Appendix 5- GRADE Summary of Findings

Summary of Findings 1: Desidustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in Non-Dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia not on dialysis
Intervention: Desidustat (any dose)
Comparator: Darbepoetin alpha

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Darbepoetin alpha	Desidustat (any dose)		
Any Adverse events up to 26 weeks in ESA naive patients	Odds ratio: 0.91 (CI 95% 0.66 - 1.26) Based on data from 588 participants in 1 study	**503** per 1000	**479** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision [1]	We are uncertain whether Desidustat (any dose) decreases adverse events up to 26 weeks in ESA-naive patients.
		Difference: **24 fewer per 1000** (CI 95% 103 fewer – 301 fewer)			
All-cause mortality up to 26 weeks in ESA naive	Odds ratio: 1.0 (CI 95% 0.32 - 3.14) Based on data from 588 participants in 1 study	**20** per 1000	**20** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision [2]	We are uncertain whether compared to conventional ESA, Desidustat has no difference in all-cause mortality up to 26 weeks in ESA-naïve patients.
		Difference: **0 fewer per 1000** (CI 95% 14 fewer - 40 more)			
Incidences of MACE and MACE plus					No studies were found that looked at incidences of MACE and MACE plus.
Progression to end stage kidney disease					No studies were found that looked at progression to end-stage kidney disease.
Need for Iron supplementation					No studies were found that looked at need for iron supplementation.
Patient requiring blood transfusion					No studies were found that looked at patient requiring blood transfusion.
	Measured by: Scale: High better	Mean	Mean	**Low**	Desidustat (any dose) probably has

Change in haemoglobin levels from baseline up to 24 weeks in ESA-naive	Based on data from 529 participants in 1 study	Difference: **MD 0.09 lower** (CI 95% 0.15 lower - 0.33 lower)		Due to serious risk of bias, Due to serious imprecision [3]	little or no difference on change in haemoglobin levels from baseline compared to ESA up to 24 weeks in ESA-naïve patients.
Quality of Life [SF 36 score] at 24 weeks ESA naive	Measured by: Scale: High better Based on data from 480 participants in 1 study	Mean	Mean	**Low** Due to serious risk of bias, Due to serious imprecision [4]	Desidustat may have little or no difference on quality of life [SF 36 score] at 24 weeks in ESA-naive patients.
		Difference: **MD 0.00 lower** (CI 95% -98.20 lower - 98.20 lower)			
Fatigue					No studies were found that looked at fatigue.
Need for Erythropoietin Stimulating Agent (ESA) up to 24 weeks in ESA-naive	Based on data from 588 participants in 1 study			**Low** Due to serious risk of bias, Due to serious imprecision [5]	There were too few ESA-naïve patients who experienced the need for Erythropoietin Stimulating Agent (ESA) up to 24 weeks, to determine whether Desidustat (any dose) made a difference.

1. **Risk of Bias: serious.** Missing intention-to-treat analysis, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals, only data from one study, inadequate Optimal information size 'OIS'. The 95% CI of the included study overlaps line of no effect (i.e., CI includes 1.0) rate.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study, inadequate Optimal information size 'OIS'; **Publication bias: no serious.** Study is commercially funded.
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, inadequate Optimal information size 'OIS'; **Publication bias: no serious.** Study is commercially funded.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, inadequate Optimal information size 'OIS'; **Publication bias: no serious.** Study is commercially funded.
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Missing intention-to-treat analysis; **Imprecision: serious**: Low number of patients, only data from one study, inadequate Optimal information size 'OIS'; **Publication bias: no serious.** Study is commercially funded.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 2: Daprodustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in Non-Dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia not on dialysis
Intervention: Daprodustat (any dose)
Comparator: rhEPO (epoetins or their biosimilars or darbepoetin)

