391	2	203	100.0%	1.56 [0.32 , 7.65]
Subtotal (95% CI)		**457**		**250**	**100.0%**	**1.56 [0.32 , 7.65]**
Total events:	6		2			
1.3.3 High-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
DIALOGUE 1 2019	1	42	0	20	100.0%	1.47 [0.06 , 34.46]
Subtotal (95% CI)		**69**		**47**	**100.0%**	**1.47 [0.06 , 34.46]**
Total events:	1		0			
1.3.4 Overall dose HIF						
Akizawa 2019	0	80	0	27		Not estimable
DIALOGUE 1 2019	1	101	0	20	20.2%	0.62 [0.03 , 14.65]
ALPS 2021	6	391	2	203	79.8%	1.56 [0.32 , 7.65]
Subtotal (95% CI)		**572**		**250**	**100.0%**	**1.29 [0.31 , 5.36]**
Total events:	7		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

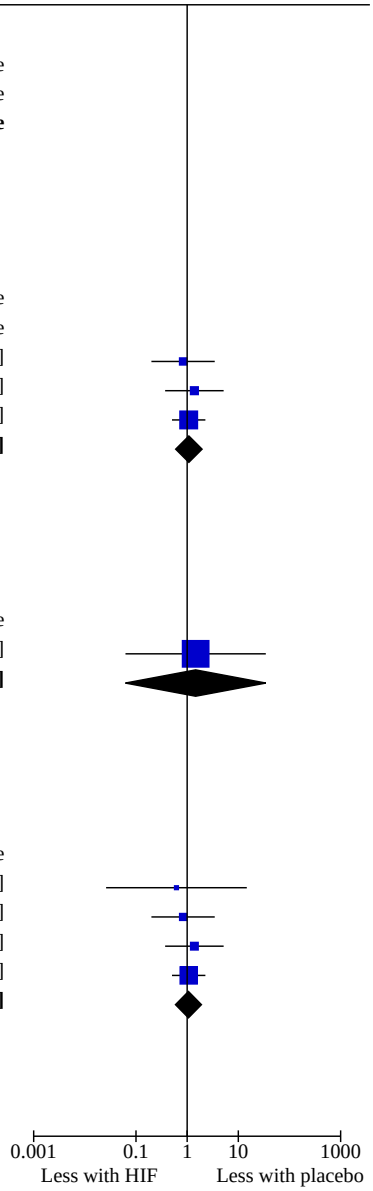
Test for overall effect: Z = 0.35 (P = 0.72)

Test for subgroup differences: Chi² = 0.03, df = 2 (P = 0.99), I² = 0%



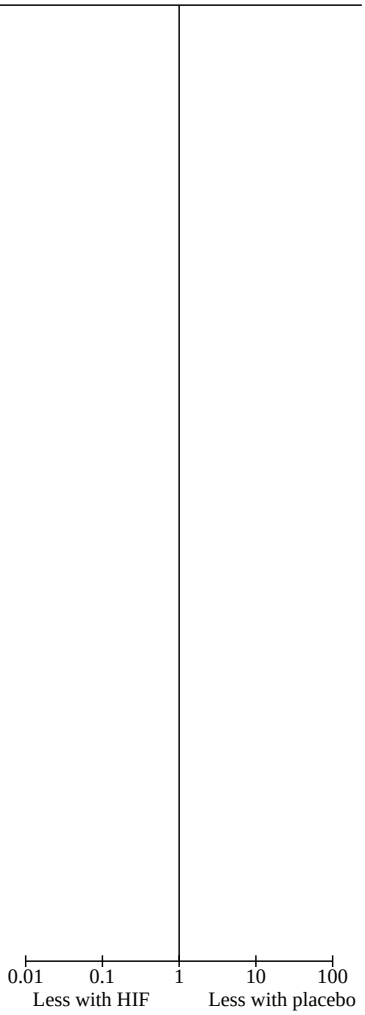
Analysis 1.4. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 4: Fatal or nonfatal myocardial infarction (overall)

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Low-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
DIALOGUE 1 2019	0	19	0	20		Not estimable
Subtotal (95% CI)		**46**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.2 Medium-dose HIF						
Akizawa 2019	0	26	0	27		Not estimable
DIALOGUE 1 2019	0	40	0	20		Not estimable
ANDES 2021	5	611	3	305	17.3%	0.83 [0.20 , 3.46]
ALPS 2021	8	391	3	203	20.3%	1.38 [0.37 , 5.16]
OLYMPUS 2021	14	1384	13	1377	62.4%	1.07 [0.51 , 2.27]
Subtotal (95% CI)		**2452**		**1932**	**100.0%**	**1.08 [0.60 , 1.96]**
Total events:	27		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
1.4.3 High-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
DIALOGUE 1 2019	1	42	0	20	100.0%	1.47 [0.06 , 34.46]
Subtotal (95% CI)		**69**		**47**	**100.0%**	**1.47 [0.06 , 34.46]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.4.4 Overall dose HIF						
Akizawa 2019	0	80	0	27		Not estimable
DIALOGUE 1 2019	1	101	0	20	3.4%	0.62 [0.03 , 14.65]
ANDES 2021	5	611	3	305	16.7%	0.83 [0.20 , 3.46]
ALPS 2021	8	391	3	203	19.6%	1.38 [0.37 , 5.16]
OLYMPUS 2021	14	1384	13	1377	60.2%	1.07 [0.51 , 2.27]
Subtotal (95% CI)		**2567**		**1932**	**100.0%**	**1.06 [0.59 , 1.90]**
Total events:	28		19			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 0.04, df = 2 (P = 0.98), I² = 0%						



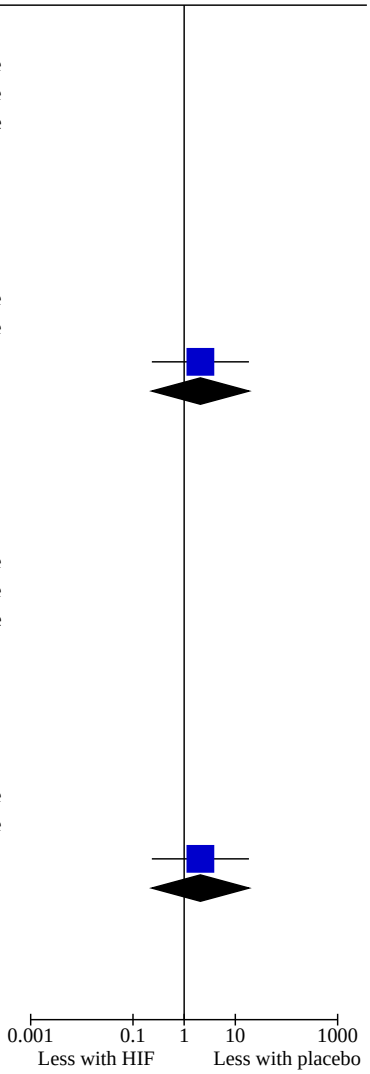
Analysis 1.5. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 5: Nonfatal stroke

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Low-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
DIALOGUE 1 2019	0	19	0	20		Not estimable
Subtotal (95% CI)		**46**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.2 Medium-dose HIF						
Akizawa 2019	0	26	0	27		Not estimable
DIALOGUE 1 2019	0	40	0	20		Not estimable
Subtotal (95% CI)		**66**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.3 High-dose HIF						
DIALOGUE 1 2019	0	42	0	20		Not estimable
Akizawa 2019	0	27	0	27		Not estimable
Subtotal (95% CI)		**69**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.4 Overall dose HIF						
Akizawa 2019	0	80	0	27		Not estimable
DIALOGUE 1 2019	0	101	0	20		Not estimable
Subtotal (95% CI)		**181**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

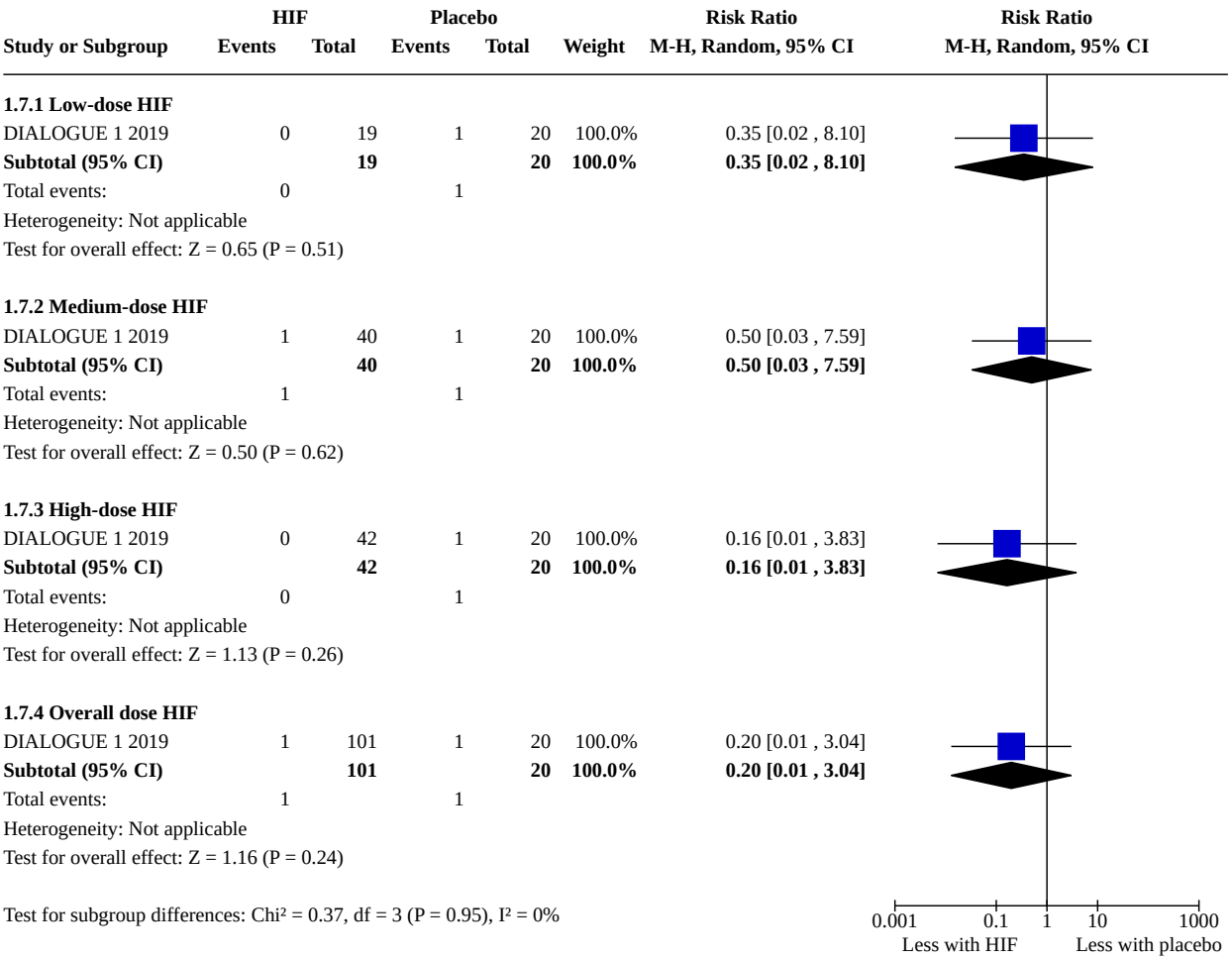


Analysis 1.6. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 6: Fatal or nonfatal stroke (overall)

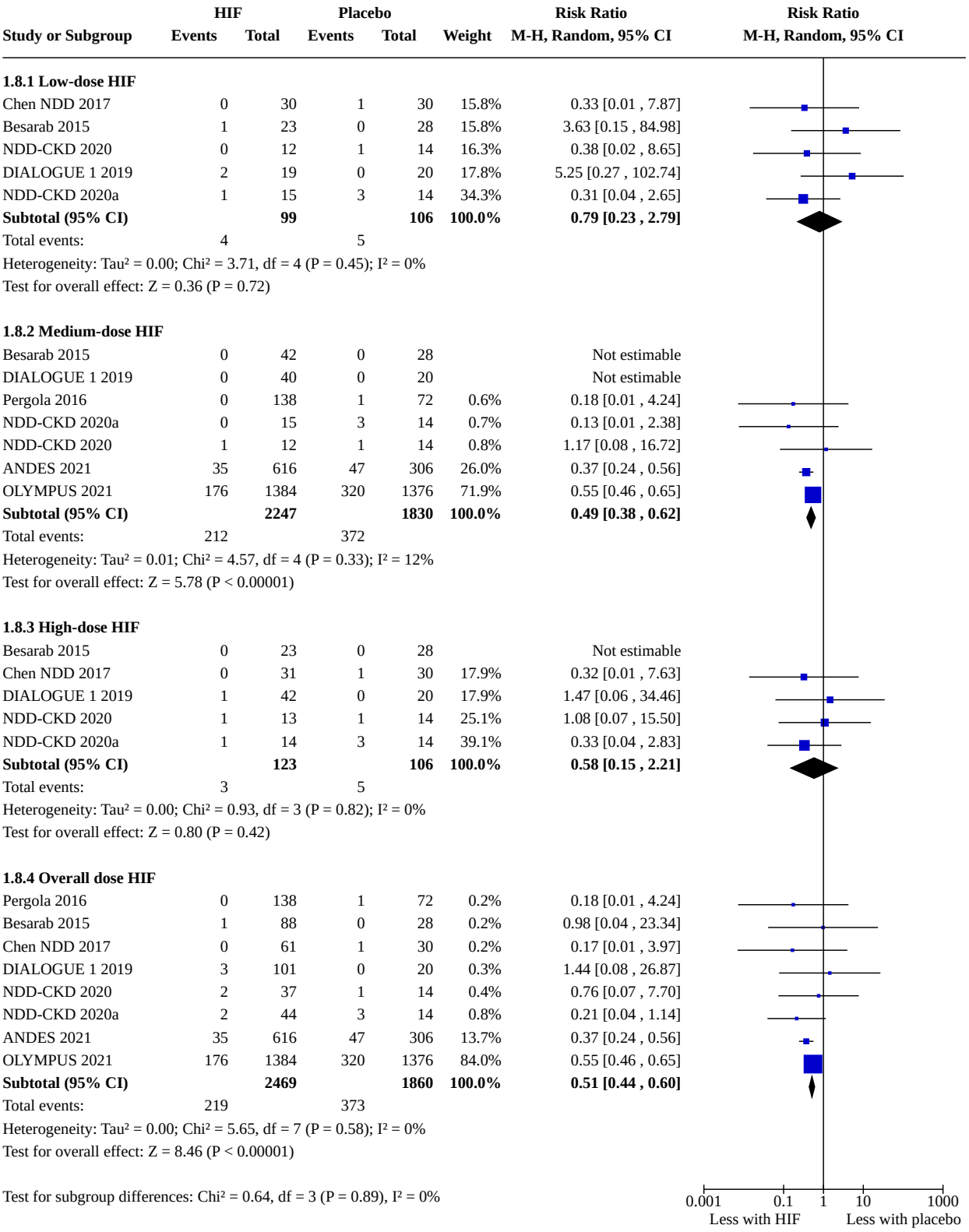
Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Low-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
DIALOGUE 1 2019	0	19	0	20		Not estimable
Subtotal (95% CI)		**46**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.2 Medium-dose HIF						
DIALOGUE 1 2019	0	40	0	20		Not estimable
Akizawa 2019	0	26	0	27		Not estimable
ALPS 2021	4	391	1	203	100.0%	2.08 [0.23 , 18.46]
Subtotal (95% CI)		**457**		**250**	**100.0%**	**2.08 [0.23 , 18.46]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.6.3 High-dose HIF						
Akizawa 2019	0	27	0	27		Not estimable
DIALOGUE 1 2019	0	42	0	20		Not estimable
Subtotal (95% CI)		**69**		**47**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.4 Overall dose HIF						
Akizawa 2019	0	80	0	27		Not estimable
DIALOGUE 1 2019	0	101	0	20		Not estimable
ALPS 2021	4	391	1	203	100.0%	2.08 [0.23 , 18.46]
Subtotal (95% CI)		**572**		**250**	**100.0%**	**2.08 [0.23 , 18.46]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 1.00), I^2 = 0%						



Analysis 1.7. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 7: Peripheral arterial events



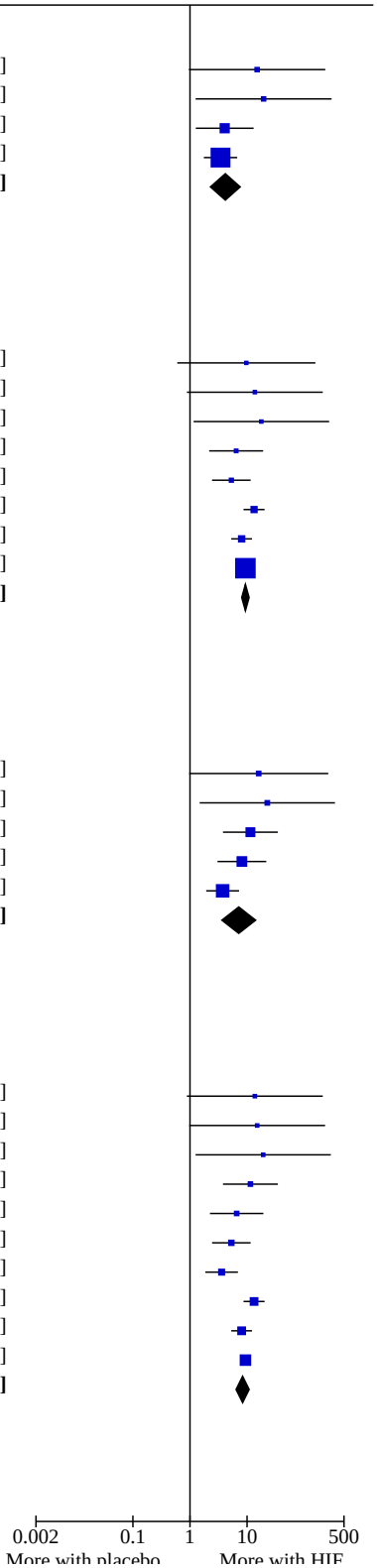
Analysis 1.8. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 8: Transfusion



Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Low-dose HIF						
Chen NDD 2017	0	30	1	30	15.8%	0.33 [0.01 , 7.87]
Besarab 2015	1	23	0	28	15.8%	3.63 [0.15 , 84.98]
NDD-CKD 2020	0	12	1	14	16.3%	0.38 [0.02 , 8.65]
DIALOGUE 1 2019	2	19	0	20	17.8%	5.25 [0.27 , 102.74]
NDD-CKD 2020a	1	15	3	14	34.3%	0.31 [0.04 , 2.65]
Subtotal (95% CI)		**99**		**106**	**100.0%**	**0.79 [0.23 , 2.79]**
Total events:	4		5			
Heterogeneity: Tau² = 0.00; Chi² = 3.71, df = 4 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.8.2 Medium-dose HIF						
Besarab 2015	0	42	0	28		Not estimable
DIALOGUE 1 2019	0	40	0	20		Not estimable
Pergola 2016	0	138	1	72	0.6%	0.18 [0.01 , 4.24]
NDD-CKD 2020a	0	15	3	14	0.7%	0.13 [0.01 , 2.38]
NDD-CKD 2020	1	12	1	14	0.8%	1.17 [0.08 , 16.72]
ANDES 2021	35	616	47	306	26.0%	0.37 [0.24 , 0.56]
OLYMPUS 2021	176	1384	320	1376	71.9%	0.55 [0.46 , 0.65]
Subtotal (95% CI)		**2247**		**1830**	**100.0%**	**0.49 [0.38 , 0.62]**
Total events:	212		372			
Heterogeneity: Tau² = 0.01; Chi² = 4.57, df = 4 (P = 0.33); I² = 12%						
Test for overall effect: Z = 5.78 (P < 0.00001)						
1.8.3 High-dose HIF						
Besarab 2015	0	23	0	28		Not estimable
Chen NDD 2017	0	31	1	30	17.9%	0.32 [0.01 , 7.63]
DIALOGUE 1 2019	1	42	0	20	17.9%	1.47 [0.06 , 34.46]
NDD-CKD 2020	1	13	1	14	25.1%	1.08 [0.07 , 15.50]
NDD-CKD 2020a	1	14	3	14	39.1%	0.33 [0.04 , 2.83]
Subtotal (95% CI)		**123**		**106**	**100.0%**	**0.58 [0.15 , 2.21]**
Total events:	3		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 3 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
1.8.4 Overall dose HIF						
Pergola 2016	0	138	1	72	0.2%	0.18 [0.01 , 4.24]
Besarab 2015	1	88	0	28	0.2%	0.98 [0.04 , 23.34]
Chen NDD 2017	0	61	1	30	0.2%	0.17 [0.01 , 3.97]
DIALOGUE 1 2019	3	101	0	20	0.3%	1.44 [0.08 , 26.87]
NDD-CKD 2020	2	37	1	14	0.4%	0.76 [0.07 , 7.70]
NDD-CKD 2020a	2	44	3	14	0.8%	0.21 [0.04 , 1.14]
ANDES 2021	35	616	47	306	13.7%	0.37 [0.24 , 0.56]
OLYMPUS 2021	176	1384	320	1376	84.0%	0.55 [0.46 , 0.65]
Subtotal (95% CI)		**2469**		**1860**	**100.0%**	**0.51 [0.44 , 0.60]**
Total events:	219		373			
Heterogeneity: Tau² = 0.00; Chi² = 5.65, df = 7 (P = 0.58); I² = 0%						
Test for overall effect: Z = 8.46 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.64, df = 3 (P = 0.89), I² = 0%						

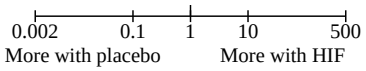
Analysis 1.9. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 9: Proportion reaching target haemoglobin

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Low-dose HIF						
Provenzano 2008	13	26	0	14	4.7%	15.00 [0.96 , 234.92]
Brigandi 2016	19	31	0	15	4.7%	19.50 [1.26 , 302.67]
Besarab 2015	10	23	3	28	24.8%	4.06 [1.26 , 13.03]
Chen NDD 2017	24	30	7	30	65.8%	3.43 [1.75 , 6.72]
Subtotal (95% CI)		**110**		**87**	**100.0%**	**4.16 [2.28 , 7.59]**
Total events:	66		10			
Heterogeneity: Tau² = 0.02; Chi² = 3.14, df = 3 (P = 0.37); I² = 5%						
Test for overall effect: Z = 4.65 (P < 0.00001)						
1.9.2 Medium-dose HIF						
Brigandi 2016	8	27	0	15	0.3%	9.71 [0.60 , 157.41]
Akizawa 2017	32	75	0	15	0.3%	13.68 [0.88 , 212.04]
Provenzano 2008	31	52	0	14	0.3%	17.83 [1.16 , 274.56]
Besarab 2015	29	42	3	28	1.9%	6.44 [2.17 , 19.13]
Pergola 2016	56	102	6	58	3.7%	5.31 [2.44 , 11.55]
ANDES 2021	530	611	20	306	12.3%	13.27 [8.68 , 20.30]
ALPS 2021	308	389	20	203	12.6%	8.04 [5.28 , 12.22]
OLYMPUS 2021	1055	1384	112	1377	68.6%	9.37 [7.83 , 11.22]
Subtotal (95% CI)		**2682**		**2016**	**100.0%**	**9.36 [8.06 , 10.86]**
Total events:	2049		161			
Heterogeneity: Tau² = 0.00; Chi² = 5.98, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 29.41 (P < 0.00001)						
1.9.3 High-dose HIF						
Brigandi 2016	4	8	0	15	5.4%	16.00 [0.97 , 264.51]
Provenzano 2008	38	50	0	14	5.7%	22.65 [1.48 , 347.14]
Chen 2019a	68	101	3	51	23.4%	11.45 [3.79 , 34.60]
Besarab 2015	23	23	3	28	26.9%	8.11 [3.03 , 21.71]
Chen NDD 2017	27	31	7	30	38.7%	3.73 [1.92 , 7.24]
Subtotal (95% CI)		**213**		**138**	**100.0%**	**7.16 [3.62 , 14.14]**
Total events:	160		13			
Heterogeneity: Tau² = 0.20; Chi² = 6.13, df = 4 (P = 0.19); I² = 35%						
Test for overall effect: Z = 5.66 (P < 0.00001)						
1.9.4 Overall dose HIF						
Akizawa 2017	32	75	0	15	0.9%	13.68 [0.88 , 212.04]
Brigandi 2016	31	66	0	15	0.9%	15.04 [0.97 , 232.99]
Provenzano 2008	82	128	0	14	0.9%	19.19 [1.25 , 293.68]
Chen 2019a	68	101	3	51	4.9%	11.45 [3.79 , 34.60]
Besarab 2015	62	88	3	28	5.1%	6.58 [2.24 , 19.32]
Pergola 2016	56	102	6	58	8.7%	5.31 [2.44 , 11.55]
Chen NDD 2017	51	61	7	30	11.1%	3.58 [1.86 , 6.92]
ANDES 2021	530	611	20	306	18.5%	13.27 [8.68 , 20.30]
ALPS 2021	308	389	20	203	18.7%	8.04 [5.28 , 12.22]
OLYMPUS 2021	1055	1384	112	1377	30.3%	9.37 [7.83 , 11.22]
Subtotal (95% CI)		**3005**		**2097**	**100.0%**	**8.36 [6.42 , 10.89]**
Total events:	2275		171			
Heterogeneity: Tau² = 0.05; Chi² = 14.31, df = 9 (P = 0.11); I² = 37%						
Test for overall effect: Z = 15.75 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.12, df = 3 (P = 0.07), I² = 57.9%						



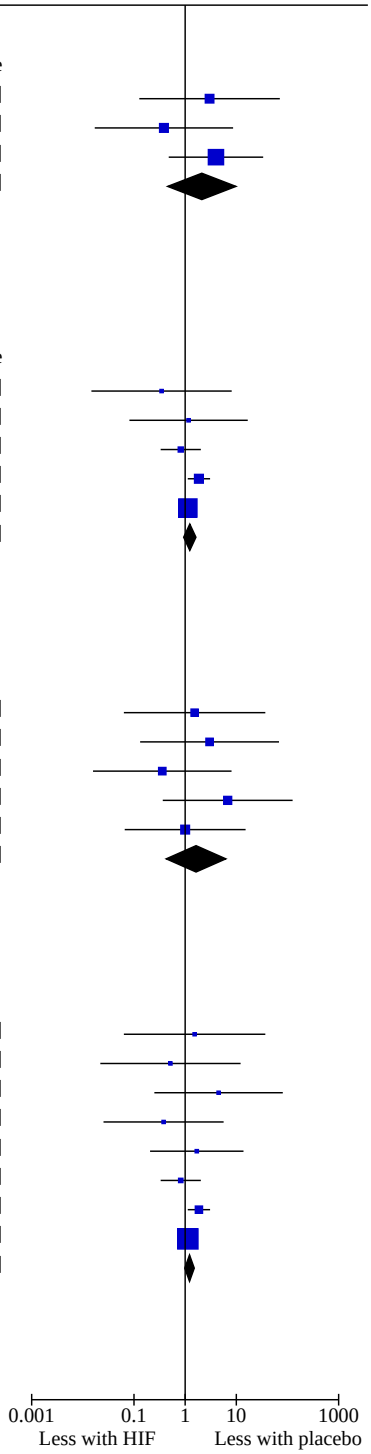
Analysis 1.9. (Continued)

Test for subgroup differences: Chi² = 7.12, df = 3 (P = 0.07), I² = 57.9%



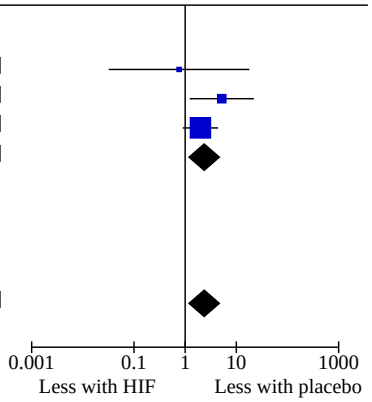
Analysis 1.10. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 10: Kidney failure

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Low-dose HIF						
Brigandi 2016	0	36	0	15		Not estimable
Chen NDD 2017	1	30	0	30	23.6%	3.00 [0.13 , 70.83]
NDD-CKD 2020	0	12	1	14	24.3%	0.38 [0.02 , 8.65]
Akizawa 2019	4	27	1	27	52.1%	4.00 [0.48 , 33.50]
Subtotal (95% CI)		**105**		**86**	**100.0%**	**2.12 [0.46 , 9.82]**
Total events:	5		2			
Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 2 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.10.2 Medium-dose HIF						
Brigandi 2016	0	41	0	15		Not estimable
Akizawa 2019	0	26	1	27	0.8%	0.35 [0.01 , 8.12]
NDD-CKD 2020	1	12	1	14	1.1%	1.17 [0.08 , 16.72]
Pergola 2016	11	138	7	72	8.7%	0.82 [0.33 , 2.02]
ANDES 2021	67	611	18	305	24.7%	1.86 [1.12 , 3.07]
ALPS 2021	135	391	62	203	64.8%	1.13 [0.88 , 1.45]
Subtotal (95% CI)		**1219**		**636**	**100.0%**	**1.23 [0.94 , 1.62]**
Total events:	214		89			
Heterogeneity: Tau² = 0.01; Chi² = 4.48, df = 4 (P = 0.34); I² = 11%						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.10.3 High-dose HIF						
Chen 2019a	1	101	0	51	17.7%	1.53 [0.06 , 36.89]
Brigandi 2016	1	15	0	15	18.4%	3.00 [0.13 , 68.26]
NDD-CKD 2020	0	13	1	14	18.5%	0.36 [0.02 , 8.06]
Chen NDD 2017	3	31	0	30	21.1%	6.78 [0.37 , 125.95]
Akizawa 2019	1	27	1	27	24.3%	1.00 [0.07 , 15.18]
Subtotal (95% CI)		**187**		**137**	**100.0%**	**1.63 [0.43 , 6.24]**
Total events:	6		2			
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						
1.10.4 Overall dose HIF						
Chen 2019a	1	101	0	51	0.4%	1.53 [0.06 , 36.89]
Brigandi 2016	1	92	0	15	0.5%	0.52 [0.02 , 12.12]
Chen NDD 2017	4	61	0	30	0.5%	4.50 [0.25 , 80.95]
NDD-CKD 2020	1	37	1	14	0.6%	0.38 [0.03 , 5.65]
Akizawa 2019	5	80	1	27	1.0%	1.69 [0.21 , 13.81]
Pergola 2016	11	138	7	72	5.5%	0.82 [0.33 , 2.02]
ANDES 2021	67	611	18	305	18.0%	1.86 [1.12 , 3.07]
ALPS 2021	135	391	62	203	73.4%	1.13 [0.88 , 1.45]
Subtotal (95% CI)		**1511**		**717**	**100.0%**	**1.22 [0.98 , 1.51]**
Total events:	225		89			
Heterogeneity: Tau² = 0.00; Chi² = 5.84, df = 7 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.81 (P = 0.07)						
Test for subgroup differences: Chi² = 0.66, df = 3 (P = 0.88), I² = 0%						



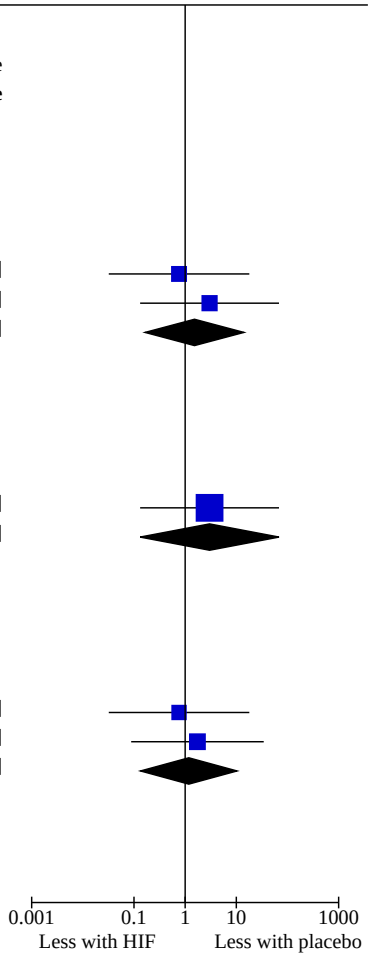
Analysis 1.11. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 11: Thrombosis

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Medium-dose HIF						
Akizawa 2017	1	78	0	19	4.6%	0.76 [0.03 , 17.95]
ALPS 2021	20	391	2	203	22.3%	5.19 [1.23 , 21.99]
OLYMPUS 2021	18	1384	9	1377	73.1%	1.99 [0.90 , 4.41]
Subtotal (95% CI)		**1853**		**1599**	**100.0%**	**2.36 [1.19 , 4.66]**
Total events:	39		11			
Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Total (95% CI)		**1853**		**1599**	**100.0%**	**2.36 [1.19 , 4.66]**
Total events:	39		11			
Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.47 (P = 0.01)						
Test for subgroup differences: Not applicable						

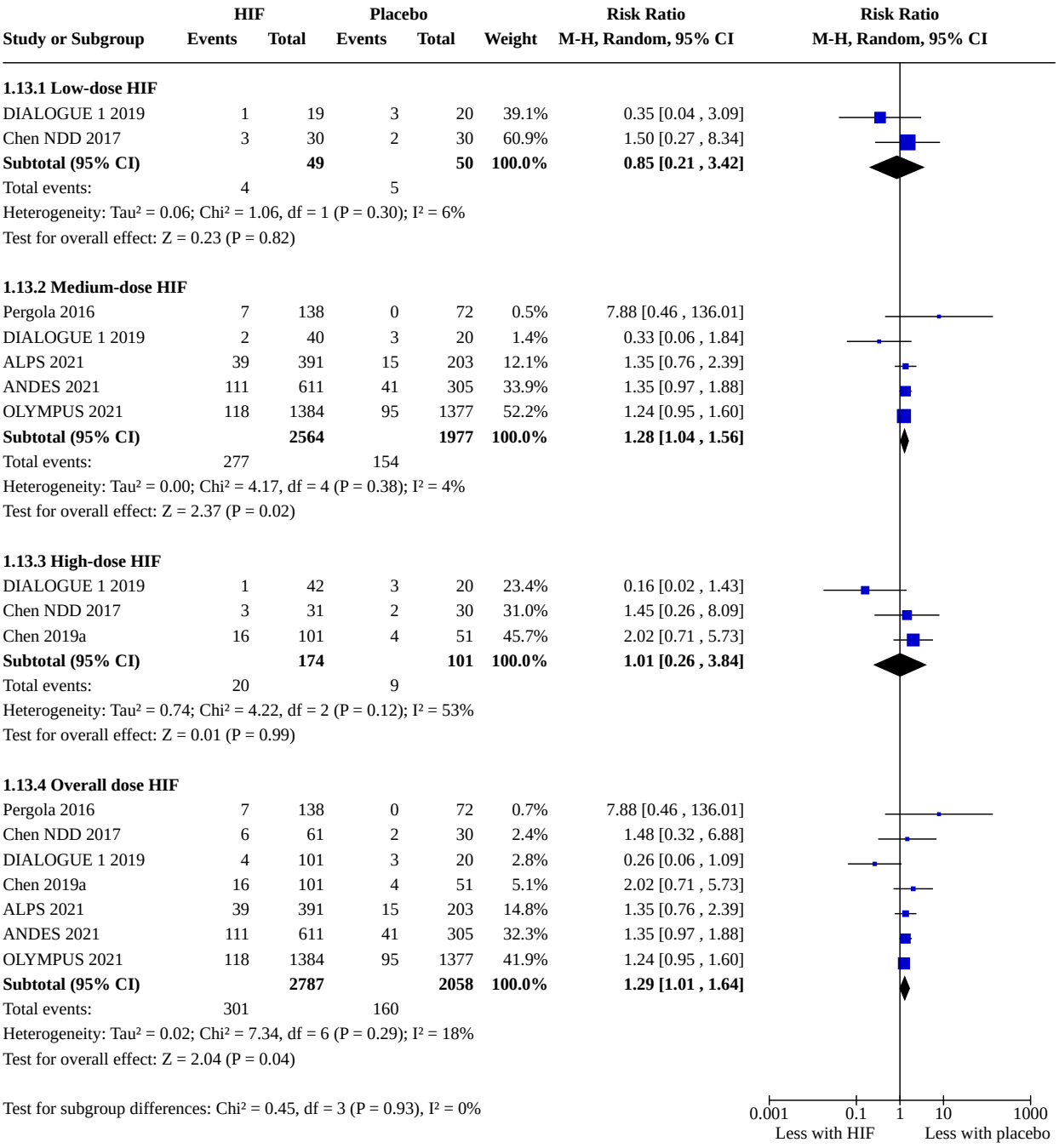


Analysis 1.12. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 12: Loss of unassisted patency (stenosis)

