KDIGO CLINICAL PRACTICE GUIDELINE FOR ANEMIA IN CHRONIC KIDNEY DISEASE

KDIGO Online Supplemental Tables
August 2012

ABBREVIATIONS AND ACRONYMS FOR SUPPLEMENTAL TABLES

5D	CKD Stage 5, Dialysis	L	Liter
α	Alfa	LVD	Left ventricular dilation
AE	Adverse event	LVH	Left ventricular hypertrophy
AKI	Acute kidney disease	µg	Microgram
Anti-HT	Antihypertensive	M	Male
AV	Arteriovenous	MACE	Major adverse cardiac event
AVR	Arteriovenous fistula	MAP	Mean arterial pressure
β	Beta	mg	Milligram
BP	Blood pressure	MI	Myocardial infarction
CHD	Coronary heart disease	mL	Milliliter
CHF	Congestive heart failure	NA	Not applicable
CI	Confidence interval	nd	Not documented
CKD	Chronic kidney disease	ng	Nanogram
CKD:5D	CKD Stage 5-Dialysis	Non-inf	Non-inferior
Cum Fe dose	Cumulative iron dose	NOS	Not otherwise specified
CV	Cardiovascular	NS	Not significant
CV Hosp	Cardiovascular hospitalization	OR	Odds ratio
CVA	Cerebrovascular accident	PD	Peritoneal dialysis
CVD	Cardiovascular disease	pmol	Picomole
DBP	Diastolic blood pressure	PO	Oral
D/C	Discontinued	PP	Per-protocol
dL	Deciliter	pt	Patient
DVT	Deep vein thrombosis	PTH	Parathyroid hormone
eGFR	estimated GFR	QoL	Quality of life
EPO	Epoetin	QW	Once weekly
ERT	Evidence review team	Q2W	Once every 2 weeks
ESA	Erythropoiesis-stimulating agent	Q4W	Once every 4 weeks
ESA vs. Pl	ESA versus Placebo	RBC	Red blood cell
ESRD	End-stage renal disease	rHuEPO	Recombinant human erythropoietin
EU	Europe	RR	Relative risk
F	Female	RRT	Renal replacement therapy
Fe	Iron	SAE	Serious adverse event
g	Gram	SBP	Systolic blood pressure
GFR	Glomerular filtration rate	SC	Subcutaneous
GI	Gastrointestinal	θ	Theta
H vs. L	High versus Low	T	Transplant
h	Hour	TIW	Three times per week
Hb	Hemoglobin	TSAT	Transferrin saturation
		U	Unit
Hct	Hematocrit	UI	Unique identifier
HD	Hemodialysis	UK	United Kingdom
HR	Hazards ratio	US	United States
HTN	Hypertension	UTI	Urinary tract infection
HX575	Recombinant human epoetin alfa	wk	Week
ITT	Intention-to-treat	XS	Cross-sectional
IU	International units	y	Year
IV	Intravenous	ζ	Zeta
kg	Kilogram		

All articles can be identified by the PubMed IDs following UI prefix

.

TABLE OF CONTENTS

Supplemental Table 1. Association between iron status and level of anemia in multivariable analyses

Country	N	Study Years	Mean Follow-up Duration	Baseline Hb (g/dL)	Baseline CKD Stage	Fe Status	Predictor	Outcome	Association
US [UI18469314]	1499	2005	XS	12.1	CKD 5D: HD	Fe deficiency 31%[1]	Fe deficiency[2]	Hb <11 g/dL	↑
UK [UI16595586]	878	2004	XS	12.9	CKD Stage1-4 T	Ferritin <100 µg/L: 47%	Lower Ferritin	Lower Hb	↑
US [UI9375826	139	1990-1994	1-5 y	Hct 24%	CKD 5D: HD initiation	TSAT 22%[3]	TSAT	Hct	↔
						Ferritin 235 U/L	Ferritin		↔
						Serum Fe 55 U/L	Serum Fe		↔

↔ Predictor not statistically significantly associated with outcome ($p<0.05$).
↑ Significant "positive" association between predictor value (as described) and increased likelihood of outcome.
↓ Significant "negative" association between predictor value (as described) and decreased likelihood of outcome.

[1] (1) Ferritin <200 ng/mL or (2) ferritin <800 ng/mL and saturation <20%. Mean ferritin = 628 ng/mL, mean transferrin saturation = 26%, mean transferrin = 176 µg/dL.
[2] Serum transferrin 2.6 , serum iron 20 , TSAT 37%.
[3] Total iron binding capacity 254

Supplemental Table 2. Summary table of RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (categorical outcomes)

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
↑Hb ≥2g/dL	DRIVE 2007 UI172677140 US	6 wk (6 wk)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 66/68	↑25% EPO 66/66	CKD 5D: HD	18%/759 ng/mL (19%/765 ng/mL)	33498 IU/wk (35128 IU/wk)	10.4 (10.2)	11.9 (11.3)	47% (29%)	--	0.041	Good

Supplemental Table 3. Summary table of RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (continuous outcomes)

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Hb													
ΔHb, g/dL	DRIVE 2007 UI172677140 US	6 wk (6 wk)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 66/68	↑25% EPO 66/66	CKD 5D: HD	18%/759 ng/mL (19%/765 ng/mL)	33498 IU/wk (35128 IU/wk)	10.4 (10.2)	11.9 (11.3)	10.4 (10.2)	1.6 (1.1)	0.014	Good
ΔHb, g/dL	DRIVE 2008 UI18216316 US	12 wks (6 wks)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 56/ 64	↑25% EPO 56/65	CKD 5D: HD	26%/934 ng/mL (21%/582 ng/mL)	37500 IU/wk (37700 IU/wk)	11.9 (11.4)	12.1 (11.6)	nd	0.2 (0.2)	NS (0.43)	Good
ESA													
Median ΔESA dose, IU/wk	DRIVE 2008 UI18216316 US	12 wks (6 wks)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 56/ 64	↑25% EPO 56/65	CKD 5D: HD	26%/934 ng/mL (21%/582 ng/mL)	37500 IU/wk (37700 IU/wk)	11.9 (11.4)	12.1 (11.6)	37500 (37700)	-7600 (+700)	0.017	Good
Median ΔESA dose, IU/kg/wk	DRIVE 2008 UI18216316 US	12 wks (6 wks)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 56/ 64	↑25% EPO 56/65	CKD 5D: HD	26%/934 ng/mL (21%/582 ng/mL)	568 IU/wk (639 IU/wk)	11.9 (11.4)	12.1 (11.6)	568 (639)	-102 (5)	nd	Good
MedianΔ ESA dose in patients with a ferritin ≤800, IU/wk	DRIVE 2008 UI18216316 US	12 wks (6 wks)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 33/34	↑25% EPO 31/33	CKD 5D: HD	24%/698 ng/mL (20/453 ng/mL)	548 IU/wk (679 IU/wk)	11.9 (11.4)	12.0 (11.5	548 (679)	445 (671)	nd	Good
Median (IQR) ΔEPO dose in patients with a ferritin >800 ng/mL, IU/kg/wk	DRIVE 2008 UI18216316 US	12 wks (6 wks)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 22/23	↑25% EPO 22/22	CKD 5D: HD	26%/1139 ng/mL (23%/762 ng/mL)	582 IU/wk (600 IU/wk)	12.0 (11.4)	12.3 (11.7)	582 (600)	605 (500)	nd	Good

Supplemental Table 4. Summary table of adverse events in RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (adverse events)

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
SAEs (patients) since beginning of DRIVE	DRIVE 2008 UI18216316 US	12 wks (6 wks)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 66/68	↑25% EPO 66/66	CKD 5D: HD	18%/759 ng/mL (19%/765 ng/mL)	33498 IU/wk (35128 IU/wk)	10.4 (10.2)	11.9 (11.3)	nd	15 (23%) [20 (30%)]	NS (>0.05)
Cardiac AEs since beginning of DRIVE										Cardiac arrest, CHF, cardiorespiratory arrest, endocarditis, MIs, pulmonary edema, and arrhythmias	6 (9%) [9 (14%)]	NS (>0.05)
GI Disorders since beginning of DRIVE										Abdominal pain, ischemic colitis, gastric erosions, acute pancreatitis, and peritonitis	1 (2%) [4 (2%)]	NS (>0.05)
Vascular Disorders since beginning of DRIVE										Gangrene, hematoma, HTN, hypotension, and TIA	3 (5%) [4 (6%)]	NS (>0.05)
Infections since beginning of DRIVE										Cellulitis, clostridial gastroenteritis, implant infections, pneumonia, sepsis, and skin and SC abscesses	4 (6%) [10 (15%)]	NS (>0.05)
SAEs (events) since beginning of DRIVE			IV Ferric gluconate [125 mg X 8] + ↑25% EPO 15/68	↑25% EPO 20/66						nd	22[4] [38]	NS (>0.05)
SAEs since end of DRIVE		6 wks (6 wks)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 56/ 64	↑25% EPO 56/65			37500 IU/wk (37700 IU/wk)	11.9 (11.4)	12.1 (11.6)	nd	8 (14%) [13 (23%)]	NS (>0.05)

[4] Total SAE's were significantly higher in the "no iron" arm over 12 weeks (Kapoian CJASN 2007), and also that those who never received iron during the 12 weeks had the highest rate of SAE's while those randomized to IV iron had the lowest rate of SAE's (Coyne NDT 2011)

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Blood disorders	DRIVE 2007 UI17267714 0 US	6 wk (6 wk)	IV Ferric gluconate [125 mg X 8] + ↑25% EPO 66/68	↑25% EPO 66/66	CKD 5D: HD	18%/759 ng/mL (19%/765 ng/mL)	33498 IU/wk (35128 IU/wk)	10.4 (10.2)	11.9 (11.3)	Anemia and coagulation disorders	1 (2%) [4 (6%)]	NS (>0.05)

Supplemental Table 5. Association between cumulative iron dose and clinical outcome in multivariable analyses

Country	N	Study Years	Mean Follow-up Duration	Baseline Hb (g/dL)	Baseline CKD Stage	Baseline Cum Fe Dose (mg)	Predictor (Comparator)	Association: Death	Association: CVD	Association: ESRD	Association: Other
US [UI15153574	31,095	96-97[5]	~1.3 y[6] (6 mo analysis)	<10: 39%	5 HD	>1800: 25%	>1800 mg	↑[7]			
							1000-1800 mg	↑[8]			
							700-1000 mg	↔			
							1-700 mg	↔			
							(vs. 0 mg)				
US [UI11856779]	16,736	93 (enrollment)	nd	nd	5 HD	≥19 100-mg vials billed for: 7.5%	>1000 mg	↑			Hospitalization ↑
							1-1000 mg	↔			Hospitalization ↔
							(vs. 0 mg)				
US [UI19245700]	1774	98-07	1-9 y	11.4	5 HD	>455 mg/mo: 59%	(vs. >455 mg/mo)	[9]			
							202-455 mg/mo	↓[10]			
							1-202 mg/mo	↓[11]			
							0 mg/mo	↔[12]			
Romania [UI18677909]	71 children										

↔ Predictor not statistically significantly associated with outcome (P<0.05).
↑ and ↓ Predictor associated with <2 times more or less risk of outcome (e.g., hazard ratio 0.5-2.0), statistically significant.
↑↑ and ↓↓ Predictor associated with 2-5 times more or less risk of outcome (e.g., hazard ratio 2-5 or 0.2-0.5), statistically significant.
↑↑↑ and ↓↓↓ Predictor associated with >5 times more or less risk of outcome (e.g., hazard ratio >5 or <0.2), statistically significant.

[5] Enrollment period
[6] 39,725 patient-years at risk
[7] Various time dependent models found no statistically significant associations.
[8] Various time dependent models found no statistically significant associations.
[9] Analysis was of survival with the highest doses of iron used as the reference. Results have been inverted for the outcome mortality.
[10] Analysis was of survival with the highest doses of iron used as the reference. Results have been inverted for the outcome mortality.
[11] Analysis was of survival with the highest doses of iron used as the reference. Results have been inverted for the outcome mortality.
[12] Analysis was of survival with the highest doses of iron used as the reference. Results have been inverted for the outcome mortality.

Supplemental Table 6. Association between iron status and clinical outcome in multivariable analyses

Country	N	Study Years	Mean Follow-up Duration	Baseline Hb (g/dL)	Baseline CKD Stage	Baseline Fe Status	Predictor (Comparator)	Association: Death	CVD	ESRD	Other
US [UI19245700]	1774	1998-2007	1-9 y	11.4	CKD 5D: HD	TSAT 30.6%[13]	≤16%	↔			
							16-20%	↔			
							20-25%	↑			
							(vs. >25%)				
						Ferritin 594 µg/L	≤100 µg/L	↑↑			
							101-300	↑↑			
							301-600	↑			
							601-1000	↔			
							(vs. >1000)				
US [UI15042544]	1283	2001	1 y	11.9	CKD 5D: HD	Serum Fe 63.6 µg/dL[14]	Lower Fe (continuous)	↑			Hospitalization ↑
						Fe saturation ratio 31.2%	Lower Fe saturation ratio (continuous)	↑			Hospitalization ↑
US [UI19118116	453	1990-2005	3 y	11.7	CKD Stage 2-5	Fe saturation 19% Ferritin 123 ng/mL[15]	Fe saturation <15 & Ferritin <100 ng/mL	↑			
							Fe saturation <15 & Ferritin ≥100 ng/mL	↔			
							Fe saturation ≥15 & Ferritin <100 ng/mL	↔			
							(vs. Fe saturation ≥15 & Ferritin ≥100 ng/mL)				
Taiwan [UI19282675]	187	2006-2007	1 y	10.1	CKD 5D: HD	TSAT	TSAT <30.6%	↔			
						Ferritin	Lower Ferritin[16] (continuous)	↓[17]			

↔ Predictor not statistically significantly associated with outcome (P<0.05).
↑ and ↓ Predictor associated with <2 times more or less risk of outcome (e.g., hazard ratio 0.5-2.0), statistically significant.
↑↑ and ↓↓ Predictor associated with 2-5 times more or less risk of outcome (e.g., hazard ratio 2-5 or 0.2-0.5), statistically significant.
↑↑↑ and ↓↓↓ Predictor associated with >5 times more or less risk of outcome (e.g., hazard ratio >5 or <0.2), statistically significant.
↑ Significant "positive" association between continuous predictor (as described) and increased risk of outcome (e.g., relative risk expressed per ng/dL difference in ferritin)
↓ Significant "negative" association between continuous predictor (as described) and decreased risk of outcome (e.g., relative risk expressed per ng/dL difference in ferritin)

[13] Serum iron 15.3 µmol/L, total iron binding capacity 44%.
[14] Total iron binding capacity 200 µg/dL; Ferritin 685 ng/mL
[15] Serum iron 58 µg/dL, Total iron binding capacity 321 µg/dL
[16] Direction of analysis inverted to be consistent with other studies.
[17] Related largely to infection-related deaths

Supplemental Table 7. Association between anemia severity (prior to erythropoietin use) and clinical outcome in multivariable analyses

Country	N	Study Years	Mean Follow-up Duration	Baseline		Predictor (Comparator)	Association				
				Hb (g/dL)	CKD Stage[18]		Death	CVD		ESRD	Other
US [UI18930570[	78,420	2003-2004[19]	10 y	11.8	CKD 5D: HD5 HD	Lower Hb (continuous)	↗				Hospitalization ↗
US [UI19207866]	5885	1997-2005	1-8 y	<10.5: 10%	CKS Stage 3-4	Hb <10.5	↑↑	CV hosp	↑	↔	
						Hb 10.5-12.5	↑		↔	↑	
						(vs. ≥12.5)					
US [UI12883982]	1942 children	1992-2001	3 y	Hct <33%: 68%	CKD 5D	Hct <33% (vs. ≥33%)	↑				
US [UI15327408]	1513	<2001	3 y	<11.3: 25%	CKD Stage 2-4	Hb <11.3				↑	ESRD or Death ↑
						Hb 11.3-12.5				↑	↔
						Hb 12.5-13.8				↑	↔
						(vs. ≥13.8)					
France[20] [UI7121651]	1453	1972-1978	nd	Hct 23.6%	CKD 5D: HD	Hct <21.6%	↑				
						Hct 21.6-25.2%	↔				
						(vs. Hct ≥25.2)					
US [UI14569102]	1269	1986-1989[21]	9 y	13.5	CKD Stage 2-4	Hb <12 [F], <13 [M] (vs no anemia)		MI or CHD death	↑↑[22]‡		
Hong Kong [UI17065681]	606	1995-2000	3 y	nd	CKD Stage 3-4	Group V[23]		MACE[24]	↔		
						Group IV			↔		
						Group III			↔		
						Group II			↔		
						(vs. Group I)					

↔ Predictor not statistically significantly associated with outcome (P<0.05).
↑ Predictor associated with <2 times greater risk of outcome (e.g., hazard ratio 0.5-2.0), statistically significant.
↑↑ Predictor associated with 2-5 times greater risk of outcome (e.g., hazard ratio 2-5 or 0.2-0.5), statistically significant.
↑↑↑ Predictor associated with >5 times greater risk of outcome (e.g., hazard ratio >5 or <0.2), statistically significant.
↗ Significant association between continuous predictor (as described) and increased risk of outcome (e.g., hazard ratio expressed per g/dL difference in Hb).

5 HD, CKD stage 5 on hemodialysis.; 5D, CKD stage 5 on dialysis (hemo- or peritoneal); CHD, coronary heart disease; CV Hosp, cardiovascular hospitalization; CVD, cardiovascular disease (incident); ESRD, end-stage renal disease (incident); F, female; M, male; MACE, major adverse cardiac event including cardiovascular death or incident myocardial infarction, acute coronary syndrome, revascularization, heart failure, and stroke.; MI, myocardial infarction; XS, cross-sectional.

[18] 5D: hemo- or peritoneal
[19] Dates of enrollment
[20] Univariable analysis. Included because this was the only study found with N≥500 performed prior to the introduction of ESA
[21] Dates of enrollment
[22] Statistical significance not reported
[23] Group I: Hct <39% (male), <32% (female). Group II: ≥39-43% (male), ≥32-36% (female). Group III: ≥43-47% (male), ≥36-40% (female). Group IV: ≥47-50% (male), ≥40-43% (female). Group V: ≥50% (male), ≥43% (female).
[24] Including cardiovascular death or incident MI, acute coronary syndrome, revascularization, heart failure, and stroke

Supplemental Table 8. Association between hyperparathyroidism and ESA responsiveness in multivariable analyses

Country	N	Study Years	Mean Follow-up Duration	Baseline Hb	Baseline CKD Stage	Baseline PTH	Predictor	Outcome	Association
US [UI19339087]	38,393	2001-2002	1 y	≤11.4: 25%	CKD 5D: HD	234	Higher PTH[25]	Hyporesponsive[26]	↑
US [UI18469314]	1499	2005	XS	12.1	CKD 5D: HD	423	Higher PTH[27]	Treated Hb <11 g/dL[28]	↑
Canada [UI11199321]	135	<2000	XS	11.0	CKD 5D: HD	2164	Higher PTH[29]	EPO U/kg/wk	↑
Sweden [UI16183417]	166	1997-2004	XS	10.3	CKD 5D: HD	253	Higher PTH[30]	EPO U/kg/wk	↑

↔ Predictor not statistically significantly associated with outcome ($p<0.05$).
↑ Significant "positive" association between higher predictor value and increased risk of outcome (e.g., under Hb target) or higher outcome value (e.g., EPO dose).

[25] PTH in pg/mL
[26] Lowest quartile of Hb slopes over time
[27] PTH in pg/mL
[28] Target 11-12.5 g/dL
[29] PTH in pg/mL
[30] PTH in pg/mL

Supplemental Table 9. Evidence profile of RCTs comparing higher vs. lower Hb targets/ESA doses in the HD-CKD and PD-CKD populations

Outcome	# of studies & study design	Total N of patients randomized	Methodologic quality of studies	Consistency across studies	Directness of the evidence, including applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative description of effect	Importance of outcome
Mortality	7 RCTs [5 H vs. L; 3 ESA vs. Pl] (High)	2790	No limitations (0)	No important inconsistencies (0)	Some uncertainty (-1)	None (0)	High for patients with CVD Moderate for others	Possible harm in Beserab study with higher risk CVD at Hb 14 g/dL vs. 10 g/dL. No benefit in other studies with other patients.	Critical
Non-fatal CV events	4 RCTs [3 H vs. L; 1 ESA vs. Pl] (High)	2104	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Overall, no benefit. Possible harm for CVA in the Parfrey study of 13.5-14.5 g/dL vs. 9.5-11.5 g/dL.	Critical
QoL	5 RCTs [4 H vs. L; 2 ESA vs. Pl] (High)	2518	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Possible benefit with higher Hb target	High
Transfusion requirement	5 RCTs [3 H vs. L; 3 ESA vs. Pl] (High)	2228	No limitations (0)	No important inconsistencies (0)	Some uncertainty[31] (-1)	None (0)	Moderate	Benefit with higher Hb target	High
Adverse events	6 RCTs [4 H vs. L; 2 ESA vs. Pl] (High)	2741						Significantly increased incidence of access thrombosis in Beserab study with higher risk CVD. Insufficient evidence for AEs in other studies.	Moderate
Total N	7 RCTs (High)	2790							
Balance of benefit and harms Trade off Improvement in QoL and transfusion requirements. Possible harm for mortality, cardiovascular events, and adverse events.							**Quality of overall evidence** Moderate		

[31] No trial specified indications for transfusions.