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		rhEPO (epoetins or their biosimilars or darbepoetin)	Daprodustat (any dose)		
Adverse events up to 52 weeks	Odds ratio: 1.18 (CI 95% 1.02 - 1.37) Based on data from 4419 participants in 3 studies	**774** per 1000	**801** per 1000	**Low** Due to very serious risk of bias [1]	Daprodustat (any dose) probably increases adverse events up to 52 weeks.
		Difference: **28 more per 1000** (CI 95% 3 more - 50 more)			
All-cause mortality up to 52 weeks	Odds ratio: 1.90 (CI 95% 0.21 - 17.31) Based on data from 250 participants in 1 study	**13** per 1000	**24** per 1000	**Low** Due to serious risk of bias, Due to very serious imprecision [2]	We are uncertain whether Daprodustat (any dose) increases all-cause mortality up to 52 weeks.
		Difference: **11 more per 1000** (CI 95% 10 fewer - 173 more)			
All-cause mortality up to 60 weeks	Odds ratio: 1.01 (CI 95% 0.85 - 1.20) Based on data from 3872 participants in 1 study	**154** per 1000	**155** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [3]	We are uncertain whether Daprodustat (any dose) has little or no difference on all-cause mortality up to 60 weeks.
		Difference: **1 more per 1000** (CI 95% 20 fewer - 25 more)			
Incidences of MACE plus up to 32 weeks	Odds ratio: 0.82 (CI 95% 0.23 - 2.87) Based on data from 250 participants in 1 study	**50** per 1000	**41** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [4]	We are uncertain whether Daprodustat (any dose) decreases incidences of MACE plus up to 32 weeks in ESA-naive/ESA-conditioned patients.
		Difference: **9 fewer per 1000** (CI 95% 38 fewer - 81 more)			
Need for Iron supplementation					No studies were found that looked at need for iron supplementation.
Need for Erythropoietin Stimulating Agent (ESA)					No studies were found that looked at need for Erythropoietin Stimulating Agent (ESA).

Incidences of MACE up to 60 weeks	Odds ratio: 1.07 (CI 95% 0.92 - 1.24) Based on data from 3872 participants in 1 study	**228** per 1000	**240** per 1000	**Very low** Due to very serious risk of bias, Due to very serious imprecision [5]	We are uncertain whether Daprodustat (any dose) increases incidences of MACE up to 60 weeks.
		Difference: **12 more per 1000** (CI 95% 14 fewer - 40 more)			
Progression to end-stage kidney disease up to 60 weeks	Odds ratio: 0.99 (CI 95% 0.83 - 1.18) Based on data from 2485 participants in 1 study	**284** per 1000	**281** per 1000	**Very low** Due to very serious risk of bias, Due to very serious imprecision [6]	We are uncertain whether Daprodustat (any dose) has little or no difference on progression to end stage kidney disease up to 60 weeks.
		Difference: **2 fewer per 1000** (CI 95% 36 fewer - 35 more)			
Patients requiring blood transfusion up to 52 weeks	Odds ratio: 0.94 (CI 95% 0.78 - 1.13) Based on data from 3870 participants in 1 study	**135** per 1000	**127** per 1000	**Very low** Due to very serious risk of bias, Due to very serious imprecision [7]	Daprodustat (any dose) may decrease blood transfusion requirement up to 52 weeks.
		Difference: **7 fewer per 1000** (CI 95% 26 fewer - 15 more)			
Health related quality of life					No studies were found that looked at health related quality of life.
Fatigue					No studies were found that looked at fatigue.
Change in haemoglobin levels from baseline up to 52 weeks	Measured by: Scale: High better Based on data from 4089 participants in 2 studies	Mean	Mean	**Low** Due to very serious risk of bias [8]	Daprodustat (any dose) probably has little or no difference on haemoglobin levels compared to conventional ESA from baseline up to 52 weeks in ESA-naive/ ESA-conditioned patients.
		Difference: **MD 0.08 lower** (CI 95% 0.08 lower - 0.08 lower)			
Change in haemoglobin levels from baseline up to 52 weeks in ESA-conditioned	Measured by: Scale: High better Based on data from 117 participants in 1 study	Mean	Mean	**Very low** Due to serious risk of bias, Due to very serious indirectness, Due to very serious imprecision [9]	Daprodustat (any dose) may have little or no difference on haemoglobin level from baseline up to 52 weeks compared to those on ESAs in ESA-conditioned patients.
		Difference: **MD 0.00 lower** (CI 95% 0.28 lower - 0.28 lower)			

1. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Publication bias: no serious.** Mostly commercially funded studies.