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Low-dose HIF						
NDD-CKD 2020a	0	15	0	15		Not estimable
Subtotal (95% CI)		**15**		**15**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.12.2 Medium-dose HIF						
Akizawa 2017	1	78	0	19	49.4%	0.76 [0.03 , 17.95]
NDD-CKD 2020a	1	15	0	15	50.6%	3.00 [0.13 , 68.26]
Subtotal (95% CI)		**93**		**34**	**100.0%**	**1.52 [0.16 , 14.05]**
Total events:	2		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.12.3 High-dose HIF						
NDD-CKD 2020a	1	15	0	15	100.0%	3.00 [0.13 , 68.26]
Subtotal (95% CI)		**15**		**15**	**100.0%**	**3.00 [0.13 , 68.26]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.12.4 Overall dose HIF						
Akizawa 2017	1	78	0	19	47.1%	0.76 [0.03 , 17.95]
NDD-CKD 2020a	2	45	0	15	52.9%	1.74 [0.09 , 34.33]
Subtotal (95% CI)		**123**		**34**	**100.0%**	**1.18 [0.13 , 10.31]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Chi² = 0.23, df = 2 (P = 0.89), I² = 0%						



Analysis 1.13. Comparison 1: Hypoxia-inducible factor (HIF) stabiliser versus placebo, Outcome 13: Hyperkalaemia



Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Low-dose HIF						
DIALOGUE 1 2019	1	19	3	20	39.1%	0.35 [0.04 , 3.09]
Chen NDD 2017	3	30	2	30	60.9%	1.50 [0.27 , 8.34]
Subtotal (95% CI)		**49**		**50**	**100.0%**	**0.85 [0.21 , 3.42]**
Total events:	4		5			
Heterogeneity: Tau² = 0.06; Chi² = 1.06, df = 1 (P = 0.30); I² = 6%						
Test for overall effect: Z = 0.23 (P = 0.82)						
1.13.2 Medium-dose HIF						
Pergola 2016	7	138	0	72	0.5%	7.88 [0.46 , 136.01]
DIALOGUE 1 2019	2	40	3	20	1.4%	0.33 [0.06 , 1.84]
ALPS 2021	39	391	15	203	12.1%	1.35 [0.76 , 2.39]
ANDES 2021	111	611	41	305	33.9%	1.35 [0.97 , 1.88]
OLYMPUS 2021	118	1384	95	1377	52.2%	1.24 [0.95 , 1.60]
Subtotal (95% CI)		**2564**		**1977**	**100.0%**	**1.28 [1.04 , 1.56]**
Total events:	277		154			
Heterogeneity: Tau² = 0.00; Chi² = 4.17, df = 4 (P = 0.38); I² = 4%						
Test for overall effect: Z = 2.37 (P = 0.02)						
1.13.3 High-dose HIF						
DIALOGUE 1 2019	1	42	3	20	23.4%	0.16 [0.02 , 1.43]
Chen NDD 2017	3	31	2	30	31.0%	1.45 [0.26 , 8.09]
Chen 2019a	16	101	4	51	45.7%	2.02 [0.71 , 5.73]
Subtotal (95% CI)		**174**		**101**	**100.0%**	**1.01 [0.26 , 3.84]**
Total events:	20		9			
Heterogeneity: Tau² = 0.74; Chi² = 4.22, df = 2 (P = 0.12); I² = 53%						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.13.4 Overall dose HIF						
Pergola 2016	7	138	0	72	0.7%	7.88 [0.46 , 136.01]
Chen NDD 2017	6	61	2	30	2.4%	1.48 [0.32 , 6.88]
DIALOGUE 1 2019	4	101	3	20	2.8%	0.26 [0.06 , 1.09]
Chen 2019a	16	101	4	51	5.1%	2.02 [0.71 , 5.73]
ALPS 2021	39	391	15	203	14.8%	1.35 [0.76 , 2.39]
ANDES 2021	111	611	41	305	32.3%	1.35 [0.97 , 1.88]
OLYMPUS 2021	118	1384	95	1377	41.9%	1.24 [0.95 , 1.60]
Subtotal (95% CI)		**2787**		**2058**	**100.0%**	**1.29 [1.01 , 1.64]**
Total events:	301		160			
Heterogeneity: Tau² = 0.02; Chi² = 7.34, df = 6 (P = 0.29); I² = 18%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Chi² = 0.45, df = 3 (P = 0.93), I² = 0%						

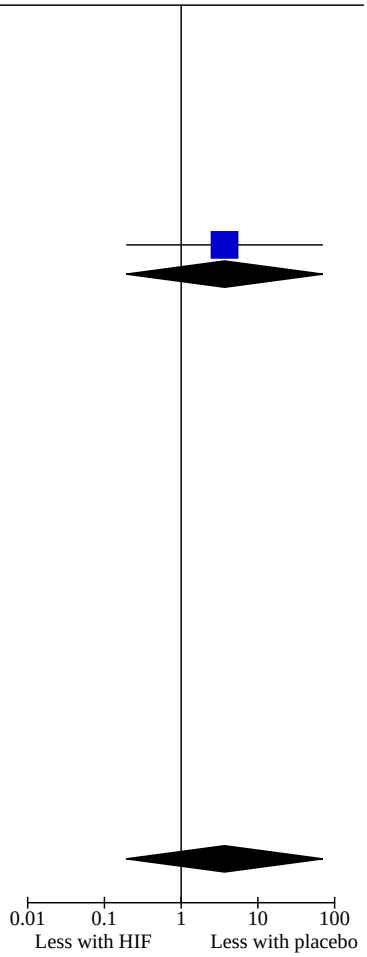
Comparison 2. Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo)

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Cardiovascular death	10	1114	Risk Ratio (M-H, Random, 95% CI)	3.68 [0.19, 70.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.1 CKD	7	850	Risk Ratio (M-H, Random, 95% CI)	3.68 [0.19, 70.21]
2.1.2 HD	2	157	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.1.3 CKD and HD	1	107	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Nonfatal myocardial infarction	3	822	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.31, 5.36]
2.2.1 CKD	3	822	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.31, 5.36]
2.3 Transfusion	8	4329	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.44, 0.60]
2.3.1 CKD	7	4271	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.44, 0.60]
2.3.2 HD	1	58	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.04, 1.14]
2.4 Proportion reaching target haemoglobin	10	5102	Risk Ratio (M-H, Random, 95% CI)	8.36 [6.42, 10.89]
2.4.1 CKD	8	4931	Risk Ratio (M-H, Random, 95% CI)	8.18 [6.13, 10.93]
2.4.2 CKD and HD	2	171	Risk Ratio (M-H, Random, 95% CI)	14.35 [2.07, 99.61]

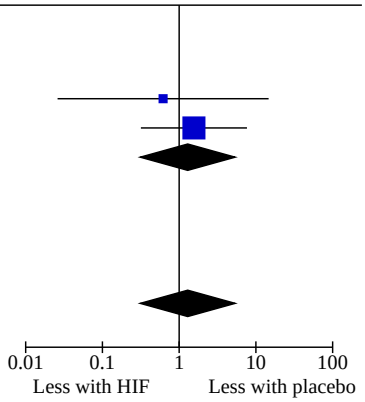
Analysis 2.1. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 1: Cardiovascular death

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 CKD						
Akizawa 2019	0	80	0	27		Not estimable
Besarab 2015	0	88	0	28		Not estimable
NDD-CKD 2020	0	37	0	14		Not estimable
Chen NDD 2017	0	61	0	30		Not estimable
DIALOGUE 1 2019	0	101	0	20		Not estimable
Chen 2019a	0	102	0	52		Not estimable
Pergola 2016	3	138	0	72	100.0%	3.68 [0.19 , 70.21]
Subtotal (95% CI)		**607**		**243**	**100.0%**	**3.68 [0.19 , 70.21]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
2.1.2 HD						
Akizawa 2017	0	78	0	19		Not estimable
NDD-CKD 2020a	0	45	0	15		Not estimable
Subtotal (95% CI)		**123**		**34**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.1.3 CKD and HD						
Brigandi 2016	0	92	0	15		Not estimable
Subtotal (95% CI)		**92**		**15**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**822**		**292**	**100.0%**	**3.68 [0.19 , 70.21]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.87 (P = 0.39)						
Test for subgroup differences: Not applicable						



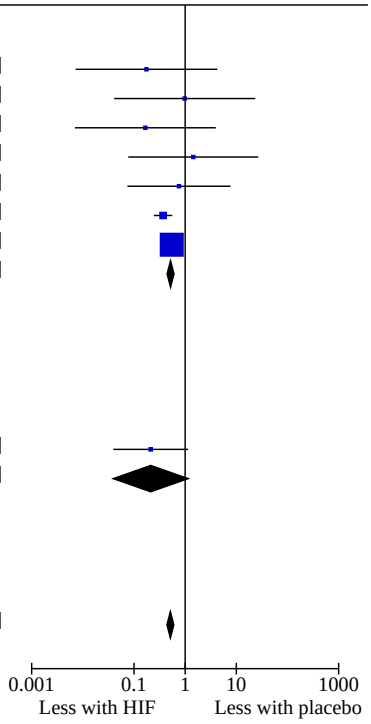
Analysis 2.2. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 2: Nonfatal myocardial infarction

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 CKD						
Akizawa 2019	0	80	0	27		Not estimable
DIALOGUE 1 2019	1	101	0	20	20.2%	0.62 [0.03 , 14.65]
ALPS 2021	6	391	2	203	79.8%	1.56 [0.32 , 7.65]
Subtotal (95% CI)		**572**		**250**	**100.0%**	**1.29 [0.31 , 5.36]**
Total events:	7		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
Total (95% CI)		**572**		**250**	**100.0%**	**1.29 [0.31 , 5.36]**
Total events:	7		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
Test for subgroup differences: Not applicable						



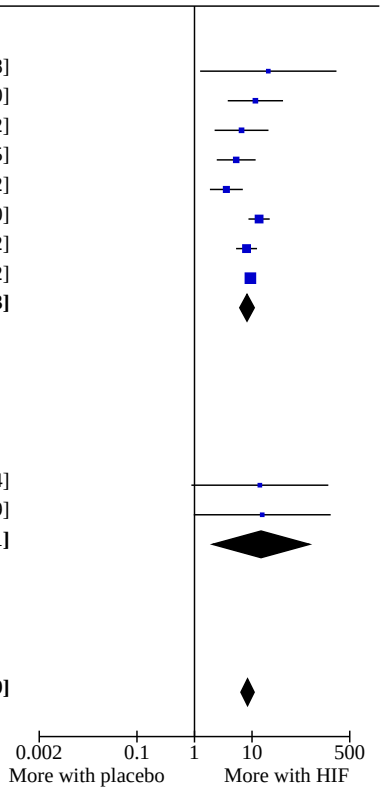
Analysis 2.3. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 3: Transfusion

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 CKD						
Pergola 2016	0	138	1	72	0.2%	0.18 [0.01 , 4.24]
Besarab 2015	1	88	0	28	0.2%	0.98 [0.04 , 23.34]
Chen NDD 2017	0	61	1	30	0.2%	0.17 [0.01 , 3.97]
DIALOGUE 1 2019	3	101	0	20	0.3%	1.44 [0.08 , 26.87]
NDD-CKD 2020	2	37	1	14	0.4%	0.76 [0.07 , 7.70]
ANDES 2021	35	616	47	306	13.7%	0.37 [0.24 , 0.56]
OLYMPUS 2021	176	1384	320	1376	84.0%	0.55 [0.46 , 0.65]
Subtotal (95% CI)		**2425**		**1846**	**99.2%**	**0.52 [0.44 , 0.60]**
Total events:	217		370			
Heterogeneity: Tau² = 0.00; Chi² = 4.58, df = 6 (P = 0.60); I² = 0%						
Test for overall effect: Z = 8.33 (P < 0.00001)						
2.3.2 HD						
NDD-CKD 2020a	2	44	3	14	0.8%	0.21 [0.04 , 1.14]
Subtotal (95% CI)		**44**		**14**	**0.8%**	**0.21 [0.04 , 1.14]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**2469**		**1860**	**100.0%**	**0.51 [0.44 , 0.60]**
Total events:	219		373			
Heterogeneity: Tau² = 0.00; Chi² = 5.65, df = 7 (P = 0.58); I² = 0%						
Test for overall effect: Z = 8.46 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.07, df = 1 (P = 0.30), I² = 6.5%						



Analysis 2.4. Comparison 2: Analyses for SOF table 1 stratifying by CKD stage (HIF versus placebo), Outcome 4: Proportion reaching target haemoglobin

Study or Subgroup	HIF Events	HIF Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 CKD						
Provenzano 2008	82	128	0	14	0.9%	19.19 [1.25 , 293.68]
Chen 2019a	68	101	3	51	4.9%	11.45 [3.79 , 34.60]
Besarab 2015	62	88	3	28	5.1%	6.58 [2.24 , 19.32]
Pergola 2016	56	102	6	58	8.7%	5.31 [2.44 , 11.55]
Chen NDD 2017	51	61	7	30	11.1%	3.58 [1.86 , 6.92]
ANDES 2021	530	611	20	306	18.5%	13.27 [8.68 , 20.30]
ALPS 2021	308	389	20	203	18.7%	8.04 [5.28 , 12.22]
OLYMPUS 2021	1055	1384	112	1377	30.3%	9.37 [7.83 , 11.22]
Subtotal (95% CI)		**2864**		**2067**	**98.2%**	**8.18 [6.13 , 10.93]**
Total events:	2212		171			
Heterogeneity: Tau² = 0.07; Chi² = 14.05, df = 7 (P = 0.05); I² = 50%						
Test for overall effect: Z = 14.23 (P < 0.00001)						
2.4.2 CKD and HD						
Akizawa 2017	32	75	0	15	0.9%	13.68 [0.88 , 212.04]
Brigandi 2016	31	66	0	15	0.9%	15.04 [0.97 , 232.99]
Subtotal (95% CI)		**141**		**30**	**1.8%**	**14.35 [2.07 , 99.61]**
Total events:	63		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Total (95% CI)		**3005**		**2097**	**100.0%**	**8.36 [6.42 , 10.89]**
Total events:	2275		171			
Heterogeneity: Tau² = 0.05; Chi² = 14.31, df = 9 (P = 0.11); I² = 37%						
Test for overall effect: Z = 15.75 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%						



Comparison 3. Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Cardiovascular death	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1.1 Low-dose HIF	6	981	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.14, 6.41]
3.1.2 Medium-dose HIF	7	7442	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.88, 1.27]
3.1.3 High-dose HIF	9	2067	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.31, 3.96]
3.1.4 Overall dose HIF	17	10340	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.26]
3.2 Fatigue	2	3471	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.16]
3.2.1 Medium-dose HIF	2	3471	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.16]
3.3 Death (any cause)	29		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.3.1 Low-dose HIF	9	1295	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.33, 2.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.2 Medium-dose HIF	15	15586	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.08]
3.3.3 High-dose HIF	13	4745	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.63, 1.37]
3.3.4 Overall dose HIF	29	21370	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.06]
3.4 Nonfatal myocardial infarction	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4.1 Low-dose HIF	2	148	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4.2 Medium-dose HIF	5	7153	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.72, 1.16]
3.4.3 High-dose HIF	4	612	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.31, 11.54]
3.4.4 Overall dose HIF	7	7765	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.10]
3.5 Fatal or nonfatal myocardial infarction (overall)	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.5.1 Low-dose HIF	2	148	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.5.2 Medium-dose HIF	9	10949	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.10]
3.5.3 High-dose HIF	8	3234	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.68, 2.19]
3.5.4 Overall dose HIF	15	14183	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.12]
3.6 Nonfatal stroke	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.6.1 Low-dose HIF	3	336	Risk Ratio (M-H, Random, 95% CI)	4.78 [0.24, 96.68]
3.6.2 Medium-dose HIF	3	6918	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.62, 1.83]
3.6.3 High-dose HIF	1	115	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.6.4 Overall dose HIF	5	7285	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.56]
3.7 Fatal or nonfatal stroke (overall)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.7.1 Low-dose HIF	4	398	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.11, 17.51]
3.7.2 Medium-dose HIF	4	6980	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.70, 1.50]
3.7.3 High-dose HIF	3	795	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.16, 1.53]
3.7.4 Overall dose HIF	7	8025	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.64, 1.40]
3.8 Nonfatal hospitalisation for heart failure	2	6836	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.00, 1.52]
3.8.1 Medium-dose HIF	2	6836	Risk Ratio (M-H, Random, 95% CI)	1.23 [1.00, 1.52]

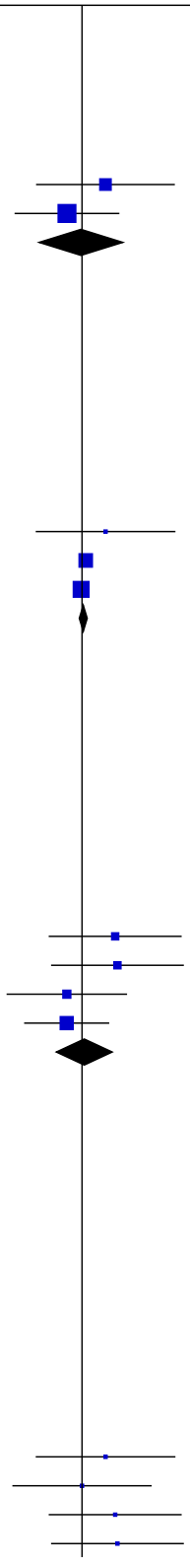
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9 Fatal or nonfatal hospitalisation for heart failure	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.9.1 Medium-dose HIF	2	6836	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.98, 1.39]
3.9.2 High-dose HIF	1	616	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.59, 1.79]
3.9.3 Overall dose HIF	3	7452	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.97, 1.36]
3.10 Peripheral arterial event	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.10.1 Low-dose HIF	2	148	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.10.2 Medium-dose HIF	2	144	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.10.3 High-dose HIF	2	179	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.10.4 Overall dose HIF	2	323	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.11 Transfusion	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.11.1 Low-dose HIF	3	192	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.23, 4.75]
3.11.2 Medium-dose HIF	7	7343	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.81, 1.02]
3.11.3 High-dose HIF	7	3443	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.62, 1.16]
3.11.4 Overall dose HIF	11	10786	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
3.12 Proportion reaching target haemoglobin	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.12.1 Low-dose HIF	7	861	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.10]
3.12.2 Medium-dose HIF	4	507	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.29]
3.12.3 High-dose HIF	9	3425	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.12]
3.12.4 Overall dose HIF	14	4601	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
3.13 Kidney failure	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.13.1 Low-dose HIF	2	361	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.20, 6.43]
3.13.2 Medium-dose HIF	7	6647	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.16]
3.13.3 High-dose HIF	2	368	Risk Ratio (M-H, Random, 95% CI)	6.88 [0.89, 53.20]
3.13.4 Overall dose HIF	9	7312	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.15]
3.14 Thrombosis	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.14.1 Medium-dose HIF	7	14532	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.71, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.14.2 High-dose HIF	4	2494	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.99, 1.83]
3.14.3 Overall dose HIF	11	17026	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.39]
3.15 Loss of unassisted patency (occlusion/stenosis)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.15.1 Low-dose HIF	1	271	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.53, 1.69]
3.15.2 Medium-dose HIF	3	800	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.29, 1.47]
3.15.3 High-dose HIF	4	1874	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.99, 2.30]
3.15.4 Overall dose HIF	8	2945	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.85, 1.59]
3.16 Access intervention	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.16.1 High-dose HIF	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.17 Cancer	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.17.1 Low-dose HIF	2	515	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.10, 3.35]
3.17.2 Medium-dose HIF	3	641	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.24, 1.74]
3.17.3 High-dose HIF	2	531	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.13, 5.85]
3.17.4 Overall dose HIF	7	1687	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.43, 1.59]
3.18 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.18.1 High-dose HIF	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.19 Hyperkalaemia	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.19.1 Low-dose HIF	2	570	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.77, 3.85]
3.19.2 Medium-dose HIF	10	15152	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.82, 1.00]
3.19.3 High-dose HIF	9	4455	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.68, 1.50]
3.19.4 Overall dose HIF	21	20177	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.04]
3.20 Pulmonary hypertension	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.20.1 Low-dose HIF	2	570	Risk Ratio (M-H, Random, 95% CI)	2.98 [0.12, 72.46]
3.20.2 Medium-dose HIF	4	7455	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.51, 2.47]
3.20.3 High-dose HIF	1	616	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.03, 2.89]
3.20.4 Overall dose HIF	7	8641	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.56, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.21 Diabetic retinopathy	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.21.1 Low-dose HIF	1	299	Risk Ratio (M-H, Random, 95% CI)	2.01 [0.18, 21.97]
3.21.2 Medium-dose HIF	6	4435	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.65, 2.15]
3.21.3 High-dose HIF	1	302	Risk Ratio (M-H, Random, 95% CI)	3.04 [0.12, 74.03]
3.21.4 Overall dose HIF	8	5036	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.71, 2.22]

Analysis 3.1. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 1: Cardiovascular death

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Low-dose HIF						
SYMPHONY ND 2021	0	107	0	109		Not estimable
DIALOGUE 4 2019	0	44	0	42		Not estimable
Akizawa 2020c	0	136	0	135		Not estimable
Chen DD 2017	0	22	0	22		Not estimable
NCT01888445	1	33	0	32	36.3%	2.91 [0.12 , 68.95]
Nangaku 2021b	1	149	2	150	63.7%	0.50 [0.05 , 5.49]
Subtotal (95% CI)		**491**		**490**	**100.0%**	**0.95 [0.14 , 6.41]**
Total events:	2		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
3.1.2 Medium-dose HIF						
Chen DD 2017	0	21	0	22		Not estimable
NCT01888445	0	32	0	32		Not estimable
MIYABI ND-M 2019	0	82	0	82		Not estimable
SYMPHONY HD 2021	0	87	0	86		Not estimable
MIYABI ND-C 2019	1	82	0	80	0.3%	2.93 [0.12 , 70.82]
ASCEND-ND 2021	109	1937	92	1935	44.7%	1.18 [0.90 , 1.55]
ASCEND-D 2021	117	1487	121	1477	55.0%	0.96 [0.75 , 1.23]
Subtotal (95% CI)		**3728**		**3714**	**100.0%**	**1.06 [0.88 , 1.27]**
Total events:	227		213			
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
3.1.3 High-dose HIF						
Chen 2019	0	204	0	100		Not estimable
Akizawa 2021	0	131	0	131		Not estimable
NCT01888445	0	33	0	32		Not estimable
DIALOGUE 4 2019	0	73	0	42		Not estimable
Chen DD 2017	0	22	0	22		Not estimable
DOLOMITES 2021	2	323	0	293	17.7%	4.54 [0.22 , 94.12]
Akizawa 2020a	2	151	0	152	17.7%	5.03 [0.24 , 103.96]
Hou 2021	1	86	1	43	21.5%	0.50 [0.03 , 7.80]
MIYABI HD-M 2019	2	153	2	76	43.1%	0.50 [0.07 , 3.46]
Subtotal (95% CI)		**1176**		**891**	**100.0%**	**1.11 [0.31 , 3.96]**
Total events:	7		3			
Heterogeneity: Tau² = 0.00; Chi² = 2.87, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.87)						
3.1.4 Overall dose HIF						
Akizawa 2021	0	131	0	131		Not estimable
Akizawa 2020c	0	136	0	135		Not estimable
SYMPHONY ND 2021	0	107	0	109		Not estimable
Chen DD 2017	0	65	0	22		Not estimable
SYMPHONY HD 2021	0	87	0	86		Not estimable
DIALOGUE 4 2019	0	117	0	42		Not estimable
Chen 2019	0	204	0	100		Not estimable
MIYABI ND-M 2019	0	82	0	82		Not estimable
MIYABI ND-C 2019	1	82	0	80	0.3%	2.93 [0.12 , 70.82]
NCT01888445	1	98	0	32	0.3%	1.00 [0.04 , 23.96]
DOLOMITES 2021	2	323	0	293	0.3%	4.54 [0.22 , 94.12]
Akizawa 2020a	2	151	0	152	0.3%	5.03 [0.24 , 103.96]



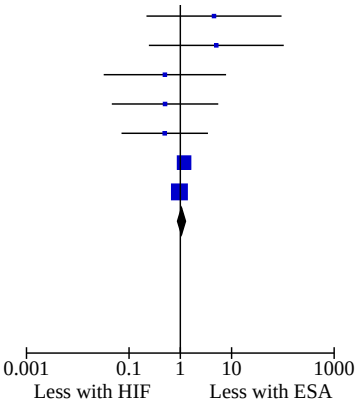
Analysis 3.1. (Continued)

DOLOMITES 2021	2	323	0	293	0.3%	4.54 [0.22 , 94.12]
Akizawa 2020a	2	151	0	152	0.3%	5.03 [0.24 , 103.96]
Hou 2021	1	86	1	43	0.4%	0.50 [0.03 , 7.80]
Nangaku 2021b	1	149	2	150	0.6%	0.50 [0.05 , 5.49]
MIYABI HD-M 2019	2	153	2	76	0.8%	0.50 [0.07 , 3.46]
ASCEND-ND 2021	109	1937	92	1935	43.4%	1.18 [0.90 , 1.55]
ASCEND-D 2021	117	1487	121	1477	53.4%	0.96 [0.75 , 1.23]
Subtotal (95% CI)		**5395**		**4945**	**100.0%**	**1.05 [0.88 , 1.26]**
Total events:	236		218			

Heterogeneity: Tau² = 0.00; Chi² = 4.81, df = 8 (P = 0.78); I² = 0%

Test for overall effect: Z = 0.59 (P = 0.56)

Test for subgroup differences: Chi² = 0.02, df = 3 (P = 1.00), I² = 0%



Analysis 3.2. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 2: Fatigue

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Medium-dose HIF						
PRO2TECT-CORRECTION 2021	23	878	29	870	46.2%	0.79 [0.46 , 1.35]
PRO2TECT-CONVERSION 2021	27	861	33	862	53.8%	0.82 [0.50 , 1.35]
Subtotal (95% CI)		**1739**		**1732**	**100.0%**	**0.80 [0.56 , 1.16]**
Total events:	50		62			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%

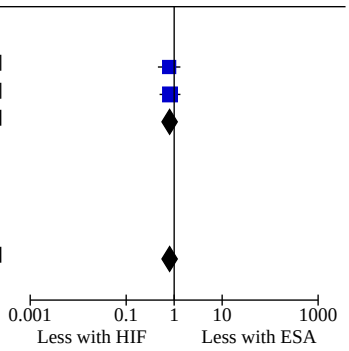
Test for overall effect: Z = 1.17 (P = 0.24)

Total (95% CI)		**1739**		**1732**	**100.0%**	**0.80 [0.56 , 1.16]**
Total events:	50		62			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%

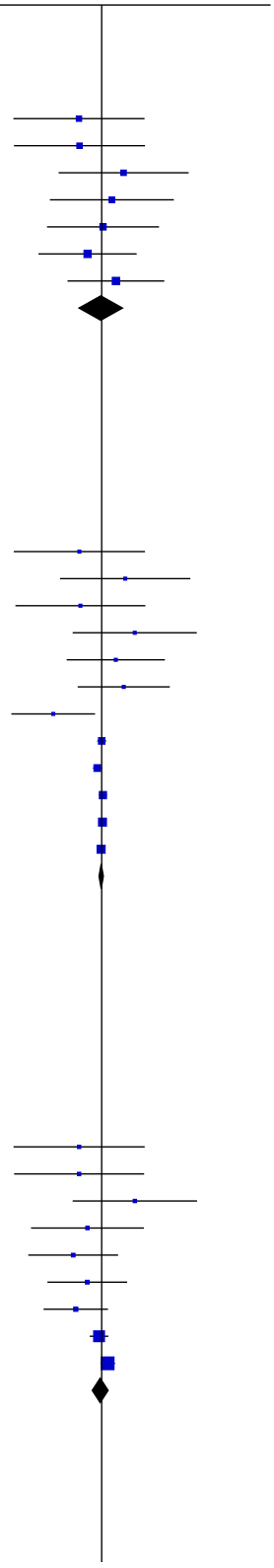
Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 3: Death (any cause)

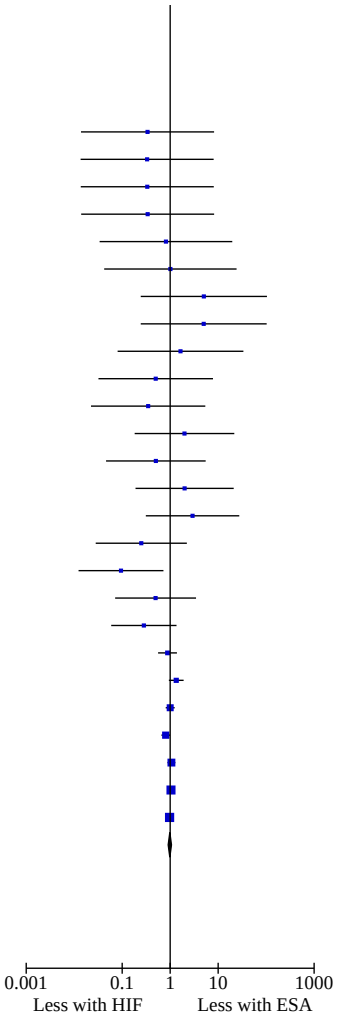
Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Low-dose HIF						
DIALOGUE 4 2019	0	44	0	42		Not estimable
Chen DD 2017	0	22	0	22		Not estimable
Akizawa 2020c	0	136	1	135	11.0%	0.33 [0.01 , 8.05]
SYMPHONY ND 2021	0	107	1	109	11.0%	0.34 [0.01 , 8.24]
NCT01888445	1	33	0	32	11.1%	2.91 [0.12 , 68.95]
Holdstock 2019	2	136	0	44	12.3%	1.64 [0.08 , 33.57]
DIALOGUE 2 2019	1	30	1	32	15.0%	1.07 [0.07 , 16.30]
Nangaku 2021b	1	149	2	150	19.5%	0.50 [0.05 , 5.49]
Holdstock 2019a	2	36	1	36	20.1%	2.00 [0.19 , 21.09]
Subtotal (95% CI)		**693**		**602**	**100.0%**	**0.96 [0.33 , 2.75]**
Total events:	7		6			
Heterogeneity: Tau² = 0.00; Chi² = 2.09, df = 6 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.93)						
3.3.2 Medium-dose HIF						
SYMPHONY HD 2021	0	87	0	86		Not estimable
NCT01888445	0	32	0	32		Not estimable
Chen DD 2017	0	21	0	22		Not estimable
Nangaku 2021a	0	151	1	153	0.1%	0.34 [0.01 , 8.23]
DIALOGUE 4 2019	1	40	0	42	0.1%	3.15 [0.13 , 75.05]
DIALOGUE 2 2019	0	30	1	32	0.1%	0.35 [0.02 , 8.39]
MIYABI ND-M 2019	2	82	0	82	0.1%	5.00 [0.24 , 102.57]
Nangaku 2021	2	162	1	161	0.2%	1.99 [0.18 , 21.70]
MIYABI ND-C 2019	3	82	1	80	0.2%	2.93 [0.31 , 27.55]
INNO2VATE 2020	1	179	11	186	0.3%	0.09 [0.01 , 0.72]
PRO2TECT-CONVERSION 2021	139	861	139	862	16.2%	1.00 [0.81 , 1.24]
INNO2VATE 2020a	147	1768	182	1769	17.1%	0.81 [0.66 , 0.99]
PRO2TECT-CORRECTION 2021	180	878	168	870	19.4%	1.06 [0.88 , 1.28]
ASCEND-D 2021	244	1487	233	1477	22.8%	1.04 [0.88 , 1.23]
ASCEND-ND 2021	252	1937	259	1935	23.3%	0.97 [0.83 , 1.14]
Subtotal (95% CI)		**7797**		**7789**	**100.0%**	**0.98 [0.88 , 1.08]**
Total events:	971		996			
Heterogeneity: Tau² = 0.01; Chi² = 13.39, df = 11 (P = 0.27); I² = 18%						
Test for overall effect: Z = 0.45 (P = 0.65)						
3.3.3 High-dose HIF						
Chen 2019	0	204	0	100		Not estimable
NCT01888445	0	32	0	32		Not estimable
Chen DD 2017	0	22	0	22		Not estimable
DIALOGUE 4 2019	0	73	0	42		Not estimable
Akizawa 2021	0	131	1	131	1.4%	0.33 [0.01 , 8.11]
DIALOGUE 2 2019	0	32	1	32	1.5%	0.33 [0.01 , 7.89]
Akizawa 2020a	2	151	0	152	1.6%	5.03 [0.24 , 103.96]
Hou 2021	1	86	1	43	1.9%	0.50 [0.03 , 7.80]
SIERRAS 2021	1	370	4	370	3.0%	0.25 [0.03 , 2.23]
MIYABI HD-M 2019	2	153	2	76	3.8%	0.50 [0.07 , 3.46]
HIMALAYAS 2021	2	522	7	517	5.6%	0.28 [0.06 , 1.36]
DOLOMITES 2021	33	323	34	293	36.3%	0.88 [0.56 , 1.38]
PYRENEES 2021	62	415	47	421	45.0%	1.34 [0.94 , 1.91]
Subtotal (95% CI)		**2514**		**2231**	**100.0%**	**0.93 [0.63 , 1.37]**
Total events:	103		97			
Heterogeneity: Tau² = 0.05; Chi² = 9.65, df = 8 (P = 0.29); I² = 17%						
Test for overall effect: Z = 0.37 (P = 0.71)						
3.3.4 Overall dose HIF						
Chen DD 2017	0	65	0	22		Not estimable



Analysis 3.3. (Continued)

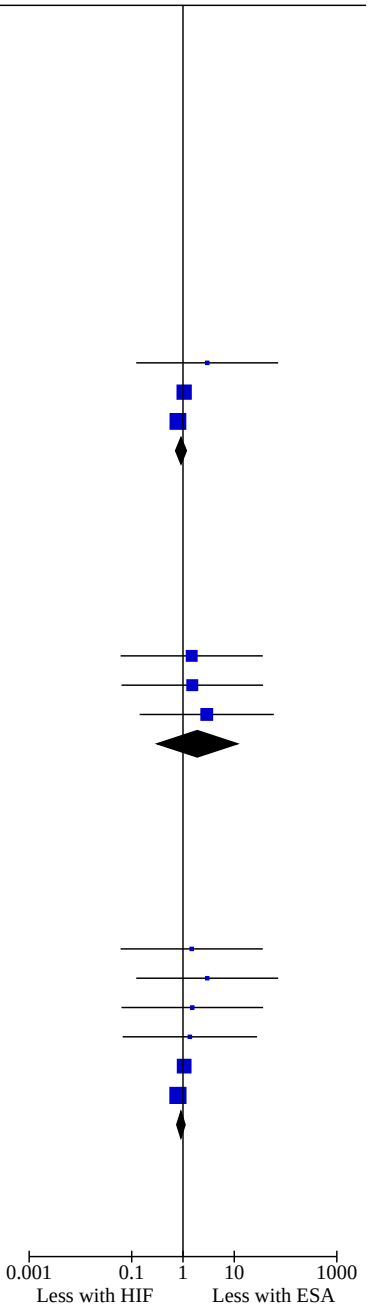
3.3.4 Overall dose HIF						
Chen DD 2017	0	65	0	22		Not estimable
SYMPHONY HD 2021	0	87	0	86		Not estimable
Chen 2019	0	204	0	100		Not estimable
Nangaku 2021a	0	151	1	153	0.1%	0.34 [0.01 , 8.23]
Akizawa 2020c	0	136	1	135	0.1%	0.33 [0.01 , 8.05]
Akizawa 2021	0	131	1	131	0.1%	0.33 [0.01 , 8.11]
SYMPHONY ND 2021	0	107	1	109	0.1%	0.34 [0.01 , 8.24]
DIALOGUE 4 2019	1	157	0	42	0.1%	0.82 [0.03 , 19.69]
NCT01888445	1	97	0	32	0.1%	1.01 [0.04 , 24.20]
Akizawa 2020a	2	151	0	152	0.1%	5.03 [0.24 , 103.96]
MIYABI ND-M 2019	2	82	0	82	0.1%	5.00 [0.24 , 102.57]
Holdstock 2019	2	136	0	44	0.1%	1.64 [0.08 , 33.57]
Hou 2021	1	86	1	43	0.1%	0.50 [0.03 , 7.80]
DIALOGUE 2 2019	1	92	1	32	0.1%	0.35 [0.02 , 5.40]
Nangaku 2021	2	162	1	161	0.1%	1.99 [0.18 , 21.70]
Nangaku 2021b	1	149	2	150	0.1%	0.50 [0.05 , 5.49]
Holdstock 2019a	2	36	1	36	0.1%	2.00 [0.19 , 21.09]
MIYABI ND-C 2019	3	82	1	80	0.1%	2.93 [0.31 , 27.55]
SIERRAS 2021	1	370	4	370	0.1%	0.25 [0.03 , 2.23]
INNO2VATE 2020	1	179	11	186	0.1%	0.09 [0.01 , 0.72]
MIYABI HD-M 2019	2	153	2	76	0.2%	0.50 [0.07 , 3.46]
HIMALAYAS 2021	2	522	7	517	0.2%	0.28 [0.06 , 1.36]
DOLOMITES 2021	33	323	34	293	3.0%	0.88 [0.56 , 1.38]
PYRENEES 2021	62	415	47	421	4.9%	1.34 [0.94 , 1.91]
PRO2TECT-CONVERSION 2021	139	861	139	862	13.1%	1.00 [0.81 , 1.24]
INNO2VATE 2020a	147	1768	182	1769	14.2%	0.81 [0.66 , 0.99]
PRO2TECT-CORRECTION 2021	180	878	168	870	17.2%	1.06 [0.88 , 1.28]
ASCEND-D 2021	244	1487	233	1477	22.5%	1.04 [0.88 , 1.23]
ASCEND-ND 2021	252	1937	259	1935	23.3%	0.97 [0.83 , 1.14]
Subtotal (95% CI)		**11004**		**10366**	**100.0%**	**0.98 [0.91 , 1.06]**
Total events:	1081		1097			
Heterogeneity: Tau² = 0.00; Chi² = 24.05, df = 25 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						