Supplemental Table 10. Summary table of RCTs comparing different Hb targets/ESA doses on key clinical outcomes in the HD-CKD and PD-CKD populations

Author Year	N	CKD stage	Baseline Hb (g/dL)	Mean follow-up months	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Clinical outcomes: CVD event (%)	Clinical outcomes: Mortality (%)	Clinical outcomes: Transfusion (%)	Clinical outcomes: QoL[32]	Quality
ESA v ESA											
Besarab 1998 UI9718377 US[33]	1233	HD-CKD	10.2	14 (median)	ESA High	14.0 (12.7-13.3)	*Non Fatal MI 19 (3%) vs. 14 (2%) NS[34]	*183 (30%) vs. 150 (24%) NS[35]	129 (21%) vs. 192 (31%) P=0.001	See QoL Table	Good
					ESA Low	10.0 (10.0)					
Parfrey 2005 UI15901766, Foley 2008 UI18922988 & 2009 UI19339412 Canada & UK	596[36]	HD-CKD	11.0	18.5	ESA High	13.5 - 14.5 (13.1)	CVA 12 (4%) vs. 4 (1%) P=0.045 Other CVD NS	13 (3%) vs. 20 (5%) per 100 pt-yr NS	0.26 vs. 0.66 per pt-yr <0.0001	See QoL Table	Good
					ESA Low	9.5 - 11.5 (10.8)					
Foley 2000 UI10972697 Canada	146[37]	HD-CKD	10.4	12	ESA High	13 – 14 (13)[38]	10 (14%) vs. 10 (14%) NS	4 (5%) vs. 3 (4%) NS	—	See QoL Table	Good
					ESA Low	9.5 - 10.5 (10.5)[39]					
CanEPO 1990-1991 UI2108751, UI2048574, UI2192412 Canada	118	HD-CKD	7.0	6	ESA High	11.5 - 13 (11.7)	—	0 (0%) vs.0 (0%) vs.1 (3%) NS	1 (2%) vs. 1 (2%) vs. 23 (60%) ESA vs. Placebo P<0.05[40]	See QoL Table	Good
					ESA Low	9.5 – 11 (10.2)					
					Placebo	(7.4)					
Furuland 2003 UI12543892 Multi	416	4-5 PD-CKD HD-CKD[41]	10.9	12	ESA High	13.5–16.0 (13.6)	—	29 (13%) vs. 27 (14%) NS	—	See QoL Table	Poor
					ESA Low	9-12 (11.3-11.7)					

[32] Refer to Hb Targets Quality of Life Table for details of quality of life measurements
[33] The data and safety monitoring board recommended that the study be terminated at the time of the third interim analysis because of concern about safety even though the futility boundary corresponding to an overall 5% level of significance had not been crossed.
[34] The primary outcome was a composite of non-fatal MI or death. RR 1.3 (95% CI 0.9; 1.8) p> 0.05.
[35] The primary outcome was a composite of non-fatal MI or death. RR 1.3 (95% CI 0.9; 1.8) p> 0.05.
[36] Of the 596 patients enrolled, 324 remained in the study for 96 weeks and were evaluated for outcomes of LVH and quality of life.
[37] 121 patients had follow-up for echocardiographic outcomes. 94 patients were evaluated for the quality of life outcome at week 48.
[38] Estimated from graph during maintenance phase
[39] Estimated from graph during maintenance phase
[40] Data at 8 weeks
[41] 294 HD-CKD, 51 PD-CKD, 72 ND-CKD patients

Author Year	N	CKD stage	Baseline Hb (g/dL)	Mean follow-up months	Arm 1 Arm 2 Arm 3	Mean Hb (g/dL) target (achieved)	Clinical outcomes				Quality
							CVD event (%)	Mortality (%)	Transfusion (%)	QoL[32]	
ESA v Placebo											
Nissenson 1995 UI7703390 US	152	PD-CKD	8	6-9	ESA Placebo	10.7-12.7 (11.2) (8.0)	—	2 (3%) vs. 1 (1%) NS	ΔU/pt/4 wk -0.21 vs. +0.42 P=0.04	—	Fair
Bahlmann 1991 UI2040200 Multi	129	HD-CKD	7.7	6	ESA Placebo	10-11.7 (10.6-10.9) (7.8)	5 (8%) vs. 11 (16%) NS	2 (3%) vs. 2 (3%) NS	9 (14%) vs. 60 (90%) P<0.05	—	Fair
ESA v Placebo in Pediatric Patients											
Morris 1993 UI8257180 UK	11	PD-CKD HD-CKD	7.3	6	ESA Placebo	10.5 -12 (11.2) (7)	—	—	—	See QoL Table	Poor

Annotations:
*Primary Outcome

Coding of Outcomes:
Mortality: all cause mortality
CVD event: Includes CHF exacerbation, MI, arrythmias, angina, interventional procedure such as CABG or angioplasty, sudden death, CVA

Supplemental Table 11. Summary table of RCTs comparing different Hb targets/ESA doses on quality of life in the HD-CKD and PD-CKD populations

Author Year	N	CKD stage / Baseline Hb (g/dL)	Follow-up	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Quality of life: Scale/Test (range)	Subscale	Time point	Favors	Net Difference[42]	P	Quality
Parfrey 2005 UI15901766, Foley 2009 UI19339412 Canada & UK	596[43]	5 (HD)	24 mo	ESA High	13.5-14.5 (13.1)	KDQOL (0-100)	Energy/Fatigue	24 wk	ESA High	4.3	<0.01	Good
								36 wk	ESA High	3.8	<0.01	
								48 wk	ESA High	1.9	<0.05	
								60 wk	ESA High	3.4	<0.01	
								72 wk	ESA High	5.8	<0.001	
								84 wk	ESA High	3.3	<0.05	
							Quality of social interaction	96 wk	Neither	--	NS	
							Burden of kidney disease	72 wk	ESA High	2.7	<0.05	
							Cognitive function	60 wk	ESA High	2.9	<0.01	
							Symptoms/Problems	96 wk	Neither	--	NS	
							Effects of kidney disease	96 wk	Neither	--	NS	
							Sexual function	72 wk	ESA High	3.3	<0.05	
							Sleep	96 wk	Neither	--	NS	
							Social support	96 wk	Neither	--	NS	
							Work status	96 wk	Neither	--	NS	
							Dialysis staff encouragement	96 wk	Neither	--	NS	
							Patient satisfaction rating	96 wk	Neither	--	NS	
							Overall health rating	96 wk	Neither	--	NS	
							Physical function	72 wk	ESA High	2.3	<0.05	
								84 wk	ESA High	2.9	<0.05	
							Role limitations-physical	84 wk	ESA high	4.9	<0.05	
							Pain	96 wk	Neither	--	NS	
							General health	72 wk	ESA High	2.2	<0.05	
							Emotional well-being	48 wk	ESA high	2.1	<0.05	
								72 wk	ESA high	2.6	<0.05	
							Role limitations-emotional	96 wk	Neither	--	NS	
							Social function	60 wk	ESA High	3.3	<0.05	
						SF-36 (0-100)	Vitality	24 wk	ESA High	4.1	0.001	
								36 wk	ESA High	3.9	0.008	
								48 wk	ESA High	3.7	0.014	
								60 wk	ESA High	3.5	0.035	
		11.0		ESA Low	9.5-11.5 (10.8)							

[42] Net difference is not reported when neither intervention is favored and therefore difference is NS

[43] 324 of the 596 patients were evaluated at 96 weeks for quality of life.

Author Year	N	CKD stage / Baseline Hb (g/dL)	Follow-up	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Quality of life						Quality
						Scale/Test (range)	Subscale	Time point	Favors	Net Difference[42]	P	
						FACIT (0-52)	Fatigue	24 mo	Neither	--	NS	
CanEPO 1990-1991 UI2108751, UI2048574, UI2192412 Canada	118	5 (HD) 7.0	6 mo	ESA High	11.5-13 (11.7)	KDQ (1-7)	Fatigue	6 mo	Neither	--	NS	Good
							Physical symptoms		Neither	--	NS	
							Relationships		Neither	--	NS	
							Depression		Neither	--	NS	
							Frustration		Neither	--	NS	
				ESA Low	9.5-11 (10.2)	SIP (0-100)	Global QoL	6 mo	Neither	--	NS	
							Physical		Neither	--	NS	
							Psychosocial		Neither	--	NS	
						TTO (0, 1)		6 mo	Neither	--	NS	
				ESA High plus ESA Low	11.5-13 (11.7) plus 9.5-11 (10.2)	KDQ (1-7)	Fatigue[44]	6 mo	ESA High or Low	1.6 or 1.4 vs. 0.4	<0.001	
							Physical symptoms[45]		ESA High or Low	1.1 or 0.9 vs. 0.1	<0.001	
							Relationships		ESA High or Low	nd	0.001	
							Depression[46]		ESA High or Low	nd	0.018	
							Frustration		Neither	--	NS	
				Placebo	(7.4)	SIP (0-100)	Global QoL	6 mo	ESA High or Low	-7.8 or -5.3 vs. -2.9	0.024	
							Physical		ESA High or Low	nd	0.005	
							Psychosocial		Neither	--	NS	
						TTO (0,1)		6 mo	Neither	--	NS	
Besarab 1998 UI9718377 US	1233	5 (HD) 10.2	14 mo	ESA High	14.0 (12.7-13.3)	SF-36 (0-100)	Vitality	12 mo	Neither	--	NS	Good
							Physical function		ESA High	nd	0.03[47]	
				ESA Low	10.0 (10.0)		General health		Neither	--	NS	
							Bodily pain		Neither	--	NS	
							Social functioning		Nether	--	NS	
							Emotional Role		Nether	--	NS	
							Mental health		Nether	--	NS	
							Physical role		Nether	--	NS	
Foley 2000 UI10972697 Canada	94	5 (HD) 10.1	48 wk	ESA High	13-14 (13)	KDQ (1-7)	Fatigue	12 mo	ESA High	nd	0.009[48]	Good
							Physical symptoms		Neither	--	NS	
				ESA Low	9.5-10.5		Depression		ESA High	nd	0.02[49]	

[44] A post hoc analysis [Keown 2010] using mixed-model repeated measures at 2, 4 and 6 mo showed consistent results.
[45] A post hoc analysis [Keown 2010] using mixed-model repeated measures at 2, 4 and 6 mo found no significance after applying a Bonferroni multiplicity adjustment (p<0.0031).
[46] A post hoc analysis [Keown 2010] using mixed-model repeated measures at 2, 4 and 6 mo found no significance after applying a Bonferroni multiplicity adjustment (p<0.0031).
[47] The physical-function score on the quality-of-life questionnaire at 12 months increased by 0.6 point for each percentage-point increase in Hct
[48] Using repeated measures of ANOVA
[49] Using repeated measures of ANOVA

Author Year	N	CKD stage / Baseline Hb (g/dL)	Follow-up	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Quality of life						Quality
						Scale/Test (range)	Subscale	Time point	Favors	Net Difference[42]	P	
					(10.5)		Relationships		ESA High	nd	0.004[50]	
							Frustration		Neither	--	NS	
							Physical function		Neither	--	NS	
							General health		Neither	--	NS	
						SF-36 (0-100)	Vitality	12 mo	Neither	--	NS	
							Bodily pain		Neither	--	NS	
							Social functioning		Neither	--	NS	
							Emotional role		Neither	--	NS	
							Mental health		Neither	--	NS	
							Physical role		Neither	--	NS	
						HUI (0,1)		12 mo	Neither	--	NS	
Furuland 2003 UI12543892 Multi	117	4-5 (PD,HD)	48 wk	ESA High	13.5–16.0 (13.6)	KDQ (1-7)	Fatigue	12 mo	ESA High	0.49	0.05	Fair
							Physical symptoms		ESA High	0.41	0.02	
							Relationship		Neither	--	NS	
		10.9		ESA Low	9-12 (11.4)		Depression		ESA High	0.40	0.02	
							Frustration		ESA High	0.0	0.05	
Pediatric Patients												
Morris 1993 UI8257180 UK	10	5 (PD,HD)	8 mo	ESA	10.5 -12 (11.2)	25-part Parental Questionnaire[51] (0-100)	Global QoL	36 wk of treatment	Neither	--	NS	Fair
		7.0		Placebo	(~6.5)		Physical performance / General health (includes school attendance)		ESA	nd	<0.02	
							Sleep		Neither	--	NS	
							Diet		Neither	--	NS	
							School performance		Neither	--	NS	
							Psychosocial		Neither	--	NS	

KEY to Quality of Life Measurement Scales/Tests:
36-item Medical Outcomes Study Short-Form Health Survey (SF-36): higher scores indicate better health
FACT-Fatigue (Functional Assessment of Cancer Therapy-Fatigue): higher scores indicate less fatigue
Health Utilities Index (HUI): 0 (death) and 1 (perfect health).
Kidney Disease Quality of Life (KDQOL): See SF-36
Kidney Diseases Questionnaire (KDQ): increased score reflects better quality of life
Sickness Impact Profile (SIP): lower scores better quality of life.
Time Trade-off (TTO): 1.0 (full health) to 0 (patient is indifferent between life and death)

[50] Using repeated measures of ANOVA
[51] 25-Part Parental Questionnaire, modified from a previously used questionnaire. [1873-appendix] Questions covered various aspects of the child's wellbeing and behavior including mood and psychological behavior, social interaction, somatic complaints and general health, sleep, diet, school functioning and physical performance. Used a VAS scale of 0-100 cm

Supplemental Table 12. Summary table of RCTs comparing different Hb targets/ESA doses on Fatigue, Vitality/Energy, and Physical function in the HD-CKD and PD-CKD populations

Author Year	N	CKD stage / Baseline Hb (g/dL)	Follow-up	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Quality of life: Scale/Test (range)	Subscale	Time point	Favors	Net Difference[52]	P	Quality
Parfrey 2005 UI15901766, Foley 2009 UI19339412 Canada & UK	596[53]	5 (HD)	24 mo	ESA High	13.5-14.5 (13.1)	KDQOL (0-100)	Energy/Fatigue	24 wk	ESA High	4.3	<0.01	Good
								36 wk	ESA High	3.8	<0.01	
								48 wk	ESA High	1.9	<0.05	
								60 wk	ESA High	3.4	<0.01	
								72 wk	ESA High	5.8	<0.001	
								84 wk	ESA High	3.3	<0.05	
		11.0		ESA Low	9.5-11.5 (10.8)	SF-36 (0-100)	Vitality	24 wk	ESA High	4.1	0.001	
								36 wk	ESA High	3.9	0.008	
								48 wk	ESA High	3.7	0.014	
								60 wk	ESA High	3.5	0.035	
						FACIT (0-52)	Fatigue	24 mo	Neither	--	NS	
CanEPO 1990-1991 UI2108751, UI2048574, UI2192412 Canada	118	5 (HD)	6 mo	ESA High	11.5-13 (11.7)	KDQ (1-7)	Fatigue	6 mo	Neither	--	NS	Good
				ESA Low								
		7.0		ESA High plus ESA Low	11.5-13 (11.7) plus 9.5-11 (10.2)	KDQ (1-7)	Fatigue[54]	6 mo	ESA High or Low	1.6 or 1.4 vs. 0.4	<0.001	
				Placebo	(7.4)							
Besarab 1998 UI9718377 US[55]	1233	5 (HD)	14 mo	ESA High	14.0 (12.7-13.3)	SF-36 (0-100)	Vitality	12 mo	Neither	--	NS	Good
		10.2		ESA Low	10.0 (10.0)		Physical function		ESA High	nd	0.03[56]	
Foley 2000 UI10972697 Canada	94	5 (HD)	48 wk	ESA High	13-14 (13)	KDQ (1-7)	Fatigue	12 mo	ESA High	nd	0.009[57]	Good
		10.1		ESA Low	9.5-10.5 (10.5)	SF-36 (0-100)	Vitality		Neither	--	NS	
							Physical role		Neither	--	NS	
Furuland 2003 UI12543892 Multi	117	4-5 (PD,HD)	48 wk	ESA High	13.5–16.0 (13.6)	KDQ (1-7)	Fatigue	12 mo	ESA High	0.49	0.05	Fair
		10.9		ESA Low	9-12 (11.4)							

[52] Net difference is not reported when neither intervention is favored and therefore difference is NS
[53] 324 of the 596 patients were evaluated at 96 weeks for quality of life.
[54] A post hoc analysis [Keown 2010] using mixed-model repeated measures at 2, 4 and 6 mo showed consistent results.
[55] The data and safety monitoring board recommended that the study be terminated at the time of the third interim analysis because of concern about safety even though the futility boundary corresponding to an overall 5% level of significance had not been crossed.
[56] The physical-function score on the quality-of-life questionnaire at 12 months increased by 0.6 point for each percentage-point increase in Hct
[57] Using repeated measures of ANOVA

KEY to Quality of Life Measurement Scales/Tests:
36-item Medical Outcomes Study Short-Form Health Survey (SF-36): higher scores indicate better health
FACT-Fatigue (Functional Assessment of Cancer Therapy-Fatigue): higher scores indicate less fatigue
Kidney Disease Quality of Life (KDQOL): See SF-36
Kidney Diseases Questionnaire (KDQ): increased score reflects better quality of life

Supplemental Table 13. Summary table of RCTs comparing different Hb targets/ESA doses on non-CVD/mortality adverse event rates in the HD-CKD and PD-CKD populations

Author Year	N	Dialysis modality	Description of Intervention	Follow-up months	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Adverse events: BP change or hypertension — Definition	BP change or hypertension — Outcome	Access thrombosis (%) — Definition	Access thrombosis (%) — Outcome	Seizures	Other reported AE — Description and Results	Total D/C of drug
ESA vs. ESA													
Besarab 1998 UI9718377 US	618	HD [58]	IV or SC ESA 1.5X pre-trial dose; adjusted after 2 weeks	14	ESA High	14.0 (12.7-13.3)	Mean SBP and DBP during the study[59]	NS	Both synthetic grafts and natural fistulae	243 (39%) vs. 176 (29%) (P= 0.001)	NS	—	0
	615		IV or SC ESA adjusted		ESA Low	10.0 (10.0)							0
Parfrey 2005 UI15901766 Canada & UK	284	HD	IV or SC ESA for 24 wks to reach target then maintained for 72 wks	24	ESA High	13.5-14.5 (13.3)	Hypertension not specified	NS	AV fistulae, permanent catheter, non site specific embolism	67 (23%) vs. 57 (19%) (NS)	—	Overall treatment emergent AE in ≥10% of patients: 284 (96%) vs. 281 (94%)[60]	nd
	281				ESA Low	9.5-11.5 (10.9)							
Furuland 2003 UI12543892 Multi	216	HD PD [61]	SC ESA TIW	12	ESA High	13.5–16.0 (13.4-14.3)	ΔMean DBP from baseline	90 vs. 83 mmHg (P= 0.02)	Complication in synthetic graft, fistulae, catheter during study	7 (5%) vs. 3(2%) in HD patients only (NS)	—	Individuals with at least 1 SAE NOS: 110 (51%) vs. 97 (38.5%) (NS) Thromboembolic event: 56 (26%)vs. 47 (24%) per arm (NS)[62]	34
	200		SC ESA TIW or no treatment		ESA Low	9-12 (11.3-11.7)							15
Foley 2000 UI10972697 Canada	73	HD	SC ESA ESA high arm had a 24 wk "ramping" phase. 24 wk maintenance was similar in both arms	11	ESA High	13-14 (13)	Mean SBP, DBP, during between groups, and use of Anti-HTN meds	For LVH: significant P=0.075 SBP and ↑Anti-HTN For LVD: NS	AV access	6 (8%) vs. 10 (14%) (NS)[63]	—	—	nd
	73				ESA Low	9.5-10.5 (10.5)							
ESA vs. Placebo													
Abraham 1991 UI1751794 US	151	HD	IV ESA TIW after HD session 100 IU/kg	2-3	ESA	12.5-13.5 (10.8)	Correlation between BP and change in Hb or rate of Hb rise	No correlation[64] ESA arm: 1 individual withdrawn for severe high BP	—	—	3 (2%) vs. 0 (0%) individuals (nd)	—	nd
	78				Placebo	(7.5)							

[58] All individuals had evidence of congestive heart failure and ischemic heart disease.

[59] Pre-study ABP had to be below 160/100 for 4 weeks prior to study. Subgroup analysis [2040]: 31 patients; Mean day & nocturnal BP readings for 24 hr were NS at baseline or at follow-up.

[60] Of these p>0.05 for all comparisons except headache was greater in the ESA high arm and skeletal pain and surgery were greater in ESA low arm. More patients in the lower target experienced skeletal pain p=0.009, surgery p=0.013, and dizziness p=0.001, and more patients in the higher target group experienced headache p=0.030, and cerebrovascular events p=0.045.

[61] Includes some pre-dialysis patients, stages 4-5.

[62] Thromboembolic events were defined by WHO classification.