2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
3. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
5. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Only data from one study, wide confidence intervals.
6. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
7. **Risk of Bias: very serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
8. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate concealment of allocation during randomization process, resulting in potential for selection bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Publication bias: no serious.** Mostly commercially funded studies.
9. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: very serious.** Only data from one study, low number of patients; **Publication bias: no serious.** Mostly commercially funded studies.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 3: Enarodustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in Non-Dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia not on dialysis
Intervention: Enarodustat (any dose)
Comparator: Darbepoetin alpha

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Darbepoetin alpha	Enarodustat (any dose)		
All-cause mortality up to 26 weeks	Odds ratio: 0.34 (CI 95% 0.01 - 8.35) Based on data from 216 participants in 1 study	**9** per 1000	**3** per 1000	**Very low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision [1]	We are uncertain whether Enarodustat (any dose) decreases all-cause mortality up to 26 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: **6 fewer per 1000** (CI 95% 9 fewer - 61 more)			
Adverse events up to 26 weeks	Odds ratio: 0.40 (CI 95% 0.21 - 0.75) Based on data from 216 participants in 1 study	**826** per 1000	**655** per 1000	**Very low** Due to very serious risk of bias, Due to very serious indirectness [2]	We are uncertain whether Enarodustat (any dose) decreases adverse events up to 26 weeks in ESA-naïve and ESA-conditioned patients.
		Difference: **171 fewer per 1000** (CI 95% 327 fewer - 45 fewer)			
Adverse events up to 26 weeks ESA-naive	Odds ratio: 0.40 (CI 95% 0.15 - 1.10) Based on data from 102 participants in 1 study	**865** per 1000	**719** per 1000	**Very low** Due to very serious risk of bias, Due to very serious indirectness, Due to very serious imprecision [3]	We are uncertain whether Enarodustat (any dose) decreases adverse events up to 26 weeks in ESA-naïve patients.
		Difference: **146 fewer per 1000** (CI 95% 375 fewer - 11 more)			
Adverse events up to 26 weeks ESA-conditioned	Odds ratio: 0.39 (CI 95% 0.17 - 0.90) Based on data from 114 participants in 1 study	**789** per 1000	**593** per 1000	**Very low** Due to very serious risk of bias, Due to very serious indirectness, Due to serious imprecision [4]	We are uncertain whether Enarodustat (any dose) decreases adverse events up to 26 weeks in ESA-conditioned patients.
		Difference: **196 fewer per 1000** (CI 95% 400 fewer - 18 fewer)			
Incidences of MACE and MACE plus					No studies were found that looked at incidences of MACE and MACE plus.

Need for Iron supplementation					No studies were found that looked at need for iron supplementation.
Need for Erythropoietin Stimulating Agent (ESA)					No studies were found that looked at need for Erythropoietin Stimulating Agent (ESA).
Progression to end-stage kidney disease					No studies were found that looked at progression to end-stage kidney disease.
Patients requiring blood transfusion					No studies were found that looked at patients requiring blood transfusion.
Health related quality of life					No studies were found that looked at health related quality of life.
Fatigue					No studies were found that looked at fatigue.
Change in haemoglobin levels from baseline up to 24 weeks	Measured by: Scale: High better Based on data from 193 participants in 1 study	Mean	Mean	**Very low** Due to very serious risk of bias, Due to very serious indirectness, Due to serious imprecision [5]	We are uncertain whether Enarodustat (any dose) has little or no difference on change in haemoglobin levels from baseline up to 24 weeks.
		Difference: **MD 0.09 lower** (CI 95% 0.08 lower - 0.26 lower)			

1. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow up, missing intention-to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: very serious.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
2. **Risk of Bias: very serious.** Missing intention-to-treat analysis, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow up; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Publication bias: no serious.** Mostly commercially funded studies.
3. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow up, missing intention-to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: very serious.** Low number of patients, only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
4. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow up, missing intention-to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.

5. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow up, missing intention-to-treat analysis; **Indirectness: very serious.** The included study was from only one country and was downgraded for lack of directness by two levels; **Imprecision: serious.** Low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 4: Molidustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in Non-Dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia not on dialysis
Intervention: Molidustat (any dose)
Comparator: Darbepoetin alpha