Test for subgroup differences: Chi² = 0.09, df = 3 (P = 0.99), I² = 0%



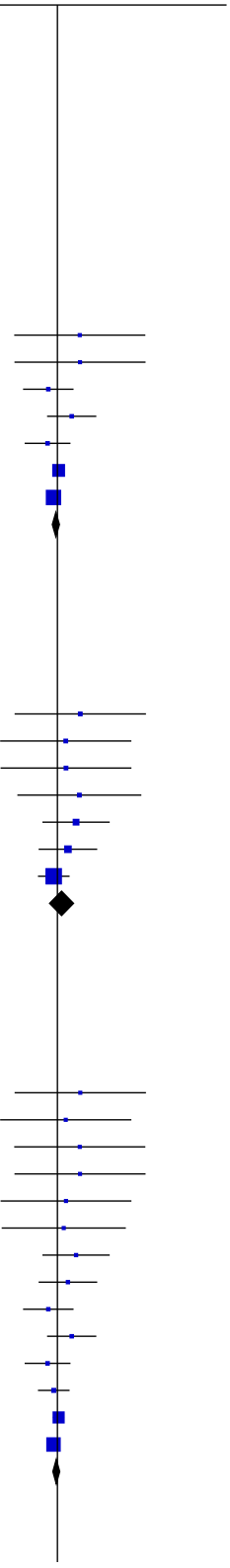
Analysis 3.4. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 4: Nonfatal myocardial infarction

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Low-dose HIF						
DIALOGUE 2 2019	0	30	0	32		Not estimable
DIALOGUE 4 2019	0	44	0	42		Not estimable
Subtotal (95% CI)		**74**		**74**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.4.2 Medium-dose HIF						
DIALOGUE 2 2019	0	30	0	32		Not estimable
DIALOGUE 4 2019	0	40	0	42		Not estimable
SYMPHONY HD 2021	1	87	0	86	0.6%	2.97 [0.12 , 71.81]
ASCEND-ND 2021	96	1937	91	1935	46.6%	1.05 [0.80 , 1.39]
ASCEND-D 2021	101	1487	126	1477	52.9%	0.80 [0.62 , 1.02]
Subtotal (95% CI)		**3581**		**3572**	**100.0%**	**0.91 [0.72 , 1.16]**
Total events:	198		217			
Heterogeneity: Tau² = 0.01; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%						
Test for overall effect: Z = 0.73 (P = 0.47)						
3.4.3 High-dose HIF						
DIALOGUE 2 2019	0	32	0	32		Not estimable
Chen 2019	1	204	0	100	32.0%	1.48 [0.06 , 35.96]
Hou 2021	1	86	0	43	32.2%	1.52 [0.06 , 36.48]
DIALOGUE 4 2019	2	73	0	42	35.9%	2.91 [0.14 , 59.12]
Subtotal (95% CI)		**395**		**217**	**100.0%**	**1.90 [0.31 , 11.54]**
Total events:	4		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.49)						
3.4.4 Overall dose HIF						
DIALOGUE 2 2019	0	92	0	32		Not estimable
Chen 2019	1	204	0	100	0.3%	1.48 [0.06 , 35.96]
SYMPHONY HD 2021	1	87	0	86	0.3%	2.97 [0.12 , 71.81]
Hou 2021	1	86	0	43	0.3%	1.52 [0.06 , 36.48]
DIALOGUE 4 2019	2	157	0	42	0.4%	1.36 [0.07 , 27.82]
ASCEND-ND 2021	96	1937	91	1935	44.1%	1.05 [0.80 , 1.39]
ASCEND-D 2021	101	1487	126	1477	54.5%	0.80 [0.62 , 1.02]
Subtotal (95% CI)		**4050**		**3715**	**100.0%**	**0.91 [0.76 , 1.10]**
Total events:	202		217			
Heterogeneity: Tau² = 0.00; Chi² = 2.93, df = 5 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 0.63, df = 2 (P = 0.73), I² = 0%						



Analysis 3.5. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 5: Fatal or nonfatal myocardial infarction (overall)

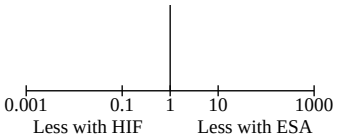
Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Low-dose HIF						
DIALOGUE 2 2019	0	30	0	32		Not estimable
DIALOGUE 4 2019	0	44	0	42		Not estimable
Subtotal (95% CI)		**74**		**74**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.2 Medium-dose HIF						
DIALOGUE 2 2019	0	30	0	32		Not estimable
DIALOGUE 4 2019	0	40	0	42		Not estimable
SYMPHONY HD 2021	1	87	0	86	0.3%	2.97 [0.12 , 71.81]
MIYABI ND-M 2019	1	82	0	82	0.3%	3.00 [0.12 , 72.58]
MIYABI ND-C 2019	4	82	6	79	2.0%	0.64 [0.19 , 2.19]
PRO2TECT-CONVERSION 2021	8	861	4	862	2.1%	2.00 [0.61 , 6.62]
PRO2TECT-CORRECTION 2021	5	878	8	870	2.4%	0.62 [0.20 , 1.89]
ASCEND-ND 2021	103	1937	97	1935	40.6%	1.06 [0.81 , 1.39]
ASCEND-D 2021	114	1487	137	1477	52.4%	0.83 [0.65 , 1.05]
Subtotal (95% CI)		**5484**		**5465**	**100.0%**	**0.93 [0.78 , 1.10]**
Total events:	236		252			
Heterogeneity: Tau² = 0.00; Chi² = 5.33, df = 6 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
3.5.3 High-dose HIF						
DIALOGUE 2 2019	0	32	0	32		Not estimable
Akizawa 2020a	1	150	0	152	3.3%	3.04 [0.12 , 74.03]
MIYABI HD-M 2019	1	153	0	76	3.3%	1.50 [0.06 , 36.39]
Hou 2021	1	86	0	43	3.3%	1.52 [0.06 , 36.48]
DIALOGUE 4 2019	2	73	0	42	3.7%	2.91 [0.14 , 59.12]
HIMALAYAS 2021	5	522	2	517	12.6%	2.48 [0.48 , 12.70]
SIERRAS 2021	5	370	3	370	16.6%	1.67 [0.40 , 6.92]
DOLOMITES 2021	12	323	13	293	57.1%	0.84 [0.39 , 1.81]
Subtotal (95% CI)		**1709**		**1525**	**100.0%**	**1.22 [0.68 , 2.19]**
Total events:	27		18			
Heterogeneity: Tau² = 0.00; Chi² = 2.51, df = 6 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
3.5.4 Overall dose HIF						
DIALOGUE 2 2019	0	92	0	32		Not estimable
Akizawa 2020a	1	150	0	152	0.3%	3.04 [0.12 , 74.03]
MIYABI HD-M 2019	1	153	0	76	0.3%	1.50 [0.06 , 36.39]
SYMPHONY HD 2021	1	87	0	86	0.3%	2.97 [0.12 , 71.81]
MIYABI ND-M 2019	1	82	0	82	0.3%	3.00 [0.12 , 72.58]
Hou 2021	1	86	0	43	0.3%	1.52 [0.06 , 36.48]
DIALOGUE 4 2019	2	157	0	42	0.3%	1.36 [0.07 , 27.82]
HIMALAYAS 2021	5	522	2	517	1.0%	2.48 [0.48 , 12.70]
SIERRAS 2021	5	370	3	370	1.3%	1.67 [0.40 , 6.92]
MIYABI ND-C 2019	4	82	6	79	1.8%	0.64 [0.19 , 2.19]
PRO2TECT-CONVERSION 2021	8	861	4	862	1.9%	2.00 [0.61 , 6.62]
PRO2TECT-CORRECTION 2021	5	878	8	870	2.2%	0.62 [0.20 , 1.89]
DOLOMITES 2021	12	323	13	293	4.6%	0.84 [0.39 , 1.81]
ASCEND-ND 2021	103	1937	97	1935	37.3%	1.06 [0.81 , 1.39]
ASCEND-D 2021	114	1487	137	1477	48.1%	0.83 [0.65 , 1.05]
Subtotal (95% CI)		**7267**		**6916**	**100.0%**	**0.95 [0.80 , 1.12]**
Total events:	263		270			
Heterogeneity: Tau² = 0.00; Chi² = 8.15, df = 13 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						



Analysis 3.5. (Continued)

Heterogeneity: Tau² = 0.00; Chi² = 8.15, df = 13 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)

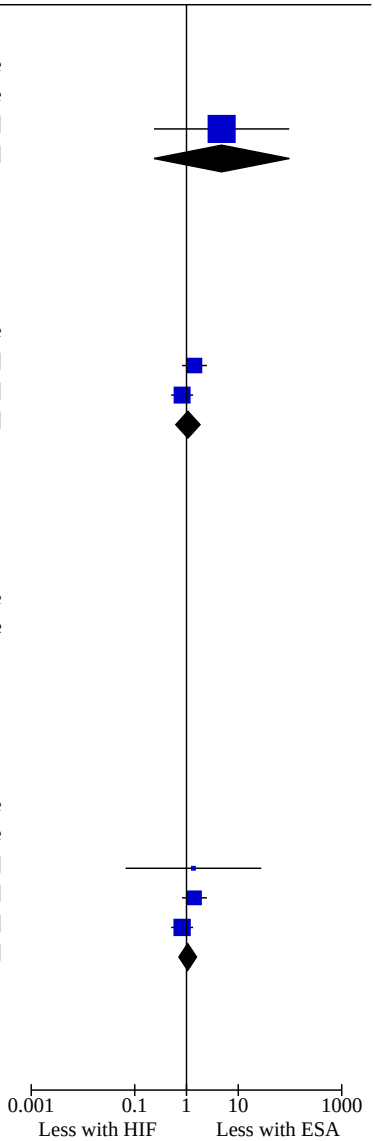
Test for subgroup differences: Chi² = 0.80, df = 2 (P = 0.67), I² = 0%



Analysis 3.6. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 6: Nonfatal stroke

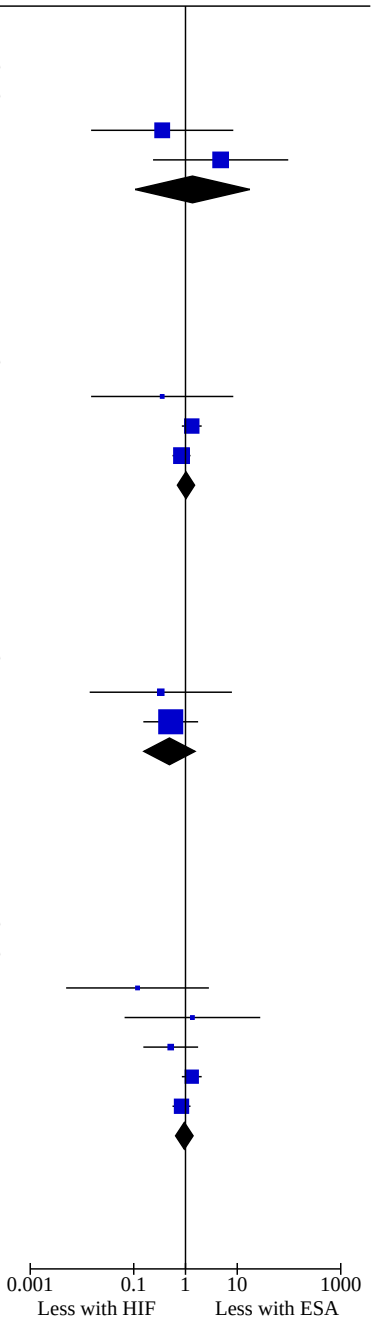
Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Low-dose HIF						
Holdstock 2019	0	134	0	45		Not estimable
Holdstock 2019a	0	36	0	35		Not estimable
DIALOGUE 4 2019	2	44	0	42	100.0%	4.78 [0.24 , 96.68]
Subtotal (95% CI)		**214**		**122**	**100.0%**	**4.78 [0.24 , 96.68]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						
3.6.2 Medium-dose HIF						
DIALOGUE 4 2019	0	40	0	42		Not estimable
ASCEND-ND 2021	30	1937	21	1935	47.0%	1.43 [0.82 , 2.48]
ASCEND-D 2021	29	1487	35	1477	53.0%	0.82 [0.51 , 1.34]
Subtotal (95% CI)		**3464**		**3454**	**100.0%**	**1.07 [0.62 , 1.83]**
Total events:	59		56			
Heterogeneity: Tau² = 0.08; Chi² = 2.14, df = 1 (P = 0.14); I² = 53%						
Test for overall effect: Z = 0.23 (P = 0.82)						
3.6.3 High-dose HIF						
DIALOGUE 4 2019	0	73	0	42		Not estimable
Subtotal (95% CI)		**73**		**42**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.6.4 Overall dose HIF						
Holdstock 2019	0	134	0	45		Not estimable
Holdstock 2019a	0	36	0	35		Not estimable
DIALOGUE 4 2019	2	157	0	42	1.7%	1.36 [0.07 , 27.82]
ASCEND-ND 2021	30	1937	21	1935	43.7%	1.43 [0.82 , 2.48]
ASCEND-D 2021	29	1487	35	1477	54.6%	0.82 [0.51 , 1.34]
Subtotal (95% CI)		**3751**		**3534**	**100.0%**	**1.06 [0.71 , 1.56]**
Total events:	61		56			
Heterogeneity: Tau² = 0.01; Chi² = 2.17, df = 2 (P = 0.34); I² = 8%						
Test for overall effect: Z = 0.27 (P = 0.79)						

Test for subgroup differences: Chi² = 0.95, df = 2 (P = 0.62), I² = 0%



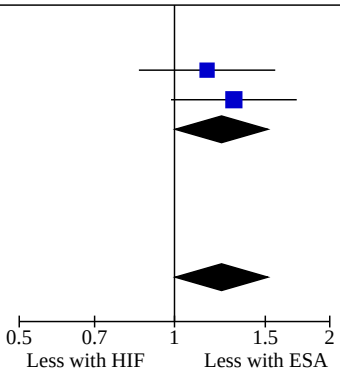
Analysis 3.7. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 7: Fatal or nonfatal stroke (overall)

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Low-dose HIF						
Holdstock 2019	0	134	0	45		Not estimable
Holdstock 2019a	0	36	0	35		Not estimable
DIALOGUE 2 2019	0	30	1	32	48.2%	0.35 [0.02 , 8.39]
DIALOGUE 4 2019	2	44	0	42	51.8%	4.78 [0.24 , 96.68]
Subtotal (95% CI)		**244**		**154**	**100.0%**	**1.37 [0.11 , 17.51]**
Total events:	2		1			
Heterogeneity: Tau² = 0.91; Chi² = 1.37, df = 1 (P = 0.24); I² = 27%						
Test for overall effect: Z = 0.24 (P = 0.81)						
3.7.2 Medium-dose HIF						
DIALOGUE 4 2019	0	40	0	42		Not estimable
DIALOGUE 2 2019	0	30	1	32	1.4%	0.35 [0.02 , 8.39]
ASCEND-ND 2021	45	1937	34	1935	46.4%	1.32 [0.85 , 2.05]
ASCEND-D 2021	43	1487	51	1477	52.2%	0.84 [0.56 , 1.25]
Subtotal (95% CI)		**3494**		**3486**	**100.0%**	**1.02 [0.70 , 1.50]**
Total events:	88		86			
Heterogeneity: Tau² = 0.03; Chi² = 2.70, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 0.11 (P = 0.91)						
3.7.3 High-dose HIF						
DIALOGUE 4 2019	0	73	0	42		Not estimable
DIALOGUE 2 2019	0	32	1	32	12.9%	0.33 [0.01 , 7.89]
DOLOMITES 2021	4	323	7	293	87.1%	0.52 [0.15 , 1.75]
Subtotal (95% CI)		**428**		**367**	**100.0%**	**0.49 [0.16 , 1.53]**
Total events:	4		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.23 (P = 0.22)						
3.7.4 Overall dose HIF						
Holdstock 2019a	0	36	0	35		Not estimable
Holdstock 2019	0	134	0	45		Not estimable
DIALOGUE 2 2019	0	92	1	32	1.5%	0.12 [0.00 , 2.83]
DIALOGUE 4 2019	2	157	0	42	1.6%	1.36 [0.07 , 27.82]
DOLOMITES 2021	4	323	7	293	9.1%	0.52 [0.15 , 1.75]
ASCEND-ND 2021	45	1937	34	1935	41.7%	1.32 [0.85 , 2.05]
ASCEND-D 2021	43	1487	51	1477	46.1%	0.84 [0.56 , 1.25]
Subtotal (95% CI)		**4166**		**3859**	**100.0%**	**0.95 [0.64 , 1.40]**
Total events:	94		93			
Heterogeneity: Tau² = 0.04; Chi² = 5.17, df = 4 (P = 0.27); I² = 23%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 1.52, df = 3 (P = 0.68), I² = 0%						



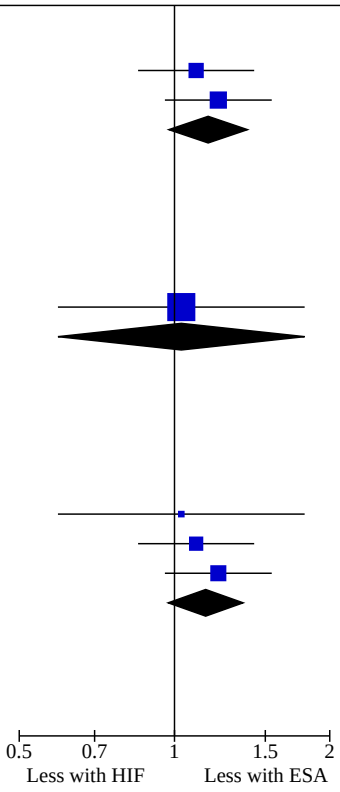
Analysis 3.8. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 8: Nonfatal hospitalisation for heart failure

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.8.1 Medium-dose HIF						
ASCEND-D 2021	85	1487	73	1477	46.0%	1.16 [0.85 , 1.57]
ASCEND-ND 2021	107	1937	82	1935	54.0%	1.30 [0.98 , 1.73]
Subtotal (95% CI)		**3424**		**3412**	**100.0%**	**1.23 [1.00 , 1.52]**
Total events:	192		155			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.00 (P = 0.05)						
Total (95% CI)		**3424**		**3412**	**100.0%**	**1.23 [1.00 , 1.52]**
Total events:	192		155			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.00 (P = 0.05)						
Test for subgroup differences: Not applicable						



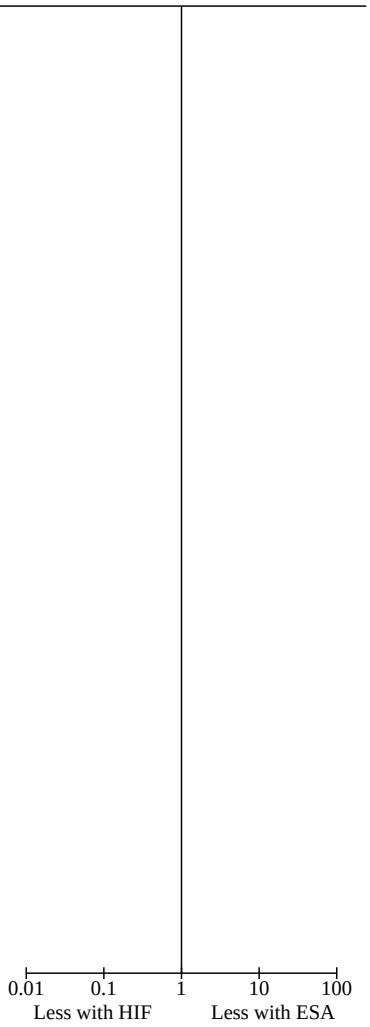
Analysis 3.9. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 9: Fatal or nonfatal hospitalisation for heart failure

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Medium-dose HIF						
ASCEND-D 2021	112	1487	101	1477	45.9%	1.10 [0.85 , 1.43]
ASCEND-ND 2021	140	1937	115	1935	54.1%	1.22 [0.96 , 1.54]
Subtotal (95% CI)		**3424**		**3412**	**100.0%**	**1.16 [0.98 , 1.39]**
Total events:	252		216			
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
3.9.2 High-dose HIF						
DOLOMITES 2021	25	323	22	293	100.0%	1.03 [0.59 , 1.79]
Subtotal (95% CI)		**323**		**293**	**100.0%**	**1.03 [0.59 , 1.79]**
Total events:	25		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
3.9.3 Overall dose HIF						
DOLOMITES 2021	25	323	22	293	9.2%	1.03 [0.59 , 1.79]
ASCEND-D 2021	112	1487	101	1477	41.6%	1.10 [0.85 , 1.43]
ASCEND-ND 2021	140	1937	115	1935	49.2%	1.22 [0.96 , 1.54]
Subtotal (95% CI)		**3747**		**3705**	**100.0%**	**1.15 [0.97 , 1.36]**
Total events:	277		238			
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 0.17, df = 2 (P = 0.92), I² = 0%						



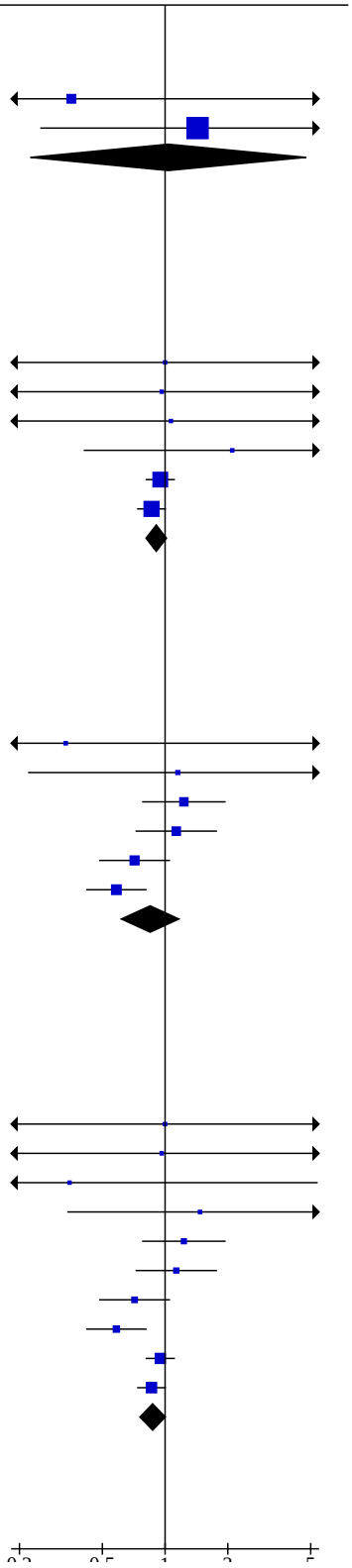
Analysis 3.10. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 10: Peripheral arterial event

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.10.1 Low-dose HIF						
DIALOGUE 2 2019	0	30	0	32		Not estimable
DIALOGUE 4 2019	0	44	0	42		Not estimable
Subtotal (95% CI)		**74**		**74**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.10.2 Medium-dose HIF						
DIALOGUE 2 2019	0	30	0	32		Not estimable
DIALOGUE 4 2019	0	40	0	42		Not estimable
Subtotal (95% CI)		**70**		**74**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.10.3 High-dose HIF						
DIALOGUE 2 2019	0	32	0	32		Not estimable
DIALOGUE 4 2019	0	73	0	42		Not estimable
Subtotal (95% CI)		**105**		**74**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.10.4 Overall dose HIF						
DIALOGUE 2 2019	0	92	0	32		Not estimable
DIALOGUE 4 2019	0	157	0	42		Not estimable
Subtotal (95% CI)		**249**		**74**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



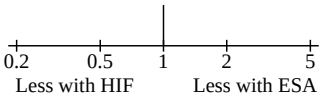
Analysis 3.11. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 11: Transfusion

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.11.1 Low-dose HIF						
Chen DD 2017	0	22	0	22		Not estimable
DIALOGUE 2 2019	0	30	1	32	23.2%	0.35 [0.02 , 8.39]
DIALOGUE 4 2019	3	44	2	42	76.8%	1.43 [0.25 , 8.15]
Subtotal (95% CI)		**96**		**96**	**100.0%**	**1.04 [0.23 , 4.75]**
Total events:	3		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
3.11.2 Medium-dose HIF						
Chen DD 2017	0	18	0	22		Not estimable
MIYABI ND-M 2019	1	82	1	82	0.2%	1.00 [0.06 , 15.72]
MIYABI ND-C 2019	1	82	1	79	0.2%	0.96 [0.06 , 15.14]
DIALOGUE 2 2019	1	30	1	32	0.2%	1.07 [0.07 , 16.30]
DIALOGUE 4 2019	4	40	2	42	0.5%	2.10 [0.41 , 10.84]
ASCEND-ND 2021	248	1937	261	1933	48.8%	0.95 [0.81 , 1.11]
ASCEND-D 2021	234	1487	270	1477	50.3%	0.86 [0.73 , 1.01]
Subtotal (95% CI)		**3676**		**3667**	**100.0%**	**0.91 [0.81 , 1.02]**
Total events:	489		536			
Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 5 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
3.11.3 High-dose HIF						
Chen DD 2017	0	20	0	22		Not estimable
DIALOGUE 2 2019	0	32	1	32	1.0%	0.33 [0.01 , 7.89]
DIALOGUE 4 2019	4	73	2	42	3.4%	1.15 [0.22 , 6.02]
DOLOMITES 2021	38	322	28	292	21.5%	1.23 [0.78 , 1.95]
HIMALAYAS 2021	38	522	33	513	22.0%	1.13 [0.72 , 1.78]
PYRENEES 2021	38	414	54	420	24.6%	0.71 [0.48 , 1.06]
SIERRAS 2021	46	369	79	370	27.5%	0.58 [0.42 , 0.82]
Subtotal (95% CI)		**1752**		**1691**	**100.0%**	**0.85 [0.62 , 1.16]**
Total events:	164		197			
Heterogeneity: Tau² = 0.07; Chi² = 9.85, df = 5 (P = 0.08); I² = 49%						
Test for overall effect: Z = 1.02 (P = 0.31)						
3.11.4 Overall dose HIF						
Chen DD 2017	0	60	0	22		Not estimable
MIYABI ND-M 2019	1	82	1	82	0.3%	1.00 [0.06 , 15.72]
MIYABI ND-C 2019	1	82	1	79	0.3%	0.96 [0.06 , 15.14]
DIALOGUE 2 2019	1	92	1	32	0.3%	0.35 [0.02 , 5.40]
DIALOGUE 4 2019	11	157	2	42	0.9%	1.47 [0.34 , 6.38]
DOLOMITES 2021	38	322	28	292	7.8%	1.23 [0.78 , 1.95]
HIMALAYAS 2021	38	522	33	513	8.1%	1.13 [0.72 , 1.78]
PYRENEES 2021	38	414	54	420	10.1%	0.71 [0.48 , 1.06]
SIERRAS 2021	46	369	79	370	13.0%	0.58 [0.42 , 0.82]
ASCEND-ND 2021	248	1937	261	1933	29.5%	0.95 [0.81 , 1.11]
ASCEND-D 2021	234	1487	270	1477	29.9%	0.86 [0.73 , 1.01]
Subtotal (95% CI)		**5524**		**5262**	**100.0%**	**0.87 [0.76 , 1.00]**
Total events:	656		730			
Heterogeneity: Tau² = 0.01; Chi² = 11.94, df = 9 (P = 0.22); I² = 25%						
Test for overall effect: Z = 1.92 (P = 0.05)						
Test for subgroup differences: Chi² = 0.32, df = 3 (P = 0.96), I² = 0%						



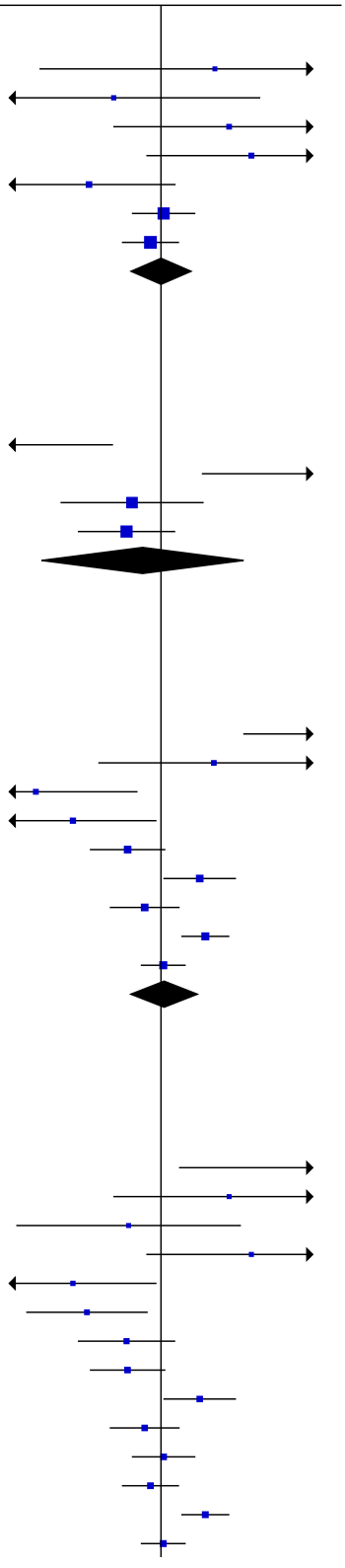
Analysis 3.11. (Continued)

Test for subgroup differences: Chi² = 0.32, df = 3 (P = 0.96), I² = 0%



Analysis 3.12. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 12: Proportion reaching target haemoglobin

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.12.1 Low-dose HIF						
Chen DD 2017	13	22	11	22	2.8%	1.18 [0.69 , 2.04]
DIALOGUE 4 2019	19	44	21	42	3.9%	0.86 [0.55 , 1.36]
Holdstock 2019a	22	30	19	32	6.0%	1.24 [0.86 , 1.77]
Holdstock 2019	78	112	20	38	7.1%	1.32 [0.96 , 1.83]
DIALOGUE 2 2019	21	30	28	32	9.8%	0.80 [0.61 , 1.05]
SYMPHONY ND 2021	93	105	94	107	33.9%	1.01 [0.91 , 1.11]
Akizawa 2020c	105	120	113	125	36.6%	0.97 [0.89 , 1.06]
Subtotal (95% CI)		**463**		**398**	**100.0%**	**1.00 [0.91 , 1.10]**
Total events:	351		306			
Heterogeneity: Tau² = 0.00; Chi² = 8.66, df = 6 (P = 0.19); I² = 31%						
Test for overall effect: Z = 0.01 (P = 0.99)						
3.12.2 Medium-dose HIF						
DIALOGUE 4 2019	9	40	21	42	14.2%	0.45 [0.23 , 0.86]
Chen DD 2017	16	18	11	22	20.9%	1.78 [1.14 , 2.78]
DIALOGUE 2 2019	24	30	28	32	31.0%	0.91 [0.73 , 1.14]
Nangaku 2021	104	162	115	161	33.8%	0.90 [0.77 , 1.05]
Subtotal (95% CI)		**250**		**257**	**100.0%**	**0.94 [0.69 , 1.29]**
Total events:	153		175			
Heterogeneity: Tau² = 0.07; Chi² = 13.26, df = 3 (P = 0.004); I² = 77%						
Test for overall effect: Z = 0.36 (P = 0.72)						
3.12.3 High-dose HIF						
Chen DD 2017	20	20	11	22	4.6%	1.95 [1.29 , 2.95]
DIALOGUE 4 2019	43	73	21	42	5.6%	1.18 [0.82 , 1.69]
DIALOGUE 2 2019	19	32	28	32	6.6%	0.68 [0.50 , 0.93]
HIMALAYAS 2021	83	522	108	517	8.3%	0.76 [0.59 , 0.99]
Akizawa 2021	101	131	112	131	14.2%	0.90 [0.80 , 1.01]
SIERRAS 2021	244	369	217	370	14.4%	1.13 [1.01 , 1.26]
Akizawa 2020a	119	150	126	151	14.5%	0.95 [0.85 , 1.06]
DOLOMITES 2021	256	286	213	273	15.9%	1.15 [1.06 , 1.24]
Chen 2019	189	204	92	100	16.1%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**1787**		**1638**	**100.0%**	**1.01 [0.91 , 1.12]**
Total events:	1074		928			
Heterogeneity: Tau² = 0.02; Chi² = 39.83, df = 8 (P < 0.00001); I² = 80%						
Test for overall effect: Z = 0.18 (P = 0.85)						
3.12.4 Overall dose HIF						
Chen DD 2017	49	60	11	22	2.0%	1.63 [1.06 , 2.52]
Holdstock 2019a	22	30	19	32	2.7%	1.24 [0.86 , 1.77]
DIALOGUE 4 2019	71	157	21	42	2.9%	0.90 [0.64 , 1.28]
Holdstock 2019	78	112	20	38	3.2%	1.32 [0.96 , 1.83]
HIMALAYAS 2021	83	522	108	517	4.4%	0.76 [0.59 , 0.99]
DIALOGUE 2 2019	64	92	28	32	6.3%	0.80 [0.66 , 0.96]
Nangaku 2021	104	162	115	161	7.7%	0.90 [0.77 , 1.05]
Akizawa 2021	101	131	112	131	9.2%	0.90 [0.80 , 1.01]
SIERRAS 2021	244	369	217	370	9.4%	1.13 [1.01 , 1.26]
Akizawa 2020a	119	150	126	151	9.6%	0.95 [0.85 , 1.06]
SYMPHONY ND 2021	93	105	94	107	10.0%	1.01 [0.91 , 1.11]
Akizawa 2020c	105	120	113	125	10.4%	0.97 [0.89 , 1.06]
DOLOMITES 2021	256	286	213	273	11.0%	1.15 [1.06 , 1.24]
Chen 2019	189	204	92	100	11.2%	1.01 [0.94 , 1.08]



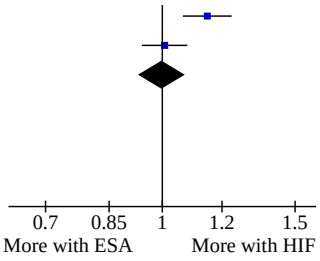
Analysis 3.12. (Continued)

DOLOMITES 2021	256	286	213	273	11.0%	1.15 [1.06 , 1.24]
Chen 2019	189	204	92	100	11.2%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**2500**		**2101**	**100.0%**	**1.00 [0.93 , 1.07]**
Total events:	1578		1289			

Heterogeneity: Tau² = 0.01; Chi² = 42.66, df = 13 (P < 0.0001); I² = 70%

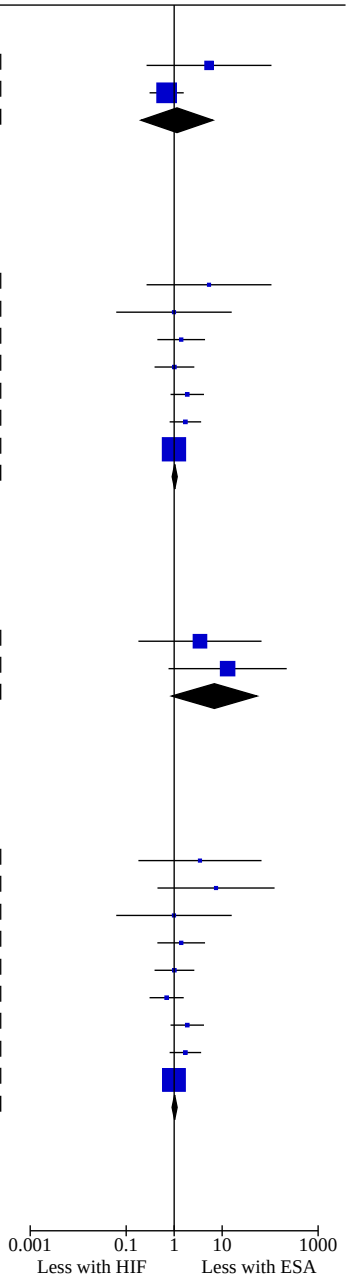
Test for overall effect: Z = 0.09 (P = 0.93)

Test for subgroup differences: Chi² = 0.17, df = 3 (P = 0.98), I² = 0%



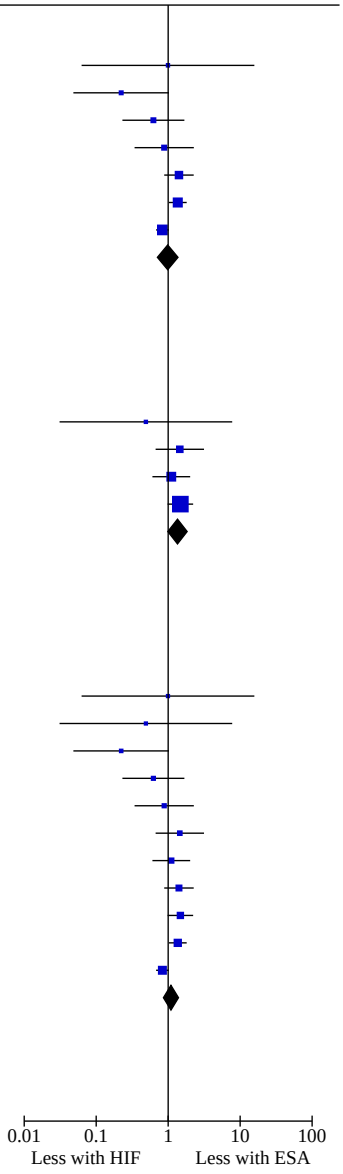
Analysis 3.13. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 13: Kidney failure