[63] Patients with ongoing access problems were specifically excluded. The event rates small and study did not have enough statistical power to detect a moderate impact on access thrombosis; the proportion using natural fistulae in the Besarab study was 23% compared to 76% in this study.

[64] No significant correlation but clinically important increases in BP appeared dose-related with earlier time to peak and peak BP achieved.

Author Year	N	Dialysis modality	Description of Intervention	Follow-up months	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Adverse events: BP change or hypertension — Definition	Adverse events: BP change or hypertension — Outcome	Adverse events: Access thrombosis (%) — Definition	Adverse events: Access thrombosis (%) — Outcome	Adverse events: Seizures	Adverse events: Other reported AE — Description and Results	Total D/C of drug
Nissenson 1995 UI7703390 US [Crossover]	78	PD	Self-admin. SC ESA TIW Blinded phase: 4,000 IU/mL; Maintenance phase: 2,000, 4,000, or 10,000 IU/mL	6-9	ESA	10.6-12.6 (11.2)	Increased DBP and anti-HTN regimen	55% vs. 20% (nd)	—	—	—	Mild and SAE: 407 AEs in 74 patients vs. 325 AE in 63 patients[65] (nd)	nd
	74				Placebo	(8.0)							

Coding of Outcomes: (Variable per Column Description)
Hypertension: includes mean changes in SBP, DBP, MAP, increase in use of anti-HTN medications, difficult to control hypertension
Access Thrombosis: synthetic grafts and fistulae

[65] Mild and severe reactions not otherwise specified. Of 408 events such in ESA group, 37% (N=149) considered mild severity but possibly related to study medication, 1% (N=5) were considered severe or life threatening possibly or definitely related to study medication. In the placebo group 26% (N=85) were considered mild severity but possibly related to study medication, <1% (N=2) were considered severe or life threatening possibly or definitely related to study medication.

Supplemental Table 14. Summary table of RCTs comparing different Hb targets/ESA doses on exercise capacity in the HD-CKD and PD-CKD populations

Author Year	N	CKD stage / Baseline Hb (g/dL)	Follow-up months	Arm1 / Arm 2 / Arm 3	Mean Hb (g/dL) target (achieved)	Primary outcome of study	Quality of life: Scale/Test	Quality of life: Description	Quality of life: Results	Quality
Parfrey 2005 UI15901766 Canada & UK	324	5 (HD) 11.0	24	ESA High ESA Low	13.5-14.5 (13.1) 9.5-11.5 (10.8)	Left ventricular volume index	6-min walk test	Patients are asked to cover as much distance in an enclosed corridor as they can in 6 minutes	NS	Good
CanEPO 1990-1991 UI2108751, UI2048574, UI2192412 Canada	118	5 (HD) 7.0	6	ESA High ESA Low Placebo	11.5 -13 (11.7) 9.5-11 (10.2) (7.4)	QoL and functional capacity[66]	Naughton stress test 6-min walk test	 Patients are asked to cover as much distance in an enclosed corridor as they can in 6 minutes	NS NS	Good
Pediatric Patients										
Morris 1993 UI8257180 UK	10	5 (PD,HD) 7.0	8	ESA Placebo	10.5 -12 (11.2) (~6.5)	QoL, diet, exercise tolerance, and PD efficiency	Exercise tolerance test	2-min walking Treadmill	NS[67] NS[68]	Poor

[66] Data shown for ESA arms vs. placebo. All statistical comparisons for ESA high vs. ESA low were not significant.
[67] Not a significant improvement but did improve over study time
[68] Only 3 children completed the treadmill test.

Supplemental Table 15. Evidence profile of RCTs comparing different higher vs. lower Hb targets/ESA doses in the ND-CKD populations

Outcome	# of studies & study design	Total N of patients randomized	Methodologic quality of studies	Consistency across studies	Directness of the evidence including applicability	Other considerations	Summary of findings: Quality of evidence for outcome	Summary of findings: Qualitative description of effect size	Summary of findings: Importance of outcome
Mortality	6 RCTs (High)	6832	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference	Critical
CVD (including mortality)	7 RCTs (High)	6962	No limitations (0)	Some inconsistency (-1)	Direct (0)	None (0)	High	No benefit. Possible harm with higher Hb target based on the CHOIR study.[69]	Critical
QoL	6 RCTs (High)	6790	No limitations (0)	Some inconsistency (-1)	Direct (0)	None (0)	Moderate	Possible benefit of higher Hb	High
Transfusion requirement	2 RCTs (High)	4641	Some limitations (-1)	No important inconsistencies (0)	Some uncertainty[70] (-1)	None (0)	Low	Possible benefit	High
Kidney disease progression	7 RCTs (High)	6614	No limitations (0)	Some inconsistency (-1)	Some uncertainty[71] (-1)	None (0)	Moderate	No difference[72]	High
Adverse events	8 RCTs (High)	7132						Possible harm with increased hypertension incidence associated with high Hb targets. Insufficient evidence for other adverse event incidence.	Moderate
Total N of patients	8 RCTs (High)	7132							
Balance of benefit and harm Trade off Possible benefit with higher target for QoL and transfusion requirements. Possible harm for cardiovascular disease and adverse events							**Quality of overall evidence** Moderate		

[69] In Singh study, statistical significance of the primary outcome is lost after multivariate adjustment for CHF, atrial fibrillation/flutter, serum albumin, reticulocyte count, and age [HR 1.24 (95% CI: 0.95;1.62), p=0.111].
[70] Indications for transfusions were not per protocol.
[71] Different degrees of blood pressure control and dietary modifications as concomitant therapies.
[72] Shorter time to dialysis in CREATE

Supplemental Table 16. Summary table of RCTs comparing different Hb targets/ESA doses on key clinical outcomes in the ND-CKD population

Author Year Country	N of patients randomized	CKD stage	Baseline Hb (g/dL)	Mean follow-up (mo)	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Clinical outcomes					Quality
							CVD event	Mortality	Kidney Disease Progression: Events	Trans-fusions	QoL[73]	
TREAT 2009 2010 UI19880844 CJASN in press Multi	4038	3-4	10.5	29	ESA High	13.0 (12.5)	632 vs. 602 HR 1.05 (0.94; 1.17) NS[74]	412 vs. 395 HR 1.05 (0.94; 1.17) NS	Death or ESRD 652 vs. 618 HR 1.06 (0.95; 1.19) ESRD 338 vs. 330 HR 1.02 (0.87; 1.18) NS	297 vs. 496 HR 0.56 (0.49; 0.65) P<0.001	At 25 wk: ↑≥3 points[75] FACT-Fatigue 963 vs. 875 RR 1.10[76] (1.04-1.18) P=0.002 ↑≥5 points[77] SF-36 Energy 611 vs. 569 RR 1.67[78] (1.53-1.82) P=0.027 ↑≥5 points[79] SF-36 Physical function 557 vs. 546 RR 1.59[80] (1.45-1.74) NS	Good
					ESA Low	<9 (10.6)						

[73] Global Scores, if documented, are provided here. Refer to Hb Targets Quality of Life Table for details of quality of life measurements.
[74] Includes Death or non-fatal CVD. MI: 124 vs. 129 [HR 0.96 (0.75; 1.22)] p=NS; Heart failure: 205 vs. 229 [HR 0.89 (0.74; 1.08)] p=NS; Myocardial ischemia: 41 vs. 49 [HR 0.84 (0.55; 1.27)] p=NS; Cardiac revascularization 84 vs. 117 [HR: 0.71 (0.54; 0.94)] p=0.02; Stroke 101 vs. 53 [HR 1.92 (1.38; 2.68)] p<0.001
[75] Considered clinically meaningful
[76] Calculated by ERT
[77] Considered clinically meaningful
[78] Calculated by ERT
[79] Considered clinically meaningful
[80] Calculated by ERT

Author Year Country	N of patients randomized	CKD stage	Baseline Hb (g/dL)	Mean follow-up (mo)	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Clinical outcomes: CVD event	Clinical outcomes: Mortality	Clinical outcomes: Kidney Disease Progression: Events	Clinical outcomes: Kidney Disease Progression: Trans-fusions	Clinical outcomes: QoL[73]	Quality
CHOIR 2006 UI17108343 US[81]	1432	3-4	10.1	16	ESA High	13.5 (12.7[82])	*125 vs. 97[83] HR 1.34 (1.03 ; 1.74) P=0.03	52 vs. 36 HR 1.48 (0.9; 2.27) NS	RRT 155 vs. 134 HR 1.19 (0.94; 1.49) NS	—	See QoL Table	Fair
					ESA Low	11.3 (11.4[84])						
CREATE 2006 UI17108342 Multi	603	3-4	11.6	36[85]	ESA High	13-15 (13.4[86])	*58 vs. 47[87] HR 1.28 (0.69; 1.89) NS	31 vs. 21 HR1.51 (0.87; 2.63)[88] NS	RRT 127 vs. 111 Shorter time to dialysis with high Hb target P=0.03	26 vs. 33 (nd)	See QoL Table	Good
					ESA Low	10.5-11.5 (11.6[89])						
Ritz 2007 UI17261422 Multi	172	1-3	11.9	15	ESA High	13-15 (13.5)	6 vs. 6[90] (nd)	----	RRT 2 vs. 3 (nd)	—	See QoL Table	Good
					ESA Low	10.5-11.5 (12.1)						
Levin 2005 UI16253719 Multi	172	3-4	11.8	22.6 (median)	ESA High	12-14 (12.8)	1 vs. 1 NS	1 vs. 3 NS[91]	RRT 8 vs. 11 NS	—	—	Good
					ESA Low	9-10.5 (11.5)						

[81] The data and safety monitoring board recommended that the study be terminated in May 2005 at the time of the second interim analysis, even though neither the efficacy nor the futility boundaries had been crossed, because the conditional power for demonstrating a benefit for the high-Hb group by the scheduled end of study was less than 5% for all plausible values of the true effect for the remaining data. Other factors that the board considered included an examination of differences between the treatment groups in adverse events, biochemical data, and QoL data.

[82] From graph. Averaged over all measurements.

[83] End point was a composite of death, myocardial infarction, hospitalization for congestive heart failure (excluding renal replacement therapy), and stroke. There was statistically significant imbalance at baseline with more individuals with CABG and HTN in higher Hb target arm. Statistical significance of the primary outcome is lost after multivariate adjustment for CHF, atrial fibrillation/flutter, serum albumin, reticulocyte count, and age [HR 1.24 (95% CI: 0.95; 1.62), p=0.111].

[84] From graph. Averaged over all measurements

[85] Follow-up in Arm 1 was 35 months; Arm 2 was 36 months.

[86] From graph. Averaged over all measurements

[87] End point was a composite of a first cardiovascular event including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for 24 hours or more.

[88] For HR inverse was taken of those reported in the article to convert to HR of higher versus lower Hb target

[89] From graph. Averaged over all measurements

[90] 6 vs. 5 patients for cardiac adverse events and 0 vs. 1 patient for ischemic stroke.

[91] All adverse events leading to death were determined to be unrelated to the study drug.

Author Year Country	N of patients randomized	CKD stage	Baseline Hb (g/dL)	Mean follow-up (mo)	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Clinical outcomes					Quality
							CVD event	Mortality	Kidney Disease Progression: Events	Trans-fusions	QoL[73]	
Roger 2004 UI14694167 Australia & New Zealand	155	3-4	11.2	24	ESA High	12-13 (12.1)	0 vs.0 NS	----	---	—	NS	Good
					ESA Low	9-10 (10.8)						
Rossert 2006 UI16632012 Multi	390[92]	3-4	11.6	11.8[93]	ESA High	13-15[94] (14.0[d,n])	3 vs. 4 (NS)	1 vs. 6 NS	—	—	See QoL Table	Poor
					ESA Low	11-12 (12.0[95])						
Macdougall 2006 UI16968726 UK[96]	197	2-5	10.9	22[97]	ESA Early	11 (11)	nd	1 vs. 6[98] NS	RRT 30 vs. 63 Mean time to dialysis or death NS	—	—	Poor
					ESA Late	11 (10.5)						

Annotations:
* Primary outcome

[92] Because of safety concerns in late 2002 related to the risk for EPO-induced pure red cell aplasia and subsequent labeling changes for SC administration of Eprex, the study was terminated prematurely by the sponsor. Thus GFR decline over 1 year could only be assessed in 163 patients (75 in Arm 1 and 88 in Arm 2) and quality of life follow-up was assessed in 177 patients with a median duration of 5.8 months between assessments.

[93] . Intended 36 months, but study stopped early. Therefore, study duration was 4 months of stabilization phase and a median of 7 months in the High Hb and 8.6 months in the Low Hb group of maintenance phase.

[94] Hemoglobin target was 14-15 g/dL for men and 13-14 g/dL in women.

[95] In the High Hb group, the achieved Hb for men was 14.2 g/dL and for women was 13.6 g/dl. In the low Hb group, the achieved Hb for men was 12.1 g/dl and for women was 11.5 g/dl. From graph. Averaged over all measurements

[96] The study, which began in 1997, was stopped early (December 2002) by the sponsor due to contraindication of the SC route of administration for EPO. Patients were followed-up for reasons of safety after their discontinuation, and were subsequently continued on a different EPO preparation to maintain their well-being. The results presented here provide some of the final available trial data in CKD patients administered EPO by the SC route before discontinuation of the study.

[97] Follow-up in Arm 1 was 24 months; Arm 2 was 21 months.

[98] Group B results include one death that occurred after dialysis started.

Supplemental Table 17. Summary table of RCTs comparing different Hb targets/ESA doses on quality of life in the ND-CKD population

Author Year Country	N	CKD stage Baseline Hb (g/dL)	Follow-up months	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Quality of life						Quality
						Scale (range)	Subscale	Timepoint	Favors	Net difference (or % improved)	P	
TREAT 2009 2010 UI19880844 CJASN in press Multi	4038	3-4	29	ESA High	13.0 (12.5)	FACT (0-52)	Fatigue	13 wk	ESA High	1.4	<0.0001	Good
							≥3 point increase[99]		ESA High	55% vs. 49%[100]	<0.05	
		10.5		ESA Low	<9 (10.6)	EQ-5D (0-100)	VAS		ESA High	1.9	<0.0001	
						FACT (0-52)	Fatigue	25 wk	ESA High	1.4	<0.001	
							≥3 point increase[101]		ESA High	55% vs. 49%	0.002	
						SF-36 (0-100)	Energy		Neither	--	NS	
							≥5 point increase[102]		ESA High	54% vs. 49%	0.03	
							Physical function		Neither	--	NS	
							≥5 point increase[103]		Neither	49% vs. 48%	NS	
							Role physical		Neither	--	NS	
							Bodily pain		Neither	--	NS	
							General health		Neither	--	NS	
							Social function		Neither	--	NS	
							Role emotional		Neither	--	NS	
							Mental health		Neither	--	NS	
						EQ-5D (0-100)	VAS		ESA High	1.6	<0.05	
						FACT (0-52)	Fatigue	49 wk	ESA High	1.2	<0.05	
							≥3 point increase[104]		ESA High	52% vs. 47%[105]	<0.05	
						SF-36 (0-100)	Energy		Neither	--	NS	
							≥5 point increase[106]		Neither	53% vs. 50%[107]	NS	
							Physical function		Neither	--	NS	
							≥5 point increase[108]		Neither	49% vs. 46%[109]	NS	
							Role physical		ESA High	2.3	<0.001	
							Bodily pain		Neither	--	NS	
							General health		Neither	--	NS	
							Social function		Neither	--	NS	
							Role emotional		Neither	--	NS	

[99] Considered clinically meaningful.
[100] Estimated from figure
[101] Considered clinically meaningful.
[102] Considered clinically meaningful.
[103] Considered clinically meaningful.
[104] Considered clinically meaningful.
[105] Estimated from figure
[106] Considered clinically meaningful.
[107] Estimated from figure
[108] Considered clinically meaningful.
[109] Estimated from figure

Author Year Country	N	CKD stage Baseline Hb (g/dL)	Follow-up months	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Quality of life						Quality
						Scale (range)	Subscale	Timepoint	Favors	Net difference (or % improved)	P	
							Mental health		Neither	--	NS	
						EQ-5D (0-100)	VAS		ESA High	1.9	<0.05	
						FACT (0-52)	Fatigue		ESA High	1.2	<0.05	
							≥3 point increase[110]	73 wk	Neither	51% vs. 49%[111]	NS	
						EQ-5D (0-100)	VAS		ESA High	1.5	<0.05	
						FACT (0-52)	Fatigue		ESA High	1.5	<0.001	
							≥3 point increase[112]		ESA High	51% vs. 45%[113]	<0.05	
						SF-36 (0-100)	Energy		ESA High	1.5	<0.001	
							≥5 point increase[114]		ESA High	54% vs. 48%[115]	<0.05	
							Physical function		ESA High	2.9	<0.05	
							≥5 point increase[116]		ESA High	48% vs. 42%[117]	<0.05	
							Role physical	97 wk	ESA High	3.6	<0.001	
							Bodily pain		Neither	--	NS	
							General health		Neither	--	NS	
							Social function		Neither	--	NS	
							Role emotional		Neither	--	NS	
							Mental health		Neither	--	NS	
						EQ-5D (0-100)	VAS		ESA High	1.6	<0.05	
CREATE 2006 UI17108342 Multi	603	3-4 / 11.6	36	ESA High / ESA Low	13-15 (13.4) / 10.5-11.5 (11.6)	SF-36 (0-100)	Vitality	1 y	ESA High	4.3[118]	<0.001	Good
							General health		ESA High	3.9[119]	0.003	
							Mental health		ESA High	4.8[120]	<0.001	
							Physical function		ESA High	5.6[121]	<0.001	
							Physical role		ESA High	7.8[122]	0.01	
							Social function		ESA High	4.2[123]	0.006	
							Vitality	2 y	ESA High	nd	0.01	
							General health		ESA High	nd	0.008	

[110] Considered clinically meaningful.
[111] Estimated from figure
[112] Considered clinically meaningful.
[113] Estimated from figure
[114] Considered clinically meaningful.
[115] Estimated from figure
[116] Considered clinically meaningful.
[117] Estimated from figure
[118] Estimated from figure
[119] Estimated from figure
[120] Estimated from figure
[121] Estimated from figure
[122] Estimated from figure
[123] Estimated from figure

Author Year Country	N	CKD stage Baseline Hb (g/dL)	Follow-up months	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Quality of life						Quality
						Scale (range)	Subscale	Timepoint	Favors	Net difference (or % improved)	P	
							Mental health		Neither	--	NS	
							Physical function		Neither	--	NS	
							Physical role		Neither	--	NS	
							Social function		Neither	--	NS	
Ritz 2007 UI17261422 Multi	172	1-3 / 11.9	15	ESA High / ESA Low	13-15 (13.5) / 10.5-11.5 (12.1)	SF-36 (0-100)	General health	15 mo	ESA High	5.0	0.04	Good
Roger 2004 UI14694167 Australia & New Zealand	155[124]	3-4 / 11.2	24	ESA High / ESA Low	12-13 (12.1) / 9-10 (10.8)	SF-36 (0-100)	Physical health	24 mo	Neither	--	NS	Good
							Mental health		Neither	--	NS	
						RQoLP (nd)	Global QoL (nd)	24 mo	Neither	--	NS	
CHOIR 2006 UI17108343 US	1432	3-4 / 10.1	16	ESA High / ESA Low	13.5 (12.7) / 11.3 (11.4)	LASA (0-100)		nd	Neither	--	NS	Fair
						KDQ (4-35)	Fatigue	nd	Neither	--	NS	
						SF-36 (0-100)	Vitality	nd	Neither	--	NS	
							Physical function		Neither	--	NS	
							General health		Neither	--	NS	
							Bodily pain		Neither	--	NS	
							Social functioning		Neither	--	NS	
							Emotional role		ESA Low	-5.1	0.01	
							Mental health		Neither	--	NS	
							Physical role		Neither	--	NS	
Rossert 2006 UI16632012 Multi	390[125]	3-4 / 11.6	7.8	ESA High / ESA Low	13-15 (14.0) / 11-12 (12.0)	SF-36 (0-100)	Vitality	4 mo	ESA High	6	0.042	Poor
							Physical function		Neither	--	NS	
							General health		Neither	--	NS	
							Bodily pain		Neither	--	NS	
							Social functioning		Neither	--	NS	
							Emotional role		Neither	--	NS	
							Mental health		Neither	--	NS	
							Physical role		Neither	--	NS	

Key for QOL Scales
36-item Medical Outcomes Study Short-Form Health Survey (SF-36): higher scores indicate better health
Kidney Diseases Questionnaire (KDQ): higher scores indicate better health
Linear Analogue Self-Assessment (LASA): higher scores indicate better function

[124] Excluded patients with unstable or poorly controlled angina, severe congestive heart failure (grade III-IV), severe chronic respiratory disease, symptomatic peripheral vascular disease, or a created arteriovenous fistula.
[125] Quality of life follow-up was assessed in 177 patients with a median duration of 5.8 months between assessments.