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Darbepoetin alpha	Molidustat (any dose)		
Treatment emergent adverse events up to 52 weeks	Odds ratio: 1.18 (CI 95% 0.52 - 2.67) Based on data from 449 participants in 3 studies	**881** per 1000	**897** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [1]	We are uncertain whether Molidustat (any dose) increases treatment emergent adverse events up to 52 weeks in ESA-naive and ESA-conditioned patients.
		Difference: **16 more per 1000** (CI 95% 87 fewer - 71 more)			
Incidence of MACE and MACE plus up to 52 weeks	Odds ratio: 5.43 (CI 95% 0.90 - 32.61) Based on data from 325 participants in 2 studies	**6** per 1000	**31** per 1000	**Very low** Due to very serious risk of bias, Due to very serious imprecision, Due to serious indirectness [2]	We are uncertain whether Molidustat (any dose) increases incidence of MACE and MACE plus up to 52 weeks ESA-naïve and ESA-conditioned.
		Difference: **26 more per 1000** (CI 95% 1 fewer - 158 more)			
	Odds ratio: 1.78 (CI 95% 0.38 - 8.28)	**10** per 1000	**17** per 1000	**Very low**	We are uncertain whether

All-cause mortality up to 52 weeks	Based on data from 449 participants in 3 studies	Difference: **8 more per 1000** (CI 95% 6 fewer - 67 more)		Due to very serious risk of bias, Due to serious imprecision [3]	Molidustat (any dose) increases all-cause mortality up to 52 weeks in ESA-naive and ESA-conditioned patients.
Need for iron supplementation [IV] up to 52 weeks	Odds ratio: 0.97 (CI 95% 0.31 - 3.09) Based on data from 325 participants in 2 studies	**37** per 1000	**35** per 1000	**Very low** Due to very serious risk of bias, Due to very serious indirectness, Due to serious imprecision [4]	We are uncertain whether Molidustat (any dose) has little or no difference on need for iron supplementation [iv] up to 52 weeks in ESA-naive and ESA-conditioned.
		Difference: **1 fewer per 1000** (CI 95% 25 fewer - 69 more)			
Need for iron supplementation [oral] up to 52 weeks	Odds ratio: 1.71 (CI 95% 1.10 - 2.66) Based on data from 325 participants in 2 studies	**398** per 1000	**530** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness, Due to serious imprecision [5]	We are uncertain whether Molidustat (any dose) increases need for iron supplementation [oral] up to 52 weeks in ESA-naive and ESA-conditioned.
		Difference: **133 more per 1000** (CI 95% 23 more - 239 more)			
Need for Erythropoietin Stimulating Agent (ESA) up to 36 weeks	Odds ratio: 0.39 (CI 95% 0.11 - 1.42) Based on data from 449 participants in 3 studies	**36** per 1000	**14** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [6]	We are uncertain whether Molidustat (any dose) decreases need for Erythropoietin Stimulating Agent (ESA) up to 36 weeks ESA-naive/ESA-conditioned patients.
		Difference: **22 fewer per 1000** (CI 95% 32 fewer - 14 more)			
Progression to end-stage kidney disease (defined by stage 5 CKD) up to 52 weeks	Odds ratio: 1.97 (CI 95% 1.04 - 3.73) Based on data from 325 participants in 2 studies	**106** per 1000	**189** per 1000	**Very low** Due to serious indirectness, Due to very serious risk of bias, Due to serious imprecision [7]	We are uncertain whether Molidustat (any dose) increases progression to end-stage kidney disease (defined by stage 5 CKD) up to 52 weeks in ESA-naive/ESA-conditioned patients.
		Difference: **83 more per 1000** (CI 95% 4 more - 201 more)			
Patients requiring blood transfusion 16 to 52 weeks	Odds ratio: 0.69 (CI 95% 0.14 - 3.47) Based on data from 449 participants in 3 studies	**16** per 1000	**11** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [8]	Molidustat (any dose) may decrease patients requiring blood transfusion 16 to 52 weeks.
		Difference: **5 fewer per 1000** (CI 95% 14 fewer - 37 more)			
Health related quality of life					No studies were found that looked

					at health related quality of life.
Fatigue					No studies were found that looked at fatigue.
Change in haemoglobin levels from baseline up to 36 weeks	Measured by: Scale: High better Based on data from 434 participants in 3 studies	Mean	Mean	**Very low** Due to serious inconsistency, Due to very serious risk of bias[9]	We are uncertain whether Molidustat (any dose) decreases haemoglobin levels from baseline up to 36 weeks in ESA-naive/ESA-conditioned patients.
		Difference: **MD 0.11 lower** (CI 95% 0.52 lower - 0.30 lower)			

1. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
2. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis, **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients; **Publication bias: no serious.** Mostly commercially funded studies.
3. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
4. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Low number of patients, wide confidence intervals.
5. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: serious.** Low number of patients; **Publication bias: no serious.** Mostly commercially funded studies.
6. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
7. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South Asian country and was downgraded for lack of directness by one level; **Imprecision: serious.** Low number of patients.
8. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
9. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:73%.; **Publication bias: no serious.** Mostly commercially funded studies.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 5: Roxadustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in Non-Dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia not on dialysis
Intervention: Roxadustat (any dose)
Comparator: Darbepoetin alpha

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Darbepoetin alpha	Roxadustat (any dose)		
Treatment emergent adverse events up to 52 weeks ESA-conditioned	Odds ratio: 1.56 (CI 95% 0.89 - 2.73) Based on data from 262 participants in 1 study	**702** per 1000	**786** per 1000	**Very low** Due to very serious risk of bias, Due to serious indirectness, Due to very serious imprecision [1]	We are uncertain whether Roxadustat (any dose) increases treatment emergent adverse events up to 52 weeks in ESA-conditioned patients.
		Difference: **84 more per 1000** (CI 95% 25 fewer - 163 more)			
Treatment emergent adverse events up to 108 weeks ESA-naive	Odds ratio: 0.89 (CI 95% 0.50 - 1.6) Based on data from 616 participants in 1 study	**925** per 1000	**916** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [2]	We are uncertain whether Roxadustat (any dose) decreases treatment emergent adverse events up to 108 weeks in ESA-naïve patients.
		Difference: **8 fewer per 1000** (CI 95% 65 fewer - 27 more)			
All-cause mortality up to 52 weeks ESA-conditioned	Odds ratio: 0.33 (CI 95% 0.01 - 8.19) Based on data from 262 participants in 1 study	**8** per 1000	**2** per 1000	**Very low** Due to very serious imprecision, Due to serious indirectness [3]	We are uncertain whether Roxadustat (any dose) decreases all-cause mortality up to 52 weeks in ESA-conditioned patients.
		Difference: **5 fewer per 1000** (CI 95% 8 fewer - 54 more)			
All-cause mortality up to 108 weeks ESA-naive	Odds ratio: 0.87 (CI 95% 0.51 - 1.47) Based on data from 616 participants in 1 study	**106** per 1000	**93** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [4]	We are uncertain whether Roxadustat (any dose) decreases all-cause mortality up to 108 weeks in ESA-naïve patients.
		Difference: **12 fewer per 1000** (CI 95% 49 fewer - 42 more)			
Incidence of MACE up to 108 weeks ESA-naive	Odds ratio: 0.82 (CI 95% 0.51 - 1.31) Based on data from 616 participants in 1 study	**140** per 1000	**117** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [5]	We are uncertain whether Roxadustat (any dose) decreases incidence of MACE up to 108 weeks in ESA-naïve patients.
		Difference: **22 fewer per 1000** (CI 95% 63 fewer - 36 more)			

Incidence of MACE plus up to 108 weeks ESA-naive	Odds ratio: 0.91 (CI 95% 0.6 - 1.38) Based on data from 616 participants in 1 study	**181** per 1000	**167** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [6]	We are uncertain whether Roxadustat (any dose) decreases incidence of MACE plus up to 108 weeks in ESA-naïve patients.
		Difference: **14 fewer per 1000** (CI 95% 64 fewer - 53 more)			
Need for Iron supplementation [bivalent oral] up to 36 weeks ESA-naive	Odds ratio: 0.78 (CI 95% 0.57 - 1.07) Based on data from 616 participants in 1 study[3]	**498** per 1000	**436** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [7]	We are uncertain whether Roxadustat (any dose) decreases need for iron supplementation [bivalent oral] up to 36 weeks in ESA-naïve patients.
		Difference: **62 fewer per 1000** (CI 95% 137 fewer - 17 more)			
Need for Iron supplementation [IV] up to 36 weeks ESA-naive	Odds ratio: 0.46 (CI 95% 0.26 - 0.81) Based on data from 616 participants in 1 study	**126** per 1000	**62** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [8]	We are uncertain whether Roxadustat (any dose) decreases need for iron supplementation [IV] up to 36 weeks in ESA-naïve patients.
		Difference: **64 fewer per 1000** (CI 95% 90 fewer - 21 fewer)			
Need for Iron supplementation [trivalent oral] up to 36 weeks ESA-naive	Odds ratio: 0.67 (CI 95% 0.49 - 0.93) Based on data from 616 participants in 1 study [7]	**447** per 1000	**351** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [9]	We are uncertain whether Roxadustat (any dose) decreases need for iron supplementation [trivalent oral] up to 36 weeks in ESA-naïve patients.
		Difference: **96 fewer per 1000** (CI 95% 163 fewer - 18 fewer)			
Need for Erythropoietin Stimulating Agent (ESA)					No studies were found that looked at need for Erythropoietin Stimulating Agent (ESA).
Progression to end-stage kidney disease					No studies were found that looked at progression to end-stage kidney disease.
Patients requiring blood transfusion up to 108 weeks	Odds ratio: 1.26 (CI 95% 0.75 - 2.11) Based on data from 614 participants in 1 study	**96** per 1000	**118** per 1000	**Very low** Due to very serious risk of bias, Due to serious imprecision [10]	Roxadustat (any dose) may worsen patients requiring blood transfusion up to 108 weeks.
		Difference: **22 more per 1000** (CI 95% 22 fewer - 87 more)			
Health related quality of life					No studies were found that looked at health related quality of life.