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.13.1 Low-dose HIF						
DIALOGUE 2 2019	2	30	0	32	24.3%	5.32 [0.27 , 106.54]
Nangaku 2021b	9	149	13	150	75.7%	0.70 [0.31 , 1.58]
Subtotal (95% CI)		**179**		**182**	**100.0%**	**1.14 [0.20 , 6.43]**
Total events:	11		13			
Heterogeneity: Tau² = 0.85; Chi² = 1.68, df = 1 (P = 0.20); I² = 40%						
Test for overall effect: Z = 0.15 (P = 0.88)						
3.13.2 Medium-dose HIF						
DIALOGUE 2 2019	2	30	0	32	0.2%	5.32 [0.27 , 106.54]
PRO2TECT-CORRECTION 2021	1	878	1	870	0.2%	0.99 [0.06 , 15.82]
PRO2TECT-CONVERSION 2021	7	861	5	862	1.1%	1.40 [0.45 , 4.40]
Nangaku 2021a	8	151	8	153	1.6%	1.01 [0.39 , 2.63]
MIYABI ND-M 2019	15	82	8	82	2.3%	1.88 [0.84 , 4.18]
MIYABI ND-C 2019	16	82	9	79	2.5%	1.71 [0.80 , 3.65]
ASCEND-ND 2021	343	1220	359	1265	92.2%	0.99 [0.87 , 1.12]
Subtotal (95% CI)		**3304**		**3343**	**100.0%**	**1.03 [0.91 , 1.16]**
Total events:	392		390			
Heterogeneity: Tau² = 0.00; Chi² = 5.72, df = 6 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.67)						
3.13.3 High-dose HIF						
Chen 2019	3	204	0	100	48.0%	3.45 [0.18 , 66.13]
DIALOGUE 2 2019	6	32	0	32	52.0%	13.00 [0.76 , 221.55]
Subtotal (95% CI)		**236**		**132**	**100.0%**	**6.88 [0.89 , 53.20]**
Total events:	9		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
3.13.4 Overall dose HIF						
Chen 2019	3	204	0	100	0.2%	3.45 [0.18 , 66.13]
DIALOGUE 2 2019	10	92	0	32	0.2%	7.45 [0.45 , 123.66]
PRO2TECT-CORRECTION 2021	1	878	1	870	0.2%	0.99 [0.06 , 15.82]
PRO2TECT-CONVERSION 2021	7	861	5	862	1.1%	1.40 [0.45 , 4.40]
Nangaku 2021a	8	151	8	153	1.6%	1.01 [0.39 , 2.63]
Nangaku 2021b	9	149	13	150	2.2%	0.70 [0.31 , 1.58]
MIYABI ND-M 2019	15	82	8	82	2.3%	1.88 [0.84 , 4.18]
MIYABI ND-C 2019	16	82	9	79	2.5%	1.71 [0.80 , 3.65]
ASCEND-ND 2021	343	1220	359	1265	89.8%	0.99 [0.87 , 1.12]
Subtotal (95% CI)		**3719**		**3593**	**100.0%**	**1.02 [0.91 , 1.15]**
Total events:	412		403			
Heterogeneity: Tau² = 0.00; Chi² = 8.01, df = 8 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
Test for subgroup differences: Chi² = 3.34, df = 3 (P = 0.34), I² = 10.3%						



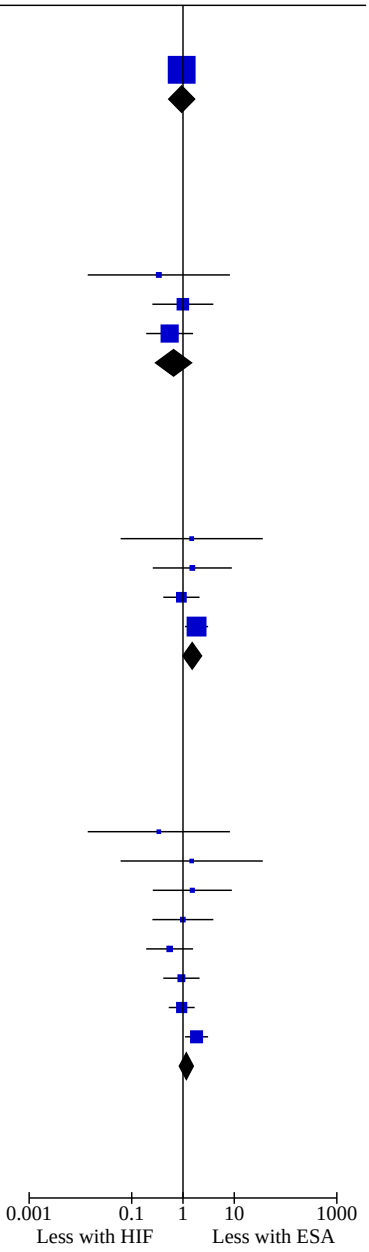
Analysis 3.14. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 14: Thrombosis

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.14.1 Medium-dose HIF						
Nangaku 2021	1	162	1	161	1.4%	0.99 [0.06 , 15.75]
PRO2TECT-CONVERSION 2021	2	861	9	862	4.1%	0.22 [0.05 , 1.03]
INNO2VATE 2020	6	179	10	186	8.3%	0.62 [0.23 , 1.68]
PRO2TECT-CORRECTION 2021	8	878	9	870	8.9%	0.88 [0.34 , 2.27]
ASCEND-ND 2021	41	1937	29	1935	20.0%	1.41 [0.88 , 2.26]
INNO2VATE 2020a	106	1768	78	1769	27.1%	1.36 [1.02 , 1.81]
ASCEND-D 2021	154	1487	184	1477	30.2%	0.83 [0.68 , 1.02]
Subtotal (95% CI)		**7272**		**7260**	**100.0%**	**0.99 [0.71 , 1.37]**
Total events:	318		320			
Heterogeneity: Tau² = 0.08; Chi² = 14.39, df = 6 (P = 0.03); I² = 58%						
Test for overall effect: Z = 0.09 (P = 0.93)						
3.14.2 High-dose HIF						
Chen 2019	1	204	1	100	1.2%	0.49 [0.03 , 7.76]
DOLOMITES 2021	16	323	10	293	15.8%	1.45 [0.67 , 3.15]
SIERRAS 2021	21	370	19	370	26.0%	1.11 [0.60 , 2.02]
PYRENEES 2021	51	414	35	420	56.9%	1.48 [0.98 , 2.22]
Subtotal (95% CI)		**1311**		**1183**	**100.0%**	**1.35 [0.99 , 1.83]**
Total events:	89		65			
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.90 (P = 0.06)						
3.14.3 Overall dose HIF						
Nangaku 2021	1	162	1	161	0.7%	0.99 [0.06 , 15.75]
Chen 2019	1	204	1	100	0.7%	0.49 [0.03 , 7.76]
PRO2TECT-CONVERSION 2021	2	861	9	862	2.3%	0.22 [0.05 , 1.03]
INNO2VATE 2020	6	179	10	186	4.8%	0.62 [0.23 , 1.68]
PRO2TECT-CORRECTION 2021	8	878	9	870	5.2%	0.88 [0.34 , 2.27]
DOLOMITES 2021	16	323	10	293	7.0%	1.45 [0.67 , 3.15]
SIERRAS 2021	21	370	19	370	9.9%	1.11 [0.60 , 2.02]
ASCEND-ND 2021	41	1937	29	1935	13.1%	1.41 [0.88 , 2.26]
PYRENEES 2021	51	414	35	420	14.9%	1.48 [0.98 , 2.22]
INNO2VATE 2020a	106	1768	78	1769	19.2%	1.36 [1.02 , 1.81]
ASCEND-D 2021	154	1487	184	1477	22.2%	0.83 [0.68 , 1.02]
Subtotal (95% CI)		**8583**		**8443**	**100.0%**	**1.09 [0.86 , 1.39]**
Total events:	407		385			
Heterogeneity: Tau² = 0.06; Chi² = 18.68, df = 10 (P = 0.04); I² = 46%						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: Chi² = 2.00, df = 2 (P = 0.37), I² = 0.1%						



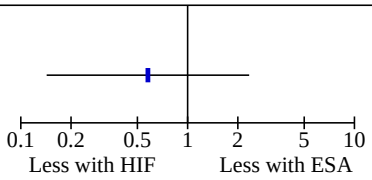
Analysis 3.15. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 15: Loss of unassisted patency (occlusion/stenosis)

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.15.1 Low-dose HIF						
Akizawa 2020c	19	136	20	135	100.0%	0.94 [0.53 , 1.69]
Subtotal (95% CI)		**136**		**135**	**100.0%**	**0.94 [0.53 , 1.69]**
Total events:	19		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
3.15.2 Medium-dose HIF						
Nangaku 2021a	0	151	1	153	6.4%	0.34 [0.01 , 8.23]
Nangaku 2021	4	162	4	161	34.8%	0.99 [0.25 , 3.91]
SYMPHONY HD 2021	5	87	9	86	58.9%	0.55 [0.19 , 1.57]
Subtotal (95% CI)		**400**		**400**	**100.0%**	**0.65 [0.29 , 1.47]**
Total events:	9		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
3.15.3 High-dose HIF						
Chen 2019	1	204	0	100	1.7%	1.48 [0.06 , 35.96]
Akizawa 2020a	3	150	2	152	5.6%	1.52 [0.26 , 8.97]
MIYABI HD-M 2019	15	153	8	76	26.7%	0.93 [0.41 , 2.10]
HIMALAYAS 2021	39	522	21	517	66.0%	1.84 [1.10 , 3.08]
Subtotal (95% CI)		**1029**		**845**	**100.0%**	**1.51 [0.99 , 2.30]**
Total events:	58		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
3.15.4 Overall dose HIF						
Nangaku 2021a	0	151	1	153	1.0%	0.34 [0.01 , 8.23]
Chen 2019	1	204	0	100	1.0%	1.48 [0.06 , 35.96]
Akizawa 2020a	3	150	2	152	3.1%	1.52 [0.26 , 8.97]
Nangaku 2021	4	162	4	161	5.2%	0.99 [0.25 , 3.91]
SYMPHONY HD 2021	5	87	9	86	8.9%	0.55 [0.19 , 1.57]
MIYABI HD-M 2019	15	153	8	76	14.9%	0.93 [0.41 , 2.10]
Akizawa 2020c	19	136	20	135	29.1%	0.94 [0.53 , 1.69]
HIMALAYAS 2021	39	522	21	517	36.8%	1.84 [1.10 , 3.08]
Subtotal (95% CI)		**1565**		**1380**	**100.0%**	**1.16 [0.85 , 1.59]**
Total events:	86		65			
Heterogeneity: Tau² = 0.00; Chi² = 6.51, df = 7 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi² = 3.96, df = 3 (P = 0.27), I² = 24.2%						

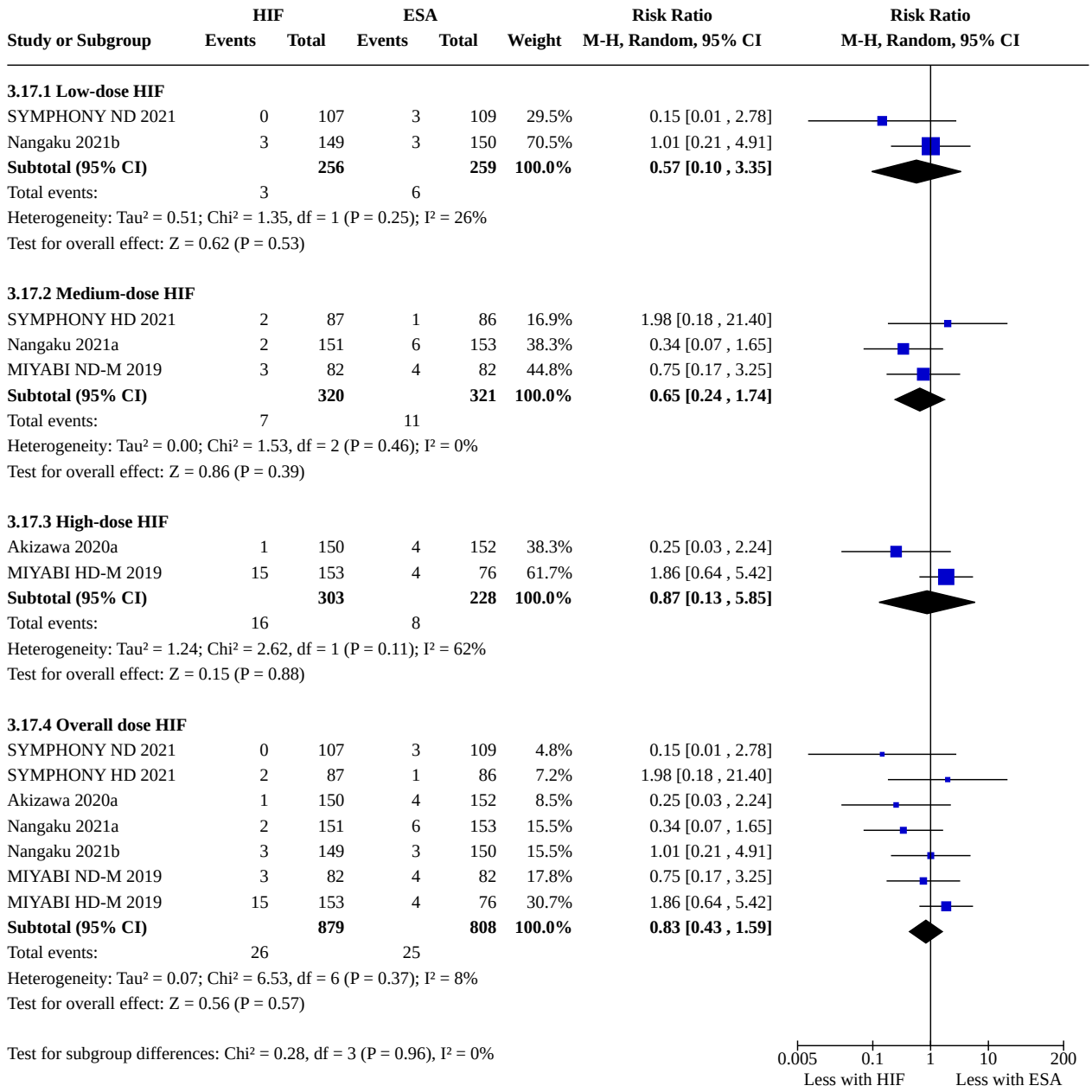


Analysis 3.16. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 16: Access intervention

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Risk Ratio M-H, Random, 95% CI
3.16.1 High-dose HIF					
MIYABI ND-C 2019	3	82	5	79	0.58 [0.14 , 2.34]

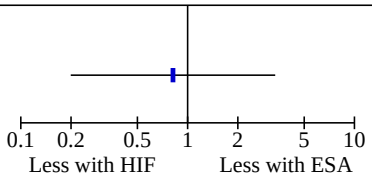


Analysis 3.17. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 17: Cancer



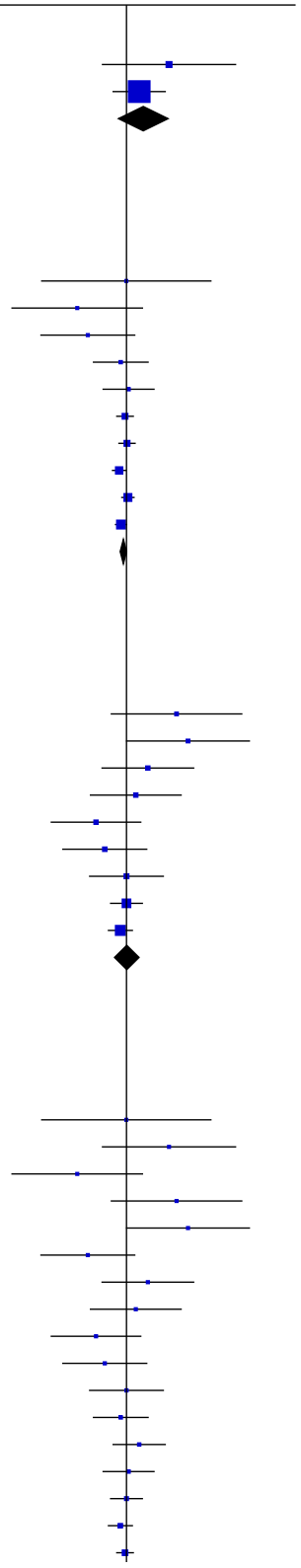
Analysis 3.18. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 18: Infection

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Risk Ratio M-H, Random, 95% CI
3.18.1 High-dose HIF					
Chen 2019	5	204	3	100	0.82 [0.20 , 3.35]



Analysis 3.19. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 19: Hyperkalaemia

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.19.1 Low-dose HIF						
Akizawa 2020c	4	136	1	135	13.6%	3.97 [0.45 , 35.07]
Nangaku 2021b	12	149	8	150	86.4%	1.51 [0.64 , 3.59]
Subtotal (95% CI)		**285**		**285**	**100.0%**	**1.72 [0.77 , 3.85]**
Total events:	16		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
3.19.2 Medium-dose HIF						
Nangaku 2021	1	162	1	161	0.1%	0.99 [0.06 , 15.75]
Nangaku 2021a	1	151	5	153	0.2%	0.20 [0.02 , 1.71]
MIYABI ND-M 2019	2	82	7	82	0.5%	0.29 [0.06 , 1.33]
INNO2VATE 2020	8	179	10	186	1.3%	0.83 [0.34 , 2.06]
MIYABI ND-C 2019	10	82	9	79	1.5%	1.07 [0.46 , 2.49]
PRO2TECT-CONVERSION 2021	81	861	85	862	13.0%	0.95 [0.71 , 1.27]
ASCEND-D 2021	91	1482	89	1474	13.6%	1.02 [0.77 , 1.35]
PRO2TECT-CORRECTION 2021	108	878	136	870	19.8%	0.79 [0.62 , 0.99]
ASCEND-ND 2021	151	1937	144	1934	22.6%	1.05 [0.84 , 1.30]
INNO2VATE 2020a	160	1768	191	1769	27.4%	0.84 [0.69 , 1.02]
Subtotal (95% CI)		**7582**		**7570**	**100.0%**	**0.90 [0.82 , 1.00]**
Total events:	613		677			
Heterogeneity: Tau² = 0.00; Chi² = 8.63, df = 9 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.88 (P = 0.06)						
3.19.3 High-dose HIF						
Akizawa 2020a	5	150	1	152	3.2%	5.07 [0.60 , 42.86]
Chen 2019	15	204	1	100	3.6%	7.35 [0.99 , 54.88]
Hou 2021	8	86	2	43	6.1%	2.00 [0.44 , 9.01]
PYRENEES 2021	4	414	3	420	6.2%	1.35 [0.30 , 6.01]
MIYABI HD-M 2019	3	153	4	76	6.4%	0.37 [0.09 , 1.62]
HIMALAYAS 2021	3	522	6	517	7.1%	0.50 [0.12 , 1.97]
Akizawa 2021	5	131	5	131	8.8%	1.00 [0.30 , 3.37]
SIERRAS 2021	25	370	25	370	26.1%	1.00 [0.59 , 1.71]
DOLOMITES 2021	38	323	42	293	32.4%	0.82 [0.55 , 1.24]
Subtotal (95% CI)		**2353**		**2102**	**100.0%**	**1.01 [0.68 , 1.50]**
Total events:	106		89			
Heterogeneity: Tau² = 0.08; Chi² = 10.73, df = 8 (P = 0.22); I² = 25%						
Test for overall effect: Z = 0.05 (P = 0.96)						
3.19.4 Overall dose HIF						
Nangaku 2021	1	162	1	161	0.2%	0.99 [0.06 , 15.75]
Akizawa 2020c	4	136	1	135	0.3%	3.97 [0.45 , 35.07]
Nangaku 2021a	1	151	5	153	0.3%	0.20 [0.02 , 1.71]
Akizawa 2020a	5	150	1	152	0.3%	5.07 [0.60 , 42.86]
Chen 2019	15	204	1	100	0.3%	7.35 [0.99 , 54.88]
MIYABI ND-M 2019	2	82	7	82	0.5%	0.29 [0.06 , 1.33]
Hou 2021	8	86	2	43	0.6%	2.00 [0.44 , 9.01]
PYRENEES 2021	4	414	3	420	0.6%	1.35 [0.30 , 6.01]
MIYABI HD-M 2019	3	153	4	76	0.6%	0.37 [0.09 , 1.62]
HIMALAYAS 2021	3	522	6	517	0.7%	0.50 [0.12 , 1.97]
Akizawa 2021	5	131	5	131	0.9%	1.00 [0.30 , 3.37]
INNO2VATE 2020	8	179	10	186	1.5%	0.83 [0.34 , 2.06]
Nangaku 2021b	12	149	8	150	1.7%	1.51 [0.64 , 3.59]
MIYABI ND-C 2019	10	82	9	79	1.8%	1.07 [0.46 , 2.49]
SIERRAS 2021	25	370	25	370	4.2%	1.00 [0.59 , 1.71]
DOLOMITES 2021	38	323	42	293	6.8%	0.82 [0.55 , 1.24]
PRO2TECT-CONVERSION 2021	81	861	85	862	12.0%	0.95 [0.71 , 1.27]



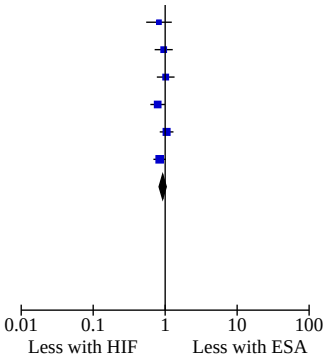
Analysis 3.19. (Continued)

DOLOMITES 2021	38	323	42	293	6.8%	0.82 [0.55 , 1.24]
PRO2TECT-CONVERSION 2021	81	861	85	862	12.0%	0.95 [0.71 , 1.27]
ASCEND-D 2021	91	1482	89	1474	12.4%	1.02 [0.77 , 1.35]
PRO2TECT-CORRECTION 2021	108	878	136	870	16.3%	0.79 [0.62 , 0.99]
ASCEND-ND 2021	151	1937	144	1934	17.9%	1.05 [0.84 , 1.30]
INNO2VATE 2020a	160	1768	191	1769	20.2%	0.84 [0.69 , 1.02]
Subtotal (95% CI)		**10220**		**9957**	**100.0%**	**0.92 [0.82 , 1.04]**
Total events:	735		775			

Heterogeneity: Tau² = 0.01; Chi² = 22.24, df = 20 (P = 0.33); I² = 10%

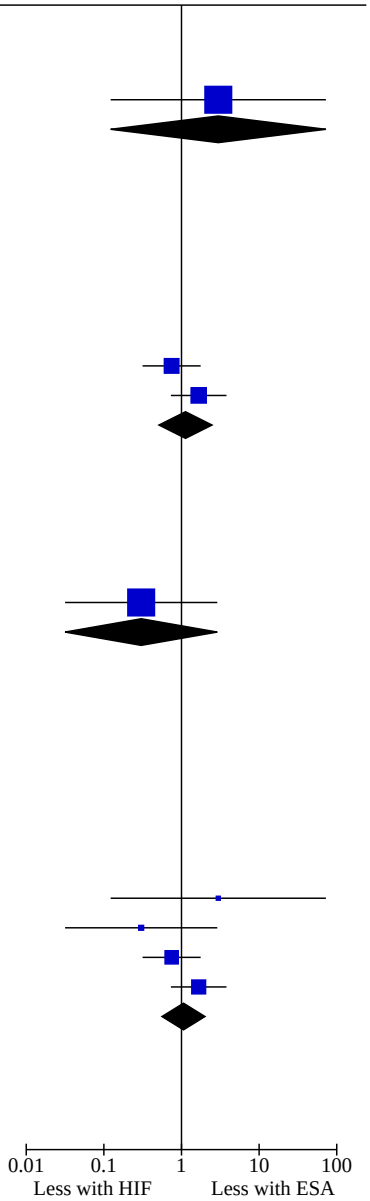
Test for overall effect: Z = 1.37 (P = 0.17)

Test for subgroup differences: Chi² = 2.65, df = 3 (P = 0.45), I² = 0%

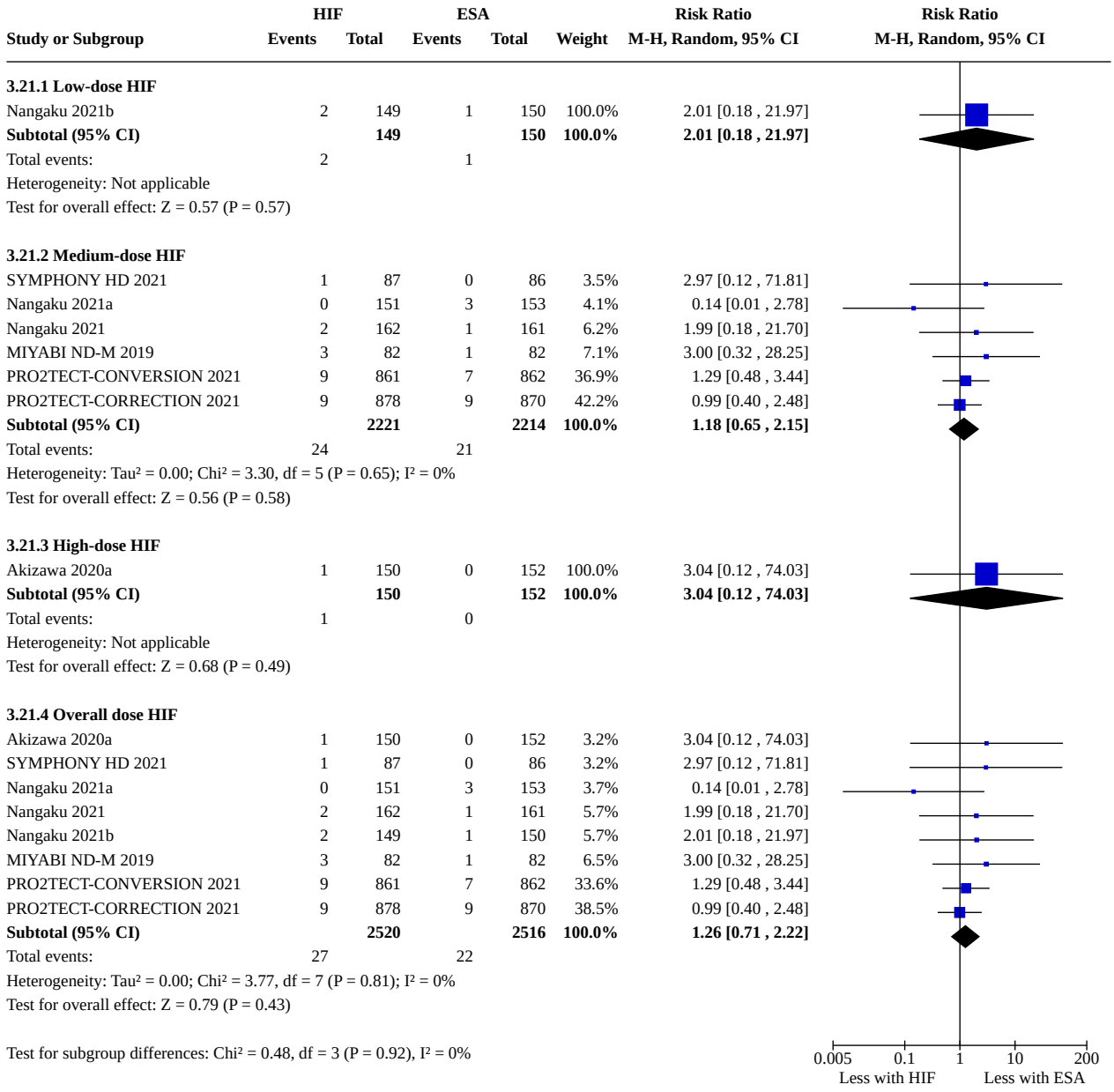


Analysis 3.20. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 20: Pulmonary hypertension

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
3.20.1 Low-dose HIF						
Nangaku 2021b	0	149	0	150		Not estimable
Akizawa 2020c	1	136	0	135	100.0%	2.98 [0.12 , 72.46]
Subtotal (95% CI)		**285**		**285**	**100.0%**	**2.98 [0.12 , 72.46]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
3.20.2 Medium-dose HIF						
Nangaku 2021a	0	151	0	153		Not estimable
Nangaku 2021	0	162	0	161		Not estimable
ASCEND-D 2021	9	1482	12	1474	48.7%	0.75 [0.32 , 1.77]
ASCEND-ND 2021	15	1937	9	1935	51.3%	1.66 [0.73 , 3.80]
Subtotal (95% CI)		**3732**		**3723**	**100.0%**	**1.13 [0.51 , 2.47]**
Total events:	24		21			
Heterogeneity: Tau² = 0.14; Chi² = 1.74, df = 1 (P = 0.19); I² = 43%						
Test for overall effect: Z = 0.30 (P = 0.77)						
3.20.3 High-dose HIF						
DOLOMITES 2021	1	323	3	293	100.0%	0.30 [0.03 , 2.89]
Subtotal (95% CI)		**323**		**293**	**100.0%**	**0.30 [0.03 , 2.89]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
3.20.4 Overall dose HIF						
Nangaku 2021a	0	151	0	153		Not estimable
Nangaku 2021	0	162	0	161		Not estimable
Nangaku 2021b	0	149	0	150		Not estimable
Akizawa 2020c	1	136	0	135	3.9%	2.98 [0.12 , 72.46]
DOLOMITES 2021	1	323	3	293	7.6%	0.30 [0.03 , 2.89]
ASCEND-D 2021	9	1482	12	1474	42.7%	0.75 [0.32 , 1.77]
ASCEND-ND 2021	15	1937	9	1935	45.7%	1.66 [0.73 , 3.80]
Subtotal (95% CI)		**4340**		**4301**	**100.0%**	**1.06 [0.56 , 2.01]**
Total events:	26		24			
Heterogeneity: Tau² = 0.05; Chi² = 3.38, df = 3 (P = 0.34); I² = 11%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi² = 1.61, df = 3 (P = 0.66), I² = 0%						



Analysis 3.21. Comparison 3: Hypoxia-inducible factor (HIF) stabiliser versus erythropoiesis-stimulating agent (ESA), Outcome 21: Diabetic retinopathy



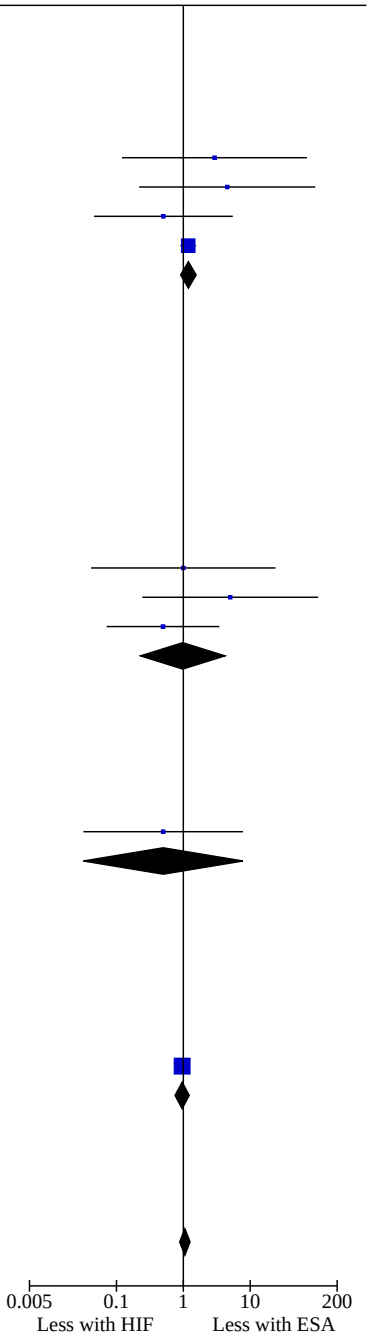
Comparison 4. Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA)

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 Cardiovascular death	17	10340	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.26]
4.1.1 CKD	7	5591	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.91, 1.55]
4.1.2 HD	7	1352	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.23, 4.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.3 PD	1	129	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.03, 7.80]
4.1.4 HD and PD	2	3268	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.23]
4.2 Fatigue	2	3471	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.16]
4.2.1 CKD	2	3471	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.16]
4.3 Nonfatal myocardial infarction	7	7765	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.10]
4.3.1 CKD	2	3996	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.80, 1.39]
4.3.2 HD	2	372	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.22, 17.59]
4.3.3 PD	1	129	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.06, 36.48]
4.3.4 HD and PD	2	3268	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.03]
4.4 Nonfatal stroke	5	7285	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.56]
4.4.1 CKD	3	4122	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.82, 2.48]
4.4.2 HD	1	199	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.07, 27.82]
4.4.3 HD and PD	1	2964	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.51, 1.34]
4.5 Transfusion	11	10786	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
4.5.1 CKD	5	4933	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.13]
4.5.2 HD and PD	6	5853	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 1.01]
4.6 Proportion reaching target haemoglobin	14	4601	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
4.6.1 CKD	6	1369	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.90, 1.16]
4.6.2 HD and PD	8	3232	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.06]

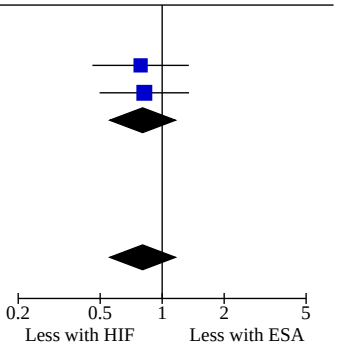
Analysis 4.1. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 1: Cardiovascular death

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 CKD						
SYMPHONY ND 2021	0	107	0	109		Not estimable
Akizawa 2021	0	131	0	131		Not estimable
MIYABI ND-M 2019	0	82	0	82		Not estimable
MIYABI ND-C 2019	1	82	0	80	0.3%	2.93 [0.12 , 70.82]
DOLOMITES 2021	2	323	0	293	0.3%	4.54 [0.22 , 94.12]
Nangaku 2021b	1	149	2	150	0.6%	0.50 [0.05 , 5.49]
ASCEND-ND 2021	109	1937	92	1935	43.4%	1.18 [0.90 , 1.55]
Subtotal (95% CI)		**2811**		**2780**	**44.7%**	**1.19 [0.91 , 1.55]**
Total events:	113		94			
Heterogeneity: Tau² = 0.00; Chi² = 1.56, df = 3 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
4.1.2 HD						
Akizawa 2020c	0	136	0	135		Not estimable
DIALOGUE 4 2019	0	117	0	42		Not estimable
SYMPHONY HD 2021	0	87	0	86		Not estimable
Chen DD 2017	0	65	0	22		Not estimable
NCT01888445	1	98	0	32	0.3%	1.00 [0.04 , 23.96]
Akizawa 2020a	2	151	0	152	0.3%	5.03 [0.24 , 103.96]
MIYABI HD-M 2019	2	153	2	76	0.8%	0.50 [0.07 , 3.46]
Subtotal (95% CI)		**807**		**545**	**1.5%**	**0.98 [0.23 , 4.19]**
Total events:	5		2			
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 2 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
4.1.3 PD						
Hou 2021	1	86	1	43	0.4%	0.50 [0.03 , 7.80]
Subtotal (95% CI)		**86**		**43**	**0.4%**	**0.50 [0.03 , 7.80]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
4.1.4 HD and PD						
Chen 2019	0	204	0	100		Not estimable
ASCEND-D 2021	117	1487	121	1477	53.4%	0.96 [0.75 , 1.23]
Subtotal (95% CI)		**1691**		**1577**	**53.4%**	**0.96 [0.75 , 1.23]**
Total events:	117		121			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
Total (95% CI)		**5395**		**4945**	**100.0%**	**1.05 [0.88 , 1.26]**
Total events:	236		218			
Heterogeneity: Tau² = 0.00; Chi² = 4.81, df = 8 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Chi² = 1.66, df = 3 (P = 0.65), I² = 0%						



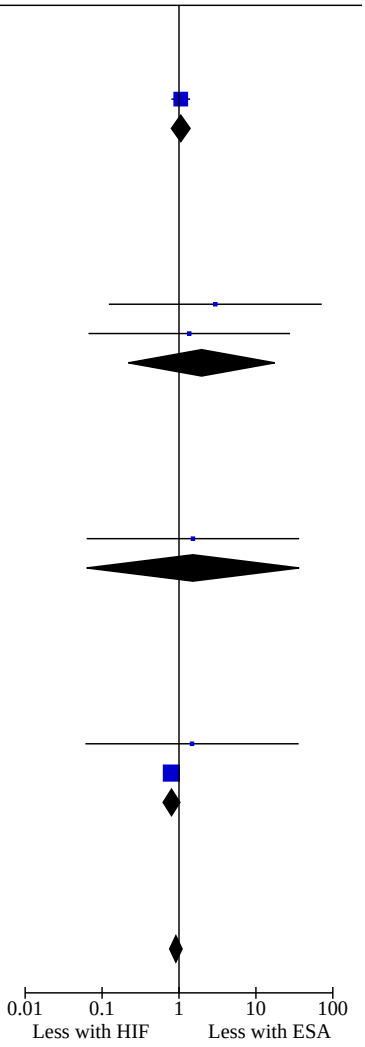
Analysis 4.2. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 2: Fatigue