Renal Quality of Life Profile (RQoLP): nd
FACT-Fatigue (Functional Assessment of Cancer Therapy-Fatigue): higher scores indicate less fatigue
EQ-5D (EuroQoL): higher scores indicate better health)

Supplemental Table 18. Summary table of RCTs comparing different Hb targets/ESA doses on Fatigue, Vitality/Energy, and Physical function in the ND-CKD population

Author Year Country	N	CKD stage Baseline Hb (g/dL)	Follow-up months	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Quality of life						Quality
						Scale (range)	Subscale	Timepoint	Favors	Net difference	P	
TREAT 2009 2010 UI19880844 CJASN in press Multi	4038	3-4 / 10.5	29	ESA High / ESA Low	13.0 (12.5) / <9 (10.6)	FACT (0-52)	Fatigue	13 wk	ESA High	1.4	<0.001	Good
							≥3 point increase[126]		ESA High	55% vs. 49%[127]	<0.05	
						FACT (0-52)	Fatigue	25 wk	ESA High	1.4	<0.001	
							≥3 point increase[128]		ESA High	55% vs. 49%	0.002	
						SF-36 (0-100)	Energy		Neither	--	NS	
							≥5 point increase[129]		ESA High	54% vs. 49%	0.03	
							Physical functioning		Neither	--	NS	
							≥5 point increase[130]		Neither	49% vs. 48%	NS	
						FACT (0-52)	Fatigue	49 wk	ESA High	1.2	<0.05	
							≥3 point increase[131]		ESA High	52% vs. 47%[132]	<0.05	
						SF-36 (0-100)	Energy		Neither	--	NS	
							≥5 point increase[133]		Neither	53% vs. 50%[134]	NS	
							Physical function		Neither	--	NS	
							≥5 point increase[135]		Neither	49% vs. 46%[136]	NS	
						FACT (0-52)	Fatigue	73 wk	ESA High	1.2	<0.05	
							≥3 point increase[137]		Neither	51% vs. 49%[138]	NS	
						FACT (0-52)	Fatigue	97 wk	ESA High	1.5	<0.001	
							≥3 point increase[139]		ESA High	51% vs. 45%[140]	<0.05	
						SF-36 (0-100)	Energy		ESA High	1.5	<0.001	

[126] Considered clinically meaningful.
[127] Estimated from figure
[128] Considered clinically meaningful.
[129] Considered clinically meaningful.
[130] Considered clinically meaningful.
[131] Considered clinically meaningful.
[132] Estimated from figure
[133] Considered clinically meaningful.
[134] Estimated from figure
[135] Considered clinically meaningful.
[136] Estimated from figure
[137] Considered clinically meaningful.
[138] Estimated from figure
[139] Considered clinically meaningful.
[140] Estimated from figure

Author Year Country	N	CKD stage Baseline Hb (g/dL)	Follow-up months	Arm 1 / Arm 2	Mean Hb (g/dL) target (achieved)	Quality of life						Quality
						Scale (range)	Subscale	Timepoint	Favors	Net difference	P	
							≥5 point increase[141]		ESA High	54% vs. 48%[142]	<0.05	
							Physical function		ESA High	2.9	<0.05	
							≥5 point increase[143]		ESA High	48% vs. 42%[144]	<0.05	
CREATE 2006 UI17108342 Multi	603	3-4	36	ESA High	13-15 (13.4)	SF-36 (0-100)	Vitality	1 y	ESA High	4.3[145]	<0.001	Good
							Physical function		ESA High	5.6[146]	<0.001	
		11.6		ESA Low	10.5-11.5 (11.6)		Vitality	2 y	ESA High	nd	0.01	
							Physical function		Neither	--	NS	
Ritz 2007 UI17261422 Multi	172	1-3	15	ESA High	13-15 (13.5)	SF-36 (0-100)	General health	15 mo	ESA High	5.0	0.04	Good
		11.9		ESA Low	10.5-11.5 (12.1)							
Roger 2004 UI14694167 Australia & New Zealand	155[147]	3-4	24	ESA High	12-13 (12.1)	SF-36 (0-100)	Physical health	24 mo	Neither	--	NS	Good
		11.2		ESA Low	9-10 (10.8)		Mental health		Neither	--	NS	
CHOIR 2006 UI17108343 US	1432	3-4	16	ESA High	13.5 (12.7)	KDQ (4-35)	Fatigue	nd	Neither	--	NS	Fair
						SF-36 (0-100)	Vitality	nd	Neither	--	NS	
		10.1		ESA Low	11.3 (11.4)		Physical function		Neither	--	NS	
Rossert 2006 UI16632012 Multi	390[148]	3-4	7.8	ESA High	13-15 (14.0)	SF-36 (0-100)	Vitality	4 mo	ESA High	6	P=0.042	Poor
		11.6		ESA Low	11-12 (12.0)		Physical function		Neither	--	NS	

Key for QOL Scales
36-item Medical Outcomes Study Short-Form Health Survey (SF-36): higher scores indicate better health
Kidney Diseases Questionnaire (KDQ): higher scores indicate better health
Linear Analogue Self-Assessment (LASA): higher scores indicate better function
Renal Quality of Life Profile (RQoLP): nd
FACT-Fatigue (Functional Assessment of Cancer Therapy-Fatigue): higher scores indicate less fatigue

[141] Considered clinically meaningful.
[142] Estimated from figure
[143] Considered clinically meaningful.
[144] Estimated from figure
[145] Estimated from figure
[146] Estimated from figure
[147] Excluded patients with unstable or poorly controlled angina, severe congestive heart failure (grade III-IV), severe chronic respiratory disease, symptomatic peripheral vascular disease, or a created arteriovenous fistula.
[148] Quality of life follow-up was assessed in 177 patients with a median duration of 5.8 months between assessments.

Supplemental Table 19. Summary table of RCTs comparing different Hb targets/ESA doses on non-CVD/mortality adverse event rates in the ND-CKD population

Author Year Country	N	CKD stage	Description of intervention	Follow-up (mo)	Arm 1) / Arm 2	Mean Hb (g/dL) target (achieved)	Adverse events: BP change or hypertension — Definition	Adverse events: BP change or hypertension — Outcome	Adverse events: Any non-CVD/mortality AE[149] — D/C of drug or withdraw (N/arm)	Adverse events: Any non-CVD/mortality AE[149] — Reason for D/C or withdraw
TREAT 2009 UI19880844 Multi	2004 2009		Initial dose of DA was 0.75 µg/kg Q2W. ESA extended to 1.50 µg/kg /mo if 2 consecutive Hb levels within 12.0-13.5 g/dL	29	ESA High ESA Low	13.0 (12.5) <9 (10.6)	Reported by investigators and not defined	491 vs. 446 (NS)	--	--
CHOIR 2006 UI17108343 US	715 717	3-4	Initially received10,000 U ESA SC QW for 3 weeks; Subsequent ESA permitted Q2W if Hb level was stable	16	ESA High ESA Low	13.5 (12.7) 11.3 (11.4)	Mean SBP from baseline to the end of the study	↓2.3 mm Hg vs. ↓2.6 mm Hg (NS)	147 (21%) vs. 160 (22%) (nd)	nd (not for RRT)
CREATE 2006 UI17108342 Multi	301 302	3-4	Initial dose of ESA 2000 IU SC QW. Dose adjustments to achieve target were permitted	36	ESA High ESA Low	13-15 (13.4) 10.5-11.5 (11.6)	HTN	89 (30%) vs. 59 (20%) P=0.005	17 vs.10 NS	nd[150]
Ritz 2007 UI17261422 Multi	88[151] 82[152]	1-3	SC ESA 2000 IU QW SC ESA 2000 IU QW if Hb <10.5 g/dL	15	ESA High ESA Low	13-15 (13.5) 10.5-11.5 (12.1)	HTN	15 (17%) vs. 9 (11%) (nd)	0	---
Levin 2005 UI16253719 Multi	85 87	3-4	SC ESA 2000 IU once weekly SC ESA 2000 IU QW if Hb <9.0 g/dL	24	ESA High ESA Low	12-14 (12.8) 9-10.5 (11.5)	Individuals with at least 1 recorded BP > 140/90[153]	51% vs. 54% NS	nd	---
Roger 2004 UI14694167 Australia & New Zealand	75 80	3-4	SC ESA SC ESA if Hb <9 g/dL	24[e]	ESA High ESA Low	12-13 (12.1) 9-10 (10.8)	2 yr adjusted Mean SBP and DBP between high and low ESA arms	Systolic: NS Diastolic: 81 vs. 78 mmHg P=0.009	0 vs. 3 (NS)	nd
Rossert 2006 UI16632012 Multi	195 195	3-4	Initial dose of ESA was 25-100 IU/kg. Therapy was given in SC doses QW. Dose adjustments were permitted in steps of 4 wks as needed to achieve target Hb level, with a permitted ↑weekly dose of 25 IU/kg.	36	ESA High ESA Low	13-15 (13.0) 11-12 (11.8)	HTN	26 (13%) vs. 22 (11%) NS	6 vs.6 (NS)	PRCA (N=2 in ESA high group), angina, pruritus

[149] Any non-CVD/mortality related adverse event that required discontinue of drug or resulted in withdraw from study.
[150] 12 of the 127 (9%) renal replacement therapy patients in the high ESA group and 8 of the 111 (7%) renal replacement therapy patients in the Low ESA group experienced a thrombotic event.
[151] Two patients from a single center were randomly assigned, but were excluded from all analysis because the center was closed due to major violation of Good Clinical Practice guidelines.
[152] Two patients from a single center were randomly assigned, but were excluded from all analysis because the center was closed due to major violation of Good Clinical Practice guidelines
[153] Statistically significant difference in ΔDBP between arms (p=0.027). However, baseline DBP was higher in Late ESA group. There were 4 episodes of hypertension as an adverse event. None were attributed to the study drug and all were resolved.

Author Year Country	N	CKD stage	Description of intervention	Follow-up (mo)	Arm 1) / Arm 2	Mean Hb (g/dL) target (achieved)	Adverse events: BP change or hypertension – Definition	Adverse events: BP change or hypertension – Outcome	Adverse events: Any non-CVD/mortality AE[149] – D/C of drug or withdraw (N/arm)	Adverse events: Any non-CVD/mortality AE[149] – Reason for D/C or withdraw
Macdougall 2006 UI16968726 UK	65	2-5	SC ESA 1000U Q2W	36	ESA High	11 (11)	HTN	14 (22%) vs. 9 (7%) nd		
	132		SC ESA 2000 U thrice weekly if Hb <9.0 g/dL		ESA Low	9-11 (10.5)				

Supplemental Table 20. ESA protocols from the major trials in CKD populations

Trial, Year Country	Population	Hb Target, g/dL (Achieved)		Drug	Initial Dose	Initial Timing of Changes	Maximum Doses Used	
		Low Target	High Target				Low Target	High Target
CanEPO 1990-1991 UI2108751, UI2048574, UI2192412 Canada	CKD 5D: HD	9.5-11 (10.2)	11.5-13 (11.7)	Epoetin alfa	100 U/kg	12 wk (high target) 8 wk (low target)	??	
CHOIR 2006 UI17108343 US	CKD Stage 3-4	11.3 (11.4)	13.5 (12.7)	Epoetin alfa	10,000 U/wk	2 wk	20,000 U/wk (per protocol)	20,000 U/wk (per protocol)
Parfrey 2005 UI15901766 Canada & UK	CKD 5D: HD	9.5-11.5 (10.8)	13.5-14.5 (13.1)	Epoetin alfa	150 IU/kg/wk	2 wk[154]	??	
Besarab 1998 UI9718377 US	CKD 5D: HD	10.0±1.0 (10.0)	14.0±1.0 (12.7-13.3)	Epoetin alfa	Low: ~150 U/kg/wk[155] High: ~225 U/kg/wk[156]	2 wk	500 U/Kg/wk (per protocol)	500 U/Kg/wk (per protocol)
CREATE 2006 UI17108342 Multiple	CKD Stage 3-4	10.5-11.5 (11.6)	13-15 (13.4)	Epoetin beta	2000 IU/wk	4 wk	20,000 U/wk (per protocol)	20,000 U/wk (per protocol)
TREAT 2009 UI19880844 Multiple	CKD Stage 3-4, DM	<9 (10.6)	13.0 (12.5)	Darbepoetin alfa	0.75 µg/kg	2 wk	1.5 µg/kg	600 µg/mo (per protocol)

Some of these data are from personal communications with the study authors.

[154] Discretionary

[155] Low Hb group started on baseline epoetin dose (coming into the trial), which was 153±119 U/Kg/wk. High Hb group was started at 1.5 times their baseline epoetin dose, which was 146±103 U/kg/wk.

[156] Low Hb group started on baseline epoetin dose (coming into the trial), which was 153±119 U/Kg/wk. High Hb group was started at 1.5 times their baseline epoetin dose, which was 146±103 U/kg/wk.

Supplemental Table 21. Evidence profile of RCTs examining IV vs. SC EPO in CKD patients with anemia

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	4 RCTs (High)	599 (276)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence	Critical
CV mortality	1 RCT (High)	114 (53)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence	Critical
CV events	0 RCTs	--	--	--	--	--	--	--	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Transfusion	2 RCTs (High)	252 (128)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	High
QoL	1 RCT (High)	83 (45)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Low	No difference	High
Hb (categorical)	3 RCTs (High)	394 (200)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Moderate	No difference[157]	Moderate
Hb (continuous)	4 RCTs (High)	559 (276)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	No difference	Moderate
ESA dose (categorical)	0 RCTs	--	--	--	--	--	--	--	Moderate
ESA dose (continuous)	4 RCTs (High)	559 (276)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	None (0)	Moderate	Benefit with SC EPO. No difference for darbepoetin.	Moderate
Adverse events	3 RCTs (High)	351 (175)						Possible harm with SC, especially in regards to pain (SC 18% vs. IV 0%)	Moderate
Total	4 RCTs	599 (276)							

Balance of potential benefits and harms:
Insufficient evidence for important clinical outcomes
No difference in Hb response
Benefit for decreasing ESA dose with SC EPO

Quality of overall evidence:
Low

[157] In one study, more patients are out of range with SC.

Supplemental Table 22. Summary table of RCTs[158] examining IV vs. SC ESA in CKD patients with anemia (categorical outcomes)

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Mortality													
All cause mortality	Bommer 2008 UI18676350 Germany	48 wk (52 wk)	IV Darbepoetin α 53/53	SC Darbepoetin α 61/61	CKD 5D	502 pg/mL (556 pg/mL)	31.1 µg (26.9 µg)	11.6 (12.0)	11.6 (11.7)	3 (6%) [5 (8%)]	RR 0.69[159] (0.16; 2.75)	NS	Good
Cerebral bleeding death										0 (%) [1 (2%)]	nd	nd	Good
Death[160]	Muirhead, 1992 UI2192414 Canada	48 wk (48 wk)	SC rHuEPO 45/64	IV rHuEPO 38/64	CKD 5D: HD	nd	147 U/kg/wk (184 U/kg/wk)	8.0 (7.7)	10.9 (11.2)	3 (5%) [12 (13%)]	RR 0.34[161] (0.09; 1.36)	NS	Good
All cause mortality	Chazot 2009 UI19407262 France	6 mo (6 mo)	SC direct switch to IV Darbepoetin α 77/77	SC indirect switch to IV Darbepoetin α after 2 mo of SC darbepoetin 77/77	CKD 5D: HD	34%/418 µg/L (35%/479 µg/L)	0.44 µg/kg/wk (0.46 µg/kg/wk)	11.6 (11.5)	11.7 (12.0)	3 (4%) [8 (10%)]	RR 0.38 (0.10; 1.36)	NS	Fair
Death	Kaufman 1998 UI9718376 US	26 wk (26 wk)	IV EPO 101/101	SC EPO 107/107	CKD 5D: HD	28%/305 ng/mL (29%/297 ng/mL)	122 U/kg/wk (117 U/kg/wk)	Hct 32% (Hct 32%)	Hct 31% (Hct 31%)	8 (8%) [11 (10%)]	RR 0.77 (0.32; 1.84)[162]	NS	Fair
CV Mortality													
Cardiac death	Bommer 2008 UI18676350 Germany	48 wk (52 wk)	IV Darbepoetin α 53/53	SC Darbepoetin α 61/61	CKD 5D	502 pg/mL (556 pg/mL)	31.1 µg (26.9 µg)	11.6 (12.0)	11.6 (11.7)	2 (4%) [2 (3%)]	RR 1.15[163] (0.17; 7.89)	NS	Good
Transfusions													
Blood transfusion	Bommer 2008 UI18676350 Germany	48 wk (52 wk)	IV Darbepoetin α 53/53	SC Darbepoetin α 61/61	CKD 5D	502 pg/mL (556 pg/mL)	31.1 µg (26.9 µg)	11.6 (12.0)	11.6 (11.7)	4 (8%) [4 (7%)]	RR1.15[164] (0.30; 4.38)	NS	Good

[158] Kaufman and Muirhead were known older studies but were not part of a systematic review.
[159] Calculated by ERT
[160] Includes those who died during 1 month placebo run-in period and after withdrawal from the study (cessation of therapy).
[161] Calculated by ERT
[162] Calculated by ERT
[163] Calculated by ERT
[164] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Transfusion	Kaufman 1998 UI9718376 US	26 wk (26 wk)	IV EPO 101/101	SC EPO 107/107	CKD 5D: HD	28%/305 ng/mL (29%/297 ng/mL)	122 U/kg/wk (117 U/kg/wk)	Hct 32% (Hct 32%)	Hct 31% (Hct 31%)	9 (12%) [7 (9%)]	RR 1.36 (0.53; 3.52)[165]	NS (0.61)	Fair
Hb													
ΔHb ≥1 g/dL	Patel 2009 UI19088467 US	4 wks (24 wks)	IV EPO 78/78	SC EPO 79/79	CKD 5D: HD	28%/315 ng/mL (27%/293 ng/mL)	49.99 U/kg/session (36 U/kg/session)	10.38 (10.37)	nd	69 (88%) [72 (91%)]	RR 0.97[166] (0.87; 1.08)	NS	Good
ΔHb >1.5 g/dL										40 (51%) [44 (56%)]	RR 0.92[167] (0.69; 1.23)	NS	Good
ΔHb 2 g/dL										25 (32%) [27 (34%)]	RR 0.94[168] (0.60; 1.46)	NS	Good
↑Hb >3.0 g/dL										1 (1%) [4 (5%)]	RR 0.25[169] (0.03; 2.22)	NS	Good
↓Hb >3.0 g/dL										3 (4%) [6 (8%)]	RR 0.51[170] (0.13; 1.95)	NS	Good
Mean number of weeks with Hb >11g/dL or <10 g/dL										12.45 (13.92)	--	0.04	Good
Mean number of ΔHb ≥1 g/dL										3.44 (4.03)	--	NS (0.08)	Good
Mean number of ΔHb>1.5 g/dL										1.27 (1.49)	--	NS (0.22)	Good
Number of ΔHb of 2 g/pt										0.63 (0.71)	nd	NS (0.42)	Good

[165] Calculated by ERT
[166] Calculated by ERT
[167] Calculated by ERT
[168] Calculated by ERT
[169] Calculated by ERT
[170] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Number of ↑Hb >3.0 g/dL										0.01 (0.05)	nd	NS (0.17)	Good
Number of ↓Hb >3.0 g/dL										0.04 (0.08)	nd	NS (0.18)	Good
Failure to achieve or maintain Hb target	Muirhead, 1992 UI2192414 Canada	48 wk (48 wk)	SC rHuEPO 45/64	IV rHuEPO 38/64	CKD 5D: HD	nd	147 U/kg/wk (184 U/kg/wk)	8.0 (7.7)	10.9 (11.2)	6[171] (9.4%) [12 (19%)]	RR 0.45[172] (0.16; 1.28)	NS[173]	Good
Patients with stable Hb levels	Chazot 2009 UI19407262 France	6 mo (6 mo)	SC direct switch to IV Darbepoetin α 77/77	SC indirect switch to IV Darbepoetin α after 2 mo of SC darbepoetin 77/77	CKD 5D: HD	34%/418.3 µg/L (35.4%/479.4µg/L)	0.44 µg/kg/wk (0.46 µg/kg/wk)	11.6 (11.5)	11.7 (12.0)	64 (83%[174]) [63 (82%)]	RD -1.0 (-12.7; 10.7)[175]	Non-inf[176]	Fair

[171] Includes 1 patient who was kept below target by physician.
[172] Calculated by ERT
[173] Without 1 patient kept below target OR=0.37 (95% CI 0.12, 1.13) p=0.08.
[174] Calculated by ERT
[175] 90% CI
[176] This study shows equivalence between groups 1 and 2 in terms of percentage of patients with Hb stability. Moreover, equivalence between groups 1 and 2 in terms of proportions of patients with Hb stability at month 3 was shown. At the end of the study, the mean intravenous darbepoetin dosages were similar between the 3 treatment groups, whatever the initial route of administration.