Fatigue					No studies were found that looked at fatigue.
Change in haemoglobin levels from baseline up to 24 weeks ESA-conditioned	Measured by: Scale: High better Based on data from 262 participants in 1 study	Mean	Mean	**Very low** Due to very serious risk of bias, Due to serious indirectness, Due to very serious imprecision [11]	Roxadustat (any dose) may have little or no difference on haemoglobin levels from baseline up to 24 weeks in ESA-conditioned patients.
		Difference: **MD 0.12 lower** (CI 95% 0.30 lower - 0.06 lower)			

1. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South-Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
2. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
3. **Risk of Bias: very serious. Indirectness: serious.** The included study was from only one non-South-Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies;
4. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
5. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
6. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
7. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
8. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
9. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
10. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Imprecision: serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
11. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, incomplete data and/or large loss to follow up, selective outcome reporting, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South-Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Only data from one study, low number of patients; **Publication bias: no serious.** Mostly commercially funded studies.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Summary of Findings 6: Vadadustat as alternative to Erythropoietin Stimulating Agents (ESAs) for management of Anaemia in Non-Dialysis dependent chronic kidney disease

Population: Adult patients (>18 years) of CKD with a diagnosis of anaemia not on dialysis
Intervention: Vadadustat (any dose)
Comparator: Darbepoetin alpha

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Darbepoetin Alpha	Vadadustat any dose		
Adverse events beyond 52 weeks ESA-naive	Odds ratio: 0.91 (CI 95% 0.66 - 1.27) Based on data from 1748 participants in 1 study	**916** per 1000	**908** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [1]	We are uncertain whether Vadadustat (any dose) decreases adverse events beyond 52 weeks in ESA-naïve patients.
		Difference: **8 fewer per 1000** (CI 95% 38 fewer - 17 more)			
Adverse events up to 52 weeks	Odds ratio: 0.77 (CI 95% 0.35 - 1.71) Based on data from 304 participants in 1 study	**922** per 1000	**901** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [2]	We are uncertain whether Vadadustat (any dose) decreases adverse events up to 52 weeks in ESA-naive and ESA-conditioned patients.
		Difference: **21 fewer per 1000** (CI 95% 117 fewer - 31 more)			
Adverse events beyond 52 weeks ESA-conditioned	Odds ratio: 1.14 (CI 95% 0.85 - 1.54) Based on data from 1723 participants in 1 study	**877** per 1000	**890** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [3]	We are uncertain whether Vadadustat (any dose) increases adverse events beyond 52 weeks in ESA-conditioned patients.
		Difference: **13 more per 1000** (CI 95% 19 fewer - 40 more)			
Incidence of MACE beyond 52 weeks	Odds ratio: 1.10 (CI 95% 0.93 - 1.29) Based on data from 3521 participants in 1 study	**199** per 1000	**214** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [4]	We are uncertain whether Vadadustat (any dose) increases incidence of MACE beyond 52 weeks in ESA-naïve and
		Difference: **16 more per 1000** (CI 95% 11 fewer - 44 more)			