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 CKD						
PRO2TECT-CORRECTION 2021	23	878	29	870	46.2%	0.79 [0.46 , 1.35]
PRO2TECT-CONVERSION 2021	27	861	33	862	53.8%	0.82 [0.50 , 1.35]
Subtotal (95% CI)		**1739**		**1732**	**100.0%**	**0.80 [0.56 , 1.16]**
Total events:	50		62			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**1739**		**1732**	**100.0%**	**0.80 [0.56 , 1.16]**
Total events:	50		62			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Not applicable						



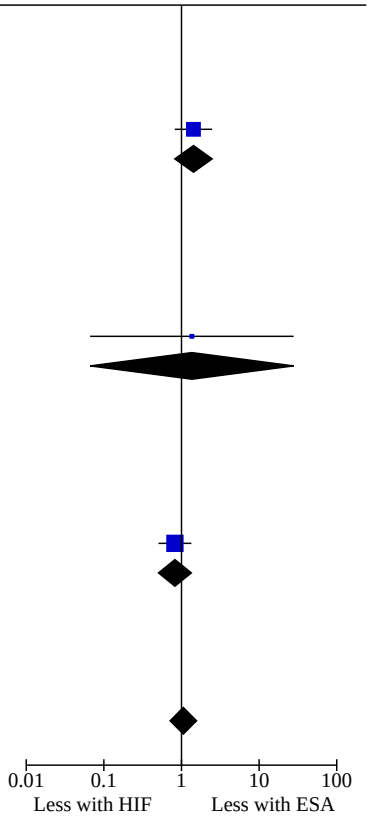
Analysis 4.3. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 3: Nonfatal myocardial infarction

Study or Subgroup	Less with HIF Events	Less with HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 CKD						
DIALOGUE 2 2019	0	92	0	32		Not estimable
ASCEND-ND 2021	96	1937	91	1935	44.1%	1.05 [0.80 , 1.39]
Subtotal (95% CI)		**2029**		**1967**	**44.1%**	**1.05 [0.80 , 1.39]**
Total events:	96		91			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
4.3.2 HD						
SYMPHONY HD 2021	1	87	0	86	0.3%	2.97 [0.12 , 71.81]
DIALOGUE 4 2019	2	157	0	42	0.4%	1.36 [0.07 , 27.82]
Subtotal (95% CI)		**244**		**128**	**0.7%**	**1.97 [0.22 , 17.59]**
Total events:	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.55)						
4.3.3 PD						
Hou 2021	1	86	0	43	0.3%	1.52 [0.06 , 36.48]
Subtotal (95% CI)		**86**		**43**	**0.3%**	**1.52 [0.06 , 36.48]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
4.3.4 HD and PD						
Chen 2019	1	204	0	100	0.3%	1.48 [0.06 , 35.96]
ASCEND-D 2021	101	1487	126	1477	54.5%	0.80 [0.62 , 1.02]
Subtotal (95% CI)		**1691**		**1577**	**54.8%**	**0.80 [0.62 , 1.03]**
Total events:	102		126			
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**4050**		**3715**	**100.0%**	**0.91 [0.76 , 1.10]**
Total events:	202		217			
Heterogeneity: Tau² = 0.00; Chi² = 2.93, df = 5 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 2.66, df = 3 (P = 0.45), I² = 0%						



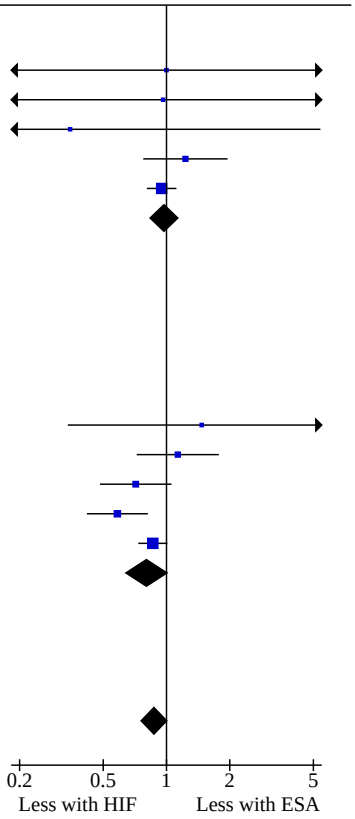
Analysis 4.4. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 4: Nonfatal stroke

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 CKD						
Holdstock 2019	0	134	0	45		Not estimable
Holdstock 2019a	0	36	0	35		Not estimable
ASCEND-ND 2021	30	1937	21	1935	43.7%	1.43 [0.82 , 2.48]
Subtotal (95% CI)		**2107**		**2015**	**43.7%**	**1.43 [0.82 , 2.48]**
Total events:	30		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
4.4.2 HD						
DIALOGUE 4 2019	2	157	0	42	1.7%	1.36 [0.07 , 27.82]
Subtotal (95% CI)		**157**		**42**	**1.7%**	**1.36 [0.07 , 27.82]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
4.4.3 HD and PD						
ASCEND-D 2021	29	1487	35	1477	54.6%	0.82 [0.51 , 1.34]
Subtotal (95% CI)		**1487**		**1477**	**54.6%**	**0.82 [0.51 , 1.34]**
Total events:	29		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
Total (95% CI)		**3751**		**3534**	**100.0%**	**1.06 [0.71 , 1.56]**
Total events:	61		56			
Heterogeneity: Tau² = 0.01; Chi² = 2.17, df = 2 (P = 0.34); I² = 8%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Chi² = 2.17, df = 2 (P = 0.34), I² = 7.8%						

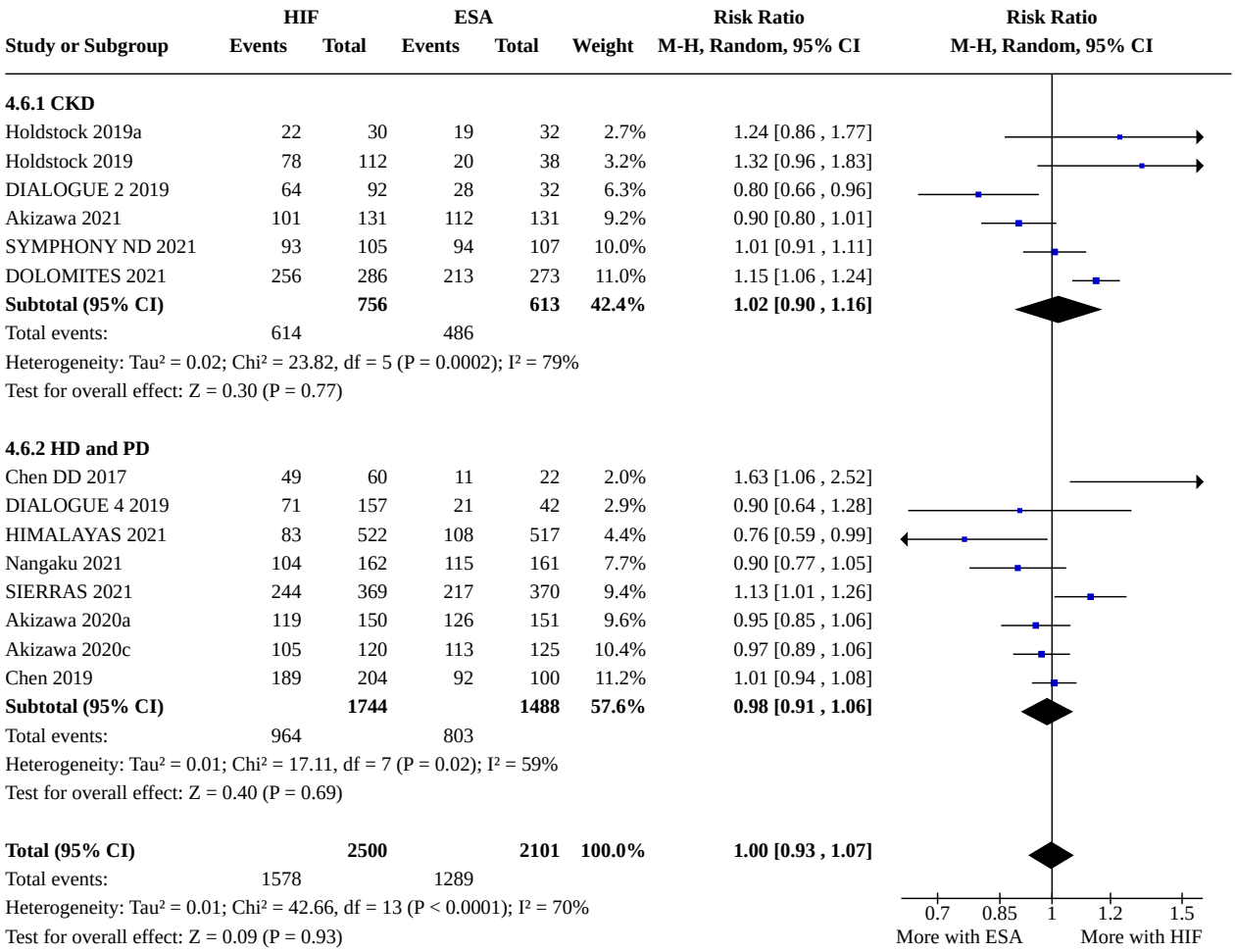


Analysis 4.5. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 5: Transfusion

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
4.5.1 CKD						
MIYABI ND-M 2019	1	82	1	82	0.3%	1.00 [0.06 , 15.72]
MIYABI ND-C 2019	1	82	1	79	0.3%	0.96 [0.06 , 15.14]
DIALOGUE 2 2019	1	92	1	32	0.3%	0.35 [0.02 , 5.40]
DOLOMITES 2021	38	322	28	292	7.8%	1.23 [0.78 , 1.95]
ASCEND-ND 2021	248	1937	261	1933	29.5%	0.95 [0.81 , 1.11]
Subtotal (95% CI)		**2515**		**2418**	**38.1%**	**0.97 [0.84 , 1.13]**
Total events:	289		292			
Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
4.5.2 HD and PD						
Chen DD 2017	0	60	0	22		Not estimable
DIALOGUE 4 2019	11	157	2	42	0.9%	1.47 [0.34 , 6.38]
HIMALAYAS 2021	38	522	33	513	8.1%	1.13 [0.72 , 1.78]
PYRENEES 2021	38	414	54	420	10.1%	0.71 [0.48 , 1.06]
SIERRAS 2021	46	369	79	370	13.0%	0.58 [0.42 , 0.82]
ASCEND-D 2021	234	1487	270	1477	29.9%	0.86 [0.73 , 1.01]
Subtotal (95% CI)		**3009**		**2844**	**61.9%**	**0.80 [0.64 , 1.01]**
Total events:	367		438			
Heterogeneity: Tau² = 0.03; Chi² = 7.39, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 1.92 (P = 0.06)						
Total (95% CI)		**5524**		**5262**	**100.0%**	**0.87 [0.76 , 1.00]**
Total events:	656		730			
Heterogeneity: Tau² = 0.01; Chi² = 11.94, df = 9 (P = 0.22); I² = 25%						
Test for overall effect: Z = 1.92 (P = 0.05)						
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 48.0%						



Analysis 4.6. Comparison 4: Analyses for SOF table 2 stratifying by CKD stage (HIF versus ESA), Outcome 6: Proportion reaching target haemoglobin



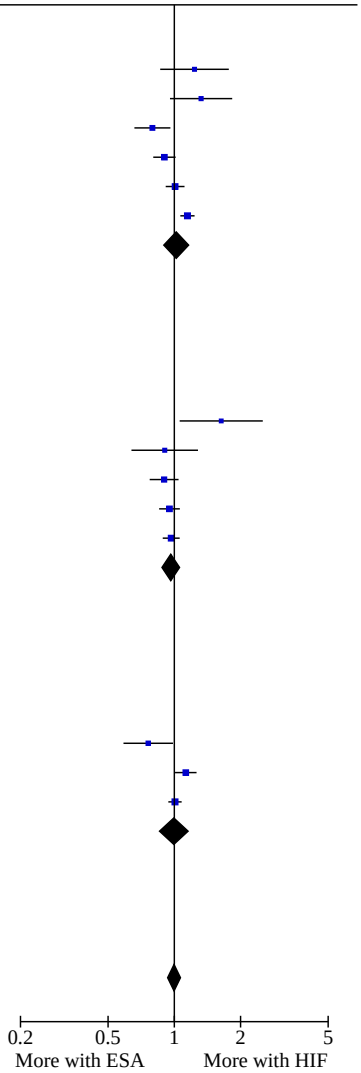
Comparison 5. Subgroup analysis: stage CKD (HIF versus ESA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Proportion reaching target haemoglobin	14	4601	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
5.1.1 CKD	6	1369	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.90, 1.16]
5.1.2 HD	5	1150	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.06]
5.1.3 HD and PD	3	2082	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.15]
5.2 Thrombosis	11	17026	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.39]
5.2.1 CKD	4	7959	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.59, 1.86]

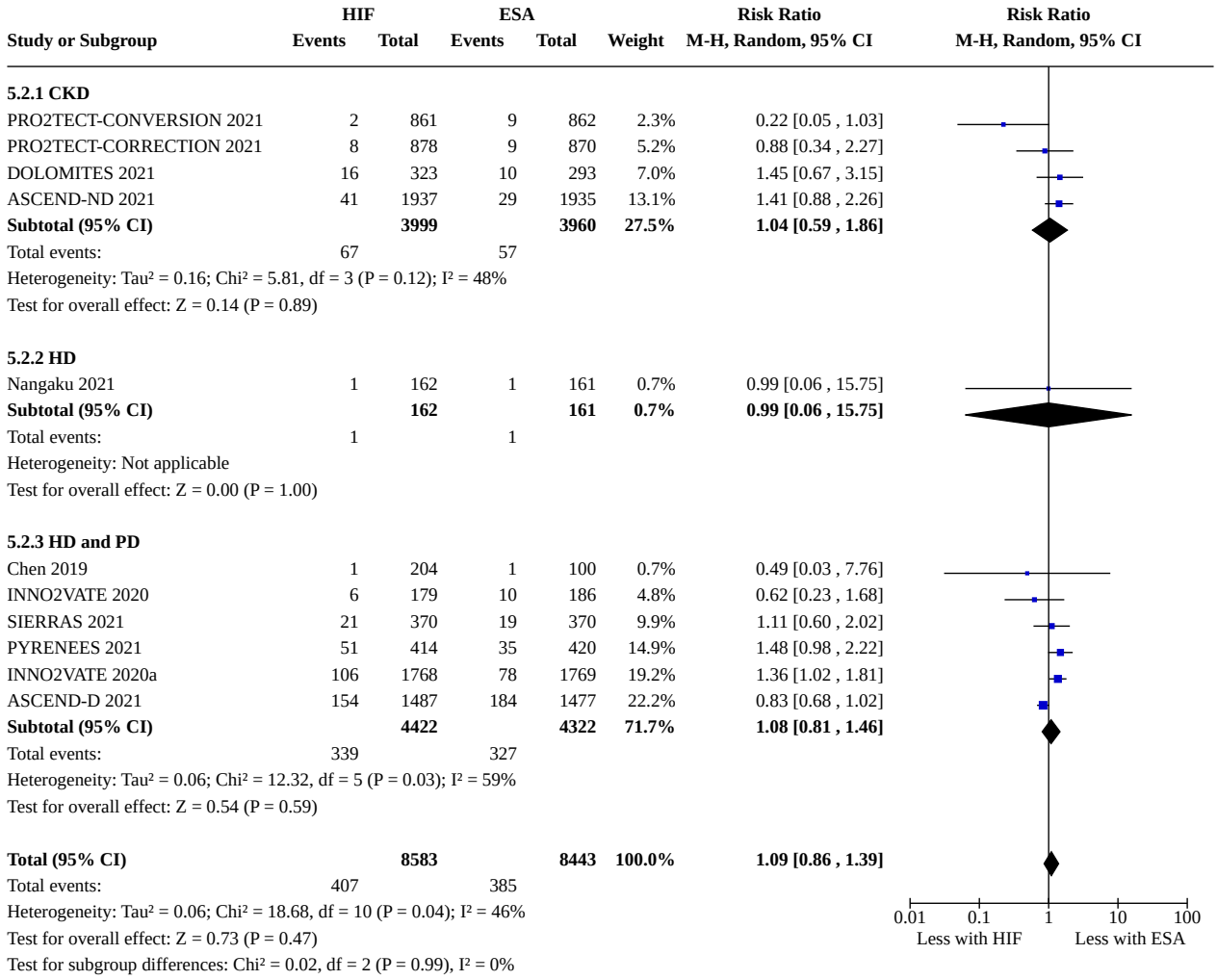
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.2.2 HD	1	323	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.06, 15.75]
5.2.3 HD and PD	6	8744	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.81, 1.46]

Analysis 5.1. Comparison 5: Subgroup analysis: stage CKD (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 CKD						
Holdstock 2019a	22	30	19	32	2.7%	1.24 [0.86 , 1.77]
Holdstock 2019	78	112	20	38	3.2%	1.32 [0.96 , 1.83]
DIALOGUE 2 2019	64	92	28	32	6.3%	0.80 [0.66 , 0.96]
Akizawa 2021	101	131	112	131	9.2%	0.90 [0.80 , 1.01]
SYMPHONY ND 2021	93	105	94	107	10.0%	1.01 [0.91 , 1.11]
DOLOMITES 2021	256	286	213	273	11.0%	1.15 [1.06 , 1.24]
Subtotal (95% CI)		**756**		**613**	**42.4%**	**1.02 [0.90 , 1.16]**
Total events:	614		486			
Heterogeneity: Tau² = 0.02; Chi² = 23.82, df = 5 (P = 0.0002); I² = 79%						
Test for overall effect: Z = 0.30 (P = 0.77)						
5.1.2 HD						
Chen DD 2017	49	60	11	22	2.0%	1.63 [1.06 , 2.52]
DIALOGUE 4 2019	71	157	21	42	2.9%	0.90 [0.64 , 1.28]
Nangaku 2021	104	162	115	161	7.7%	0.90 [0.77 , 1.05]
Akizawa 2020a	119	150	126	151	9.6%	0.95 [0.85 , 1.06]
Akizawa 2020c	105	120	113	125	10.4%	0.97 [0.89 , 1.06]
Subtotal (95% CI)		**649**		**501**	**32.6%**	**0.96 [0.88 , 1.06]**
Total events:	448		386			
Heterogeneity: Tau² = 0.00; Chi² = 6.68, df = 4 (P = 0.15); I² = 40%						
Test for overall effect: Z = 0.80 (P = 0.43)						
5.1.3 HD and PD						
HIMALAYAS 2021	83	522	108	517	4.4%	0.76 [0.59 , 0.99]
SIERRAS 2021	244	369	217	370	9.4%	1.13 [1.01 , 1.26]
Chen 2019	189	204	92	100	11.2%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**1095**		**987**	**25.0%**	**0.99 [0.86 , 1.15]**
Total events:	516		417			
Heterogeneity: Tau² = 0.01; Chi² = 8.41, df = 2 (P = 0.01); I² = 76%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Total (95% CI)		**2500**		**2101**	**100.0%**	**1.00 [0.93 , 1.07]**
Total events:	1578		1289			
Heterogeneity: Tau² = 0.01; Chi² = 42.66, df = 13 (P < 0.0001); I² = 70%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 0.52, df = 2 (P = 0.77), I² = 0%						



Analysis 5.2. Comparison 5: Subgroup analysis: stage CKD (HIF versus ESA), Outcome 2: Thrombosis

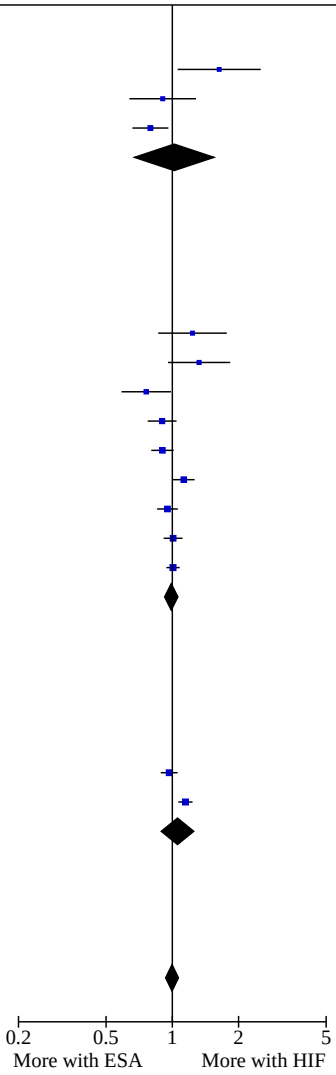


Comparison 6. Subgroup analysis: duration of therapy (HIF versus ESA)

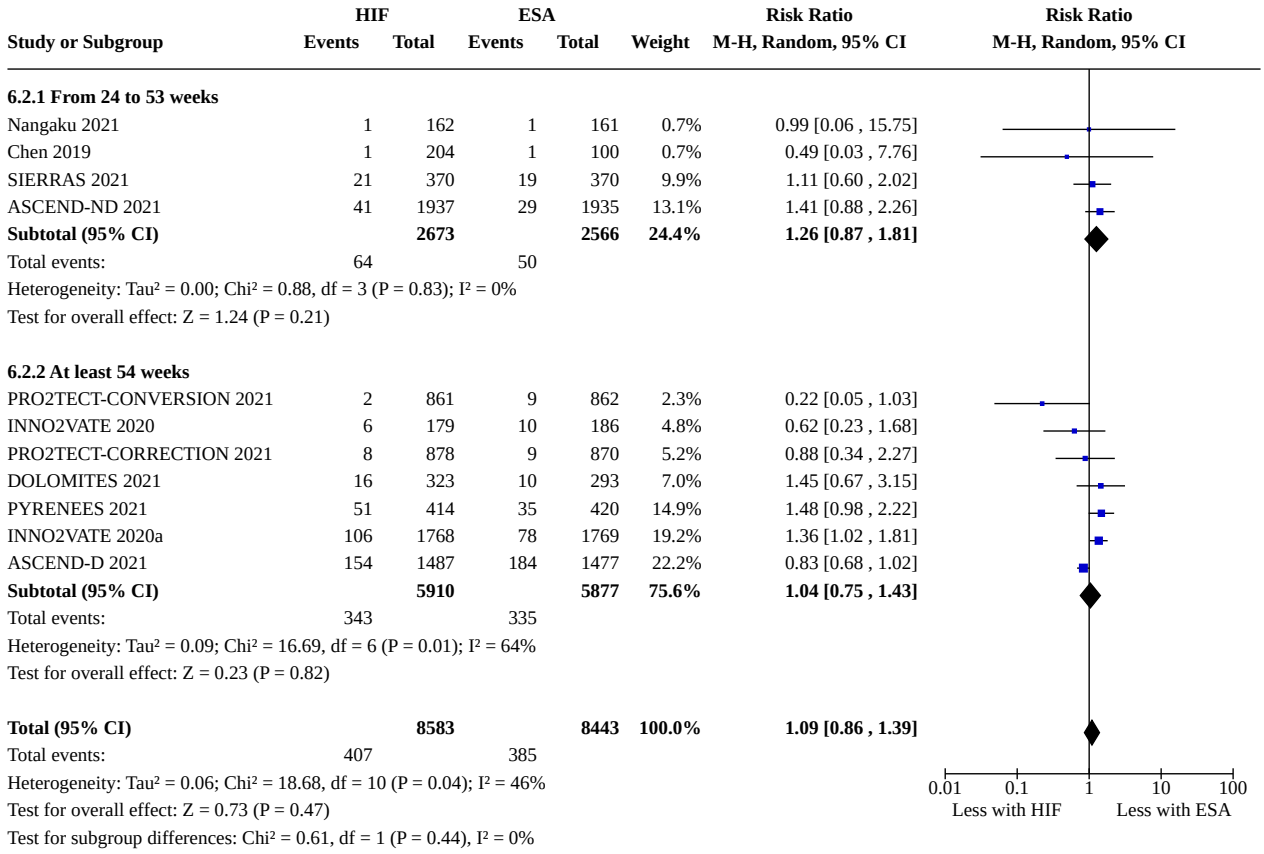
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Proportion reaching target haemoglobin	14	4601	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
6.1.1 From 8 to 23 weeks	3	405	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.55]
6.1.2 From 24 to 53 weeks	9	3392	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
6.1.3 At least 54 weeks	2	804	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.89, 1.25]
6.2 Thrombosis	11	17026	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.39]
6.2.1 From 24 to 53 weeks	4	5239	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.87, 1.81]
6.2.2 At least 54 weeks	7	11787	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.75, 1.43]

Analysis 6.1. Comparison 6: Subgroup analysis: duration of therapy (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 From 8 to 23 weeks						
Chen DD 2017	49	60	11	22	2.0%	1.63 [1.06 , 2.52]
DIALOGUE 4 2019	71	157	21	42	2.9%	0.90 [0.64 , 1.28]
DIALOGUE 2 2019	64	92	28	32	6.3%	0.80 [0.66 , 0.96]
Subtotal (95% CI)		**309**		**96**	**11.2%**	**1.02 [0.67 , 1.55]**
Total events:	184		60			
Heterogeneity: Tau² = 0.11; Chi² = 10.37, df = 2 (P = 0.006); I² = 81%						
Test for overall effect: Z = 0.09 (P = 0.93)						
6.1.2 From 24 to 53 weeks						
Holdstock 2019a	22	30	19	32	2.7%	1.24 [0.86 , 1.77]
Holdstock 2019	78	112	20	38	3.2%	1.32 [0.96 , 1.83]
HIMALAYAS 2021	83	522	108	517	4.4%	0.76 [0.59 , 0.99]
Nangaku 2021	104	162	115	161	7.7%	0.90 [0.77 , 1.05]
Akizawa 2021	101	131	112	131	9.2%	0.90 [0.80 , 1.01]
SIERRAS 2021	244	369	217	370	9.4%	1.13 [1.01 , 1.26]
Akizawa 2020a	119	150	126	151	9.6%	0.95 [0.85 , 1.06]
SYMPHONY ND 2021	93	105	94	107	10.0%	1.01 [0.91 , 1.11]
Chen 2019	189	204	92	100	11.2%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**1785**		**1607**	**67.3%**	**0.99 [0.92 , 1.06]**
Total events:	1033		903			
Heterogeneity: Tau² = 0.01; Chi² = 18.57, df = 8 (P = 0.02); I² = 57%						
Test for overall effect: Z = 0.32 (P = 0.75)						
6.1.3 At least 54 weeks						
Akizawa 2020c	105	120	113	125	10.4%	0.97 [0.89 , 1.06]
DOLOMITES 2021	256	286	213	273	11.0%	1.15 [1.06 , 1.24]
Subtotal (95% CI)		**406**		**398**	**21.4%**	**1.06 [0.89 , 1.25]**
Total events:	361		326			
Heterogeneity: Tau² = 0.01; Chi² = 8.61, df = 1 (P = 0.003); I² = 88%						
Test for overall effect: Z = 0.62 (P = 0.53)						
Total (95% CI)		**2500**		**2101**	**100.0%**	**1.00 [0.93 , 1.07]**
Total events:	1578		1289			
Heterogeneity: Tau² = 0.01; Chi² = 42.66, df = 13 (P < 0.0001); I² = 70%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 0.50, df = 2 (P = 0.78), I² = 0%						



Analysis 6.2. Comparison 6: Subgroup analysis: duration of therapy (HIF versus ESA), Outcome 2: Thrombosis

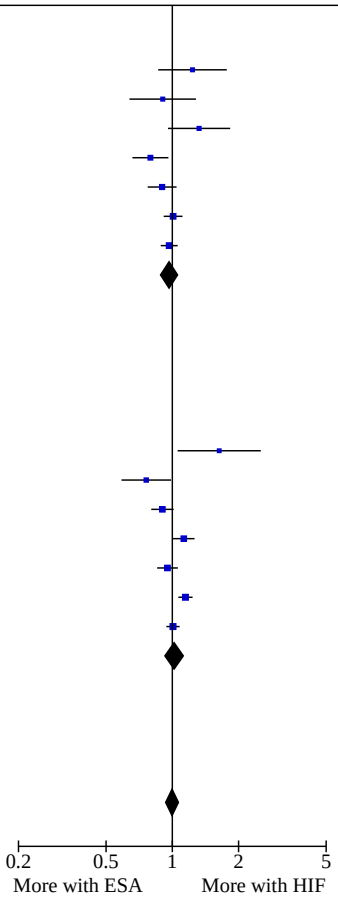


Comparison 7. Subgroup analysis: frequency of administration (HIF versus ESA)

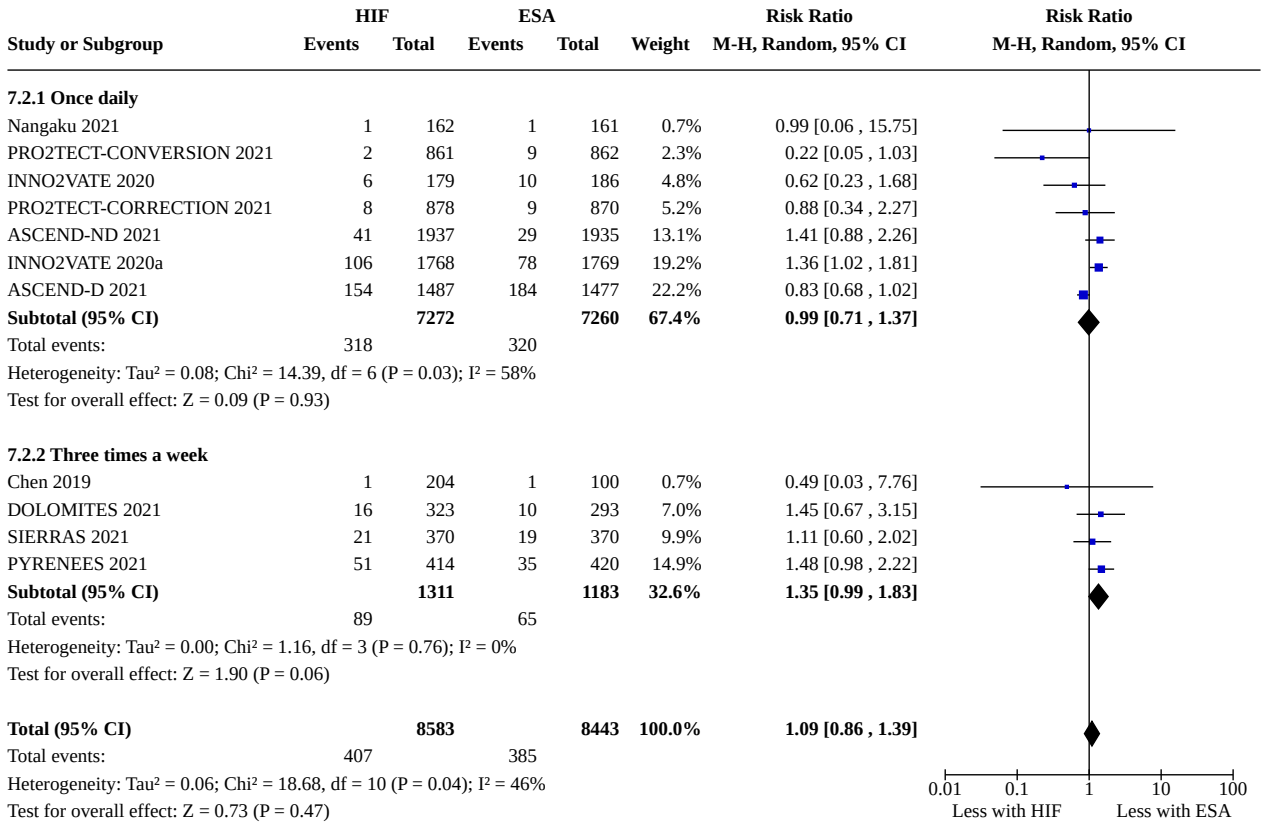
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Proportion reaching target haemoglobin	14	4601	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
7.1.1 Once a day	7	1315	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.06]
7.1.2 Three times a week	7	3286	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.93, 1.12]
7.2 Thrombosis	11	17026	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.39]
7.2.1 Once daily	7	14532	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.71, 1.37]
7.2.2 Three times a week	4	2494	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.99, 1.83]

Analysis 7.1. Comparison 7: Subgroup analysis: frequency of administration (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Once a day						
Holdstock 2019a	22	30	19	32	2.7%	1.24 [0.86 , 1.77]
DIALOGUE 4 2019	71	157	21	42	2.9%	0.90 [0.64 , 1.28]
Holdstock 2019	78	112	20	38	3.2%	1.32 [0.96 , 1.83]
DIALOGUE 2 2019	64	92	28	32	6.3%	0.80 [0.66 , 0.96]
Nangaku 2021	104	162	115	161	7.7%	0.90 [0.77 , 1.05]
SYMPHONY ND 2021	93	105	94	107	10.0%	1.01 [0.91 , 1.11]
Akizawa 2020c	105	120	113	125	10.4%	0.97 [0.89 , 1.06]
Subtotal (95% CI)		**778**		**537**	**43.3%**	**0.97 [0.88 , 1.06]**
Total events:	537		410			
Heterogeneity: Tau² = 0.01; Chi² = 11.29, df = 6 (P = 0.08); I² = 47%						
Test for overall effect: Z = 0.75 (P = 0.45)						
7.1.2 Three times a week						
Chen DD 2017	49	60	11	22	2.0%	1.63 [1.06 , 2.52]
HIMALAYAS 2021	83	522	108	517	4.4%	0.76 [0.59 , 0.99]
Akizawa 2021	101	131	112	131	9.2%	0.90 [0.80 , 1.01]
SIERRAS 2021	244	369	217	370	9.4%	1.13 [1.01 , 1.26]
Akizawa 2020a	119	150	126	151	9.6%	0.95 [0.85 , 1.06]
DOLOMITES 2021	256	286	213	273	11.0%	1.15 [1.06 , 1.24]
Chen 2019	189	204	92	100	11.2%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**1722**		**1564**	**56.7%**	**1.02 [0.93 , 1.12]**
Total events:	1041		879			
Heterogeneity: Tau² = 0.01; Chi² = 27.57, df = 6 (P = 0.0001); I² = 78%						
Test for overall effect: Z = 0.38 (P = 0.70)						
Total (95% CI)		**2500**		**2101**	**100.0%**	**1.00 [0.93 , 1.07]**
Total events:	1578		1289			
Heterogeneity: Tau² = 0.01; Chi² = 42.66, df = 13 (P < 0.0001); I² = 70%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 0.62, df = 1 (P = 0.43), I² = 0%						



Analysis 7.2. Comparison 7: Subgroup analysis: frequency of administration (HIF versus ESA), Outcome 2: Thrombosis

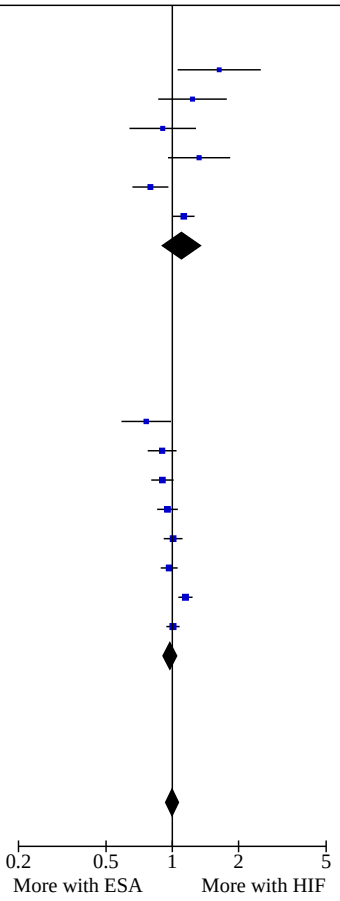


Comparison 8. Subgroup analysis: phase 2 versus phase 3 studies (HIF versus ESA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Proportion reaching target haemoglobin	14	4601	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.93, 1.07]
8.1.1 Phase 2	6	1356	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.90, 1.34]
8.1.2 Phase 3	8	3245	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.05]
8.2 Thrombosis	11	17026	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.39]
8.2.1 Phase 2	1	740	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.60, 2.02]
8.2.2 Phase 3	10	16286	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.83, 1.42]

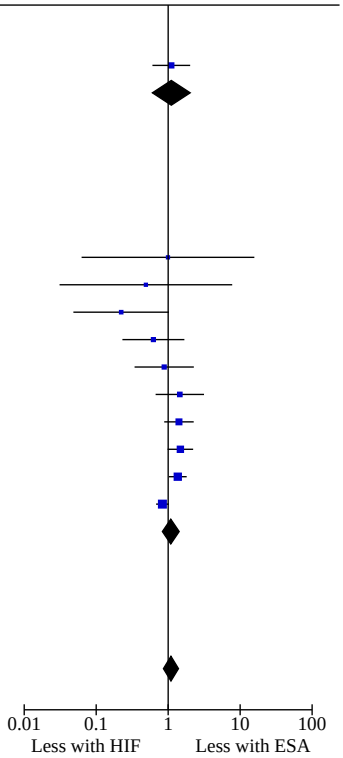
Analysis 8.1. Comparison 8: Subgroup analysis: phase 2 versus phase 3 studies (HIF versus ESA), Outcome 1: Proportion reaching target haemoglobin