Supplemental Table 23. Summary table of RCTs[177] examining IV vs. SC ESA in CKD patients with anemia (continuous outcomes)

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
QoL													
KDQ Physical	Muirhead, 1992 UI2192414 Canada	48 wk (48 wk)	SC rHuEPO 45/64	IV rHuEPO 38/64	CKD 5D: HD	nd	147 U/kg/wk (184 U/kg/wk)	8.0 (7.7)	10.9 (11.2)	4.3 (4.3)	+0.9 (+1.0)	NS	Fair
KDQ Fatigue										4.5 (4.3)	+0.5 (+0.8)	NS	
KDQ Relation-ships										5.2 (4.9)	+0.2 (+0.5)	NS	
KDQ Depression										5.1 (5.0)	+0.3 (+0.4)	NS	
KDQ Frustration										5.3 (4.9)	+0.1 (+0.3)	NS	
KDQ Global Physical										4.5 (4.4)	+0.6 (+0.7)	NS	
KDQ Global Emotional										5.2 (4.9)	+0.2 (+0.4)	NS	
Hb/Hct													
ΔHb, g/dL	Bommer 2008 UI18676350 Germany	48 wk (52 wk)	IV Darbepoetin α 53/53	SC Darbepoetin α 61/61	CKD 5D	502 pg/mL (556 pg/mL)	31.1 µg (26.9 µg)	11.6 (12.0)	11.6 (11.7)	11.6 (12.0)	+0.36 -0.04 ,0.76 (range)	NS (0.073)	Good
Hb, g/dL	Muirhead, 1992 UI2192414 Canada	48 wk (48 wk)	SC rHuEPO 45/64	IV rHuEPO 38/64	CKD 5D: HD	nd	147 U/kg/wk (184 U/kg/wk)	8.0 (7.7)	10.9 (11.2)	8.0 (7.7)	+2.9 (+3.5)	NS	Good
Hb, g/dL	Chazot 2009 UI19407262 France	6 mo (6 mo)	SC direct switch to IV Darbepoetin α 77/77	SC indirect switch to IV Darbepoetin α after 2 mo of SC darbepoetin 77/77	CKD 5D: HD	34%/418 µg/L (35%/479 µg/L)	0.44 µg/kg/wk (0.46 µg/kg/wk)	11.6 (11.5)	11.7 (12.0)	11.6 (11.5)	+0.1 (+0.5)	nd	Fair
ΔHct, %	Kaufman 1998 UI9718376 US	26 wk (26 wk)	IV EPO 101/101	SC EPO 107/107	CKD 5D: HD	28%/305 ng/mL (29%/297 ng/mL)	122 U/kg/wk (117 U/kg/wk)	Hct 32% (Hct 32%)	Hct 31% (Hct 31%)	32% (32%)	-0.9% (-0.7%)	NS (0.60)	Fair

[177] Kaufman and Muirhead were known older studies but were not part of a systematic review.

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
ESA dose													
ΔDarbepoetin doses, µg/wk	Bommer 2008 UI18676350 Germany	48 wk (52 wk)	IV Darbepoetin α 53/53	SC Darbepoetin α 61/61	CKD 5D	502 pg/mL (556 pg/mL)	31.1 µg (26.9 µg)	11.6 (12.0)	11.6 (11.7)	31.7 (25.8)	Net Δ -1.25	NS (0.67)	Good
EPO dose (U/kg/wk)	Muirhead, 1992 UI2192414 Canada	48 wk (48 wk)	SC rHuEPO 45/64	IV rHuEPO 38/64	CKD 5D: HD	nd	147 U/kg/wk (184 U/kg/wk)	8.0 (7.7)	10.9 (11.2)	0	147 (184)	NS	Good
EPO dose (U/kg/wk)		Stabilization (32-48 wk)								0	206 (274)	0.02	
Time to stabilization (wk)										--	14.9 (17.3)	0.006	
Darbepoetin dose, µg/kg/wk	Chazot 2009 UI19407262 France	6 mo (6 mo)	SC direct switch to IV Darbepoetin α 77/77	SC indirect switch to IV Darbepoetin α after 2 mo of SC darbepoetin 77/77	CKD 5D: HD	34%/418 µg/L (35.4%/479 µg/L)	0.44 µg/kg/wk (0.46 µg/kg/wk)	11.6 (11.5)	11.7 (12.0)	0.45 (0.46)	-0.01 (0)	nd	Fair
ΔWeekly EPO dose, U/kg/wk	Kaufman 1998 UI9718376 US	26 wk (26 wk)	IV EPO 101/101	SC EPO 107/107	CKD 5D: HD	28%/305 ng/mL (29%/297 ng/mL)	122 U/kg/wk (117 U/kg/wk)	Hct 32% (Hct 32%)	Hct 31% (Hct 31%)	122 (117)	+18.3 (-21.9)	<0.001	Fair

Supplemental Table 24. Summary table of adverse events in RCTs[178] examining IV vs. SC EPO in CKD patients with anemia

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Total	Bommer 2008 UI18676350 Germany	48 wk (52 wk)	IV Darbepoetin α 53/53	SC Darbepoetin α 61/61	CKD 5D	502 pg/mL (556 pg/mL)	31.1 µg (26.9 µg)	11.6 (12.0)	11.6 (11.7)	All	18 (34%) [38 (62%)]	0.005[179]
SAEs										Including death	6 (11%) [24 (39%)]	0.003[180]
Related to darbepoeitin										Classified as related to by the investigators	5 (9%) [4 (7%)]	NS[181]
Total AE	Chazot 2009 UI19407262 France	6 mo (6 mo)	SC direct switch to IV Darbepoetin α 77/77	SC indirect switch to IV Darbepoetin α after 2 mo of SC darbepoetin 77/77	CKD 5D: HD	34%/418 µg/L (35.4%/479 µg/L)	0.44 µg/kg/wk (0.46 µg/kg/wk)	11.6 (11.5)	11.7 (12.0)	Mild or moderate	25 (32%) [22 (29%)]	NS
Seizure	Muirhead, 1992 UI2192414 Canada	48 wk (48 wk)	SC rHuEPO 45/64	IV rHuEPO 38/64	CKD 5D: HD	nd	147 U/kg/wk (184 U/kg/wk)	8.0 (7.7)	10.9 (11.2)	nd (none HTN)	4 (7%) [1 (2%)]	nd
Serious HTN										PreHD DBP>110 or HTN seizure	18 (30%) [22 (36%)]	nd
Thrombotic events										Dialysis access or extracorporeal circuit	24 (39%) [30 (48%)]	nd
Failure of access										nd	21% [18%]	nd
SC pain										nd	11 (18%) [0 (0%)]	nd

[178] Kaufman and Muirhead were known older studies but were not part of a systematic review.
[179] Calculated by ERT
[180] Calculated by ERT
[181] Calculated by ERT

Supplemental Table 25. Evidence profile of RCTs examining different dosing schedules in CKD patients with anemia

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	7 RCTs (High)	2803 (1884)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence	Critical
CV mortality	2 RCTs (High)	803 (570)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence	Critical
CV events	2 RCTs (High)	949 (711)	No limitations (0)	NA	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence	Critical
ESRD	1 RCT (High)	644 (322)	Some limitations (-1)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Very low	Insufficient evidence	Critical
Transfusion	5 RCTs (High)	2003 (1282)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence	High
QoL	1 RCT (High)	519 (489)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Sparse (-1)	Moderate	No difference	High
Hb (categorical)	3 RCTs (High)	1257 (739)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference	Moderate
Hb (continuous)	8 RCTs (High)	3006 (2086)	No limitations (0)	Important inconsistencies (0)	Direct (0)	None (0)	Moderate	No difference[182]	Moderate
ESA dose (categorical)	0 RCTs	--	--	--	--	--	--	--	Moderate
ESA dose (continuous)	4 RCTs (High)	1003 (638)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	Benefit of C.E.R.A every two weeks vs. once every month and epoetin every week vs. IV darbepoetin every week or epoetin three times per week	Moderate
Adverse events	6 RCTs (High)	2803 (1984)						No difference in major adverse events	Moderate
Total	8 RCTs	3006 (2086)							

[182] In one study, there was a benefit for IV darbepoetin alfa every week or epoetin alfa three times per week over epoetin alfa every week in dialysis patients.

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
	Balance of potential benefits and harms: Insufficient evidence for important clinical outcomes. No difference in Hb response. Benefit for more frequent ESA administration for cumulative dose.[183]						**Quality of overall evidence:** Very low		

[183] Varies by preparation

Supplemental Table 26. Summary table of RCTs examining different dosing schedules in CKD patients with anemia (categorical outcomes)

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Q2W vs. Q4W													
Mortality													
All cause mortality	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol-EPO β Q2W 223/223	Methoxy polyethylene glycol- EPO β Q4W 224/224	CKD 5D	27%/453 µg/L (28%/522 µg/L)	Median 57µg/2 wk (175 µg/4 wk)	119.7 g/L (118.5 g/L)	118.0 g/L (116.1 g/L)	19 (9%) [15 (7%)]	RR 1.26[184] (0.66;2.42)	NS	Fair
Total death	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO Q4W 215/215	29 mL/min (28 mL/min)	519 pmol/L (559 pmol/L)	4529 IU/wk (5423 IU/wk)	11.12 (11.17)	11.0 (11.0)	3 (3%) [9 (4%)]	RR 0.33[185] (0.09; 1.20)	NS	Good
Deaths	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	C.E.R.A Q4W 191/191	CKD 5D: HD & PD	30%/418 ng/mL (28%/427 ng/mL)	56 µg/2wk (150 µg/4wk)	11.70 (11.66)	11.70 (11.46)	13 (7%) [18 (10%)]	RR 0.73[186] (0.37;1.44)	NS	Fair
Death [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	C.E.R.A. Q4W 72/72	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	2 (2%) [1 (1%)]	RR 1.97 (0.18, 21.28)[187]	NS (0.576)	Fair
Death	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 20,000 units Q2W 131/131	EPO α 40,000 units Q4W 126/126	nd	26% /179 (25%/227)	9,681 U (9,748 U)	11.9 (11.9)	11.9 (11.4)	1 (1%) [2 (2%)]	RR 0.96 (0.06, 15.21)[188]	NS	Fair
CV mortality													
Sudden cardiac death	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO Q4W 215/215	29 mL/min (28 mL/min)	518.60 pmol/L (558.97 pmol/L)	4529 IU/wk (5423 IU/wk)	11.12 (11.17)	11.0 (11.0)	0 (0%) [0 (0%)]	--	---	Good

[184] Calculated by ERT
[185] Calculated by ERT
[186] Calculated by ERT
[187] Calculated by ERT
[188] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
ESRD													
Dialysis	Pergola, 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO Q4W 215/215	29 mL/min (28 mL/min)	518.60 pmol/L (558.97 pmol/L)	4529 IU/wk (5423 IU/wk)	11.12 (11.17)	11.0 (11.0)	2 (2%) [4 (2%)]	RR 1.00[189] (0.19; 5.40)	NS	Fair
CV events													
Cardiac arrest	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO Q4W 215/215	29 mL/min (28 mL/min)	518.60 pmol/L (558.97 pmol/L)	4529 IU/wk (5423 IU/wk)	11.12 (11.17)	11.0 (11.0)	0 (0%) [1 (1%)]	--	---	Good
Thrombosis	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 20,000 units Q2W 131/131	EPO α 40,000 units Q4W 126/126	nd	26% /179 (25%/227)	9,681 U (9,748 U)	11.9 (11.9)	11.9 (11.4)	3 (2%) [3 (2%)]	RR 0.96 (0.20, 4.68)[190]	NS	Fair
Transfusion													
Transfusion	Levin, 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol-EPO β Q2W 223/223	Methoxy polyethylene glycol- EPO β Q4W 224/224	CKD 5D	27%/453 µg/L (28%/522 µg/L)	Median 57µg/2 wk (175 µg/4 wks)	119.7 g/L (118.5 g/L)	118.0 g/L (116.1 g/L)	21 (10%) [16 (7%)]	RR 1.31[191] (0.70; 2.44)	NS	Fair
Transfusion	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO Q4W 215/215	29 mL/min (28 mL/min)	518.60 pmol/L (558.97 pmol/L)	4529 IU/wk (5423 IU/wk)	11.12 (11.17)	11.0 (11.0)	6 (6%) [14 (7%)]	RR 0.86[192] (0.34; 2.18)	NS	Fair
Transfusion	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	C.E.R.A Q4W 191/191	CKD 5D: HD & PD	30%/418 ng/mL (28%/427 ng/mL)	56 µg/2wk (150 µg/4wk)	11.70 (11.66)	11.70 (11.46)	6% [11%]	--	---	Good

[189] Calculated by ERT
[190] Calculated by ERT
[191] Calculated by ERT
[192] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Transfusions [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	C.E.R.A. Q4W 72/72	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	2 (3%) [0 (0%)]	nd	nd	Fair
Hb													
Hb maintained within 10 g/L	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol-EPO β Q2W 223/223	Methoxy polyethylene glycol- EPO β Q4W 224/224	CKD 5D	27%/453 µg/L (28%/522 µg/L)	Median 57µg/2 wk (175 µg/4 wks)	119.7 g/L (118.5 g/L)	118.0 g/L (116.1 g/L)	133 (68%) [127 (68%)]	RR 1.00[193] (0.87; 1.15)	NS	Fair
Hb maintained within ±1.0 g/dL	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	C.E.R.A Q4W 191/191	CKD 5D: HD & PD	30%/418 ng/mL (28%/427 ng/mL)	56 µg/2wk (150 µg/4wk)	11.70 (11.66)	11.70 (11.46)	76% [66%]	--	---	Good
Hb maintained within 10-13.5 g/dL										92% [88%]	--	---	Good
Hb levels maintained within ±1 g/dL of the response value [ITT]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	C.E.R.A. Q4W 72/72	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	55 (76%) [50 (70%)]	RR 1.08 (0.89, 1.33)[194]	NS (0.428)	Fair
Q2W vs. Q3W													
Mortality													
Death	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 20,000 units Q2W 131/131	Epoetin α 30,000 units Q3W 132/132	nd	26% /179 (26%/205)	9,681 U (9,489 U)	11.9 (11.9)	11.9 (11.2)	2 (2%) [3 (2%)]	RR 1.01 (0.21, 4.90)[195]	NS	Fair

[193] Calculated by ERT
[194] Calculated by ERT
[195] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
CV events													
Thrombosis	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 20,000 units Q2W 131/131	Epoetin α 30,000 units Q3W 132/132	nd	26% /179 (26%/205)	9,681 U (9,489 U)	11.9 (11.9)	11.9 (11.2)	3 (2%) [5 (4%)]	RR 0.60 (0.15, 2.48)[196]	NS	Fair
Q3W vs. Q4W													
Mortality													
Death	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 30,000 units Q3W 132/132	Epoetin α 40,000 units Q4W 126/126	nd	26%/205 (25%/227)	9,489 U (9,748 U)	11.9 (11.9)	11.2 (11.4)	1 (1%) [2 (2%)]	RR 0.48 (0.04, 5.20)[197]	NS	Fair
CV event													
Thrombosis	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 30,000 units Q3W 132/132	Epoetin α 40,000 units Q4W 126/126	nd	26%/205 (25%/227)	9,489 U (9,748 U)	11.9 (11.9)	11.2 (11.4)	5 (4%) [3 (2%)]	RR 1.59 (0.39, 6.52)[198]	NS	Fair
Q4W vs. QW-TIW													
Mortality													
All cause mortality	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q4W 224/224	EPO α or β QW-TIW 226/226	CKD 5D	28%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	118.5 g/L (119.1 g/L)	116.1 g/L (118.2 g/L)	15 (7%) [17 (8%)]	RR 0.90[199] (0.46; 1.76)	NS	Fair
Transfusion													
Transfusion	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q4W 224/224	EPO α or β QW-TIW 226/226	CKD 5D	28%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	118.5 g/L (119.1 g/L)	116.1 g/L (118.2 g/L)	16 (7%) [17 (8%)]	RR 0.96[200] (0.50; 1.86)	NS	Fair

[196] Calculated by ERT
[197] Calculated by ERT
[198] Calculated by ERT
[199] Calculated by ERT
[200] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Hb													
Hb maintained within 10 g/L	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q4W 224/224	EPO α or β QW-TIW 226/226	CKD 5D	28%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	118.5 g/L (119.1 g/L)	116.1 g/L (118.2 g/L)	127 (68%) [138 (67%)]	RR 1.00[201] (0.87; 1.15)	NS	Fair
Q2W vs. QW-TIW													
Mortality													
All cause mortality	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q2W 223/223	EPO α or β QW-TIW 226/226	CKD 5D	27%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	119.7 g/L (119.1 g/L)	118.0 g/L (118.2 g/L)	19 (9%) [17 (8%)]	RR 1.14[202] (0.61; 2.13)	NS	Fair
Total death	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	29 mL/min (31 mL/min)	553pmol/L (510 pmol/L)	6662 IU/wk (5039 IU/wk)	9.81 (9.63)	11.1 (11.4)	4 (3%) [4 (3%)]	RR 0.98[203] (0.25; 3.85)	NS	Good
CV mortality													
Cardiac death	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	29 mL/min (31 mL/min)	553pmol/L (510 pmol/L)	6662 IU/wk (5039 IU/wk)	9.81 (9.63)	11.1 (11.4)	0 (0%) [0 (0%)]	--	---	Good
Transfusion													
Transfusion	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q2W 223/223	EPO α or β QW-TIW 226/226	CKD 5D	27%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	119.7 g/L (119.1 g/L)	118.0 g/L (118.2 g/L)	21 (10%) [17 (8%)]	RR 1.26[204] (0.69; 2.33)	NS	Fair

[201] Calculated by ERT
[202] Calculated by ERT
[203] Calculated by ERT
[204] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Transfusion	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	29 mL/min (31 mL/min)	553pmol/L (510 pmol/L)	6662 IU/wk (5039 IU/wk)	9.81 (9.63)	11.1 (11.4)	14 (11%) [37[205] (3%)]	RR 0.37[206] (0.21; 0.65)	0.002[207]	Fair
Hb													
Hb maintained within 10 g/L	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q2W 223/223	EPO α or β QW-TIW 226/226	CKD 5D	27%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	119.7 g/L (119.1 g/L)	118.0 g/L (118.2 g/L)	133 (68%) [138 (67%)]	RR 1.01[208] (0.88; 1.15)	NS	Fair
QW vs. QW or TIW													
Mortality													
Death	Locatelli 2008 UI18587731 Multi	28 wks (28 wks)	EPO α QW 213/217	IV Darbepoetin α QW or EPO α TIW 68/70	CKD 5D: HD	31%/402 ng/mL (32%/402 ng/mL)	6.791 IU/wk (6.210 IU/wk)	11.57 (11.57)	10.92 (11.64)	1 (5%) [0 (0%)]	--	---	Good
Total death	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α QW 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	30 mL/min (31 mL/min)	573.81 pmol/L (510.23 pmol/L)	5035 IU/wk (5039 IU/wk)	9.71 (9.63)	11.3 (11.4)	6 (5%) [4 (3%)]	RR 1.48[209] (0.43; 5.10)	NS[210]	Good
Death	Locatelli 2002 UI12087569 EU	24 wks (24 wks)	SC EPO β QW 75/84	SC EPO β TIW 71/89	5D: HD	26%/422 ng/mL (27%/461 ng/mL)	81 IU/kg (78 IU/kg)	Hct 33.1% (33.3%)	Hct 33% (33.2%)[211]	1 (1%) [5 (7%)]	RR 0.19[212] (0.02; 1.58)	NS	Good

[205] Calculated by ERT
[206] Calculated by ERT
[207] Calculated by ERT
[208] Calculated by ERT
[209] Calculated by ERT
[210] Calculated by ERT
[211] Estimated from graph
[212] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
CV mortality													
Cardiac death	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α QW 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	30 mL/min (31 mL/min)	573.81 pmol/L (510.23 pmol/L)	5035 IU/wk (5039 IU/wk)	9.71 (9.63)	11.3 (11.4)	1 (1%) [0 (0%)]	--	---	Good
Transfusion													
Transfusion	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α QW 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	30 mL/min (31 mL/min)	573.81 pmol/L (510.23 pmol/L)	5035 IU/wk (5039 IU/wk)	9.71 (9.63)	11.3 (11.4)	88 (7%) [37 (3%)][213]	RR 2.34[214] (1.75; 3.14)	0.000[215]	Fair
Transfusion	Locatelli 2002 UI12087569 EU	24 wks (24 wks)	SC EPO β QW 75/84	SC EPO β TIW 71/89	5D: HD	26%/422 ng/mL (27%/461 ng/mL)	81 IU/kg (78 IU/kg)	Hct 33.1% (33.3%)	Hct 33% (33.2%)[216]	6 (8%) [8 (11%)]	RR 0.71 (0.26; 1.94)	NS	Fair
Q4W vs. QW													
Mortality													
Total death	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q4W 215/215	EPO QW 108/108	28 mL/min (28 mL/min)	558.97 pmol/L (513.97 pmol/L)	5423 IU/wk (2967 IU/wk)	11.17 (11.03)	11.0 (11.0)	9 (4%) [4 (4%)]	RR 1.13[217] (0.36; 3.59)	NS	Good
Death	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 40,000 units Q4W 126/126	EPO α 10,000 units QW 130/130	nd	25%/227 (25%/198)	9,748 U (9,265 U)	11.9 (11.9)	11.4 (12.2)	1 (1%) [1 (1%)]	RR 1.04 (0.07, 16.44)[218]	NS	Fair
CV mortality													
Sudden cardiac death	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q4W 215/215	EPO QW 108/108	28 mL/min (28 mL/min)	558.97 pmol/L (513.97 pmol/L)	5423 IU/wk (2967 IU/wk)	11.17 (11.03)	11.0 (11.0)	0 (0%) [2 (2%)]	--	---	Good