					ESA-conditioned patients.
Incidence of MACE plus beyond 52 weeks	Odds ratio: 1.04 (CI 95% 0.89 - 1.21) Based on data from 3521 participants in 1 study	**245** per 1000	**252** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [5]	We are uncertain whether Vadadustat (any dose) increases incidence of MACE plus beyond 52 weeks.
		Difference: **7 more per 1000** (CI 95% 21 fewer - 37 more)			
All-cause mortality beyond 52 weeks ESA-conditioned	Odds ratio: 1.00 (CI 95% 0.77 - 1.29) Based on data from 1723 participants in 1 study	**161** per 1000	**161** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [6]	We are uncertain if Vadadustat (any dose) has little or no difference on all-cause mortality beyond 52 weeks in ESA-conditioned patients.
		Difference: **0 fewer per 1000** (CI 95% 32 fewer - 37 more)			
All-cause mortality up to 52 weeks	Odds ratio: 0.34 (CI 95% 0.01 - 8.30) Based on data from 304 participants in 1 study	**7** per 1000	**2** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [7]	We are uncertain whether Vadadustat (any dose) decreases all-cause mortality up to 52 weeks in ESA-naive and ESA-conditioned patients.
		Difference: **5 fewer per 1000** (CI 95% 7 fewer - 48 more)			
All-cause mortality beyond 52 weeks ESA-naive	Odds ratio: 1.08 (CI 95% 0.85 - 1.36) Based on data from 1748 participants in 1 study	**193** per 1000	**205** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [8]	We are uncertain whether Vadadustat (any dose) increases all-cause mortality beyond 52 weeks in ESA-naïve patients.
		Difference: **12 more per 1000** (CI 95% 24 fewer - 52 more)			
All-cause mortality beyond 52 weeks	Odds ratio: 1.01 (CI 95% 0.85 - 1.2) Based on data from 3521 participants in 1 study	**177** per 1000	**178** per 1000	**Very low** Due to serious risk of bias, Due to very serious imprecision [9]	Vadadustat (any dose) may have little or no difference on all-cause mortality beyond 52 weeks in ESA-naive and ESA-conditioned patients.
		Difference: **1 more per 1000** (CI 95% 22 fewer - 28 more)			
Need for Iron supplementation [oral] up to 52 weeks	Odds ratio: 1.26 (CI 95% 0.78 - 2.05) Based on data from 304 participants in 1 study	**288** per 1000	**337** per 1000	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [10]	We are uncertain whether Vadadustat (any dose) increases need for iron supplementation [oral] up to 52 weeks in ESA-naive and ESA-conditioned patients.
		Difference: **50 more per 1000** (CI 95% 48 fewer - 165 more)			
Need for Erythropoietin					No studies were found that looked

Stimulating Agent (ESA)					at need for Erythropoietin Stimulating Agent (ESA).
Progression to end-stage kidney disease					No studies were found that looked at progression to end-stage kidney disease.
Patients requiring blood transfusion					No studies were found that looked at patients requiring blood transfusion.
Health related quality of life					No studies were found that looked at health related quality of life.
Fatigue					No studies were found that looked at fatigue.
Change in haemoglobin levels from baseline up to 52 weeks ESA-naive	Measured by: Scale: High better Based on data from 3780 participants in 2 studies	Mean	Mean	**Very low** Due to serious risk of bias, Due to very serious inconsistency [11]	We are uncertain whether Vadadustat (any dose) have little or no difference on haemoglobin levels from baseline up to 52 weeks in ESA-naïve patients.
		Difference: **MD 0.00 lower** (CI 95% 0.04 lower - 0.05 lower)			

1. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South-Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious.** The included study was from only one non-South-Asian country and was downgraded for lack of

directness by one level; **Imprecision: very serious.** Wide confidence intervals, low number of patients, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.

8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
9. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Imprecision: very serious.** Only data from one study, wide confidence intervals; **Publication bias: no serious.** Mostly commercially funded studies.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Indirectness: serious**. The included study was from only one non-South-Asian country and was downgraded for lack of directness by one level; **Imprecision: very serious.** Low number of patients, wide confidence intervals, only data from one study; **Publication bias: no serious.** Mostly commercially funded studies.
11. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis; **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2: 99 %., point estimates vary widely, the confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., the direction of the effect is not consistent between the included studies; **Publication bias: no serious.** Mostly commercially funded studies.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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