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Phase 2						
Chen DD 2017	49	60	11	22	2.0%	1.63 [1.06 , 2.52]
Holdstock 2019a	22	30	19	32	2.7%	1.24 [0.86 , 1.77]
DIALOGUE 4 2019	71	157	21	42	2.9%	0.90 [0.64 , 1.28]
Holdstock 2019	78	112	20	38	3.2%	1.32 [0.96 , 1.83]
DIALOGUE 2 2019	64	92	28	32	6.3%	0.80 [0.66 , 0.96]
SIERRAS 2021	244	369	217	370	9.4%	1.13 [1.01 , 1.26]
Subtotal (95% CI)		**820**		**536**	**26.5%**	**1.10 [0.90 , 1.34]**
Total events:	528		316			
Heterogeneity: Tau² = 0.04; Chi² = 18.08, df = 5 (P = 0.003); I² = 72%						
Test for overall effect: Z = 0.94 (P = 0.35)						
8.1.2 Phase 3						
HIMALAYAS 2021	83	522	108	517	4.4%	0.76 [0.59 , 0.99]
Nangaku 2021	104	162	115	161	7.7%	0.90 [0.77 , 1.05]
Akizawa 2021	101	131	112	131	9.2%	0.90 [0.80 , 1.01]
Akizawa 2020a	119	150	126	151	9.6%	0.95 [0.85 , 1.06]
SYMPHONY ND 2021	93	105	94	107	10.0%	1.01 [0.91 , 1.11]
Akizawa 2020c	105	120	113	125	10.4%	0.97 [0.89 , 1.06]
DOLOMITES 2021	256	286	213	273	11.0%	1.15 [1.06 , 1.24]
Chen 2019	189	204	92	100	11.2%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**1680**		**1565**	**73.5%**	**0.97 [0.91 , 1.05]**
Total events:	1050		973			
Heterogeneity: Tau² = 0.01; Chi² = 26.11, df = 7 (P = 0.0005); I² = 73%						
Test for overall effect: Z = 0.72 (P = 0.47)						
Total (95% CI)		**2500**		**2101**	**100.0%**	**1.00 [0.93 , 1.07]**
Total events:	1578		1289			
Heterogeneity: Tau² = 0.01; Chi² = 42.66, df = 13 (P < 0.0001); I² = 70%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.8%						



Analysis 8.2. Comparison 8: Subgroup analysis: phase 2 versus phase 3 studies (HIF versus ESA), Outcome 2: Thrombosis

Study or Subgroup	HIF Events	HIF Total	ESA Events	ESA Total	Weight	Risk Ratio M-H, Random, 95% CI
8.2.1 Phase 2						
SIERRAS 2021	21	370	19	370	9.9%	1.11 [0.60 , 2.02]
Subtotal (95% CI)		**370**		**370**	**9.9%**	**1.11 [0.60 , 2.02]**
Total events:	21		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
8.2.2 Phase 3						
Nangaku 2021	1	162	1	161	0.7%	0.99 [0.06 , 15.75]
Chen 2019	1	204	1	100	0.7%	0.49 [0.03 , 7.76]
PRO2TECT-CONVERSION 2021	2	861	9	862	2.3%	0.22 [0.05 , 1.03]
INNO2VATE 2020	6	179	10	186	4.8%	0.62 [0.23 , 1.68]
PRO2TECT-CORRECTION 2021	8	878	9	870	5.2%	0.88 [0.34 , 2.27]
DOLOMITES 2021	16	323	10	293	7.0%	1.45 [0.67 , 3.15]
ASCEND-ND 2021	41	1937	29	1935	13.1%	1.41 [0.88 , 2.26]
PYRENEES 2021	51	414	35	420	14.9%	1.48 [0.98 , 2.22]
INNO2VATE 2020a	106	1768	78	1769	19.2%	1.36 [1.02 , 1.81]
ASCEND-D 2021	154	1487	184	1477	22.2%	0.83 [0.68 , 1.02]
Subtotal (95% CI)		**8213**		**8073**	**90.1%**	**1.09 [0.83 , 1.42]**
Total events:	386		366			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 18.65$, df = 9 (P = 0.03); $I^2 = 52\%$						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**8583**		**8443**	**100.0%**	**1.09 [0.86 , 1.39]**
Total events:	407		385			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 18.68$, df = 10 (P = 0.04); $I^2 = 46\%$						
Test for overall effect: Z = 0.73 (P = 0.47)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.96), $I^2 = 0\%$						



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Hypoxia-Inducible Factor-Proline Dioxygenases] explode all trees 2. MeSH descriptor: [Prolyl-Hydroxylase Inhibitors] this term only 3. ("HIF prolyl-hydroxylase inhibitor*"):ti,ab,kw 4. (hypoxia-inducible factor stabiliser*):ti,ab,kw 5. (hypoxia-inducible factor-proline dioxygenase*):ti,ab,kw 6. (roxadustat):ti,ab,kw 7. (molidustat):ti,ab,kw 8. (daprodustat):ti,ab,kw 9. (vadadustat):ti,ab,kw 10.(enarodustat):ti,ab,kw 11.(desidustat):ti,ab,kw 12.(FG-4592):ti,ab,kw 13.("BAY-85 3934"):ti,ab,kw 14.(GSK1278863):ti,ab,kw

(Continued)

15.(AKB-6548):ti,ab,kw
16.(JTZ-951):ti,ab,kw
17.(ZYAN-1):ti,ab,kw
18.{or 1-17}
19.MeSH descriptor: [Kidney Diseases] explode all trees
20.MeSH descriptor: [Renal Replacement Therapy] explode all trees
21.MeSH descriptor: [Renal Insufficiency] explode all trees
22.MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees
23.dialysis:ti,ab,kw (Word variations have been searched)
24.haemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched)
25.hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched)
26.hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched)
27.kidney disease* or renal disease* or kidney failure or renal failure:ti,ab,kw (Word variations have been searched)
28.ESRF or ESKF or ESRD or ESKD:ti,ab,kw (Word variations have been searched)
29.CKF or CKD or CRF or CRD:ti,ab,kw (Word variations have been searched)
30.CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched)
31.predialysis or pre-dialysis:ti,ab,kw (Word variations have been searched)
32.(kidney transplant*):ti,ab,kw
33.(renal transplant*):ti,ab,kw
34.{or #19-#33}
35.{and #18, #34}

MEDLINE	1. Hypoxia-Inducible Factor-Proline Dioxygenases/ 2. Prolyl-Hydroxylase Inhibitors/ 3. HIF prolyl-hydroxylase inhibitor$.tw. 4. hypoxia-inducible factor stabiliser$.tw. 5. hypoxia-inducible factor-proline dioxygenase$.tw. 6. roxadustat.tw. 7. daprodustat.tw. 8. molidustat.tw. 9. vadadustat.tw. 10.enarodustat.tw. 11.desidustat.tw. 12.FG-4592.tw. 13.ASP1517.tw 14.AZD9941.tw 15.BAY85-3934.tw. 16.GSK1278863.tw. 17.AKB-6548.tw. 18.JTZ-951.tw 19.ZYAN-1.tw. 20.or/1-19 21.Kidney Diseases/ 22.exp Renal Replacement Therapy/ 23.Renal Insufficiency/ 24.exp Renal Insufficiency, Chronic/ 25.Diabetic Nephropathies/ 26.diabetic kidney disease$.tw. 27.diabetic nephropath$.tw. 28.exp Hypertension, Renal/ 29.dialysis.tw.

(Continued)

	30.(haemodialysis or haemodialysis).tw. 31.(hemofiltration or haemofiltration).tw. 32.(hemodiafiltration or haemodiafiltration).tw. 33.(kidney disease* or renal disease* or kidney failure or renal failure).tw. 34.(ESRF or ESKF or ESRD or ESKD).tw. 35.(CKF or CKD or CRF or CRD).tw. 36.(CAPD or CCPD or APD).tw. 37.(predialysis or pre-dialysis).tw. 38.Uremia/ 39.(uremic or ur?emia).tw. 40.or/19-37 41.and/20,40
EMBASE	1. exp hypoxia inducible factor prolyl hydroxylase inhibitor/ 2. HIF prolyl-hydroxylase inhibitor$.tw. 3. hypoxia-inducible factor stabiliser$.tw. 4. hypoxia-inducible factor-proline dioxygenase$.tw. 5. roxadustat.tw. 6. molidustat.tw. 7. daprodustat.tw. 8. vadadustat.tw. 9. enarodustat.tw. 10.desidustat.tw. 11.FG-4592.tw. 12.ASP1517.tw 13.AZD9941.tw 14.BAY85-3934.tw. 15.GSK1278863.tw. 16.AKB-6548.tw. 17.JTZ-951.tw. 18.ZYAN-1.tw 19.or/1-18 20.exp renal replacement therapy/ 21.kidney disease/ 22.chronic kidney disease/ 23.kidney failure/ 24.chronic kidney failure/ 25.mild renal impairment/ 26.stage 1 kidney disease/ 27.moderate renal impairment/ 28.severe renal impairment/ 29.end stage renal disease/ 30.renal replacement therapy-dependent renal disease/ 31.diabetic nephropathy/ 32.kidney transplantation/ 33.renovascular hypertension/ 34.(haemodialysis or haemodialysis).tw. 35.(hemofiltration or haemofiltration).tw. 36.(hemodiafiltration or haemodiafiltration).tw. 37.dialysis.tw. 38.(CAPD or CCPD or APD).tw. 39.(kidney disease* or renal disease* or kidney failure or renal failure).tw.

(Continued)

	40.(CKF or CKD or CRF or CRD).tw. 41.(ESRF or ESKF or ESRD or ESKD).tw. 42.(predialysis or pre-dialysis).tw. 43.((kidney or renal) adj (transplant* or graft* or allograft*)).tw. 44.or/18-41 45.and/19,44

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias*: Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias*: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias*: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

(Continued)

	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias*: No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias*: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias*: The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

Appendix 3. Studies reporting adverse events

Study ID	Intervention	Control	Adverse events in the intervention arm	Adverse events in the control arm	Comments
Akizawa 2017	**Daprodustat (4, 6, 8, 10 mg)**	**Placebo**	Death (0/78), nasopharyngitis (5/78), hypertension (2/78), cerebral haemorrhage (0/78),	Death (0/19), nasopharyngitis (0/19), hypertension (0/19), cerebral haemorrhage	"On-therapy AEs were reported in a total of 32 subjects. All AEs were reported as single in-

(Continued)

			pyoderma gangrenosum (1/78) Further data were available on the NCT02019719: any AE (26/78), SAE (0/78), cerebral haemorrhage (0/78), ear discomfort (1/78), gastritis atrophic (1/78), stomatitis (1/78), vomiting (1/78), pyrexia (1/78), peripheral oedema (1/78), seasonal allergy (1/78), nasopharyngitis (5/78), pharyngitis (1/78), pharyngitis bacterial (1/78), upper respiratory tract infection (1/78), AVF thrombosis (1/78), burns second degree (1/78), injury (1/78), procedural hypotension (1/78), shunt stenosis (1/78), decreased appetite (1/78), back pain (2/78), arthralgia (1/78), lumbar spinal stenosis (1/78), dyspnoea 0(/78), dermatitis (2/78), blister rupture (1/78), drug eruption (1/78), haemorrhage subcutaneous (1/78), rash (0/78), hypertension (2/78)	(1/19) pyoderma gangrenosum (0/19) Further data were available on the NCT02019719: any AE (5/19), SAE (1/19), cerebral haemorrhage (1/19), ear discomfort (0/19), gastritis atrophic (0/19), stomatitis (0/19), vomiting (0/19), pyrexia (1/19), peripheral oedema (0/19), seasonal allergy (0/19), nasopharyngitis (0/19), pharyngitis (0/19), pharyngitis bacterial (0/19), upper respiratory tract infection (0/19), AVF thrombosis (0/19), burns second degree (0/19), injury (0/19), procedural hypotension (0/19), shunt stenosis (0/19), decreased appetite (1/19), back pain (0/19), arthralgia (0/19), lumbar spinal stenosis (0/19), dyspnoea (1/19), dermatitis (1/19), blister rupture (0/19), drug eruption (0/19), haemorrhage subcutaneous (0/19), rash (1/19), hypertension (0/19)	stances in each treatment group, except for nasopharyngitis, which was reported in 1 subject in the 4 mg group and 2 subjects each in the 8 and 10 mg groups. Two non-serious AEs of hypertension, in 1 subject each in the 6 and 10 mg groups, were assessed as treatment-related by the investigator. There were 2 serious on-therapy AEs reported in the study: cerebral haemorrhage in the placebo group and pyoderma gangrenosum in the 10 mg group. The cerebral haemorrhage was assessed as treatment-related by the investigator. No deaths occurred during the study."
Akizawa 2019	**Roxadustat (50, 70, 100 mg)**	**Placebo**	SAE (11/80), death (0/80), MI (0/80), stroke (0/80), GI (22/80), diarrhoea (8/80), nausea (5/80), infections/infestations (32/80), nasopharyngitis (21/80), renal/urinary disorders (5/80), declining kidney function (5/80) musculoskeletal and connective tissue disorders (11/80), muscle spasms (1/80), respiratory, thoracic, and mediastinal disorders (5/80), cough (1/80), initiation of dialysis (4/80)	SAE (2/27), death (0/27), MI (0/27), stroke (0/27), GI (2/27), diarrhoea (1/27), nausea (0/27), infections/infestations (9/27), nasopharyngitis (6/27), renal/urinary disorders (1/27), declining kidney function (1/27), musculoskeletal and connective tissue disorders (4/27), muscle spasms (2/27), respiratory, thoracic, and mediastinal disorders (2/27), cough (2/27), initiation of dialysis (0/27)	"The incidence of overall TEAEs ranged between 70.4% (placebo) and 88.5% (70 mg roxadustat). No major adverse cardiac events (i.e., myocardial infarction, stroke, death) occurred in roxadustat-treated patients. Two cases of congestive heart failure (one with 50 mg TIW and one with placebo) occurred during the study; the case in the placebo-treated patient was considered drug-related. In terms of clinically relevant arrhythmias, two cases of atrial fibrillation occurred. A total of six cases of declining kidney function

(Continued)

					were reported (placebo TIW, n = 1; roxadustat 50 mg TIW, n = 4; roxadustat 100 mg TIW, n = 1)ed (one with placebo and one with 70 mg TIW). Discontinuation due to progressive disease requiring initiation of dialysis occurred in three patients (11.1%) in the roxadustat 50-mg TIW group and one patient (3.7%) in the roxadustat 100-mg TIW group. Two cases of hepatic dysfunction occurred in patients treated with placebo TIW."
Akizawa 2020a	**Roxadustat**	**Darbepoetin alfa**	SAE (31/150), angina pectoris (5/150), acute MI (1/150), aortic valve stenosis (0/150), atrioventricular block complete (0/150), bradycardia (1/150), cardiac failure (0/150), cardiac failure congestive (1/150), coronary artery stenosis (1/150), myocardial ischemias (0/150), sudden hearing loss (1/150), GI haemorrhage (1/150), vascular stent occlusion (1/150), cellulitis (2/150), UTI (1/150), shunt stenosis (6/150), shunt occlusion (3/150), joint dislocation (1/150), subcutaneous hematoma (0/150), spinal column injury (1/150), lumbar spinal stenosis (1/150), basal cell carcinoma (0/150), gastric cancer (1/150), malignant neoplasm of renal pelvis (0/150), transitional cell carcinoma (0/150), lip and/or oral cavity cancer (0/150), cerebral infarction (1/150), psychiatric disorders (0/150), asthma (1/150), pulmonary oedema (0/150), surgical and medical procedures (1/150), DVT (2/150), orthostatic hypotension (1/150), venous occlusion (1/150), peripher-	SAE (22/152), angina pectoris (2/152), acute MI (0/152), aortic valve stenosis (1/152), atrioventricular block complete (1/152) bradycardia (0/152), cardiac failure (1/152), cardiac failure congestive (0/152), coronary artery stenosis (0/152), myocardial ischemias (1/152), sudden hearing loss (0/152), GI haemorrhage (0/152), vascular stent occlusion (0/152), cellulitis (0/152), UTI (0/152), shunt stenosis (6/152), shunt occlusion (2/152), joint dislocation (0/152), subcutaneous hematoma (1/152), spinal column injury (0/152), lumbar spinal stenosis (0/152), basal cell carcinoma (1/152), gastric cancer (0/152), malignant neoplasm of renal pelvis (4/152), transitional cell carcinoma (4/152), lip and/or oral cavity cancer (4/152), cerebral infarction (0/152), psychiatric disorders (1/152), asthma (0/152), pulmonary oedema (1/152), surgical and medical procedures (2/152), DVT (0/152), orthostatic hypotension	"The proportion of patients who reported TEAEs was similar in the roxadustat (129/150; 86.0%) and DA (126/152; 82.9%) groups. The incidence of serious TEAEs was 20.7% (31/150) and 14.5% (22/152) in the roxadustat and DA groups, respectively. Serious TEAEs considered potentially drug related were reported in 3.3%(5/150) and 3.9%(6/152) of patients in the roxadustat and DA groups, respectively. The incidence of TEAEs leading to withdrawal of treatment and, in turn, withdrawal from the study, was 8.7% (13/150) and 5.3% (8/ 152) in the roxadustat and DA groups, respectively. Two deaths were reported during the study, both of which occurred in the roxadustat group. TEAEs included nasopharyngitis, shunt stenosis, diarrhoea, contusion, and vomiting. The incidences of nasopharyngitis and vomiting were higher in the roxadustat group than in the DA group. Retinal haemor-

(Continued)

			al arterial occlusive disease (0/150), subclavian vein stenosis (1/150), retinal haemorrhage (5/150), dental caries (5/150), nasopharyngitis (52/150), contusion (10/150), wound (3/150), procedural hypotension (5/150), hyperkalaemia (5/150), back pain (3/150), skin exfoliation (6/150), internal haemorrhage (2/150), vertigo (1/150), eye disorders (5/150), faeces soft (0/150), general disorders and administration site conditions (3/150), nervous system disorders (2/150), psychiatric disorders (2/150), eczema (0/150)	(0/152), venous occlusion (0/152), peripheral arterial occlusive disease (1/152), subclavian vein stenosis (0/152), retinal haemorrhage (6/152), dental caries (0/152), nasopharyngitis (40/152), contusion (10/152), wound (5/152), procedural hypotension (1/152), hyperkalaemia (1/152), back pain (7/152), skin exfoliation (2/152), internal haemorrhage (6/152), vertigo (2/152,) eye disorders (4/152), faeces soft (1/152), general disorders and administration site conditions (1/152), nervous system disorders (2/152), psychiatric disorders (0/152), eczema (1/152)	rhage was reported as a TEAE in 3.3% (5/150) and 3.9%(6/152) of patients in the roxadustat and DA groups, respectively."
Akizawa 2020c	**Daprodustat**	**Darbepoetin alfa**	Death (0/136), nasopharyngitis (57/136), pharyngitis (10/136), gastroenteritis (7/136), shunt stenosis (19/136), contusion (17/136), skin abrasion (10/1360, procedural hypotension (11/136), diarrhoea (20/136), vomiting (15/136), nausea (9/136), constipation (8/136), abdominal discomfort (3/136), back pain (6/136), arthralgia (5/136), muscle spasms (7/136), pain in extremity (1/136), headache (8/136), pyrexia (7/136), hypertension (5/136), arteriosclerosis coronary artery (0/136), cardiac failure (1/136), cerebral infarction (1/136), pulmonary oedema (0/136), retinal vein occlusion (2/136), retinal artery occlusion (0/136), shunt events (4/136), venous occlusion (1/136), gastritis erosive (2/136), chronic gastritis (0/136), duodenal perforation (1/136), gastric ulcer	Death (1/135), nasopharyngitis (57/135), pharyngitis (10/135), gastroenteritis (7/135), shunt stenosis (19/135), contusion (17/135), skin abrasion (10/135), procedural hypotension (11/135), diarrhoea (20/135), vomiting (15/135), nausea (9/135), constipation (8/135), abdominal discomfort (3/135), back pain (6/135), arthralgia (5/135), muscle spasms (7/135), pain in extremity (1/135), headache (8/135), pyrexia (7/135), hypertension (5/135), arteriosclerosis coronary artery (1/135), cardiac failure (2/135), cerebral infarction (1/135), pulmonary oedema (1/135), retinal vein occlusion (1/135), retinal artery occlusion (1/135), shunt events (4/135), venous occlusion (0/135), gastritis erosive (2/135), chronic gastritis (1/135), duodenal perforation (0/135),	"Most participants in both treatment groups experienced one or more AEs (93% daprodustat, 97% darbepoetin alfa). Of the AEs occurring in $5% of participants in any group (Table 4), contusion and diarrhoea were more frequent ($5% difference) in the daprodustat group, whereas nasopharyngitis and extremity pain was more frequent ($5% difference) in the darbepoetin alfa group. Hyperkalaemia was reported in 3% of participants in the daprodustat group versus 1% in the darbepoetin alfa group. SAEs occurred in 15% (daprodustat) and 27% (darbepoetin alfa) of participants. SAEs reported in two or more participants ($1%) in any treatment group were shunt stenosis (3% daprodustat, 4% darbepoetin alfa), shunt occlusion (,1% dapro-

(Continued)

			(0/136), haemorrhagic erosive gastritis (0/136), macular oedema (2/136), anterior chamber angle neovascularization (2/136), retinal haemorrhage (0/136), hypertensive cardiomyopathy (0/136), pulmonary hypertension (1/136), pancreatic carcinoma (0/136), rheumatoid arthritis (0/136), thrombosis and/or tissue ischemias secondary to excessive erythropoiesis (0/136)	gastric ulcer (1/135), haemorrhagic erosive gastritis (1/135), macular oedema (2/135), anterior chamber angle neovascularization (1/135), retinal haemorrhage (1/135), hypertensive cardiomyopathy (1/135), pulmonary hypertension (0/135), pancreatic carcinoma (1/135), rheumatoid arthritis (1/135), thrombosis and/or tissue ischemias secondary to excessive erythropoiesis (0/135)	dustat, 2% darbepoetin alfa), shunt malfunction (0% daprodustat, 1% darbepoetin alfa), pneumonia (,1% daprodustat, 1% darbepoetin alfa), sepsis (0% daprodustat, 1% darbepoetin alfa), and cardiac failure congestive (0% daprodustat, 1% darbepoetin alfa). No deaths were reported in the daprodustat group. One fatal event (sepsis) was reported during the follow-up period in the darbepoetin alfa group."
Akizawa 2020f	**Roxadustat**	**Darbepoetin alfa**	The incidence of TEAEs was 78.6% in roxadustat	The incidence of TEAEs was 70.2% in darbepoetin alfa. No other clear information were provided	"The incidence of TEAEs observed during the 24-week treatment period was 78.6% in roxadustat (CG), 70.2% in DA (CG), and 77.1% in roxadustat (RG). Common TEAEs included nasopharyngitis, CKD, hyperkalaemia, and hypertension; rates of these were comparable between groups. The incidence of serious TEAEs (TESAEs) was 17.6% (23/131 patients) in the roxadustat (comparative) group, 13.0% (17/131 patients) in the DA (comparative) group."
Akizawa 2021	**Roxadustat**	**Darbepoetin alfa**	TEAE (103/131), serious TEAE (23/131) Overall (103/131); GI disorders (32/131); constipation (5/131); diarrhoea (3/131); dental caries (3/131); nausea (5/131); general disorders and administration site conditions (13/131); oedema, peripheral (5/131); pyrexia (5/131); infections and infestations (42/131); nasopharyngitis (25/131); pneumonia (4/131); gastroenteritis (5/131); cystitis (0/131); pharyngitis (0/131);	TEAE (92/131), serious TEAE (17/131) Overall (92/131); GI disorders (19/131); constipation (4/131); diarrhoea (5/131); dental caries (1/131); nausea (1/131); general disorders and administration site conditions (13/131); oedema, peripheral (4/131); pyrexia (4/131); infections and infestations (48/131); nasopharyngitis (34/131); pneumonia (4/131); gastroenteritis (1/131); cystitis (2/131); pharyn-	"In the SAF, the incidence of TEAEs was comparable across treatment arms. The incidence of TEAEs was 78.6% (103/131 patients) in the roxadustat (comparative) group, 70.2% (92/131 patients) in the DA (comparative) group."

(Continued)

			Injury, poisoning and procedural complications (15/131); contusion (4/131); investigations (8/131); blood potassium increased (0/131); metabolism and nutrition disorders (15/131); hyperkalaemia (5/131); hypoglycaemia (1/131); musculoskeletal and connective tissue disorders (12/131); back pain (4/131); nervous system disorders (16/131); headache (3/131); renal and urinary disorders (15/131); CKD (9/131); skin and subcutaneous tissue disorders (7/131); eczema (1/131); vascular disorders (5/131); hypertension (3/131)	gitis (1/131); injury, poisoning and procedural complications (10/131); contusion (2/131); investigations (6/131); blood potassium increased (4/131); metabolism and nutrition disorders (16/131); hyperkalaemia (5/131); hypoglycaemia (0/131); musculoskeletal and connective tissue disorders (13/131); back pain (5/131); nervous system disorders (9/131); headache (4/131); renal and urinary disorders (13/131); CKD (9/131); skin and subcutaneous tissue disorders (11/131); eczema (3/131); vascular disorders (6/131); hypertension (5/131)	
ALPS 2021	**Roxadustat**	**Placebo**	All AE (343/391), SAE (61.6%), death (45/391), kidney failure (135/391), hypertension (87/391), oedema peripheral (45/391), GFR decreased (43/391), hyperkalaemia (39/391), viral upper respiratory tract infection (38/391), nausea (37/391), diarrhoea (33/391), pneumonia (28/391), iron deficiency (26/391), anaemia (24/391), headache (21/391), AVF thrombosis (20/391), pruritus (20/391), asthenia (19/391), hyperuricaemia (9/391), azotaemia (10/391), AKI (1/391), sepsis (6/391), peritonitis (5/391), pyelonephritis chronic (5/391), device related infection (4/391), MI (8/391), acute MI (6/391), atrial fibrillation (3/391), cardiac failure chronic (3/391), coronary artery disease (1/391), hip fracture (4/391), DVT (4/391), hypertensive crisis (4/391), cerebrovascular accident (5/391), Ischaemic stroke (4/391),	All AE (176/203), SAE (56.7%), death (20/203), kidney failure (62/203), hypertension (28/203), oedema peripheral (21/203), GFR decreased (23/203), hyperkalaemia (15/203), viral upper respiratory tract infection (9/203), nausea (6/203), diarrhoea (7/203), pneumonia (14/203), iron deficiency (8/203), anaemia (37/203), headache (11/203), AVF thrombosis (2/203), pruritus (2/203), asthenia (12/203), hyperuricaemia (11/203), azotaemia (8/203), AKI (2/203), sepsis (0/203), peritonitis (1/203), pyelonephritis chronic (2/203), device related infection (0/203), MI (3/203), acute MI (2/203), atrial fibrillation (3/203), cardiac failure chronic (3/203), coronary artery disease (2/203), hip fracture (0/203), DVT (0/203), hyper-	"The overall incidence of TEAEs was comparable between groups: 87.7% of patients in the roxadustat group and 86.7% of patients in the placebo group were reported to have experienced TEAEs. A comparable proportion of patients in both groups (47.3% roxadustat, 43.3% placebo) had TEAEs ≥ Grade 3 in severity. A greater proportion of patients in the roxadustat group (20.7%) experienced TEAEs considered related to treatment by the investigator compared with the placebo group (13.3%). In the roxadustat group 61.6% of patients 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. A total of 45 patients in the roxadustat group and 20 in the

(Continued)

			diabetic neuropathy (0/391), pleural effusion (3/391), pulmonary oedema (3/391), hydrothorax (0/391), diabetic metabolic decompensation (1/391), asthenia (1/391), multiple organ dysfunction syndrome (1/391), catheter site haemorrhage (0/391), peripheral swelling (0/391)	tensive crisis (5/203), cerebrovascular accident (0/203), Ischaemic stroke (1/203), diabetic neuropathy (2/203), pleural effusion (3/203), pulmonary oedema (2/203), hydrothorax (2/203), diabetic metabolic decompensation (2/203), asthenia (2/203), multiple organ dysfunction syndrome (2/203), catheter site haemorrhage (2/203), peripheral swelling (2/203)	placebo group experienced death. The most common TEAE in both groups were end stage renal disease, hypertension, oedema peripheral and glomerular filtration rate decreased."
ANDES 2021	**Roxadustat**	**Placebo**	Hyperkalaemia (111/611), constipation (105/611), viral upper respiratory tract infection (98/611), hypertension (95/611), oedema peripheral (89/611), nausea (85/611), upper respiratory tract infection (79/611), diarrhoea (78/611), UTI (68/611), kidney failure (67/611), headache (66/611), insomnia (63/611), dizziness (58/611), cough (57/611), back pain (55/611), CKD (54/611), pruritus (54/611), vomiting (54/611), hypoglycaemia (53/611), AKI (49/611), oedema (48/611), arthralgia (45/611), pneumonia (44/611), decreased appetite (41/611), muscle spasms (41/611), hyperphosphataemia (40/611), dyspepsia (39/611), pain in extremity (39/611), pyrexia (39/611), abdominal pain (35/611), bronchitis (34/611), dyspnoea (34/611), cellulitis (32/611), gout (32/611), asthenia (31/611), hypotension (31/611), metabolic acidosis (29/611), anaemia (17/611), cardiac failure congestive (23/611), hyponatraemia (15/611), azotaemia (13/611), hypoglycaemia (13/611),	Hyperkalaemia (41/305), constipation (34/305), viral upper respiratory tract infection (40/305), hypertension (27/305), oedema peripheral (28/305), nausea (29/305), upper respiratory tract infection (48/305), diarrhoea (31/305), UTI (29/305), kidney failure (18/305), headache (26/305), insomnia (9/305), dizziness (32/305), cough (28/305), back pain (18/305), CKD (21/305), pruritus (19/305), vomiting (20/305), hypoglycaemia (15/305), AKI (11/305), oedema (9/305), arthralgia (24/305), pneumonia (18/305), decreased appetite (8/305), muscle spasms (9/305), hyperphosphataemia (10/305), dyspepsia (12/305), pain in extremity (14/305), pyrexia (9/305), abdominal pain (13/305), bronchitis (13/305), dyspnoea (23/305), cellulitis (7/305), gout (20/305), asthenia (11/305), hypotension (10/305), metabolic acidosis (18/305), anaemia (44/305), cardiac failure congestive (9/305), hyponatraemia (3/305), azotaemia (5/305), hy-	"The incidences of TEAEs and TESAEs were comparable. [...] TEAEs were reported by 92.3% (564/611) of roxadustat and 89.5% (273/305) of placebo treated patients, corresponding to incidence rates of 554.4 and 594.5/100 PEY. The most common TEAEs in the roxadustat or placebo group were hyperkalaemia (13.6 vs. 12.5/100 PEY), constipation (12.2 vs. 10.3/100 PEY), viral upper respiratory tract infection (16.9 vs. 15.4/100 PEY), upper respiratory tract infection (12.8 vs. 18.0/100 PEY), and hypertension (11.3 vs. 10.1/100 PEY) (Table 2). The incidence rates of TESAEs were 74.2 and 66.0/100 PEY among roxadustat- vs. placebo-treated patients. Incidence rates for fatal TESAEs were 3.8 and 2.9, respectively."

(Continued)

			peritonitis (13/611), pulmonary oedema (4/611), arthralgia (32/611), diabetes mellitus inadequate control (6/611), acute MI (5/611), fluid overload (3/611), gastroenteritis (2/611), chronic obstructive pulmonary disease (1/611)	poglycaemia (4/305), peritonitis (1/305), pulmonary oedema (6/305), arthralgia (19/305), diabetes mellitus inadequate control (0/305), acute MI (3/305), fluid overload (3/305), gastroenteritis (4/305), chronic obstructive pulmonary disease (3/305)	
ASCEND-D 2021	**Daprodustat**	**Darbepoetin alfa** (PD patients) **ESA** (HD patients)	SAE (773/1482); AE (1307/1482); thrombosis or tissue ischemias due to excessive erythropoiesis (20/1482); cardiomyopathy (15/1482); pulmonary-artery hypertension (9/1482); cancer-related death or tumour progression or recurrence (47/1482); oesophageal or gastric erosions (60/1482); proliferatives retinopathy, macular oedema, or choroidal neovascularization (38/1482); exacerbation of rheumatoid arthritis (2/1482); worsening of hypertension (293/1482)	Data were reported on 1474 participants SAE (748/1474); AE (1252/1474); thrombosis or tissue ischemias due to excessive erythropoiesis (11/1474); cardiomyopathy (16/1474); pulmonary-artery hypertension (12/1474); cancer-related death or tumour progression or recurrence (51/1474);oesophageal or gastric erosions (81/1474); proliferatives retinopathy, macular oedema, or choroidal neovascularization (35/1474); exacerbation of rheumatoid arthritis (1/1474); worsening of hypertension (302/1474)	"Serious adverse events during the trial were reported in 773 patients (52.2%) in the daprodustat group and in 748 (50.7%) in the ESA group."
ASCEND-ID 2021	**Daprodustat**	**Darbepoetin alfa**	Worsening of hypertension: 24% Rates of AE: 76% Rescue treatment: 3%	Worsening of hypertension: 19% Rates of AE: 72% Rescue treatment: 3%	"Rescue treatment was the same in both groups (3%). While the number of subjects with worsening of hypertension (24% Dapro vs 19% Darbe) was numerically higher, the overall effect of daprodustat on BP was similar to Darbe. Rates of AEs were similar (76% Dapro vs 72% Darbe)."
ASCEND-ND 2021	**Daprodustat**	**Darbepoetin alfa**	SAE (850/1937); AE (1545/1937); thrombosis or tissue ischemias due to excessive erythropoiesis (5/1937); cardiomyopathy (6/1937); pulmonary-artery hypertension (15/1937); can-	SAE (703/1933); AE (1487/1933); thrombosis or tissue ischemias due to excessive erythropoiesis (13/1933); cardiomyopathy (7/1933); pulmonary-artery hyper-	"Serious adverse events that started or worsened after the initiation of trial treatment were reported in 850 of 1937 patients in the daprodustat group (43.9%) and 703 of 1933 pa-

(Continued)

			cer-related death or tumour progression or recurrence (72/1937); oesophageal or gastric erosions (70/1937); proliferatives retinopathy, macular oedema, or choroidal neovascularization (54/1937); exacerbation of rheumatoid arthritis (2/1937); worsening of hypertension (344/1937)	tension (9/1933); cancer-related death or tumour progression or recurrence (49/1933); oesophageal or gastric erosions (41/1933); proliferatives retinopathy, macular oedema, or choroidal neovascularization (44/1933); exacerbation of rheumatoid arthritis (4/1933); worsening of hypertension (363/1933)	tients in the darbepoetin alfa group (36.4%)."
Besarab 2015	**Roxadustat (0.7, 1, 1.5, 2 mg/kg)**	**Placebo**	Any treatment-related AE: 52/88 Diarrhoea (8/88), headache (6/88), back pain (4/88), fatigue (4/88), hyperkalaemia (4/88), peripheral oedema (3/88), dizziness (2/88), insomnia (2/88), seasonal allergy (1/88), UTI (1/88), SAE (4/88), death (0/88), constipation (1/88), gastro oesophageal reflux disease (2/88), nausea (1/88), abdominal discomfort (0/88), abdominal pain (1/88), abdominal pain upper (1/88), ascites (1/88), dyspepsia (1/88), gastritis (1/88), GI disorder (1/88), lip swelling (1/88), influenza (1/88), bronchitis (1/88), candidiasis (0/88), cystitis (1/88), onychomycosis (0/88), sinusitis (1/88), tooth abscess (1/88), tooth infection (1/88), upper respiratory tract infection (1/88), hyperuricaemia (2/88), acidosis (1/88), anorexia (1/88), decreased appetite (1/88), diabetes mellitus (1/88), gout (1/88), hyperglycaemia (1/88), hypernatraemia (1/10), hyperphosphataemia (1/88), hypoglycaemia (1/88), metabolic acidosis (1/88), type 2 diabetes mellitus (1/88), vitamin D deficiency	Any treatment-related AE: 13/28 Diarrhoea (2/28), headache (1/28), back pain (1/28), fatigue (0/28), hyperkalaemia (0/28), peripheral oedema (0/28), dizziness (0/28), insomnia (1/28), seasonal allergy (2/28), UTI (3/28), SAE (4/28), death (0/28), constipation (1/28), gastro oesophageal reflux disease (0/28), nausea (1/28), abdominal discomfort (1/28), abdominal pain (1/28), abdominal pain upper (0/28), ascites (0/28), dyspepsia (0/28), gastritis (0/28), GI disorder (0/28), lip swelling (0/28), influenza (1/28), bronchitis (0/28), candidiasis (1/28), cystitis (0/28), onychomycosis (1/28), sinusitis (0/28), tooth abscess (0/28), tooth infection (0/28), upper respiratory tract infection (0/28), hyperuricaemia (0/28), acidosis (0/28), anorexia (0/28), decreased appetite (0/28), diabetes mellitus (0/28), gout (0/28), hyperglycaemia (0/28), hypernatraemia (0/10), hyperphosphataemia (0/28), hypoglycaemia (0/28), metabolic acidosis (0/28), type 2 diabetes mellitus (0/28),	"AEs were reported by 52 (59%) roxadustat-treated and 13 (46%) placebo subjects; the most common AEs were expected in CKD and did not differ clinically differ between groups. Serious AEs (SAEs) were reported by four (5%) roxadustat-treated subjects and one (4%) placebo patient; the SAEs in roxadustat treated subjects included vascular access complications, femoral neck fracture, noncardiac chest pain and dyspnoea. The vascular access complication was reported in a patient with graft infection 4 days after arteriovenous (AV) graft placement whose baseline eGFR was 18.4 mL/min. Initial Hb was 9.3 g/dL. Despite a good Hb response for 6 weeks, a left arm AV graft was placed to prepare for future dialysis. Four days later, the patient presented with signs and symptoms compatible with 'graft' infection and was treated with clindamycin and vancomycin. No CV SAEs and no death occurred during study. The incidences of seizure, thromboembolic and CV events during roxadustat treat-

(Continued)

	(1/88), muscle spasms (1/88), myalgia (2/88), arthralgia (1/88), neck pain (0/88), osteoarthritis (0/88), osteoporosis (1/88), oedema peripheral (3/88), asthenia (0/88), chills (1/88), non-cardiac chest pain (1/88), oedema (1/88), pyrexia (1/88), neuropathy peripheral (1/88), drug eruption (1/88), erythema (1/88), increased tendency to bruise (1/88), intertrigo (1/88), pruritus (1/88), rash (1/88), skin lesion (1/88), skin ulcer (1/88), stasis dermatitis (0/88), sinus bradycardia (0/88), bradycardia (1/88), bundle branch block right (0/88), cardiac failure congestive (1/88), pericarditis (0/88), ventricular extrasystoles (1/88), AVF site complication (1/88), excoriation (1/88), femoral neck fracture (1/88), foot fracture (1/88), laceration (1/88), procedural pain (1/88), skin laceration (1/88), immune system disorders (1/88), depression (1/88), renal impairment (2/88), micturition urgency (1/88), AKI (0/88), allergic sinusitis (1/88), cough (1/88), dyspnoea (1/88), postnasal drip (1/88), wheezing (1/88), hot flush (1/88), hypertension (1/88), hypotension (0/88), vasculitis (0/88), anaemia (2/88), hyperparathyroidism secondary (1/88), hypothyroidism (1/88), diabetic retinopathy (1/88), eyelid oedema (1/88), breast cyst (1/88), prostatitis (1/88), ear pain (1/88), gallbladder polyp (1/88), benign breast neoplasm (1/88), nail operation (1/88)	vitamin D deficiency (0/28), muscle spasms (1/28), myalgia (1/28), arthralgia (0/28), neck pain (0/28), osteoarthritis (1/28), osteoporosis (1/28), oedema peripheral (0/28), asthenia (0/28), chills (1/28), non-cardiac chest pain (1/28), oedema (1/28), pyrexia (0/28), neuropathy peripheral (0/28), drug eruption (0/28), erythema (0/28), increased tendency to bruise (0/28), intertrigo (0/28), pruritus (0/28), rash (0/28), skin lesion (0/28), skin ulcer (0/28), stasis dermatitis (1/28), sinus bradycardia (2/28), bradycardia (0/28), bundle branch block right (1/28), cardiac failure congestive (0/28), pericarditis (1/28), ventricular extrasystoles (0/28), AVF site complication (0/28), excoriation (0/28), femoral neck fracture (0/28), foot fracture (0/28), laceration (0/28), procedural pain (0/28), skin laceration (0/28), immune system disorders (3/28), depression (0/28), renal impairment (0/28), micturition urgency (0/28), AKI (1/28), allergic sinusitis (0/28), cough (0/28), dyspnoea (0/28), postnasal drip (0/28), wheezing (0/28), hot flush (0/28), hypertension (0/28), hypotension (1/28), vasculitis (1/28), anaemia (0/28), hyperparathyroidism secondary (0/28), hypothyroidism (0/28), diabetic retinopathy (0/28), eyelid oedema (0/28), breast cyst (0/28), prostatitis (0/28), ear pain (0/28), gallbladder polyp (0/28), benign	ment are of special interest in this population; no such AEs were reported. Two episodes of moderate exacerbation of hypertension were reported by one site investigator as AEs in the same patient who had a prior history of hypertension, received the lowest roxadustat dose 0.7 mg/kg BIW and gained excessive fluid weight. No hypertension exacerbation or other AEs of special interest were reported in the higher dose groups, and overall, no safety signal was detected from the ABPM. No evidence of liver toxicity or sustained increases of liver enzymes or serum bilirubin were reported in this study."