[213] Calculated by ERT
[214] Calculated by ERT
[215] Calculated by ERT
[216] Estimated from graph
[217] Calculated by ERT
[218] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
ESRD													
Dialysis	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q4W 215/215	EPO QW 108/108	28 mL/min (28 mL/min)	558.97 pmol/L (513.97 pmol/L)	5423 IU/wk (2967 IU/wk)	11.17 (11.03)	11.0 (11.0)	4 (2%) [2 (2%)]	RR 1.00[219] (0.19; 5.40)	NS	Fair
CV events													
Cardiac arrest	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q4W 215/215	EPO QW 108/108	28 mL/min (28 mL/min)	558.97 pmol/L (513.97 pmol/L)	5423 IU/wk (2967 IU/wk)	11.17 (11.03)	11.0 (11.0)	0 (0%) [0 (0%)]	--	---	Good
Thrombosis	Provenzano, 2005 UI16114787 US	16 wks (16 wks)	EPO α 40,000 units Q4W 126/126	EPO α 10,000 units QW 130/130	nd	25%/227 (25%/198)	9,748 U (9,265 U)	11.9 (11.9)	11.4 (12.2)	3 (2%) [2 (2%)]	RR 1.55 (0.26, 9.11)[220]	NS	Fair
Transfusion													
Transfusion	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q4W 215/215	EPO QW 108/108	28 mL/min (28 mL/min)	558.97 pmol/L (513.97 pmol/L)	5423 IU/wk (2967 IU/wk)	11.17 (11.03)	11.0 (11.0)	14 (7%) [4 (4%)]	RR 1.76[221] (0.59; 5.21)	NS	Fair
Q3W vs. QW													
Mortality													
Death	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 30,000 units Q3W 132/132	EPO α 10,000 units QW 130/130	nd	26%/205 (25%/198)	9, 489 U (9, 265 U)	11.9 (11.9)	11.2 (12.2)	3 (2%) [1 (1%)]	RR 02.95 (0.31, 28.04)[222]	NS	Fair
CV event													
Thrombosis	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 30,000 units Q3W 132/132	EPO α 10,000 units QW 130/130	nd	26%/205 (25%/198)	9, 489 U (9, 265 U)	11.9 (11.9)	11.2 (12.2)	5 (4%) [2 (2%)]	RR 2.48 (0.49, 12.56)[223]	NS	Fair

[219] Calculated by ERT
[220] Calculated by ERT
[221] Calculated by ERT
[222] Calculated by ERT
[223] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Q2W vs. QW													
Mortality													
Total death	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α QW 125/125	29 mL/min (30 mL/min)	552.74 pmol/L (573.81 pmol/L)	6662 IU/wk (5035 IU/wk)	9.81 (9.71)	11.1 (11.3)	4 (3%) [6 (5%)]	RR 0.67[224] (0.19; 2.31)	NS[225]	Good
Total death	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO QW 108/108	29 mL/min (28 mL/min)	518.60 pmol./L (513.97 pmol/L)	4529 IU/wk (2967 IU/wk)	11.12 (11.03)	11.0 (11.0)	3 (3%) [4 (4%)]	RR 0.76[226] (0.17; 3.30)	NS	Good
Death	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 20,000 units Q2W 131/131	EPO α 10,000 units QW 130/130	nd	26%/179 (25% /198)	9,681 U (9,265 U)	11.9 (11.9)	11.9 (12.2)	2 (2%) [1 (1%)]	RR 1.98 (0.18, 21.62)[227]	NS	Fair
CV mortality													
Cardiac death	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α QW 125/125	29 mL/min (30 mL/min)	552.74 pmol/L (573.81 pmol/L)	6662 IU/wk (5035 IU/wk)	9.81 (9.71)	11.1 (11.3)	0 (0%) [1 (1%)]	--	---	Good
Sudden cardiac death	Pergola, 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO QW 108/108	29 mL/min (28 mL/min)	518.60 pmol./L (513.97 pmol/L)	4529 IU/wk (2967 IU/wk)	11.12 (11.03)	11.0 (11.0)	0 (0%) [2 (2%)]	--	---	Good
ESRD													
Dialysis	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO QW 108/108	29 mL/min (28 mL/min)	518.60 pmol./L (513.97 pmol/L)	4529 IU/wk (2967 IU/wk)	11.12 (11.03)	11.0 (11.0)	2 (2%) [2 (2%)]	RR 1.01[228] (0.14; 7.04)	NS	Fair

[224] Calculated by ERT
[225] Calculated by ERT
[226] Calculated by ERT
[227] Calculated by ERT
[228] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
CV events													
Cardiac arrest	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO QW 108/108	29 mL/min (28 mL/min)	518.60 pmol./L (513.97 pmol/L)	4529 IU/wk (2967 IU/wk)	11.12 (11.03)	11.0 (11.0)	0 (0%) [0 (0%)]	--	---	Good
Thrombosis	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 20,000 units Q2W 131/131	EPO α 10,000 units QW 130/130	nd	26%/179 (25% /198)	9,681 U (9,265 U)	11.9 (11.9)	11.9 (12.2)	3 (2%) [2 (2%)]	RR 1.49 (0.25, 8.76)[229]	NS	Fair
Transfusion													
Transfusion	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α QW 125/125	29 mL/min (30 mL/min)	552.74 pmol/L (573.81 pmol/L)	6662 IU/wk (5035 IU/wk)	9.81 (9.71)	11.1 (11.3)	14 (11%) [8 (7%)][230]	RR 1.75[231] (0.76; 4.02)	NS[232]	Fair
Transfusion	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO QW 108/108	29 mL/min (28 mL/min)	518.60 pmol./L (513.97 pmol/L)	4529 IU/wk (2967 IU/wk)	11.12 (11.03)	11.0 (11.0)	6 (6%) [4 (4%)]	RR 1.51[233] (0.44; 5.21)	NS	Fair
Hb													
Target Hb >10 g/dL maintained without ↑EPO >60%	Mircescu 2006 UI16931218 Romania	12 wk (24 wk)	EPO β Q2W 102/104	EPO β QW 101/103	CKD 5D: HD	36%/333 ng/mL (36%/339 ng/mL)	67.8 IU/kg (71.8 IU/kg)	11.4 (11.4)	11.41 (11.38)	73% [62%]	--	---	Good
Target Hb >10 g/dL maintained without ↑EPO >60%										75% [69%]	--	---	Good

[229] Calculated by ERT
[230] Calculated by ERT
[231] Calculated by ERT
[232] Calculated by ERT
[233] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Target Hb >10 g/dL maintained without ↑EPO >60%										66% [62%]	--	---	Good
Target Hb >10 g/dL maintained without ↑EPO >60%										66% [64%]	--	---	Good

Supplemental Table 27. Summary table of RCTs examining different dosing schedules in CKD patients with anemia (continuous outcomes)

Outcome	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Q2W vs. Q4W													
QoL													
Mean ΔLASA energy score	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 20,000 units Q2W 94/131	Epoetin α 40,000 units Q4W 93/126	nd	26% /179 (25%/227)	9,681 U (9,748 U)	11.9 (11.9)	11.9 (11.4)	52.9 (49.1)	2.7 (6.1)	nd	Fair
Mean ΔLASA activity score										53.3 (52.2)	3.5 (5.0)	nd	Fair
Mean ΔLASA overall QOL score										62.9 (59.5)	0.7 (1.6)	nd	Fair
Mean Δtotal KDQ score										22.7 (22.8)	0.1 (-0.2)	nd	Fair
Hb													
ΔHb, g/L [PP]	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol-EPO β Q2W 223/223	Methoxy polyethylene glycol- EPO β Q4W 224/224	CKD 5D	27%/453 µg/L (28%/522 µg/L)	Median 57µg/2 wk (175 µg/4 wk)	119.7 g/L (118.5 g/L)	118.0 g/L (116.1 g/L)	119.7 (118.5)	-0.71 (-2.20; 0.77) [-0.25 (-1.79; 1.29)][234]	---	Fair
ΔHb g/dL	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO Q4W 215/215	29 mL/min (28 mL/min)	519 pmol/L (559 pmol/L)	4529 IU/wk (5423 IU/wk)	11.12 (11.17)	11.0 (11.0)	11.12 (11.17)	-0.10 (-0.19)	---	Good
Difference of least squares means										11.12 (11.17)	-0.03 (-0.09)	---	Good
ΔHb, g/dL [PP]	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	C.E.R.A Q4W 191/191	CKD 5D: HD & PD	30%/418 ng/mL (28%/427 ng/mL)	56 µg/2wk (150 µg/4wk)	11.70 (11.66)	11.70 (11.46)	11.70 (11.66)	0.032 (-0.131)	---	Good

[234] After adjusting for covariates

Outcome	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Hb, g/dL [ITT]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	C.E.R.A. Q4W 72/72	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	8-11 g/dL (8-11g/dL)	+0.92 to +3.92 (+0.7 to 3.7)[235]	nd	Fair
Mean ΔHb g/dL	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 20,000 units Q2W 114/131	Epoetin α 40,000 units Q4W 104/126	nd	26% /179 (25%/227)	9,681 U (9,748 U)	11.9 (11.9)	11.9 (11.4)	11.9 (11.9)	0.0 (-0.5)	nd	Fair
ESA dose													
Median doses	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	C.E.R.A Q4W 191/191	CKD 5D: HD & PD	30%/418 ng/mL (28%/427 ng/mL)	56 µg/2wk (150 µg/4wk)	11.70 (11.66)	11.70 (11.46)	60 µg/2wk (120 µg/4wk)	-4 µg/2wk (+30 µg/4wk)	---	Good
Q2W vs., Q3W													
QoL													
Mean ΔLASA energy score	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 20,000 units Q2W 94/131	Epoetin α 30,000 units Q3W 101/132	nd	26% /179 (26%/205)	9,681 U (9,489 U)	11.9 (11.9)	11.9 (11.2)	52.9 (51.3)	2.7 (5.9)	nd	Fair
Mean ΔLASA activity score										53.3 (53.4)	3.5 (6.0)	nd	Fair
Mean ΔLASA overall QOL score										62.9 (63.5)	0.7 (1.3)	nd	Fair
Mean Δtotal KDQ score										22.7 (23.0)	0.1 (-0.4)	nd	Fair
Hb													
Mean ΔHb g/dL	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 20,000 units Q2W 114/131	Epoetin α 30,000 units Q3W 114/132	nd	26% /179 (26%/205)	9,681 U (9,489 U)	11.9 (11.9)	11.9 (11.2)	11.9 (11.9)	0.0 (-0.7)	nd	Fair
Q3W vs., Q4W													
QoL													

[235] The Hb was given in a range at baseline (taken from the inclusion criteria). Therefore the achieved Hb is also given in a range of what the difference could be.

Outcome	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Mean ΔLASA energy score	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 30,000 units Q3W 101/132	Epoetin α 40,000 units Q4W 93/126	nd	26%/205 (25%/227)	9,489 U (9,748 U)	11.9 (11.9)	11.2 (11.4)	51.3 (49.1)	5.9 (6.1)	nd	Fair
Mean ΔLASA activity score										53.4 (52.2)	6.0 (5.0)	nd	Fair
Mean ΔLASA overall QOL score										63.5 (59.5)	1.3 (1.6)	nd	Fair
Mean Δtotal KDQ score										23.0 (22.8)	-0.4 (-0.2)	nd	Fair
Hb													
Mean ΔHb g/dL	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 30,000 units Q3W 114/132	Epoetin α 40,000 units Q4W 104/126	nd	26%/205 (25%/227)	9,489 U (9,748 U)	11.9 (11.9)	11.2 (11.4)	11.9 (11.9)	-0.7 (-0.5)	nd	Fair
Q4W vs. QW-TIW													
Hb													
ΔHb, g/L [PP]	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q4W 224/224	EPO α or β 1-3X/wk 226/226	CKD 5D	28%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	118.5 g/L (119.1 g/L)	116.1 g/L (118.2 g/L)	118.5 (119.1)	-0.25 (-1.79; 1.29) [-0.75 (-2.26; 0.75)][236]	---	Fair
Difference ΔHb [ITT]											0.025 (-2.20; 2.70)	Non-inf[237]	Fair
Q2W vs. QW-TIW													
Hb													
ΔHb, g/L [PP]	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q2W 223/223	EPO α or β 1-3X/wk 226/226	CKD 5D	27%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	119.7 g/L (119.1 g/L)	118.0 g/L (118.2 g/L)	119.7 (119.1)	-0.71 (-2.20; 0.77) [-0.75 (-2.26; 0.75)][238]	---	Fair

[236] After adjusting for covariates
[237] The lower limit of 97.5% CI was > pre-defined -7.5g/L non-inferiority threshold indicating that methoxy polyethylene glycol-epoetin is non-inferior to epoetin (p<0.0001)
[238] After adjusting for covariates

Outcome	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Difference ΔHb [ITT]										119.7 (119.1)	-0.31 (-2.13; 2.76)	Non-inf[239]	Fair
ΔHb g/dL	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	29 mL/min (31 mL/min)	553pmol/L (510 pmol/L)	6662 IU/wk (5039 IU/wk)	9.81 (9.63)	11.1 (11.4)	9.81 (9.63)	1.27 (1.81)	Non-inf[240]	Good
QW vs. QW or TIW													
Hb													
ΔHb, g/dL	Locatelli 2008 UI18587731 Multi	28 wks (28 wks)	EPO α QW 213/217	IV Darbepoetin α QW or EPO α TIW 68/70	CKD 5D: HD	31%/402 ng/mL (32%/402 ng/mL)	6.791 IU/wk (6.210 IU/wk)	11.57 (11.57)	10.92 (11.64)	11.57 (11.57)	-0.65 (+0.07)	<0.001	Good
ΔHb g/dL	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α QW 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	30 ml/min (31 ml/min)	573.81 pmol/L (510.23 pmol/L)	5035 IU/wk (5039 IU/wk)	9.71 (9.63)	11.3 (11.4)	9.71 (9.63)	1.59 (1.81)	Non-inf[241]	Good
ΔHct% [PP]	Locatelli 2002 UI12087569 EU	24 wks (24 wks)	SC EPO β QW 75/84	SC EPO β TIW 71/89	5D: HD	26%/422 ng/mL (27%/461 ng/mL)	81 IU/kg (78 IU/kg)	Hct 33.1% (33.3%)	Hct 33% (33.2%)[242]	33.1% (33.3%)	-0.1 (-0.1)	nd[243]	Fair
ESA dose													
ESA dose, IU/week	Locatelli 2008 UI18587731 Multi	28 wks (28 wks)	EPO α QW 213/217	IV Darbepoetin α QW or EPO α TIW 68/70	CKD 5D: HD	31%/402 ng/mL (32%/402 ng/mL)	6.791 IU/wk (6.210 IU/wk)	11.57 (11.57)	10.92 (11.64)	6,791 (6,210)	1,636 (-133)	<0.001	Good
Normalized ESA dose, IU/kg/g										6,791 (6,210)	+24.9 (-2.9)	<0.001	Good
Normalized ESA dose, IU/kg/g Hb/wk										6,791 (6,210)	+3.1 (-0.2)	<0.001	Good

[239] The lower limit of 97.5% CI was > pre-defined -7.5g/L non-inferiority threshold indicating that methoxy polyethylene glycol-epoetin is non-inferior to epoetin (p<0.0001)

[240] The lower limit of the 95% CI for the estimated treatment difference for both comparisons QW versus TIW (-0.380; 0.0037) and Q2W vs. TIW (-0.641; -0.221) was above the prespecified noninferiority margin of -1 g/dL.

[241] The lower limit of the 95% CI for the estimated treatment difference for both comparisons QW vs. TIW (-0.380; 0.0037) and Q2W vs. TIW (-0.641; -0.221) was above the prespecified noninferiority margin of -1 g/dL.

[242] Estimated from graph

[243] The difference in mean time-adjusted AUC for hematocrit between the two treatment groups was -0.54 volume%. The mean value and 90% CI (-1.27; 0.19) were within the pre-specified range.

Outcome	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Median ΔEPO dose IU/kg/wk [PP]	Locatelli 2002 UI12087569 EU	24 wks (24 wks)	SC EPO β QW 75/84	SC EPO β TIW 71/89	5D: HD	26%/422 ng/mL (27%/461 ng/mL)	81 IU/kg (78 IU/kg)	Hct 33.1% (33.3%)	Hct 33% (33.2%)[244]	81 (78)	1.0 (0.0)	nd[245]	Fair
Q3W vs. QW													
QoL													
Mean ΔLASA energy score	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 30,000 units Q3W 132/132	EPO α 10,000 units QW 130/130	nd	26%/205 (25%/198)	9, 489 U (9, 265 U)	11.9 (11.9)	11.2 (12.2)	51.3 (48.3)	5.9 (6.8)	nd	Fair
Mean ΔLASA activity score										53.4 (49.1)	6.0 (4.6)	nd	Fair
Mean ΔLASA overall QOL score										63.5 (58.7)	1.3 (3.3)	nd	Fair
Mean Δtotal KDQ score										23.0 (21.7)	-0.4 (1.1)	nd	Fair
Hb													
Mean ΔHb g/dL	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 30,000 units Q3W 132/132	EPO α 10,000 units QW 130/130	nd	26%/205 (25%/198)	9, 489 U (9, 265 U)	11.9 (11.9)	11.2 (12.2)	11.9 (11.9)	-0.7 (0.3)	nd	Fair
Q2W vs. QW													
QoL													
Mean ΔLASA energy score	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 20,000 units Q2W 131/131	EPO α 10,000 units QW 130/130	nd	26%/179 (25% /198)	9,681 U (9,265 U)	11.9 (11.9)	11.9 (12.2)	52.9 (48.3)	2.7 (6.8)	nd	Fair
Mean ΔLASA activity score										53.3 (49.1)	3.5 (4.6)	nd	Fair

[244] Estimated from graph

[245] The ratio of mean weekly epoetin beta doses was 1.11. This value and the 90% CI of the ratio (0.99; 1.23) were within the pre-specified range.

Outcome	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Mean ΔLASA overall QOL score										32.9 (58.7)	0.7 (3.3)	nd	Fair
Mean Δtotal KDQ score										22.7 (21.7)	0.1 (1.1)	nd	Fair
Hb													
Mean Hb levels, g/dL	Mircescu 2006 UI16931218 Romania	12 wk (24 wk)	EPO β Q2W 102/104	EPO β QW 101/103	CKD 5D: HD	36%/333 ng/mL (36%/339 ng/mL)	67.8 IU/kg (71.8 IU/kg)	11.4 (11.4)	11.41 (11.38)	11.38 (11.32)	+0.04 (+0.06)	Non-inf[246]	Good
Difference between groups in mean Hb, g/dL										11.4 (11.4)	0.028 (-0.21; 0.26)	---	Good
ΔHb g/dL	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α QW 125/125	29 mL/min (30 mL/min)	552.74 pmol/L (573.81 pmol/L)	6662 IU/wk (5035 IU/wk)	9.81 (9.71)	11.1 (11.3)	9.81 (9.71)	1.27 (1.59)	---	Good
Difference of least squares means	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α QW 125/125	29 mL/min (30 mL/min)	552.74 pmol/L (573.81 pmol/L)	6662 IU/wk (5035 IU/wk)	9.81 (9.71)	11.1 (11.3)	9.81 (9.71)	-0.43 (-0.17)	---	Good
ΔHb g/dL	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO QW 108/108	29 mL/min (28 mL/min)	518.60 pmol./L (513.97 pmol/L)	4529 IU/wk (2967 IU/wk)	11.12 (11.03)	11.0 (11.0)	11.12 (11.03)	-0.10 (-0.02)	Non-inf[247]	Good
Difference in Hb at 16 wks, g/dL	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 20,000 units Q2W 131/131	EPO α 10,000 units QW 130/130	nd	26%/179 (25% /198)	9,681 U (9,265 U)	11.9 (11.9)	11.9 (12.2)	11.9 (11.9)	+0.3 (-0.6, 0.1)	0.001[248]	Fair
Mean ΔHb g/dL											0.0 (0.3)	nd	Fair
ESA dose													

[246] The 2 treatment schedules were considered to have similar efficacy if mean Hb level in group 2w did not differ by more than +/-0.5 g/dL compared with group 1w during the assessment period

[247] The lower limit of the 95% CI for the estimated treatment difference for both comparisons, Q2W (-0.208; 0.153) vs. QW, and Q4W (-0.249; 0.063) vs. QW, was above the prespecified noninferiority margin of -1 g/dL. These analyses were adjusted for the baseline Hb level.

[248] One-sided p-value testing non-inferiority from QW

Outcome	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT/Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Mean cumulative EPO doses/wk	Mircescu 2006 UI16931218 Romania	12 wk (24 wk)	EPO β Q2W 102/104	EPO β QW 101/103	CKD 5D: HD	36%/333 ng/mL (36%/339 ng/mL)	67.8 IU/kg (71.8 IU/kg)	11.4 (11.4)	11.41 (11.38)	70.8 (72.5)	+0.957 (+0.991)	---	Good
Ratio of Q2W to QW mean cumulative EPO doses										70.8 (72.5)	0.94 (0.81; 1.08)	Non-inf[249]	Good
Q4W vs. QW													
QoL													
Mean ΔLASA energy score	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 40,000 units Q4W 126/126	EPO α 10,000 units QW 130/130	nd	25%/227 (25%/198)	9,748 U (9,265 U)	11.9 (11.9)	11.4 (12.2)	49.1 (48.3)	6.1 (6.8)	nd	Fair
Mean ΔLASA activity score										52.2 (49.1)	5.0 (4.6)	nd	Fair
Mean ΔLASA overall QOL score										59.5 (58.7)	1.6 (3.3)	nd	Fair
Mean Δtotal KDQ score										22.8 (21.7)	-0.2 (1.1)	nd	Fair
Hb													
ΔHb g/dL	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q4W 215/215	EPO QW 108/108	28 mL/min (28 mL/min)	558.97 pmol/L (513.97 pmol/L)	5423 IU/wk (2967 IU/wk)	11.17 (11.03)	11.0 (11.0)	11.17 (11.03)	-0.19 (-0.02)	Non-inf[250]	Good
Difference in Hb at 16 wks, g/dL	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 40,000 units Q4W 126/126	EPO α 10,000 units QW 130/130	nd	25%/227 (25%/198)	9,748 U (9,265 U)	11.9 (11.9)	11.4 (12.2)	11.9 (11.9)	+0.8 (-1.2, -0.5)	0.008[251]	Fair
Mean ΔHb g/dL											-0.5 (0.3)	nd	Fair

[249] A range of 0.8 to 1.25 for the ratio is considered sufficient to define bioequivalence. Equivalence of drug use in the 2 arms was accepted if the entire 95% CI for this ratio was within these limits

[250] The lower limit of the 95% CI for the estimated treatment difference for both comparisons, Q2W (-0.208; 0.153) vs. QW, and Q4W (-0.249; 0.063) vs. QW, was above the prespecified noninferiority margin of -1 g/dL. These analyses were adjusted for the baseline Hb level.

[251] One-sided p-value testing non-inferiority from QW

Supplemental Table 28. Summary table of adverse events in RCTs examining different dosing schedules in CKD patients with anemia

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Q2W vs. Q4W												
Any AE	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol-EPO β Q2W 223/223	Methoxy polyethylene glycol- EPO β Q4W 224/224	CKD 5D	27%/453 µg/L (28%/522 µg/L)	Median 57µg/2 wk (175 µg/4 wk)	119.7 g/L (118.5 g/L)	118.0 g/L (116.1 g/L)	Diarrhea, nasopharyngitis HTN, AV graft thrombosis, upper respiratory tract infection, headache, fluid overload, muscle spasms	203 (92%) [202 (92%)]	NS[252]
SAEs										Sepsis, pneumonia, AV graft thrombosis	5 (2%) [6 (3%)]	NS[253]
AEs leading to D/C										Adverse events leading to withdrawal	9 (4%) [6 (3%)]	NS[254]
AEs related to treatment										Judged to be related to treatment	12 (5%) [10 (5%)]	NS[255]
SAEs related to treatment										Judged to be related to treatment	3 (1%) [2 (1%)]	NS[256]
Thromboembolic vascular events	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO Q4W 215/215	29 mL/min (28 mL/min)	519 pmol/L (559 pmol/L)	4529 IU/wk (5423 IU/wk)	11.12 (11.17)	11.0 (11.0)	Clinical safety events	5 (5%) [7 (3%)]	NS[257]
Treatment emergent AEs										HTN, UTI, edema, and hyperkalemia	77 (72%) [170 (79%)]	NS[258]

[252] Calculated by ERT
[253] Calculated by ERT
[254] Calculated by ERT
[255] Calculated by ERT
[256] Calculated by ERT
[257] Calculated by ERT
[258] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
SAEs										Most commonly reported: CHF, acute renal failure, chest pain, and anemia	28 (26%) [56 (26%)]	NS[259]
D/C										D/C from the study	15 (14%) [41 (19%)]	NS[260]
AEs leading to study D/C										D/C from the study because of an AE	4 (4%) [11 (5%)]	NS[261]
Hypertension	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	C.E.R.A Q4W 191/191	CKD 5D: HD & PD	30%/418 ng/mL (28%/427 ng/mL)	56 µg/2wk (150 µg/4wk)	11.70 (11.66)	11.70 (11.46)	---	27 (14%) [30 (16%)]	---
Procedural hypertension										---	17 (9%) [29 (15%)]	---
Any AE										---	171 (90%) [177 (93%)]	---
Serious AE										---	70 (37%) [73 (38%)]	---
AE leading to D/C										---	1 (1%) [0 (0%)]	---
SAE [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	C.E.R.A. Q4W 72/72	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	None considered to be treatment related	11[262] (15%) [11 (15%)]	NS (0.972)
AE related to study medication [safety]										Related to study medication	1 (1%) [0 (0%)][263]	nd

[259] Calculated by ERT
[260] Calculated by ERT
[261] Calculated by ERT
[262] Event rate calculated by ERT
[263] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Any AE [safety]										At least 1 AE mild or moderate in intensity	48 (67%) [46 (64%)][264]	NS (0.814)
HTN [safety]										nd	1 (1%) [3 (4%)][265]	NS (0.330)
HTN	Provenzano 2005 US UI16114787	16 wks (16 wks)	Epoetin α 20,000 units Q2W 130/131	Epoetin α 40,000 units Q4W 124/126	nd	26% /179 (25%/227)	9,681 U (9,748 U)	11.9 (11.9)	11.9 (11.4)	nd	8 (6%) [9 (7%)]	NS
Drug D/C										Withdrew from the study due to adverse events	3 (2%) [5 (4%)]	NS
Q2W vs. Q3W												
HTN	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 20,000 units Q2W 130/131	Epoetin α 30,000 units Q3W 131/132	nd	26% /179 (26%/205)	9,681 U (9,489 U)	11.9 (11.9)	11.9 (11.2)	nd	8 (6%) [9 (7%)]	NS
Drug D/C										Withdrew from the study due to adverse events	3 (2%) [5 (4%)]	NS
Q3W vs. Q4W												
HTN	Provenzano 2005 UI16114787 US	16 wks (16 wks)	Epoetin α 30,000 units Q3W 131/132	Epoetin α 40,000 units Q4W 124/126	nd	26%/205 (25%/227)	9,489 U (9,748 U)	11.9 (11.9)	11.2 (11.4)	nd	9 (7%) [9 (7%)]	NS
Drug D/C										Withdrew from the study due to adverse events	5 (4%) [5 (4%)]	NS
Q4W vs. QW-TIW												

[264] Calculated by ERT
[265] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Any AE	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q4W 224/224	EPO α or β 1-3X/wk 226/226	CKD 5D	28%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	118.5 g/L (119.1 g/L)	116.1 g/L (118.2 g/L)	Diarrhea, nasopharyngitis HTN, AV graft thrombosis, upper respiratory tract infection, headache, fluid overload, muscle spasms	202 (92%) [214 (95%)]	NS[266]
SAEs										Sepsis, pneumonia, AV graft thrombosis	6 (3%) [9 (4%)]	NS[267]
AEs leading to withdrawal										Adverse events leading to withdrawal	6 (3%) [1 (0.4%)]	NS[268]
AEs related to treatment										Judged to be related to treatment	10 (5%) [4 (2%)]	NS[269]
SAEs related to treatment										Judged to be related to treatment	2 (1%) [1 (0.4%)]	NS[270]
Q2W vs. QW-TIW												

[266] Calculated by ERT
[267] Calculated by ERT
[268] Calculated by ERT
[269] Calculated by ERT
[270] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Any AE	Levin 2007 UI17950856 Multi	52 wks (52 wks)	Methoxy polyethylene glycol- EPO β Q2W 223/223	EPO α or β 1-3X/wk 226/226	CKD 5D	27%/453 µg/L (31%/522 µg/L)	Median 57µg/2 wk (10,800 IU/wk)	119.7 g/L (119.1 g/L)	118.0 g/L (118.2 g/L)	Diarrhea, nasopharyngitis HTN, AV graft thrombosis, upper respiratory tract infection, headache, fluid overload, muscle spasms	203 (92%) [214 (95%)]	NS[271]
SAEs										Sepsis, pneumonia, AV graft thrombosis	5 (2%) [9 (4%)]	NS[272]
AEs leading to withdrawal										Adverse events leading to withdrawal	9 (4%) [1 (0.4%)]	NS[273]
AEs related to treatment										Judged to be related to treatment	12 (5%) [4 (2%)]	NS[274]
SAEs related to treatment										Judged to be related to treatment	3 (1%) [1 (0.4%)]	NS[275]
Total AEs	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	29 mL/min (31 mL/min)	553pmol/L (510 pmol/L)	6662 IU/wk (5039 IU/wk)	9.81 (9.63)	11.1 (11.4)	AEs that occurred after the first dose of study drug	107 (86%) [98 (80%)	NS[276]
Drug related AEs										Possible, probable, or very likely related to study drug	15 (12%) [11 (9%)	NS[277]

[271] Calculated by ERT
[272] Calculated by ERT
[273] Calculated by ERT
[274] Calculated by ERT
[275] Calculated by ERT
[276] Calculated by ERT
[277] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
SAEs										Cardiac failure congestive, CRF, hypoglycemia, MI, AKI, pneumonia, GI heme, hip fracture, dehydration, syncope, UTI, anemia, chest pain, DVT, dyspnea, fall, diarrhea, osteoarthritis, upper GI heme	42 (34%) [36 (29%)	NS[278]
Confirmed thromboembolic vascular events										---	8 (6%) [2 (2%)	NS[279]
AEs leading to study D/C										---	5 (4%) [3 (2%)	NS[280]
QW vs. QW or TIW												
Total AEs	Locatelli 2008 UI18587731 Multi	28 wks (28 wks)	EPO α QW 213/217	IV Darbepoetin α QW or EPO α TIW 68/70	CKD 5D: HD	31%/402 ng/mL (32%/402 ng/mL)	6.791 IU/wk (6.210 IU/wk)	11.57 (11.57)	10.92 (11.64)	---	157 (72%) [50 (71%)]	NS
Mild events										---	109[281] (51%) [34 (50%)]	NS[282]
Moderate events										---	89[283] (42%) [23 (34%)]	NS[284]

[278] Calculated by ERT
[279] Calculated by ERT
[280] Calculated by ERT
[281] Calculated by ERT
[282] Calculated by ERT
[283] Calculated by ERT
[284] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Marked events	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α QW 125/125	EPO α TIW (22wk), then QW (22wk) 123/123	30 mL/min (31 mL/min)	573.81 pmol/L (510.23 pmol/L)	5035 IU/wk (5039 IU/wk)	9.71 (9.63)	11.3 (11.4)	---	32[285] (15%) [11 (16%)]	NS[286]
AEs considered possibly related to study treatment										---	0 (0%) [1 (2%)]	---
AEs considered possibly related to study treatment										Hb >14 g/dL, anemia, reduction in Hb, increase in Hb and asthenia	11/402 3/123	NS[287]
SAEs										nd	54 (25%) [16 (23%)]	NS[288]
Total AEs										AEs that occurred after the first dose of study drug	98 (78%) [98 (80%)	NS[289]
Drug related AEs										Possible, probable, or very likely related to study drug	11 (9%) [11 (9%)	NS[290]

[285] Calculated by ERT
[286] Calculated by ERT
[287] Calculated by ERT
[288] Calculated by ERT
[289] Calculated by ERT
[290] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
SAEs										Cardiac failure congestive, CRF, hypoglycemia, MI, AKI, pneumonia, GI heme, hip fracture, dehydration, syncope, UTI, anemia, chest pain, DVT, dyspnea, fall, diarrhea, osteoarthritis, upper GI heme	41 (33%) [36 (29%)	NS[291]
Confirmed thromboembolic vascular events										---	5 (4%) [2 (2%)	NS[292]
AEs leading to study D/C										---	3 (2%) [3 (2%)	NS[293]
SAEs										nd	22 (27%) [30 (34%)]	NS[295]
AEs	Locatelli 2002 UI12087569 EU	24 wks (24 wks)	SC EPO β QW 75/84	SC EPO β TIW 71/89	5D: HD	26%/422 ng/mL (27%/461 ng/mL)	81 IU/kg (78 IU/kg)	Hct 33.1% (33.3%)	Hct 33% (33.2%)[294]	Hypotension, HTN, pain in extremity, diarrhea, cough, muscle cramps, headache, pruritis, upper respiratory tract infection	46 (55%) [47 (53%)]	NS[296]

[291] Calculated by ERT
[292] Calculated by ERT
[293] Calculated by ERT
[294] Estimated from graph
[295] Calculated by ERT
[296] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Q3W vs. QW												
HTN	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 30,000 units Q3W 132/132	EPO α 10,000 units QW 130/130	nd	26%/205 (25%/198)	9, 489 U (9, 265 U)	11.9 (11.9)	11.2 (12.2)	nd	9 (7%) [9 (7%)]	NS
Drug D/C										Withdrew from the study due to adverse events	5 (4%) [3 (2%)]	NS
Q2W vs. QW												
Total AEs	Pergola 2009 UI19808215 US	44 wks (44 wks)	EPO α Q2W 125/125	EPO α QW 125/125	29 mL/min (30 mL/min)	552.74 pmol/L (573.81 pmol/L)	6662 IU/wk (5035 IU/wk)	9.81 (9.71)	11.1 (11.3)	AEs that occurred after the first dose of study drug	107 (86%) [98 (78%)	NS[297]
Drug related AEs										Possible, probable, or very likely related to study drug	15 (12%) [11 (9%)	NS[298]
SAEs										Cardiac failure congestive, CRF, hypoglycemia, MI, AKI, pneumonia, GI heme, hip fracture, dehydration, syncope, UTI, anemia, chest pain, DVT, dyspnea, fall, diarrhea, osteoarthritis, upper GI heme	42 (34%) [41 (33%)	NS[299]

[297] Calculated by ERT
[298] Calculated by ERT
[299] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Confirmed thromboembolic vascular events										---	8 (6%) [5 (4%)	NS[i300]
AEs leading to study D/C										---	5 (4%) [3 (2%)	NS[301]
Thromboembolic vascular events										Clinical safety events	5 (5%) [3 (3%)]	NS[302]
Treatment emergent AEs										HTN, UTI, edema, and hyperkalemia	77 (72%) [84 (78%)]	NS[303]
SAEs	Pergola 2010 UI20185602 US	37 wks (37 wks)	EPO Q2W 107/107	EPO QW 108/108	29 mL/min (28 mL/min)	518.60 pmol./L (513.97 pmol/L)	4529 IU/wk (2967 IU/wk)	11.12 (11.03)	11.0 (11.0)	Most commonly reported: CHF, acute renal failure, chest pain, and anemia	28 (26%) [24 (22%)]	NS[304]
D/Cs										D/C from the study	15 (14%) [13 (12%)]	NS[305]
AEs leading to study D/C										D/C from the study because of an AE	4 (4%) [3 (3%)]	NS[306]
HTN	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 20,000 units Q2W 131/131	EPO α 10,000 units QW 130/130	nd	26%/179 (25% /198)	9,681 U (9,265 U)	11.9 (11.9)	11.9 (12.2)	nd	8 (6%) [9 (7%)]	NS
Drug D/C										Withdrew from the study due to adverse events	5 (4%) [3 (2%)]	NS
Q4W vs. QW												
Thromboembolic vascular events	Pergola 2010 UI20185602	37 wks (37 wks)	EPO Q4W 215/215	EPO QW 108/108	28 mL/min (28 mL/min)	558.97 pmol/L	5423 IU/wk (2967 IU/wk)	11.17 (11.03)	11.0 (11.0)	Clinical safety events	7 (3%) [3 (3%)]	NS[307]

[300] Calculated by ERT
[301] Calculated by ERT
[302] Calculated by ERT
[303] Calculated by ERT
[304] Calculated by ERT
[305] Calculated by ERT
[306] Calculated by ERT
[307] Calculated by ERT

Adverse Event	Author, Year, Country,	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline Stat / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Treatment emergent AEs	US					(513.97 pmol/L)				HTN, UTI, edema, and hyperkalemia	170 (79%) [84 (78%)]	NS[308]
SAEs										Most commonly reported: CHF, acute renal failure, chest pain, and anemia	56 (26%) [24 (22%)]	NS[309]
D/C										D/C from the study	41 (19%) [13 (12%)]	NS[310]
AEs leading to study D/C										D/C from the study because of an AE	11 (5%) [3 (3%)]	NS[311]
HTN	Provenzano 2005 UI16114787 US	16 wks (16 wks)	EPO α 40,000 units Q4W 126/126	EPO α 10,000 units QW 130/130	nd	25%/227 (25%/198)	9,748 U (9,265 U)	11.9 (11.9)	11.4 (12.2)	nd	9 (7%) [9 (7%)]	NS
Drug D/C										Withdrew from the study due to adverse events	5 (4%) [3 (2%)]	NS

[308] Calculated by ERT
[309] Calculated by ERT
[310] Calculated by ERT
[311] Calculated by ERT

Supplemental Table 29. Evidence profile of RCTs examining ESA vs. ESA in CKD patients with anemia

Outcome	# of studies and study design	Total N (treatment)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	15 RCTs (High)	5719 (3000)	No limitations (0)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Moderate	Insufficient evidence	Critical
CV mortality	1 RCT (High)	324 (162)	No limitations (0)	NA	Direct (0)	Sparse (-1) Imprecision (-1)	Low	Insufficient evidence	Critical
CV events	1 RCT (High)	522 (347)	Serious limitations (-2)	NA	Direct (0)	Imprecision (-1)	Very Low	Insufficient evidence	Critical
ESRD	0 RCTs	--	--	--	--	--	--	--	Critical
Transfusion	17 RCTs (High)	6590 (3527)	Some limitations (-1)	No important inconsistencies (0)	Direct (0)	Imprecision (-1)	Low	Insufficient evidence	High
QoL	1 RCT (High)	324 (162)	Some limitations (-1)	NA	Direct (0)	Sparse (-1)	Low	Possible benefit for darbepoetin alfa for Physical Role and Vitality vs. C.E.R.A.[312]	High
Hb (categorical)	13 RCTs (High)	5006 (2786)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference	Moderate
Hb (continuous)	16 RCTs (High)	5763 (3099)	No limitations (0)	No important inconsistencies (0)	Direct (0)	None (0)	High	No difference	Moderate
ESA dose (categorical)	4 RCT (High)	1608 (715)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	No difference	Moderate
ESA dose (continuous)	7 RCTs (High)	3102 (1796)	No limitations (0)	NA	Direct (0)	Sparse (-1)	Moderate	No difference[313]	Moderate
Adverse events	16 RCTs (High)	6285 (3514)						No difference in major adverse events	Moderate
Total	18 RCTs	7032 (3807)							

Balance of potential benefits and harms:
Insufficient evidence for important clinical outcomes.
No difference for Hb response.

Quality of overall evidence:
Low

[312] Statistical comparisons were not performed.
[313] EPO is better if C.E.R.A. is given every four weeks but not for C.E.R.A given every two weeks.