(Continued)

				breast neoplasm (0/28), nail operation (0/28)	
Brigandi 2016	**GSK1278863**	**Placebo**	**CKD participants**: nausea (6/61), dyspepsia (2/61), vomiting (3/61), hypotension (3/61), abdominal pain upper (2/61), dizziness (2/61), insomnia (2/61), idiopathic thrombocytopenic purpura (1/61), acute coronary syndrome (1/61), abdominal discomfort (1/61), diarrhoea (1/61), pancreatitis acute (1/61), chest pain (1/61), malaise (1/61), carbon dioxide abnormal (1/61), anorexia (1/61), dehydration (1/61), hyperuricaemia (1/61), arthritis (1/61), headache (1/61), lethargy (1/61), AKI (1/61), reduced kidney function (1/61), death (0/61) SAE: acute coronary syndrome, AKI, diabetic ketoacidosis, ketoacidosis, hyperglycaemia, hypotension, lower respiratory tract infection, AKI, dehydration, respiratory failure, pneumonia (no information on number of patients were reported). **HD participants**: abdominal pain (1/31), nausea (0/31), decreased appetite (0/31), death (0/31) SAE: atrial fibrillation, hepatitis acute, peripheral arterial occlusive disease (no information on number of patients were reported)	**CKD participants**: nausea (0/9), dyspepsia (1/9), vomiting (0/9), hypotension (0/9), abdominal pain upper (0/9), dizziness (0/9), insomnia (0/9), idiopathic thrombocytopenic purpura (0/9), acute coronary syndrome (0/9), abdominal discomfort (0/9), diarrhoea (0/9), pancreatitis acute (0/9), chest pain (0/9), malaise (0/9), carbon dioxide abnormal (0/9), anorexia (0/9), dehydration (0/9), hyperuricaemia (0/9), arthritis (0/9), headache (0/9), lethargy (0/9), AKI (0/9), reduced kidney function (0/9), death (0/9) SAE: impaired liver functions, sciatica, pyrexia, peripheral arterial occlusive disease (no information on number of patients were reported). **HD participants**: abdominal pain (0/6), nausea (1/6), decreased appetite (1/6), death (0/6) SAE (0/6)	"AEs, regardless of causality, were reported by 35 of 61 (57%) patients with CKD-3/4/5 and 15 of 31 (48%) patients with CKD-5D receiving GSK1278863. Overall, the frequency of AE reports was similar in the placebo arms in both groups. The most common AE in the CKD-3/4/5 group was nausea (n = 9 [13%]; 3 [21%] with 25 mg and 6 [40%] with 100 mg). In the CKD-3/4/5 group, 16 of 70 (23%) patients had investigator-assessed drug-related AEs, of which nausea was the most common (reported by 6 of 70 [9%] of patients). In the CKD-5D group, the most commonly reported AEs were anaemia and hypotension, each occurring in 2 (5%) patients. In this population, a total of 2 patients reported investigator-assessed drug-related AEs of abdominal pain in 1 patient (10-mg dose) and nausea and decreased appetite, both in 1 patient receiving placebo. Early termination from the study due to AEs was reported by 6 (9%) and 3 (8%) patients in the CKD-3/ 4/5 and CKD-5D groups, respectively, and none was considered drug-related by the investigator. In the CKD-3/4/5 group, serious AEs were reported for 7 individuals. Only 2 patients, both in the 100-mg group, had possibly related serious AEs. In the CKD-5D group, 3 individuals had serious AEs. No deaths

(Continued)

					were reported during the study."
Chen 2019	**Roxadustat**	**EPO alfa**	Any AE during treatment (96/204), upper respiratory tract infection (37/204), hypertension (25/204), hyperkalaemia (15/204), chest discomfort (13/204), vomiting (12/204), asthenia (12/204), alanine aminotransferase increased (11/204), dizziness (10/204), hypotension (10/204), muscle spasms (5/204), any SAE during treatment (29/204), blood or lymphatic system disorder (1/204), cardiac disorder (5/204), endocrine disorder (1/204), GI disorder (2/204), hepatobiliary disorder (2/204), immune system disorder (2/204), infection or infestation (5/204), injury, poisoning, or procedural complication (7/204), metabolism or nutrition disorder (1/204), nervous system disorder (3/204), product issue (0/204), renal or urinary disorder (4/204), reproductive system or breast disorder (1/204), vascular disorder (2/204), death (0/204)	Any AE during treatment (36/100), upper respiratory tract infection (11/100), hypertension (16/100), hyperkalaemia (1/100), chest discomfort (0/100), vomiting (2/100), asthenia (2/100), alanine aminotransferase increased (4/100), dizziness (6/100), hypotension (6/100), muscle spasms (5/100), any SAE during treatment (10/100), blood or lymphatic system disorder (0/100), cardiac disorder (1/100), endocrine disorder (0/100), GI disorder (0/100), hepatobiliary disorder (0/100), immune system disorder (0/100), infection or infestation (3/100), injury, poisoning, or procedural complication (5/100), metabolism or nutrition disorder (0/100), nervous system disorder (0/100), product issue (1/100), renal or urinary disorder (0/100), reproductive system or breast disorder (0/100), vascular disorder (0/100), death (0/100)	“A total of 159 of 204 patients (77.9%) treated with roxadustat and 63 of 100 patients (63.0%) treated with epoetin alfa reported having at least one adverse event during treatment. The most frequently reported event was upper respiratory infection, which occurred in 37 patients (18.1%) in the roxadustat group and in 11 (11.0%) in the epoetin alfa group. A total of 29 patients (14.2%) treated with roxadustat and 10 (10.0%) treated with epoetin alfa reported having at least one serious adverse event during treatment. The most frequently reported serious adverse event was vascular-access complication, which occurred in similar proportions of the treatment groups (6 patients [2.9%] in the roxadustat group and 3 patients [3.0%] in the epoetin alfa group). No deaths occurred during the reporting period. Adverse events that occurred in at least 5% of the patients in either group. Hyperkalemia was reported more frequently in the roxadustat group than in the epoetin alfa group in this open-label trial. The proportion of patients with potassium values within categories from 5.5 mmol/L or less, more than 5.5 to 6.0 mmol/L, more than 6.0 to 6.5 mmol per liter, and more than 6.5 mmol/L at baseline and at weeks 13 and 27 were generally sim-

(Continued)

					ilar in the treatment groups."
Chen 2019a	**Roxadustat**	**Placebo**	Any AE (37/101), hyperkalaemia (16/101), metabolic acidosis (12/101), anaemia (0/101), diarrhoea (0/101), peripheral oedema (7/101), pyrexia (2/101), upper respiratory tract infection (5/101), gout (1/101), back pain:0/101), dizziness (1/101), hypertension (6/101), any SAE (9/101), serious anaemia (0/101), corona-artery disease (0/101), GI haemorrhage (1/101), acute cholecysts (0/101), cholelithiasis (0/101), lung infection (1/101), serious hyperkalaemia (2/101), hypokalaemia (1/101), serious metabolic acidosis (1/101), kidney failure (1/101), chronic GN (1/101), azotaemia (0/101), renal impairment (0/101), dysfunctional uterine bleeding (0/101), acute respiratory failure (0/101), rash (1/101), hypertension (1/101)	Any AE (25/51), hyperkalaemia (4/51), metabolic acidosis (1/51), anaemia (3/51), diarrhoea (3/51), peripheral oedema (3/51), pyrexia (3/51), upper respiratory tract infection (4/51), gout (3/51), back pain (3/51), dizziness (4/51), hypertension (2/51), any SAE (6/51), serious anaemia (1/51), corona-artery disease (1/51), GI haemorrhage (0/51), acute cholecysts (1/51), cholelithiasis (1/51), lung infection (1/51), serious hyperkalaemia (0/51), hypokalaemia (0/51), serious metabolic acidosis (0/51), kidney failure (0/51), chronic GN (0/51), azotaemia (1/51), renal impairment:1/51), dysfunctional uterine bleeding (1/51), acute respiratory failure (1/51), rash (0/51), hypertension (0/51)	"During the randomized phase, at least one adverse event was reported in 69 of 101 patients (68%) in the roxadustat group (14.4 patient-years) and in 38 of 51 patients (75%) in the placebo group. Hyperkalemia and metabolic acidosis were reported more often in the roxadustat group than in the placebo group (in 16 patients [16%] in the roxadustat group and in 4 patients [8%] in the placebo group for hyperkalaemia and in 12 patients [12%] and 1 patient [2%], respectively, for metabolic acidosis). Serious adverse events, which were consistent with those generally seen in patients with chronic kidney disease, were reported in 9 patients (9%) in the roxadustat group and in 6 patients (12%) in the placebo group. There were no deaths during the randomized phase of the trial. An increase in the level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) occurred in 2 patients in the roxadustat group and 1 patient in the placebo group (2% in each group)"
Chen DD 2017	**Roxadustat**	**EPO alfa**	Death (0/60), SAE (0/60)	Death (0/22), SAE (0/22)	"No SAEs occurred during the DD study. No deaths or major adverse cardiac events occurred in FG-4592 subjects. In the DD study, 32 subjects (43%) among the total of 74 FG-4592-treated subjects and 4 subjects (18%) among the total of 22 epoetin al-

(Continued)

					fa-treated subjects reported having at least one TEAE. One adverse event of rash in the mid-dose FG-4592 arm in the DD study led to treatment discontinuation."
Chen NDD 2017	**Roxadustat**	**Placebo**	Death (0/61), SAE (0/61), muscle spasms (1/61), diarrhoea (2/61), vomiting (2/61), abdominal discomfort (0/61), nausea (4/61), dizziness (3/61), headache (2/61), hypertension (4/61), hyperkalaemia (6/61), liver injury (0/61), decreased appetite (0/61), TSAT decreased (8/61), CKD (4/61), nasopharyngitis (2/61), upper respiratory tract infection (3/61	Death (0/30), SAE (0/30), muscle spasms (0/30), diarrhoea (1/30), vomiting (0/30), abdominal discomfort (1/30), nausea (1/30), dizziness (3/30), headache (0/30), hypertension (0/30), hyperkalaemia (2/30), liver injury (1/30), decreased appetite (0/30), TSAT decreased (1/30), CKD (0/30), nasopharyngitis (0/30), upper respiratory tract infection (3/30	"Treatment-emergent serious adverse events (SAEs) were reported in four (13.3%) placebo-treated subjects and eight (13.1%) FG-4592-treated subjects in the blinded NDD study; no SAEs were deemed related to FG-4592. One cardiovascular SAE of unstable angina was reported in a placebo-treated subject but no such events were reported in FG-4592-treated subjects. No deaths or major adverse cardiac events occurred in FG-4592 subjects. Nineteen (63%) placebo-treated subjects and 36 (59%) FG-4592 subjects reported at least one treatment emergent adverse event (TEAE) in the NDD study. One placebo-treated but no FG4592-treated subjects had elevations 3> upper limit of normal of either ALT or AST. Two adverse events of urinary tract infection and worsening chronic renal failure in the low-dose FG4592 arm in the NDD study (a decline in eGFR from 11 mL/ min at screening to 8 mL/ min at EOT) led to treatment discontinuation."
DIALOGUE 1 2019	**Molidustat (25, 50, 75, 100 mg)**	**Placebo**	Hyperparathyroidism secondary (1/101), constipation (5/101), diarrhoea (4/101), vomiting (0/101), nasopharyngitis (7/101), UTI (4/101), hyperkalaemia (4/101),	Hyperparathyroidism secondary (3/20), constipation (1/20), diarrhoea (1/20), vomiting (1/20), nasopharyngitis (2/20), UTI (3/20), hyperkalaemia (3/20),	"The incidences of treatment-emergent adverse events (TEAEs) and serious TEAEs in the molidustat combined-dose group were numerically lower than

(Continued)

			dizziness (5/101), hypertension (10/101), acute MI (1/101), stroke (0/101), arterial occlusive disease (1/101), peripheral arterial occlusive disease (0/101), peripheral artery thrombosis (1/101), peripheral venous disease (0/101), death (0/101)	dizziness (3/20), hypertension (5/20), acute MI (0/20), stroke (1/20), arterial occlusive disease (0/20), peripheral arterial occlusive disease (1/20), peripheral artery thrombosis (0/20), peripheral venous disease (1/20), death (0/20)	those seen in the placebo group. One increase in alanine transaminase levels in the placebo group of DIALOGUE 1 was reported."
DIALOGUE 2 2019	**Molidustat (25, 50, 75, mg)**	**Darbepoetin alfa**	Diarrhoea (5/92), peripheral oedema (8/92), CKD (10/92), hypertension (14/92), acute MI (10/92), stroke (0/92), arterial occlusive disease (0/92), peripheral arterial occlusive disease (0/92), peripheral artery thrombosis (1/92), peripheral venous disease (0/92), death (1/92)	Diarrhoea (1/32), peripheral oedema (2/32), CKD (0/3), hypertension (4/32), acute MI (0/32), stroke (1/32), arterial occlusive disease (0/32), peripheral arterial occlusive disease (0/32), peripheral artery thrombosis (0/32), peripheral venous disease (0/32), death (1/32)	"The incidence of TEAEs in DIALOGUE 2 was numerically higher in the molidustat combined-dose group than in the darbepoetin group, and the incidence of study drug-related TEAEs in both DIALOGUE 2 and DIALOGUE 4 was numerically higher in the molidustat groups than in the darbepoetin/epoetin groups. Study drug-related serious TEAEs occurred in only one and two patients in the molidustat groups of DIALOGUE 2 and DIALOGUE 4, respectively (hyponatraemia, prolonged QT interval, and hypotension)."
DIALOGUE 4 2019	**Molidustat (25, 50, 75, 150 mg)**	**Epoetin alfa or beta**	Diarrhoea (12/157), nausea (8/157), vomiting (6/157), nasopharyngitis (9/157), Hb decreased (10/157), Hb increased (13/157), hypertension (17/157), acute MI (2/157), stroke (2/157), arterial occlusive disease (0/157), peripheral arterial occlusive disease (0/157), peripheral artery thrombosis (0/157), peripheral venous disease (0/157), venous occlusion (1/157), death (1/157)	Diarrhoea (2/42), nausea (2/42), vomiting (0/42), nasopharyngitis (1/42), Hb decreased (2/42), Hb increased (2/42), hypertension (8/42), acute MI (0/42), stroke (0/42), arterial occlusive disease (0/42), peripheral arterial occlusive disease (0/42), peripheral artery thrombosis (0/42), peripheral venous disease (0/42), death (0/42)	"The incidence of study drug-related TEAEs in both DIALOGUE 2 and DIALOGUE 4 was numerically higher in the molidustat groups than in the darbepoetin/epoetin groups. Study drug-related serious TEAEs occurred in only one and two patients in the molidustat groups of DIALOGUE 2 and DIALOGUE 4, respectively (hyponatraemia, prolonged QT interval, and hypotension)"
DOLOMITES 2021	**Roxadustat**	**Darbepoetin**	Total SAEs (209/323). The complete list is available in the results posted in the NCT02021318 Acute MI (5/323), cardiac arrest (3/323), coronary	Total SAEs (181/293). The complete list is available in the results posted in the NCT02021318	"Common TEAEs in both groups were end-stage renal disease, hypertension, decreased eGFR, and peripheral edema."

(Continued)

			artery disease (1/323), MI (3/323), glaucoma (0/323), abdominal pain (1/323), diarrhoea (3/323), vomiting (1/323), cardiac death (2/323), chest pain (2/323), sudden death (14/323), liver injury (0/323), kidney transplant failure (0/323), catheter site infection (0/323), renal cyst infection (2/323), AVF site complication (3/323), arterial bypass occlusion (1/323), shunt occlusion (0/323), tibia fracture (0/323), vascular access site thrombosis (0/323), diabetes mellitus (2/323), cerebral ischemias (1/323), Ischaemic stroke (0/323), depression (1/323), AKI (7/323), CKD (1/323), kidney failure (108/323), GFR decreased (33/323), pulmonary hypertension (1/323), thrombosis (1/323) **Other AEs (not including serious)** GFR decrease: 33/323 **Overall data > 5% reported in the Astellas website** AVF thrombosis (16/323), hyperkalaemia (38/323)	Acute MI (8/293), cardiac arrest (3/293) coronary artery disease (3/293), MI (0/293), glaucoma (1/293), abdominal pain (1/293), diarrhoea (2/293), vomiting (0/293), cardiac death (0/293), chest pain (1/293), sudden death (1/293), liver injury (1/293), renal transplant failure (1/293), catheter site infection (1/293), renal cyst infection (0/293), AVF site complication (1/293), arterial bypass occlusion (0/293), shunt occlusion (1/293), tibia fracture (1/293), vascular access site thrombosis (1/293), diabetes mellitus (0/293), cerebral ischemias (0/293), Ischaemic stroke (3/293), depression (0/293), AKI (7/293), CKD (0/293), kidney failure (106/293), GFR decreased (28/293), pulmonary hypertension (3/293), thrombosis (0/293) **Other AEs (not including serious)** GFR decrease: 28/293 **Overall data > 5% reported in the Astellas website** AVF thrombosis (10/293), hyperkalaemia (42/293)	
HIMALAYAS 2021	**Roxadustat**	**EPO alfa**	The following are related > 5% AEs Hypertension (99/522), diarrhoea (72/522), muscle spasms (60/522), AVF thrombosis (59/522), headache (57/522), hypotension (54/522), hyperphosphataemia (52/522), nausea (45/522), pneumonia (42/522), constipation (35/522), vomiting	The following are related to > 5% AEs Hypertension (88/517), diarrhoea (38/517), muscle spasms (39/517), AVF thrombosis (46/517), headache (44/517), hypotension (35/517), hyperphosphataemia (35/517), nausea (30/517), pneumonia (40/517), constipation (23/517), vom-	"More than 85%of patients in the roxadustat and epoetin alfa groups experienced one or more TEAE during treatment. The most frequently reported TEAE in the roxadustat group was hypertension, which occurred in 19.0%of patients in the roxadustat group and

(Continued)

			(32/522), AVF site complication (31/522), pruritus (30/522), fluid overload (29/522), cough (28/522), dizziness (28/522), hyperkalaemia (26/522), procedural hypotension (26/522), hyperparathyroidism, secondary (25/522), back pain (18/522) AEs < 1% were reported in table 8 of Provenano 2021	iting (17/517), AVF site complication (43/517), pruritus (22/517), fluid overload (28/517), cough (21/517), dizziness (24/517), hyperkalaemia (36/517), procedural hypotension (31/517), hyperparathyroidism, secondary (27/517), back pain (27/517) AEs < 1% were reported in table 8 of Provenano 2021	17.0% in the epoetin alfa group. Hyperkalemia rates were lower in the roxadustat versus epoetin alfa group (5.0% versus 7.0%). In the roxadustat and epoetin alfa groups, 44.8% and 42.2%, respectively, experienced one or more TESAE during treatment (Table 8). There were 63 (12.1%) fatal TEAEs in the roxadustat group and 59 (11.4%) in the epoetin alfa group."
Holdstock 2019	**Daprodustat**	**EPO**	AEs and frequency of MACE and component endpoints in the combined daprodustat (both Holdstock 2019 and Holdstock 2019a) Note: cumulative data for all-cause death, MI, stroke, blood transfusion and hospitalisation due to heart failure were reported	AEs and frequency of MACE and component endpoints in the combined control group (both Holdstock 2019 and Holdstock 2019a) To note that cumulative data for all-cause death, MI, stroke, blood transfusion and hospitalisation due to heart failure were reported	"Other adverse events included sequelae of excessive erythropoiesis, fatal CV and thromboembolic events, cardiomyopathy, pulmonary artery hypertension, cancer, oesophageal and gastric erosions, exacerbation of rheumatoid arthritis, and retinal and choroidal neovascularization. The proportion of these events was the same in both groups (8%). One participant with advanced CKD and gout who was randomized to daprodustat 1 mg met the protocol-defined liver stopping criteria 2 weeks after treatment initiation, with alanine aminotransferase (ALT) increased."
Holdstock 2019a	**Daprodustat**	**EPO**	AEs and frequency of MACE and component endpoints in the combined daprodustat (both Holdstock 2019 and Holdstock 2019a)	AEs and frequency of MACE and component endpoints in the combined control group (both Holdstock 2019 and Holdstock 2019a)	"Other adverse events included sequelae of excessive erythropoiesis, fatal CV and thromboembolic events, cardiomyopathy, pulmonary artery hypertension, cancer, oesophageal and gastric erosions, exacerbation of rheumatoid arthritis, and retinal and choroidal neovascularization. The pro-

(Continued)

					portion of these events was the same in both groups (8%). One participant with advanced CKD and gout who was randomized to daprodustat 1 mg met the protocol-defined liver stopping criteria 2 weeks after treatment initiation, with alanine aminotransferase (ALT) increased."
Hou 2021	**Roxadustat**	**ESA**	Upper respiratory tract infection (2/86), hypertension (5/86), hyperkalaemia (8/86), chest discomfort (2/86), vomiting (3/86), asthenia (2/86), alanine aminotransferase increased (2/86), dizziness (0/86), hypotension (1/86), muscle spasms (0/86), constipation (1/86), pruritus (1/86), peritonitis (1/86), ostealgia (2/86), headache (3/86), insomnia (5/86)	Upper respiratory tract infection (1/43), hypertension (3/43), hyperkalaemia (2/43), chest discomfort (1/43), vomiting (1/43), asthenia (1/43), alanine aminotransferase increased (0/43), dizziness (1/43), hypotension (1/43), muscle spasms (1/43), constipation (0/43), pruritus (0/43), peritonitis (1/43), ostealgia (0/43), headache (2/43), insomnia (0/43)	"Common adverse events included hyperkalaemia, hypertension, and insomnia." "During treatment, serious adverse events (SAEs) were reported in 2 (2%) roxadustat-treated subjects and 1 (2%) ESAs-treated patient. One SAE of MI was reported in a roxadustat-treated subject, and he discontinued the trial. A 66-year-old patient in the roxadustat group with hypertension died in the intensive care unit (death cause: acute heart failure) during follow-up. A 61-year-old patient with diabetes in the ESAs group died on day 84 due to heart failure." "Overall, 38 of 86 patients (44%) treated with roxadustat and 15 of 43 patients (35%) treated with ESAs incurred at least one adverse event during treatment."
INNO2VATE 2020	**Vadadustat**	**Darbepoetin alfa**	Any AE: 150/179 Hypertension (29/179), diarrhoea (18/179), pneumonia (13/179), hyperkalaemia (8/179), fluid overload (13/179), fall (11/179), headache (8/179), hypotension (7/179), nausea (14/179), vomiting (13/179), UTI	Any AE: 159/186 Hypertension (24/186), diarrhoea (18/186), pneumonia (15/186), hyperkalaemia (10/186), fluid overload (6/186), fall (9/186), headache (11/186), hypotension (16/186), nausea (13/186), vom-	"In the incident DD-CKD trial, 83.8% of the patients in the vadadustat group and 85.5% of the patients in the darbepoetin alfa group had at least one adverse event after the start of treatment. The incidence of serious adverse events was 49.7%

(Continued)

			(11/179), dialysis-related complication (8/179), cough (11/179), AVF site complication (8/179), dyspnoea (13/179), upper respiratory tract infection (5/179), pain in extremity (8/179), sepsis (6/179), AVF thrombosis (6/179), nasopharyngitis (10/179), back pain (7/179), hypoglycaemia (5/179), atrial fibrillation (5/179), bronchitis (5/179), procedural hypotension (11/179)	iting (10/186), UTI (16/186), dialysis-related complication (11/186), cough (5/186), AVF site complication (9/186), dyspnoea (10/186), upper respiratory tract infection (9/186), pain in extremity (6/186), sepsis (9/186), AVF thrombosis (10/186), nasopharyngitis (8/186), back pain (4/186), hypoglycaemia (9/186), atrial fibrillation (6/186), bronchitis (7/186), procedural hypotension (12/186)	in the vadadustat group and 56.5% in the darbepoetin alfa group."
INNO2VATE 2020a	**Vadadustat**	**Darbepoetin alfa**	Any AE: 1562/1768 Hypertension (187/1768), diarrhoea (230/1768), pneumonia (195/1768), hyperkalaemia (160/1768), fluid overload (156/1768), fall (150/1768), headache (160/1768), hypotension (146/1768), nausea (149/1768), vomiting (120/1768), UTI (110/1768), dialysis-related complication (99/1768), cough (99/1768), AVF site complication (94/1768), dyspnoea (92/1768), upper respiratory tract infection (99/1768), pain in extremity (91/1768), sepsis (89/1768), AVF thrombosis (106/1768), nasopharyngitis (92/1768), back pain (76/1768), hypoglycaemia (92/1768), atrial fibrillation (69/1768), bronchitis (67/1768), procedural hypotension (69	Any AE: 1580/1769 Hypertension (244/1769), diarrhoea (178/1769), pneumonia (172/1769), hyperkalaemia (191/1769), fluid overload (173/1769), fall (159/1769), headache (135/1769), hypotension (141/1769), nausea (134/1769), vomiting (124/1769), UTI (117/1769), dialysis-related complication (122/1769), cough (121/1769), AVF site complication (120/1769), dyspnoea (119/1769), upper respiratory tract infection (112/1769), pain in extremity (117/1769), sepsis (101/1769), AVF thrombosis (78/1769), nasopharyngitis (84/1769), back pain (99/1769), hypoglycaemia (78/1769), atrial fibrillation (95/1769), bronchitis (95/1769), procedural hypotension (74/1769)	"In the prevalent DD-CKD trial, 88.3% of the patients in the vadadustat group and 89.3% of the patients in the darbepoetin alfa group had at least one adverse event after the start of treatment. The incidence of serious adverse events was 55.0% and 58.3%, respectively."
Meadowcroft 2019	**Daprodustat**	**Placebo**	AE: diarrhoea (16/177), nasopharyngitis (15/177), nausea (13/177), headache (9/177), hypertension (9/177), hyperkalaemia (8/177), back pain (7/177), any	AE: diarrhoea (2/39), nasopharyngitis (5/39), nausea (0/39), headache (2/39), hypertension (1/39), hyperkalaemia (0/39), back pain (4/39), any	"On the AEs most frequently reported, diarrhoea, nausea, hypertension and hyperkalaemia were reported more often in the combine daprodus-

(Continued)

	MACE (7/177), death (any cause) (5/177), MI (3/177), stroke (0/177), hospitalisation due to heart failure (5/177) SAE (31/177), cardiac arrest (3/177), thrombosis related to vascular access (3/177), cancer (3/177), oesophageal and gastric erosions (3/177), pulmonary artery hypertension (2/177), elevations of estimated sPAP (2/177), macular oedema in (2/177), exacerbation of RA (1/177)	MACE (0/39), death (any cause) (0/39), MI (0/39), stroke (0/39), hospitalisation due to heart failure (1/39) SAE (10/39), cardiac arrest (0/177), thrombosis related to vascular access (2/39), cancer (0/39), oesophageal and gastric erosions (0/39), pulmonary artery hypertension (0/39), elevations of estimated sPAP (0/39), macular oedema in (0/39), exacerbation of RA (0/39)	tat group, while nasopharyngitis and back pain were reported more often in the control group. [...] Serious adverse events were reported in 31 participants in the daprodustat group and 10 participants in the control group. the most common adverse events. The most common Serious AEs in the intervention group were myocardial infarction and cardiac arrest, in 3 participants each, followed by unstable angina, cardiac failure, hypertensive crisis, lobar pneumonia and pulmonary oedema in 2 participants each. In the control group no specific serious AEs were reported in more than one participant." "Thrombosis events related to vascular access were reported in 6 (3%) daprodustat participants and 2 (5%) control participants. Also reported for the combined daprodustat group were cancer progression or recurrence in 3 (2%) participants (2 retrospectively identified as pre-existing but undiagnosed, and 1 basal cell carcinoma); oesophageal and gastric erosions in 3 (2%) participants; pulmonary artery hypertension, reported as elevations of estimated sPAP, in 2 (1%) participants; macular edema in 2 (1%) participants, based on review of ophthalmology exam data; and an exacerbation of RA in 1 (<1%) participants with pre-existing RA"

(Continued)

MIYABI HD-M 2019	**Molidustat**	**Darbepoetin alfa**	AE (TEAEs) (95.4%), serious TEAEs (24.2%), TEAEs with an outcome of death (1.3%) or AEs of special interest (4.6%)	AE (TEAEs) (94.7%), serious TEAEs (18.4%), TEAEs with an outcome of death (2.6%) or AEs of special interest (3.9%)	"There were no apparent between-group differences in incidence of treatment-emergent adverse events (TEAEs) (molidustat, 95.4%; darbepoetin alfa, 94.7%), serious TEAEs (24.2%; 18.4%), TEAEs with an outcome of death (1.3%; 2.6%) or AEs of special interest (4.6%; 3.9%)."
MIYABI ND-C 2019	**Molidustat**	**Darbepoetin alfa**	AEs: 84.1%; the most common AEs were nasopharyngitis (20.7%) and worsening CKD (13.4%) Constipation (10/82), dental caries (1/82), diarrhoea (8/82), nausea (6/82), stomatitis (1/82), pyrexia (1/82), bronchitis (5/82), nasopharyngitis (26/82), pneumonia (6/82), contusion (10/82), hyperkalaemia (10/82), back pain (8/82), muscle spasms (2/82), CKD worsening (16/82), cough (2/82), eczema (3/82), AVF operation (3/82), hypertension (8/82)	AEs: 91.1%; the most common AEs were nasopharyngitis (25.3%) and worsening CKD (6.3%) Constipation (8/82), dental caries (4/82), diarrhoea (3/82), nausea (4/82), stomatitis (4/82), pyrexia (5/82), bronchitis (3/82), nasopharyngitis (21/82), pneumonia (2/82), contusion (3/82), hyperkalaemia (9/82), back pain (3/82), muscle spasms (5/82), CKD worsening (9/82), cough (4/82), eczema (4/82), AVF operation (5/82), hypertension (4/82)	"AEs were experienced in 84.1% of patients in the MO group and in 91.1% of patients in the DA group up to 36 weeks. The most common AEs occurred ≥ 5% of patients in any group were nasopharyngitis (20.7% and 25.3%, respectively) and worsening of chronic kidney disease (13.4% and 6.3%, respectively)." "Severe TEAEs were also observed in 17.1% of patients for molidustat and 7.6% for darbepoetin. The most common TEAEs were nasopharyngitis (31.7% for molidustat and 26.6% for darbepoetin) and worsening of CKD (19.5% for molidustat and 11.4% for darbepoetin)."
MIYABI ND-M 2019	**Molidustat**	**Darbepoetin alfa**	Constipation (7/82), diarrhoea (7/82), large intestine polyp (0/82), oedema, peripheral (7/82), influenza (6/82), nasopharyngitis (28/82), pneumonia (4/82), hyperkalaemia (2/82), hypoglycaemia (6/82), back pain (6/82), insomnia (5/82), CKD worsening (15/82), hypertension (2/82)	Constipation (7/82), diarrhoea (10/82), large intestine polyp (5/82), oedema, peripheral (2/82), influenza (1/82), nasopharyngitis (33/82), pneumonia (5/82), hyperkalaemia (7/82), hypoglycaemia (0/82), back pain (3/82), insomnia (4/82), CKD worsening (8/82), hypertension (5/82)	"The proportion of patients who reported at least 1 treatment-emergent adverse event (TEAE) was 92.7% for molidustat and 96.3% for darbepoetin."
Nangaku 2021	**Vadadustat**	**Darbepoetin alfa**	Nasopharyngitis (19.8%), diarrhoea (10.5%), and shunt stenosis (8.0%)	Nasopharyngitis (28.6%), diarrhoea	"A similar proportion of patients reported at least one AE during the

(Continued)

	The incidence rates of SAE were 13.0% CV event, cardiac failure (13/162), cerebral infarction (1/162), carotid artery stenosis (1/162), cerebellar infarction (1/162), intracranial aneurysm (1/162), lacunar infarction (1/162), thrombotic cerebral infarction (1/162), subarachnoid haemorrhage (0/162), cardiac failure congestive (2/162), angina pectoris (1/162), coronary artery stenosis (1/162), myocardial ischemias (1/162), angina unstable (1/162), arteriosclerosis coronary artery (1/162), cardiac failure (1/162), pulmonary oedema (2/162), subdural hematoma (1/162), coronary artery restenosis (0/162), retinal disorder (21/162), retinal haemorrhage (16/162), diabetic retinopathy (2/162), macular oedema (1/162), retinal oedema (1/162), retinal vein occlusion (1/162), vitreous floaters (1/162), cystoid macular oedema (1/162), chorioretinopathy (1/162), retinal detachment (0/162), retinal vascular disorder (0/162), vitreous detachment (0/162), vitreous haemorrhage (0/162), retinal aneurysm (0/162), age-related macular degeneration (0/162), malignancy (7/162), breast cancer (1/162), gastric cancer (1/162), seborrhoeic keratosis (1/162), cholesteatoma (1/162), laryngeal papilloma (1/162), squamous cell carcinoma of skin (1/162), uterine leiomyoma (1/162), pyogenic granuloma (0/162), thymoma (0/162), prostate (9.9%), and shunt stenosis (12.4%) The incidence rates of SAEs were 10.6% CV event, cardiac failure (15/161), cerebral infarction (5/161), carotid artery stenosis (1/161), cerebellar infarction (1/161), intracranial aneurysm (0/161), lacunar infarction (0/161), thrombotic cerebral infarction (0/161), subarachnoid haemorrhage (1/161), cardiac failure congestive (0/161), angina pectoris (3/161), coronary artery stenosis (2/161), myocardial ischemias (1/161), angina unstable (0/161), arteriosclerosis coronary artery (0/161), cardiac failure (0/161), pulmonary oedema (1/161), subdural hematoma (0/161), coronary artery restenosis (1/161), retinal disorder (16/161), retinal haemorrhage (10/161), diabetic retinopathy (1/161), macular oedema (3/161), retinal oedema (0/161), retinal vein occlusion (0/161), vitreous floaters (0/161), cystoid macular oedema (0/161), chorioretinopathy (0/161), retinal detachment (1/161), retinal vascular disorder (1/161), vitreous detachment (1/161), vitreous haemorrhage (1/161), retinal aneurysm (1/161), age-related macular degeneration (1/161), malignancy (9/161), breast cancer (1/161), gastric cancer (1/161), seborrhoeic keratosis (1/161), cholesteatoma (0/161), laryngeal papilloma (0/161), squamous cell carcinoma	52-week treatment period: 95.1% (154 of 162 patients) and 98.1% (158 of 161 patients) in the vadadustat and darbepoetin alfa groups, respectively, as presented in Table 3. During the 52-week treatment period, 11.1% and 3.7% of patients in the vadadustat and darbepoetin alfa groups, respectively, reported at least one ADR, and 25.3 and 27.3% of those in the vadadustat and darbepoetin alfa groups, respectively, reported at least one serious AE; however, none of the serious events was considered to be related to study treatment."

(Continued)

			cancer (0/162), pancreatic neoplasm (0/162), urethral neoplasm (0/162), renal cell carcinoma (0/162), GI submucosal tumour (0/162), hyperkalaemia (1/162), thromboembolism (12/162), cerebral infarction (1/162), cerebellar infarction (1/162), lacunar infarction (1/162), thrombotic cerebral infarction (1/162), retinal vein occlusion (1/162), peripheral arterial occlusive disease (3/162), thrombophlebitis (0/162), peripheral artery occlusion (0/162), shunt occlusion (4/162), shunt thrombosis (1/162), AVF thrombosis (0/162), pulmonary hypertension (0/162)	of skin (0/161), uterine leiomyoma (0/161), pyogenic granuloma (1/161), thymoma (1/161), prostate cancer (1/161), pancreatic neoplasm (1/161), urethral neoplasm (1/161), renal cell carcinoma (1/161), GI submucosal tumour (1/161), hyperkalaemia (1/161), thromboembolism (14/161), cerebral infarction (5/161), cerebellar infarction (1/161), lacunar infarction (0/161), thrombotic cerebral infarction (0/161), retinal vein occlusion (0/161), peripheral arterial occlusive disease (3/161), thrombophlebitis (1/161), peripheral artery occlusion (1/161), shunt occlusion (4/161), shunt thrombosis (0/161), AVF thrombosis (1/161), pulmonary hypertension (0/161)	
Nangaku 2021a	**Vadadustat**	**Darbepoetin alfa**	AE: 72.2% The most common AEs in the VDT group were nasopharyngitis (VDT: 14.6%, DA: 12.4%), diarrhoea (VDT: 10.6%, DA: 3.3%), and constipation (VDT: 5.3%, DA: 3.9%) The incidence rate of SAEs was 13.9% Nasopharyngitis (37/151), diarrhoea (18/151), constipation (14/151), contusion (11/151), peripheral oedema (11/151), vomiting (10/151), CKD (9/151), renal impairment (8/151), pyrexia (8/151), pruritus (7/151), cystitis (6/151), eczema (5/151), hypertension (2/151), CV events (9/151), cardiac failure, chronic (3/151), cardiac failure, congestive (2/151), intracra-	AE: 73.2% The incidence rate of SAEs was 14.4% Nasopharyngitis (43/153), diarrhoea (8/153), constipation (11/153), contusion (7/153), peripheral oedema (5/153), vomiting (3/153), CKD (14/153), renal impairment (8/153), pyrexia (1/153), pruritus (8/153), cystitis (9/153), eczema (8/153), hypertension (11/153), CV events (5/153), cardiac failure, chronic (0/153), cardiac failure, congestive (0/153), intracranial aneurysm (1/153), cardiac failure (0/153), myocardial ischemias (0/153), subarachnoid haemorrhage (0/153), cardiac failure, acute (2/153), lacunar infarction (2/153), cerebral	"At least one adverse event (AE) was seen in 72.2% (VDT) and 73.2% (DA) subjects. The most common AEs in the VDT group were nasopharyngitis (VDT: 14.6%, DA: 12.4%), diarrhoea (VDT: 10.6%, DA: 3.3%), and constipation (VDT: 5.3%, DA: 3.9%). The incidence rates of serious AEs were 13.9% (VDT) and 14.4% (DA). [...] In the vadadustat group, nine patients reported a CV event or cardiac failure, four reported at least one retinal disorder event, two reported a malignancy, one reported an event of hyperkalaemia, and one reported a thromboembolism. There were no patients with pulmonary hypertension. All AEs of special interest,

(Continued)

			nial aneurysm (1/151), cardiac failure (1/151), myocardial ischemias (1/151), subarachnoid haemorrhage (1/151), cardiac failure, acute (0/151), lacunar infarction (0/151), cerebral infarction (0/151), retinal disorders (1/151), retinal haemorrhage (2/151), macular oedema (1/151), retinal exudates (1/151), retinal vein occlusion (1/151), age-related macular degeneration (1/151), diabetic retinopathy (0/151), scintillating scotoma (0/151), vitreous floaters (0/151), retinal aneurysm (0/151), macular fibrosis (0/151), malignancy (2/151), colon adenoma (1/151), oral papilloma (1/151), basal cell carcinoma (0/151), gastric cancer (0/151), keratoacanthoma (0/151), renal cancer (0/151), seborrhoeic keratosis (0/151), skin papilloma (0/151), renal cancer metastatic (0/151), kidney angiomyolipoma (0/151), hyperkalaemia (1/151), thromboembolism (1/151), retinal vein occlusion (1/151), lacunar infarction (0/151), cerebral infarction (0/151), acute MI (0/151), pulmonary embolism (0/151), shunt occlusion (0/151), pulmonary hypertension (0/151)	infarction (1/153), retinal disorders (0/153), retinal haemorrhage (5/153), macular oedema (0/153), retinal exudates (0/153), retinal vein occlusion (0/153), age-related macular degeneration (0/153), diabetic retinopathy (3/153), scintillating scotoma (1/153), vitreous floaters (1/153), retinal aneurysm (1/153), macular fibrosis (1/153), malignancy (6/153), colon adenoma (0/153), oral papilloma (0/153), basal cell carcinoma (1/153), gastric cancer (1/153), keratoacanthoma (1/153), renal cancer (1/153), seborrhoeic keratosis (1/153), skin papilloma (1/153), renal cancer metastatic (1/153), kidney angiomyolipoma (1/153), hyperkalaemia (5/153), thromboembolism (6/153), retinal vein occlusion (0/153), lacunar infarction (2/153), cerebral infarction (1/153), Acute MI (1/153), pulmonary embolism (1/153), shunt occlusion (1/153), pulmonary hypertension (0/153)	except one retinal haemorrhage, were considered to be not related to vadadustat."
Nangaku 2021b	**Daprodustat**	**Mircera**	Nasopharyngitis (49/149), constipation (10/149), back pain (12/149), renal impairment (9/149), hyperkalaemia (12/149), pruritus (12/149), CKD (6/149), influenza (8/149), contusion (5/149), diarrhoea (5/149), BP increased (8/149), hypertension (4/149), muscle spasms (4/149)	Nasopharyngitis (56/150), constipation (18/150), back pain (11/150), renal impairment (13/150), hyperkalaemia (8/150), pruritus (5/150), CKD (10/150), influenza (8/150), contusion (8/150), diarrhoea (7/150), BP increased (4/150), hypertension	"There was no meaningful difference in the frequencies of adverse events."

(Continued)

				(8/150), muscle spasms (7/150)	
NCT01888445	**Roxadustat (dose 50, 75, 100 mg)**	**Darbepoetin alfa**	Treatment 1 (33 participants), treatment 2 (32 participants), treatment 3 (32 participants) TEAEs: treatment 1 (24, 72.7%), treatment 2 (26. 81.3%), treatment 3 (27, 84.4%) Drug-related TEAEs: treatment 1 (8, 24.2%), treatment 2 (7. 21.9%), treatment 3 (12, 37.5%) Deaths: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0) Serious TEAEs: treatment 1 (4, 12.1%), treatment 2 (7, 21.9%), treatment 3 (4. 12.5%) Drug-related serious TEAEs: treatment 1 (0), treatment 2 (2, 6.3%), treatment 3 (1, 3.1%) Eye disorders: treatment 1 (3, 9.1%), treatment 2 (2, 6.3%), treatment 3 (8, 25.0%) Retinal haemorrhage: treatment 1 (2, 6.1%), treatment 2 (2, 6.3%), treatment 3 (5, 15.6%) GI disorders: treatment 1 (7, 21.2%), treatment 2 (11, 34.4%), treatment 3 (13, 40.6%) Constipation: treatment 1 (1. 3.0%), treatment 2 (2, 6.3%), treatment 3 (2, 6.3%) Diarrhoea: treatment 1 (2, 6.1%), treatment 2 (1, 3.1%), treatment 3 (2, 6.3%) Nausea treatment: 1 (3, 9.1%), treatment 2 (2, 6.3%), treatment 3 (4, 12.5%) Vomiting: treatment 1 (2, 6.1%), treatment 2 (2, 6.3%), treatment 3 (7, 21.9%) Infections and infestations: treatment 1 (12, 36.4%), treatment 2 (12,	Control: 32 participants. TEAEs: 25 (78.1%) Drug-related TEAEs: 2 (6.3%) Deaths: 0 Serious TEAEs: 2 (6.3%) Drug-related serious TEAEs: 0 Eye disorders: 4 (12.5%) Retinal haemorrhage: 0 GI disorders: 9 (28.1%) Constipation: 2 (6.3%) Diarrhoea: 2 (6.3%) Nausea: 1 (3.1%) Vomiting: 2 (6.3%) Infections and infestations: 15 (46.9%) Nasopharyngitis: 14 (43.8%) Cardiac disorders: 0 Cardiac failure congestive: 0. Myocardial ischemias control 0 GI disorders: 1 (3.1%). Gastric ulcer: 1 (3.1%) Ileus: 0 Vomiting: 0 General disorders and administration site conditions: 0 Gait disturbance: 0 Pneumonia bacterial: 0 Viral upper respiratory tract infection: 0 Injury, poisoning and procedural complications: 0 Vascular graft occlusion: 0 Investigations treatment: 0 Hb decreased: 0 Liver function test abnormal: 0 Metabolism and nutrition disorders: 0 Decreased appetite: 0 Nervous system disorders: 0 Cerebral infarction: 0 Dizziness: 0 Lacunar infarction: 0	"The proportion of patients experiencing drug-related TEAEs and serious TEAEs in the ASP1517 groups was higher than that in the darbepoetin alfa group. The common (incidence > 5%) TEAEs in the pooled ASP1517 group included nasopharyngitis, vomiting, nausea, retinal haemorrhage, constipation, and diarrhoea. The common (incidence > 5%) TEAEs in the darbepoetin alfa group included nasopharyngitis, procedural hypotension, hyperparathyroidism secondary, constipation, diarrhoea, vomiting, excoriation, and back pain. The common (incidence > 1%) drug-related TEAEs included vomiting, nausea, retinal haemorrhage, hypertension and blood pressure increased in the pooled ASP1517 group and macular fibrosis and hypertension in the darbepoetin alfa group. One patient in the ASP1517 50 mg group died of embolism venous and the event was considered unrelated to the study treatment. Other than this patient, the outcome of patients with serious TEAEs was reported as recovered or recovering. Drug-related TEAEs leading to discontinuation of study treatment were reported in 2 (6.3%) patients each in the ASP1517 70 mg and 100 mg groups. A potential drug-induced liver injury case was reported in 1 patient, which was considered

(Continued)

37.5%), treatment 3 (9, 28.1%)
Nasopharyngitis: treatment 1 (10, 30.3%), treatment 2 (10, 31.3%), treatment 3 (8, 25.0%)

Cardiac disorders: treatment 1 (2, 6.1%), treatment 2 (0), treatment 3 (2, 6.3%)
Cardiac failure, congestive: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (2, 6.3%)
Myocardial ischemias: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0)
GI disorders: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (1, 3.1%)
Gastric ulcer: treatment 1 (0), treatment 2 (0), treatment 3 (0)
Ileus: treatment 1 (0), treatment 2 (0): treatment 3 (1, 3.1%)
Vomiting: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0)
General disorders and administration site conditions: treatment 1 (0), treatment 2 (0), treatment 3 (1, 3.1%)
Gait disturbance: treatment 1 (0), treatment 2 (0), treatment 3 (1, 3.1%)
Pneumonia bacterial: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0)
Viral upper respiratory tract infection: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0)
Injury, poisoning and procedural complications: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0)
Vascular graft occlusion: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0)
Investigations: treatment 1 (1, 3.0%), treatment 2 (1, 3.1%), treatment 3 (0)
Respiratory, thoracic and mediastinal disorders: 0
Pneumonia aspiration: 0
Surgical and medical procedures: 0
Gastric polypectomy: 0
Intestinal polypectomy: 0
Vascular disorders: 1 (3.1%)
Embolism venous: 0
Haematoma: 1 (3.1%)

unrelated to the study treatment because both AST and ALT remained within normal ranges during the study treatment and the event occurred approximately 2 weeks after discontinuation of the study treatment. No notable safety concerns were reported in other clinical laboratory evaluations, vital signs, ECGs or other safety-related observations. Due to an apparent imbalance between the occurrences of retinal haemorrhage events reported as adverse events, it was decided to conduct a descriptive aggregate analysis of the same ophthalmological images following centralized and masked grading by experienced graders. When interpreting treatment outcomes, one needs to consider that the ASP1517 and darbepoetin treatment groups were generally well balanced in terms of factors related to the efficacy of ASP1517 at baseline. Differences between groups were present in terms of factors that predicted new retinal pathology including longer dialysis vintage duration and a higher number of subjects with a status of laser therapy prior to treatment in the darbepoetin treated patients. At screening retinal haemorrhages were seen in 15.5% of the study population prior to any study intervention in the analysis. During treatment, a total of 9 (10.1%) patients in the pooled

(Continued)

	Hb decreased: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0) Liver function test abnormal: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0) Metabolism and nutrition disorders: treatment 1 (0): treatment 2 (0), treatment 3 (1, 3.1%) Decreased appetite: treatment 1 (0), treatment 2 (0), treatment 3 (1, 3.1%) Nervous system disorders: treatment 1 (0), treatment 2 (2, 6.3%), treatment 3 (1, 3.1%) Cerebral infarction: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0) Dizziness: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0) Lacunar infarction: treatment 1 (0), treatment 2 (0), treatment 3 (1, 3.1%) Respiratory, thoracic and mediastinal disorders: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0) Pneumonia aspiration: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0) Surgical and medical procedures: treatment 1 (0), treatment 2 (2, 6.3%), treatment 3 (0) Gastric polypectomy: treatment 1 (0), treatment 2 (1, 3.1%), treatment 3 (0) Intestinal polypectomy: treatment 1 (0), treatment 2 (2, 6.3%), treatment 3 (0) Vascular disorders: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0) Embolism, venous: treatment 1 (1, 3.0%), treatment 2 (0), treatment 3 (0) Haematoma: treatment 1 (0), treatment 2 (0), treatment 3 (0)	ASP1517 group and 2 (6.5%) patients in the darbepoetin group displayed new or worsening retinal haemorrhage. For the group of patients without haemorrhages at baseline, the incidence of new or worsening retinal haemorrhages after the start of treatment was comparable between pooled ASP1517 and darbepoetin treatment groups, 8.0% vs 7.1%, respectively. When new or worsening retinal haemorrhage assessments were presented by baseline status, low patient numbers in the group with retinal haemorrhages at baseline made it difficult to interpret the data but the incidence prior to and during treatment appeared similar. No change in retinal thickness was observed over the course of the study in the ASP1517 and darbepoetin alfa treatment groups."

(Continued)

NDD-CKD 2020	**Vadadustat (150, 300, 600 mg)**	**Placebo**	Death (0/37), SAE (7/37), duodenal ulcer haemorrhage (0/37), hepatic function abnormal (1/37), influenza (0/37), lung infection (1/37), spinal compression1 fracture (0/37), AKI (1/37), kidney failure (1/37), renal impairment (0/37), asthma (0/37), interstitial lung disease (1/37), arteriovenous shunt procedure (3/37)	Death (0/14), SAE (4/14), duodenal ulcer haemorrhage (1/14), hepatic function abnormal (0/14), influenza (0/14), lung infection (0/14), spinal compression fracture (10/14), AKI (0/14), kidney failure (0/14), renal impairment (1/14), asthma (1/14), interstitial lung disease (0/14), arteriovenous shunt procedure (0/14)	"During the primary efficacy period, the incidence of treatment-emergent adverse events (AEs) with placebo and vadadustat 150, 300 and 600mg was 36, 33, 58 and 54% (NDD-CKD) and 40, 53, 73 and 40% (DDCKD), respectively. The most common AEs during the primary efficacy period were nausea and hypertension (NDD-CKD) and diarrhoea, nasopharyngitis and shunt stenosis (DD-CKD). Of 23 serious AEs in 18 patients, 1 was deemed related (hepatic function abnormal); no deaths were reported."
NDD-CKD 2020a	**Vadadustat (150, 300, 600 mg)**	**Placebo**	Death (0/45), SAE (6/45), pericarditis (1/45), cholecystitis acute (1/45), enteritis infectious (1/45), AFVS complication (0/45), shunt stenosis (1/45), toxic encephalopathy (1/45), gastric ulcer haemorrhage (1/45), shunt stenosis (1/45), cerebral haemorrhage (1/45), anxiety (1/45)	Death (0/15), SAE (1/15), pericarditis (0/15), cholecystitis acute (0/15), enteritis infectious (0/15), AFVS complication (1/15), shunt stenosis (0/15), toxic encephalopathy (0/15), gastric ulcer haemorrhage (0/15), shunt stenosis (0/15), cerebral haemorrhage (0/15), anxiety (0/15)	"During the primary efficacy period, the incidence of treatment-emergent adverse events (AEs) with placebo and vadadustat 150, 300 and 600mg was 36, 33, 58 and 54% (NDD-CKD) and 40, 53, 73 and 40% (DDCKD), respectively. The most common AEs during the primary efficacy period were nausea and hypertension (NDD-CKD) and diarrhoea, nasopharyngitis and shunt stenosis (DD-CKD). Of 23 serious AEs in 18 patients, 1 was deemed related (hepatic function abnormal); no deaths were reported."
Pergola 2016	**Vadadustat**	**Placebo**	SAE (33/138), initiation of dialysis (11/138), diarrhoea (14/138), nausea (14/138), constipation (5/138), GI haemorrhage (0/138), fatigue (12/138), oedema peripheral (10/138), UTI (9/138), upper respiratory tract infection (2/138), hyperkalaemia (7/138), headache (8/138),	SAE 11 (15.3%), initiation of dialysis (7/72), diarrhoea (3/72), nausea (3/72), constipation (4/72), GI haemorrhage (4/72), fatigue (5/72), oedema peripheral (7/72), UTI (6/72), upper respiratory tract infection (5/72), hyperkalaemia (0/72), headache (2/72), dizzi-	"The percentage of patients who experienced at least 1 adverse events was comparable between the vadadustat and placebo groups (74.6% vs. 73.6%). Occurrence of at least 1 drug related AE was reported in 25.4% of vadadustat-treated patients (35 of 138) and

(Continued)

			dizziness (7/138), AKI (10/138), CKD (7/138), dyspnoea (6/138), hypertension (11/138), hypotension (6/138), death (3/138)	ness (3/72), AKI (4/72), CKD (3/72), dyspnoea (4/72), hypertension (2/72), hypotension (4/72), death (0/72)	11.1% of placebo-treated patients (8 of 72). Most commonly reported drug-related AEs in the vadadustat group included diarrhoea (4.3%) and nausea (4.3%), whereas diarrhoea (2.8%) was the most commonly reported drug-related AE in the placebo group. Hypertension was reported as an AE in 8.0% of vadadustat-treated patients (11 of 138) and 2.8% of those treated with placebo (2 of 72). A total of 33 vadadustat-treated patients (23.9%) reported at least 1 serious adverse event (SAE), as did 11 placebo treated patients (15.3%); the higher incidence of SAEs was primarily due to a higher incidence of renal-related SAEs in the vadadustat group (10.1%) compared with the placebo group (2.8%). The requirement for initiation of dialysis was evenly balanced between the vadadustat (11 of 138, 8.0%) and placebo (7 of 72, 9.7%) groups."
PRO2TECT-CONVERSION 2021	**Vadadustat**	**Darbepoetin alfa**	Any AE (767/878), death (139/878), diarrhoea (119//878), kidney failure (237/878), fall (69/878), hyperkalaemia (81/878), hypertension (124/878), peripheral oedema (85/878), pneumonia (86/878), UTI (105/878), nausea (73/878)	All data were related to 861 participants: Any AE (756/861), death 139/861), diarrhoea (76/861), kidney failure (245/861), fall (65/861), hyperkalaemia (85/861), hypertension (128/861), peripheral oedema (87/861), pneumonia (84/861), UTI (125/861), nausea (58/861)	"The full list of AEs is provided in the supplementary materials."
PRO2TECT-CORRECTION 2021	**Vadadustat**	**Darbepoetin alfa**	Any AE (798/870), death (180/870), diarrhoea (122/870), kidney failure (305/870), fall (84/870), hyperkalaemia (108/870), hypertension (155/870),	Any AE (797/862), death (168/862), diarrhoea (87/862), kidney failure (306/862), fall (87/862), hyperkalaemia (136/862), hy-	"The full list of AEs is provided in the supplementary materials."

(Continued)

			peripheral oedema (110/870), pneumonia (86/870), UTI (113/870), nausea (88/870)	pertension (192/862), peripheral oedema (91/862), pneumonia (75/862), UTI (104/862), nausea (71/862)	
Provenzano 2008	**FG2216 (375, 625, 1250 mg)**	**Placebo**	Death (1/128) (not reported in which treatment group)	Death (0/14)	"There were 41 SAE in 25 participants, 2 were assessed as possibly related to FG2216, including 1 death due to fulminant hepatitis."
PYRENEES 2021	**Roxadustat**	**EPO alfa**	Hypertension (74/414), AVF thrombosis (50/414), headache (36/414), diarrhoea (35/414), bronchitis (33/414), hypotension (33/414), iron deficiency (30/414), nausea (29/414), viral upper respiratory tract infection (29/414), pneumonia (23/414), AVF site complication (23/414), hyperparathyroidism, secondary (22/414), anaemia (21/414), atrial fibrillation (20/414), muscle spasms (15/414), upper respiratory tract infection (14/414), fall (13/414), peritonitis (10/414), sepsis (8/414), bronchitis (5/414), gangrene (5/414), UTI (4/414), gastroenteritis (0/414), femur fracture (2/414), shunt thrombosis (1/414), atrial fibrillation (12/414), acute MI (9/414), cardiac failure (8/414), angina pectoris (5/414), cardiac failure, congestive (5/414), cardiac arrest (4/414), myocardial ischemias (4/414), MI (1/414), supraventricular tachycardia (1/414), DVT (4/414), peripheral arterial occlusive disease (2/414), peripheral ischemias (2/414), respiratory, thoracic and mediastinal disorders (29/414), pleural effusion (6/414), pulmonary oedema (6/414), dyspnoea (4/414), pulmonary em-	Hypertension (79/420), AVF thrombosis (31/420), headache (29/420), diarrhoea (35/420), bronchitis (29/420), hypotension (27/420), iron deficiency (51/420), nausea (8/420), viral upper respiratory tract infection (39/420), pneumonia (27/420), AVF site complication (21/420), hyperparathyroidism, secondary (16/420), anaemia (16/420), atrial fibrillation (25/420), muscle spasms (33/420), upper respiratory tract infection (22/420), fall (21/420), peritonitis (3/420), sepsis (9/420), bronchitis (3/420), gangrene (4/420), UTI (0/420), gastroenteritis (6/420), femur fracture (5/420), shunt thrombosis (14/420), atrial fibrillation (8/420), acute MI (11/420), cardiac failure (9/420), angina pectoris (6/420), cardiac failure, congestive (1/420), cardiac arrest (8/420), myocardial ischemias (4/420), MI (6/420), supraventricular tachycardia (5/420), DVT (0/420), peripheral arterial occlusive disease (4/420), peripheral ischemias (4/420), respiratory, thoracic and mediastinal disorders (21/420), pleural effusion (2/420), pulmonary	"The overall incidence of TEAEs and TEAEs PEY during the safety emergent period was comparable between treatment groups, with the overall event profile largely driven by events in the Infections and Infestations (most commonly viral upper respiratory tract infections and bronchitis in both treatment groups), Injury, Poisoning and Procedural Complications (with a greater incidence of arteriovenous (AV) fistula thrombosis in the roxadustat treatment group, mainly in the subgroup of patients receiving roxadustat compared with epoetin), Vascular Disorders (most commonly hypertension in both treatment groups) and gastrointestinal Disorders (with a greater incidence of diarrhoea and nausea in the roxadustat treatment group) MedDRA SOCs. TEAEs with an increased incidence in the roxadustat treatment group were mostly in the gastrointestinal Disorders, Skin and Subcutaneous Disorders, Nervous System Disorders and General Disorders and Administration Site Conditions SOCs. There were imbalances in the overall incidence of nausea

(Continued)

			bolism (4/414), general disorders and administration site conditions (28/414), pyrexia (4/414), duodenal ulcer (4/414), GI haemorrhage (0/414), nervous system disorders 15/414), cerebral infarction (0/414), metabolism and nutrition disorders (12/414), hyperkalaemia (4/414), product Issues (6/414), device malfunction (4/414), blood and lymphatic system disorders (5/414)	oedema (2/420), dyspnoea (4/420), pulmonary embolism (1/420), general disorders and administration site conditions (20/420), pyrexia (4/420), duodenal ulcer (0/420), GI haemorrhage (6/420), nervous system disorders (21/420), cerebral infarction (4/420), metabolism and nutrition disorders (12/420), hyperkalaemia (3/420), product Issues (1/420), device malfunction (0/420), blood and lymphatic system disorders (8/420)	and arteriovenous fistulae thrombosis, with a greater number in the roxadustat treatment group, and upper respiratory tract/viral upper respiratory tract infections, iron deficiency and muscle spasms occurring in a greater number of patients in the ESA treatment group. Hypertension and hypotension were seen in both treatment groups in comparable amounts. Differences were apparently due to the increased incidences of deaths and serious TEAEs over time in patients receiving roxadustat compared with epoetin alfa."
Provenzano 2016	**Roxadustat (part 1 and part 2)**	**EPO alfa**	Data were reported considering all participants in the intervention group both in part 1 and part 2. Separate data were not reported	Data were reported considering all participants in the control group both in part 1 and part 2. Separate data were not reported	"AE and SAE rates were consistent with background disease of this ESRD population. In the safety population, 69 of 108 (63.9%) roxadustat treated and 22 of 36 (61%) epoetin alfa–treated participants had at least 1 AE. Thirty-two of 144 (22.2%) participants in the safety population had a total of 50 treatment-emergent SAEs. Of roxadustat-treated participants, 26 of 108 (24.1%) had at least 1 SAE. The only SAE considered as possibly related to roxadustat treatment was acute pancreatitis. Of epoetin alfa–treated participants, 6 of 36 (17%) had at least 1 SAE. Three roxadustat-treated participants died during the study."
SIERRAS 2021	**Roxadustat**	**EPO alfa**	Nausea (63/370), hypertension (62/370), vomiting (60/370), hyperkalaemia (60/370), AVF site complica-	Nausea (60/370), hypertension (47/370), vomiting (57/370), hyperkalaemia (56/370), AVF site complica-	"At least 1 TEAE was experienced by 91.6% (event rate/100 PEY: 728.1) and 91.4% (event rate/100 PEY: 728.5) of

(Continued)

tion (58/370), dyspnoea (56/370), diarrhoea (54/370), cough (50/370), pain in extremity (49/370), constipation (44/370), upper respiratory tract infection (43/370), pneumonia (42/370), hypotension (41/370), headache (42/370), anaemia (40/370), fluid overload (40/370), back pain (39/370), non-cardiac chest pain (37/370), AVF thrombosis (37/370), fall (37/370), acute MI (34/370), abdominal pain (33/370), pyrexia (33/370), UTI (32/370), arteriovenous graft thrombosis (31/370), cardiac failure, congestive (30/370), asthenia (27/370), viral upper respiratory tract infection (26/370), arthralgia (26/370), bronchitis (25/370), cellulitis (25/370), sepsis (25/370), hypoglycaemia (25/370), dizziness (25/370), oedema, peripheral (23/370), pruritus (22/370), cardiac arrest (21/370), tachycardia (20/370), atrial fibrillation (19/370), abdominal pain, upper (19/370), limb injury (19/370), acute respiratory failure (19/370), peripheral swelling (18/370), coronary artery disease (17/370), muscle spasms (17/370), syncope (17/370), anxiety (16/370), pain (15/370), musculoskeletal pain (15/370), insomnia (15/370), bradycardia (14/370), contusion (14/370), pleural effusion (14/370), GI haemorrhage (13/370), iron deficiency (12/370), angina pectoris (11/370), face oedema (10/370), vascular graft complication (10/370), pulmonary oedema (7/370)	tion (72/370), dyspnoea (67/370), diarrhoea (70/370), cough (69/370), pain in extremity (59/370), constipation (49/370), upper respiratory tract infection (40/370), pneumonia (52/370), hypotension (43/370), headache (40/370), anaemia (54/370), fluid overload (47/370), back pain (39/370), non-cardiac chest pain (41/370), AVF thrombosis (42/370), fall (58/370), acute MI (26/370), abdominal pain (31/370), pyrexia (34/370), UTI (31/370), arteriovenous graft thrombosis (28/370), cardiac failure, congestive (33/370), asthenia (21/370), viral upper respiratory tract infection (26/370), arthralgia (37/370), bronchitis (29/370), cellulitis (30/370), sepsis (27/370), hypoglycaemia (30/370), dizziness (30/370), oedema, peripheral (34/370), pruritus (21/370), cardiac arrest (23/370), tachycardia (19/370), atrial fibrillation (26/370), abdominal pain, upper (18/370), limb injury (17/370), acute respiratory failure (29/370), peripheral swelling (26/370), coronary artery disease (22/370), muscle spasms (25/370), syncope (21/370), anxiety (21/370), pain (19/370), musculoskeletal pain (20/370), insomnia (25/370), bradycardia (21/370), contusion (20/370), pleural effusion (24/370), GI haemorrhage (19/370), iron deficiency (23/370), angina pectoris (23/370), face oedema (19/370), vas-	patients in the roxadustat and epoetin alfa groups."

(Continued)

				cular graft complication (24/370), pulmonary oedema (24/370)	
SYMPHONY HD 2021	**Enarodustat**	**Darbepoetin alfa**	Retinal disorders (6/87), retinal haemorrhage (3/87), chorioretinopathy (1/87), diabetic retinopathy (1/87), macular oedema (1/87), vitreous haemorrhage (1/87), malignant or unspecified tumours (2/87), malignant neoplasm of renal pelvis (0/87), neoplasm skin (1/87), renal cancer (1/87), hypertension (4/87), embolic and thrombotic events (6/87), shunt occlusion (4/87), acute MI (1/87), arterial occlusive disease (0/87), lacunar infarction (1/87), pulmonary embolism (1/87)	Retinal disorders (3/86), retinal haemorrhage (3/86), chorioretinopathy (0/86), diabetic retinopathy (0/86), macular oedema (0/86), vitreous haemorrhage (0/86), malignant or unspecified tumours (1/86), malignant neoplasm of renal pelvis (1/86), neoplasm skin (0/86), renal cancer (0/86), hypertension (2/86), embolic and thrombotic events (5/86), shunt occlusion (4/86), acute MI (0/86), arterial occlusive disease (1/86), lacunar infarction (0/86), pulmonary embolism (0/86)	"In this study, 76/87 subjects (87.4%) in the enarodustat arm and 72/86 subjects (83.7%) in the DA arm experienced at least 1 AE. No death occurred in this study. Serious AEs occurred in 13 subjects (14.9%) in the enarodustat arm and 12 subjects (14.0%) in the DA arm, none of which were judged to be related to the study drug. Four subjects (4.6%) in the enarodustat arm and 3 subjects (3.5%) in the DA arm discontinued the study due to AE. AEs that occurred in ≥5% of subjects in any arm are listed in Table 2. The most frequent AE was viral upper respiratory tract infection in each arm. Vomiting and gastroenteritis in the enarodustat arm were observed at least twice as often as in the DA arm, but were considered unrelated to the study drug in both arms."
SYMPHONY ND 2021	**Enarodustat**	**Darbepoetin alfa**	Any AEs (70/107), viral upper respiratory tract infection (19/107), diarrhoea (3/107), upper respiratory tract inflammation (2/107), contusion (1/107), embolic and thrombotic events (0/107), hypertension (5/107), BP increased (4/107), hypertension (1/107), malignant or unspecified tumours (0/107), malignant neoplasm of renal pelvis (0/107), gastric cancer (0/107), soft tissue neoplasm (0/107), retinal disorders (4/107), retinal haemorrhage (2/107),	Any AEs (90/109), viral upper respiratory tract infection (25/109), diarrhoea (9/109), upper respiratory tract inflammation (7/109), contusion (6/109), embolic and thrombotic events (0/109), hypertension (5/109), BP increased (2/109), hypertension (3/109), malignant or unspecified tumours (3/109), malignant neoplasm of renal pelvis (1/109), gastric cancer (1/109), soft tissue neoplasm (1/109), retinal disorders (1/109), retinal haemorrhage	"There were no apparent differences in the incidence of adverse events between arms (65.4% [enarodustat], 82.6% [DA])." "Except for death, 15 serious adverse events (SAEs) occurred in 13 subjects in the enarodustat arm, and 14 SAEs occurred in 11 subjects in the DA arm. Four SAEs (fluid retention, hyperkalaemia, edema, and pneumonia) were judged to be related to enarodustat. Overall, 65.4% of subjects receiving enarodu-

(Continued)

	retinal tear (1/107), retinal detachment (1/107), macular oedema (1/107), diabetic retinal oedema (0/107)	(0/109), retinal tear (0/109), retinal detachment (0/109), macular oedema (0/109), diabetic retinal oedema (1/109)	stat and 82.6% of subjects receiving DA experienced at least one AE."

Footnotes:AE - adverse events; AKI - acute kidney injury; AVF - arteriovenous fistula; BP - blood pressure; CKD - chronic kidney disease; DVT - deep vein thrombosis; EPO - erythropoietin; GFR - glomerular filtration rate: MACE - major adverse cardiovascular events; MI - myocardial infarction; SAE - serious adverse events; TEAE - treatment-emergent adverse event; TSAT - transferrin saturation; UTI - urinary tract infection

WHAT'S NEW

Date	Event	Description
26 August 2022	Amended	Acknowledgements updated

HISTORY

Protocol first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: PN, AT, MR, SP
2. Study selection: PN, EH, MR, DH, VS
3. Extract data from studies: PN, EH, MR, DH, VS
4. Enter data into RevMan: PN, SP
5. Carry out the analysis: PN, EH, SP
6. Interpret the analysis: all authors
7. Draft the final review: PN, EH, SP
8. Disagreement resolution: SP, GS
9. Update the review: PN, SP, JC, GS

DECLARATIONS OF INTEREST

- Patrizia Natale: no relevant interests were disclosed
- Suetonia C Palmer: no relevant interests were disclosed
- Allison Jaure: no relevant interests were disclosed
- Elisabeth M Hodson: no relevant interests were disclosed
- Marinella Ruospo: no relevant interests were disclosed
- Tess E Cooper: no relevant interests were disclosed
- Deirdre Hahn: no relevant interests were disclosed
- Valeria Saglimbene: no relevant interests were disclosed
- Jonathan Craig: no relevant interests were disclosed
- Giovanni FM Strippoli: no relevant interests were disclosed

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included death (any cause), fatal or nonfatal MI, fatal or nonfatal stroke and thrombosis as outcomes.

We have combined data for loss of unassisted patency (including both stenosis/occlusions), and need for access intervention (including both surgically or by radiological guided angioplasty).

We have performed subgroup analyses considering the frequency of HIF stabilisers therapy.

Due to the short follow-up, we have added the proportion of patients requiring blood transfusion and the proportion of patients reaching the target Hb in the Summary of Findings tables, instead of cancer and infection.

NOTES

Acknowledgement section updated

INDEX TERMS

Medical Subject Headings (MeSH)

*Anemia [drug therapy] [etiology]; *Cardiovascular Diseases; Cause of Death; Fatigue; Hypoxia; Iron [therapeutic use]; *Renal Insufficiency, Chronic [therapy]

MeSH check words

Adult; Humans