Supplemental Table 30. Summary table of RCTs examining ESA vs. ESA in CKD patients with anemia (categorical outcomes)

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Darbepoetin vs. EPO													
Mortality													
Death	Nissenson 2002 UI12087569 US & Canada	28 wks (28 wks)	IV Darbepoetin α QW + placebo 169/169	IV EPO TIW+ placebo 335/335	5D: HD	32%/411ng/mL (32%/425 ng/mL)	14,177 U/wk (13,576 U/wk)	11.2 (11.2)	11.36 (12.8)	9 (5%) [23 (7%)]	RR 0.78[314] (0.37; 1.64)	NS	Fair
Death	Tolman 2005 UI15788469 UK	9 mo (9 mo)	SC Darbepoetin α QW 112/112	SC EPO β TIW 105/105	5D: HD	478 µg/L (499 µg/L)	Median 91 IU/kg/wk (79 IU/kg/wk)	11.86 (11.73)	11.9 (11.5)	13 (12%) [11 (10%)]	RR 1.11 (0.52; 2.36)	NS	Fair
Death	Vanrenterghem 2002 UI12427142 Multi	52 wk (52 wk)	Darbepoetin α 347/347	rHuEPO 175/175	5D: HD, PD	305.8 µg/L (288.7 µg/L)	6000 IU/wk (6000 IU/wk)	11.0 (11.0)	11.5 (11.0)	41 12%) [11 (6%)]	RR 1.86[315] (0.98;3.53)	NS (0.062)	Fair
		2 y (52 wk)								25% [21%]	--	nd	Fair
Annualized death rate										13% [11%]	--	NS	Fair
CV events													
Cerebrovascular disorder	Vanrenterghem 2002 UI12427142 Multi	52 wk (52 wk)	Darbepoetin α 347/347	rHuEPO 175/175	5D: HD, PD	305.8 µg/L (288.7 µg/L)	6000 IU/wk (6000 IU/wk)	11.0 (11.0)	11.5 (11.0)	2% (1%)	--	nd	Poor
MI										2% (1%)	--	nd	Poor
Transient ischemic attack										0% (1%)	--	nd	Poor
Transfusion													
Transfusions	Nissenson 2002 UI12087569 US & Canada	28 wks (28 wks)	IV Darbepoetin α QW + placebo 169/169	IV EPO TIW+ placebo 335/335	5D: HD	32%/411ng/mL (32%/425 ng/mL)	14,177 U/wk (13,576 U/wk)	11.2 (11.2)	11.36 (12.8)	16 (10%) [37 (11%)]	RR 0.86[316] (0.49; 1.50)	NS	Fair
Transfusions	Tolman 2005 UI15788469 UK	9 mo (9 mo)	SC Darbepoetin α QW 112/112	SC EPO β TIW 105/105	5D: HD	478 µg/L (499 µg/L)	Median 91 IU/kg/wk (79 IU/kg/wk)	11.86 (11.73)	11.9 (11.5)	8 (10%) [11 (14%)]	RR 0.73 (0.31; 1.71)	NS	Fair
Transfusions	Vanrenterghem 2002 UI12427142 Multi	2 y (52 wk)	Darbepoetin α 347/347	rHuEPO 175/175	5D: HD, PD	305.8 µg/L (288.7 µg/L)	6000 IU/wk (6000 IU/wk)	11.0 (11.0)	11.5 (11.0)	4% [5%]	--	nd	Fair

[314] Calculated by ERT
[315] Calculated by ERT
[316] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
ESA dose													
%Dose changes	Nissenson 2002 UI12087569 US & Canada	28 wks (28 wks)	IV Darbepoetin α QW + placebo 169/169	IV EPO TIW+ placebo 335/335	5D: HD	32%/411ng/mL (32%/425 ng/mL)	14,177 U/wk (13,576 U/wk)	11.2 (11.2)	11.36 (12.8)	74 (44%) [164 (49%)]	RR 0.89 (0.73; 1.10)	NS	Fair
EPO ζ vs. EPO α													
Mortality													
Total all cause mortality	Krivoshiev 2008 UI18394266 EU	24 wks (24 wks)	EPO ζ 300/305	EPO α 298/304	CKD 5D: HD	---	182.20 IU/kg/wk (166.14 IU/kg/wk)	8.07 (8.04)	11.60 (11.61)	13 (4%) [16 (5%)]	RR 0.81[317] (0.40;1.65)	NS	Good
Mortality possibly related to drug										1 (0.3%) [0 (0%)]	---	---	Good
Death [safety]	Krivoshiev 2010 UI20369312 Multi	28 wks (28 wks)	EPO ζ 232/232	EPO α 230/230	CKD 5D: HD	nd	97.0 IU/kg/wk (86.0 IU/kg/wk)	10.56 (10.40)	10.94 (11.02)	16 (7%) [7 (3%)]	RR 2.27 (0.95, 5.40)[318]	NS (0.065)	Good
Transfusion													
Transfusion	Krivoshiev 2008 UI18394266 EU	24 wks (24 wks)	EPO ζ 273/305	EPO α 268/304	CKD 5D: HD	---	182.20 IU/kg/wk (166.14 IU/kg/wk)	8.07 (8.04)	11.60 (11.61)	10 (4%) [13 (5%)]	RR 0.76[319] (0.34;1.69)	NS	Good
Transfusion	Wizemann 2008 UI18208642 Germany & Poland	24 wk (24 wk)	EPO ζ 239/313	EPO α 239/313	CKD 5D: HD	---	---	11.6 (11.7)	11.35 (11.54)	3 (1%) [2 (1%)]	RR 1.50[320] (0.25; 8.90)	NS	Good
Transfusions [PP]	Krivoshiev 2010 UI20369312 Multi	28 wks (28 wks)	EPO ζ 154/232	EPO α 165/230	CKD 5D: HD	nd	97.0 IU/kg/wk (86.0 IU/kg/wk)	10.56 (10.40)	10.94 (11.02)	2 (1%) [1 (1%)]	RR 2.14 (0.20, 23.40)[321]	NS (0.532)	Good

[317] Calculated by ERT
[318] Calculated by ERT
[319] Calculated by ERT
[320] Calculated by ERT
[321] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Hb													
Hb maintenance success[322]	Krivoshiev 2008 UI18394266 EU	24 wks (24 wks)	EPO ζ 273/305	EPO α 268/304	CKD 5D: HD	---	182.20 IU/kg/wk (166.14 IU/kg/wk)	8.07 (8.04)	11.60 (11.61)	236 (86%) [227 (85%)]	95% CI [test-reference] (-4.2%; 7.7%)	NS	Good
Hb treatment success[323]										230 (84%) [230 (86%)]	RR 0.98[324] (0.91; 1.05)	NS	Good
Permanent ∆Hb >1 g/dL	Wizemann 2008 UI18208642 Germany & Poland	24 wk (24 wk)	EPO ζ 239/313	EPO α 239/313	CKD 5D: HD	---	---	11.6 (11.7)	11.35 (11.54)	11% [11%]	--	NS	Good
Transient ∆Hb >1g/dL										132 (55%) [134 (56%)]	RR 0.99[325] (0.84; 1.16)	NS	Good
Patients with Hb values outside the target range										161 (67%) [152 (64%)]	RR 1.06[326] (0.91; 1.24)	NS	Good
Hb values outside the target range [PP]	Krivoshiev 2010 UI20369312 Multi	28 wks (28 wks)	EPO ζ 154/232	EPO α 165/230	CKD 5D: HD	nd	97.0 IU/kg/wk (86.0 IU/kg/wk)	10.56 (10.40)	10.94 (11.02)	134 (87%) [143 (87%)]	RR 1.00 (0.92, 1.09)[327]	NS (0.927)	Good
Permanent ∆Hb >1 g/dL [PP]										66 (43%) [59 (36%)]	RR 1.18 (0.90, 1.56)[328]	NS (0.238)	Good
Transient ∆Hb >1 g/dL [PP]										131 (85%) [148 (90%)]	RR 0.95 (0.87, 1.03)[329]	NS (0.216)	Good
Hb>13 g/dL [safety]			EPO ζ 232/232	EPO α 230/230						180 (78%) [174 (76%)]	RR 1.03 (0.93, 1.13)[330]	NS (0.624)	Good

[322] Hb concentration of ≥11.0 ±1.0 g/dL for at least 4 consecutive weeks
[323] Hb concentration of ≥11.0-12.0 g/dL for 2 consecutive weeks without any blood transfusion within the preceding 3 months
[324] Calculated by ERT
[325] Calculated by ERT
[326] Calculated by ERT
[327] Calculated by ERT
[328] Calculated by ERT
[329] Calculated by ERT
[330] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
ESA dose													
Permanent ∆EPO dose	Wizemann 2008 UI18208642 Germany & Poland	24 wk (24 wk)	EPO ζ 239/313	EPO α 239/313	CKD 5D: HD	---	---	11.6 (11.7)	11.35 (11.54)	94 (39%) [98 (41%)]	RR 0.96[331] (0.77; 1.19)	NS	Good
Transient ∆EPO dose										141 (59%) [155 (65%)]	RR 0.91[332] (0.75; 1.05)	NS	Good
Permanent dosage changes [PP]	Krivoshiev 2010 UI20369312 Multi	28 wks (28 wks)	EPO ζ 154/232	EPO α 165/230	CKD 5D: HD	nd	97.0 IU/kg/wk (86.0 IU/kg/wk)	10.56 (10.40)	10.94 (11.02)	135 (88%) [136 (82%)]	RR 1.06 (0.97, 1.17)[333]	NS (0.190)	Good
Transient dosage changes [PP]										139 (90%) [141 (86%)]	RR 1.06 (0.97, 1.15)[334]	NS (0.189)	Good
EPO θ vs. EPO β													
Mortality													
All cause mortality [ITT]	Gertz, 2010 UI20812790 Multi	13-24 wk (24 wk)	EPO θ 180/180	EPO β 90/90	CKD 5D: HD	nd	102.5 IU/kg (97.5 IU/kg)	10.87 (10.87)	10.60 (10.66)	10 (6%) [7 (8%)]	RR 0.71 (0.28, 1.81)	NS	Good
Transfusion													
Transfusion requirement [ITT]	Gertz, 2010 UI20812790 Multi	13-24 wk (24 wk)	EPO θ 180/180	EPO β 90/90	CKD 5D: HD	nd	102.5 IU/kg (97.5 IU/kg)	10.87 (10.87)	10.60 (10.66)	7 (4%) [4 (4%)]	RR 0.88 (0.26, 2.91)	NS	Good
Hb													
%Hb values w/in range (baseline ±1 g/dL and 9.5-12.0 g/dL), per pt [PP]	Gertz, 2010 UI20812790 Multi	13-24 wk (24 wk)	EPO θ 150/180	EPO β 74/90	CKD 5D: HD	nd	102.5 IU/kg (97.5 IU/kg)	10.87 (10.87)	10.60 (10.66)	66% [67%]	Ratio 0.99 (0.87, 1.13)	NS	Good

[331] Calculated by ERT
[332] Calculated by ERT
[333] Calculated by ERT
[334] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Hb values w/in range (baseline ±1 g/dL and 9.5-12.0 g/dL), % pts/wk [PP]										59-72%, (60-74%)	--	NS	Fair
HX575 vs. EPO α													
Transfusion													
Transfusions	HaagWeber 2009 UI19863881 Germany & Austria	24-28 wk (≥ 54 wk)	HX575 203/314	EPO α 114/164	CKD 5D: HD	25%/677 ng/mL (26%/672 ng/mL)	6906 IU/wk (6477 IU/wk)	11.7 (12.0)	11.7 (11.9)	15 (7%) [8 (7%)]	RR 0.99 (0.43; 2.29)	NS	Fair
Hb													
Responders definition I[335]	HaagWeber 2009 UI19863881 Germany & Austria	24-28 wk (≥24 wk)	HX575 304/314	EPO α 161/164	CKD 5D: HD	25%/677 ng/mL (26%/672 ng/mL)	6906 IU/wk (6477 IU/wk)	11.7 (12.0)	11.7 (11.9)	81% [84%]	---	---	Fair
Responders definition II[336]										70% [64%]	---	---	Fair
C.E.R.A. vs. EPO													
Mortality													
Death	Spinowitz 2009 UI18004064 Multi	36 wks (36 wks)	C.E.R.A. Q2W 123/168	EPO QW-TIW 133/168	CKD 5D: HD & PD	29%/515 ng/mL (30%/482 ng/mL)	60 µg/2wk (7,310 IU/wk)	11.85 (11.83)	11.99 (11.82)	7 (4%) [10 (6%)]	RR 0.76 (0.30; 1.93)[337]	NS	Good
Deaths	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191	CKD 5D: HD & PD	30%/418 ng/mL (31%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	13 (7%) [12 (6%)]	RR 1.09[338] (0.51; 2.33)	---	Fair
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		28%/427 ng/mL (31%/435 ng/mL)	150 µg/4wk (5500 IU/wk)	11.66 (11.65)	11.46 (11.52)	18 (10%) [12 (6%)]	RR 1.50[339] (0.74; 3.03)	---	

[335] Patients with mean Hb value during the baseline and evaluation periods within the target range of 10.0–13.0 g/dL
[336] Responders according to Definition I with mean weekly epoetin dosages during baseline and evaluation periods differing by ≤ 25%
[337] Calculated by ERT
[338] Calculated by ERT
[339] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Deaths	Levin 2007 UI17950856 Multi	52 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226	CKD 5D: HD & PD	27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	19 (9%) [17 (8%)]	RR 1.14[340] (0.61; 2.13)	NS	Good
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	15 (7%) [17 (8%)]	RR 0.90 (0.46; 1.76)	NS	
Transfusion													
RBC transfusion	Spinowitz 2009 UI18004064 Multi	36 wks (36 wks)	C.E.R.A. Q2W 123/168	EPO QW to TIW 133/168	CKD 5D: HD & PD	29%/515 ng/mL (30%/482 ng/mL)	60 µg/2wk (7,310 IU/week)	11.85 (11.83)	11.99 (11.82)	34 (28%) [59 (44%)]	RR 0.62[341] (0.44; 0.88)[342]	NS	Fair
RBC transfusion	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191	CKD 5D: HD & PD	30%/418 ng/mL (31%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	6% [10%]	--	---	Good
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		28%/427 ng/mL (31%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	11% [10%]	--	---	
RBC transfusions	Levin 2007 UI17950856 Multi	52 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226	CKD 5D: HD & PD	27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	21 (10%) [17 (8%)]	RR 1.26[343] (0.69; 2.33)	NS	Good
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	16 (7%) [17 (8%)]	RR 0.96[344] (0.50; 1.86)	NS	

[340] Calculated by ERT
[341] Calculated by ERT
[342] Calculated by ERT
[343] Calculated by ERT
[344] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Hb													
Hb within ±1.0 g/dL of baseline value	Spinowitz 2009 UI18004064 Multi	36 wks (36 wks)	C.E.R.A. Q2W 123/168	EPO QW-TIW 133/168	CKD 5D: HD & PD	29%/515 ng/mL (30%/482 ng/mL)	60 µg/2wk (7,310 IU/week)	11.85 (11.83)	11.99 (11.82)	86[345] (69%) [90 (68%)]	RR 1.03 (0.88; 1.22)[346]	NS	Good
Hb within ±1.0 g/dL of baseline value Maintained Hb 10-13.5 g/dL	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191	CKD 5D: HD & PD	30%/418 ng/mL (31%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	76% [72%]	--	---	Good
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		28%/427 ng/mL (31%/435 ng/mL)	150 µg/4wk (5500 IU/wk)	11.66 (11.65)	11.46 (11.52)	66% [72%]	--	---	
			C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191		30%/418 ng/mL (31%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	92% [88%]	--	---	
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		28%/427 ng/mL (31%/435 ng/mL)	150 µg/4wk (5500 IU/wk)	11.66 (11.65)	11.46 (11.52)	88% [88%]	--	---	
Hb within 10 g/dL of baseline value	Levin 2007 UI17950856 Multi	52 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q2W 196/223	EPO QW-TIW 205/226	CKD 5D: HD & PD	27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	133 (68%) [138 (67%)]	RR 1.01[347] (0.88; 1.15)	NS	Good
			Methoxy polyethylene glycol-EPO β Q4W 188/224	EPO QW-TIW 205/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	127 (68%) [138 (67%)]	RR 1.00[348] (0.87; 1.15)	NS	

[345] Calculated by ERT
[346] Calculated by ERT
[347] Calculated by ERT
[348] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
C.E.R.A. vs. Darbepoetin α													
Mortality													
All cause mortality	Canaud 2008 UI18586762 Multi	52 wk (52 wk)	C.E.R.A. 157/157	Darbepoetin α 156/156	CKD 5D	28%/nd (28%/nd)	0.35 µg/kg/wk (0.44 µg/kg/wk)	12.0 (11.9)	12.1 (11.8)	13 (9%) [12 (8%)]	RR 1.08[349] (0.51; 2.28)	NS	Fair
All cause death	Macdougall 2008 UI18287255 Multi	28 wks (28 wks)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD Stage 3-4	24%/175 µg/L (24%/186 µg/L)	0.34 µg/kg (0.19 µg/kg)	10.2 (10.2)	12.18 (12.01)	8 (5%) [9 (6%)]	RR 0.89[350] (0.35; 2.26)	NS	Good
Death [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	Darbepoetin α QW/Q2W 151/151	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.89)	2 (2%) [6 (4%)]	RR 0.69 (0.14, 3.33)[351]	NS (0.644)	Fair
			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	1 (1%) [6 (4%)]	RR 0.35 (0.04, 2.85)[352]	NS (0.326)	Fair
Death (safety)	Carrera 2010 UI20522670 Multi	52 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q4W 245/245	Darbepoetin α Q2W 244/245	CKD 5D: HD	27%/427 µg/L (27%/446 µg/L)	Median 30.0 µg/wk (20.0 µg/wk)	12.09 g/dL (12.07 g/dL)	11.8 (10.7)[353]	14 (6%) [14 (6%)]	RR 1.00 (0.49, 2.04)[354]	NS	Good
Death (safety)	Roger 2011 UI21505096 Multi	28 wk (20 wk)	C.E.R.A Q4W 153/153	Darbepoetin α QW/Q2W 154/154	CKD Stage 3-4	24%/186 µg/L (23.8%/207 µg/L)	Median 80 µg/4wk (110 µg/4wk)[355]	9.53 g/dL (9.53 g/dL)	11.3 g/dL (11.5 g/dL[356])	4 (3%) [7 (5%)]	RR 0.58 (0.17, 1.92)[357]	NS	Good

[349] Calculated by ERT
[350] Calculated by ERT
[351] Calculated by ERT
[352] Calculated by ERT
[353] Estimated from figure
[354] Calculated by ERT
[355] Estimated from figure
[356] Estimated from figure
[357] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
CV mortality													
CV death	Macdougall 2008 UI18287255 Multi	28 wks (28 wks)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD Stage 3-4	24%/175 µg/L (24%/186 µg/L)	0.34 µg/kg (0.19 µg/kg)	10.2 (10.2)	12.18 (12.01)	7 (4%) [5 (3%)]	RR 1.41[358] (0.46; 4.35)	NS	Good
Transfusion													
Transfusion[359]	Canaud 2008 UI18586762 Multi	52 wk (52 wk)	C.E.R.A. 157/157	Darbepoetin α 156/156	CKD 5D	28.4%/nd (28.0%/nd)	0.35 µg/kg/wk (0.44 µg/kg/wk)	12.0 (11.9)	12.1 (11.8)	19 (12%) [16 (10%)]	RR1.18[360] (0.63; 2.21)	NS	Fair
Transfusion	Macdougall 2008 UI18287255 Multi	28 wks (28 wks)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD Stage 3-4	24%/175 µg/L (24%/186 µg/L)	0.34 µg/kg (0.19 µg/kg)	10.2 (10.2)	12.18 (12.01)	5[361] (3%) [11[362] (7%)	RR 0.45[363] (0.16; 1.28)	NS	Fair
Transfusions [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	**C.E.R.A. Q2W 73/73**	Darbepoetin α QW/Q2W 151/151	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.89)	2 (3%) [4 (3%)]	RR 1.03 (0.19, 5.52)[364]	NS (0.969)	Fair
			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	0 (0%) [4 (3%)]	nd	nd	Fair
Transfusions	Carrera 2010 UI20522670 Multi	52 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q4W 245/245	Darbepoetin α Q2W 244/245	CKD 5D: HD	27%/427 µg/L (27%/446 µg/L)	Median 30.0 µg/wk (20.0 µg/wk)	12.09 g/dL (12.07 g/dL)	11.8 (10.7)[365]	39 (16%) [32 (13%)]	RR 1.21[366] (0.79, 1.87)	NS	Good

[358] Calculated by ERT
[359] At least one RBC transfusion during the dose-titration and evaluation period)
[360] Calculated by ERT
[361] Calculated by ERT
[362] Calculated by ERT
[363] Calculated by ERT
[364] Calculated by ERT
[365] Estimated from figure
[366] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Transfusions	Roger 2011 UI21505096 Multi	28 wk (20 wk)	C.E.R.A Q4W 153/153	Darbepoetin α QW/Q2W 154/154	CKD Stage 3-4	24%/186 µg/L (23.8%/207 µg/L)	Median 80 µg/4wk (110 µg/4wk)[367]	9.53 g/dL (9.53 g/dL)	11.3 g/dL (11.5 g/dL[368])	5 (3%) [10 (7%)]	RR.0.50 (0.18, 1.44)[369]	NS	Good
Hb													
Hb response rate	Macdougall 2008 UI18287255 Multi	28 wks (28 wks)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD Stage 3-4	24%/175 µg/L (24%/186 µg/L)	0.34 µg/kg (0.19 µg/kg)	10.2 (10.2)	12.18 (12.01)	159[370] (98%) [156[371] (96%)	Response rate 95% CI (93.80; 99.32)[372]	Non-inf[373]	Good
Hb levels maintained within ±1 g/dL of the response value [ITT]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	Darbepoetin α QW/Q2W 151/151	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.89)	55 (76%) [103 (68%)]	RR 1.10 (0.93, 1.31)[374]	NS (0.253)	Fair
Hb levels maintained within ±1 g/dL of the response value [ITT]			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	50 (70%) [103 (68%)]	RR 1.12 (0.95, 1.33)[375]	NS (0.188)	Fair
Hb response rate	Carrera 2010 UI20522670	52 wk (52 wk)	Methoxy polyethylene	Darbepoetin α Q2W	CKD 5D: HD	27%/427 µg/L	Median 30.0 µg/wk	12.09 g/dL (12.07 g/dL)	11.8 (10.7)[376]	157 (64%) [99 (40%)]	RR 1.59 (1.33, 1.90)	<0.0001	Good

[367] Estimated from figure
[368] Estimated from figure
[369] Calculated by ERT
[370] Calculated by ERT
[371] Calculated by ERT
[372] The 95% CI for the C.E.R.A. response rate was 93.80 to 99.32%
[373] The lower limit was greater than the predefined 60% response (p<0.0001), it could be concluded that C.E.R.A. once every 2 wk effectively corrected anemia.
[374] Calculated by ERT
[375] Calculated by ERT
[376] Estimated from figure

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
Proportion of patients without Hb response when treated with darbepoetin	Multi		glycol-EPO β Q4W 245/245	245/245		(27%/446 µg/L)	(20.0 µg/wk)			24% (50%)	nd	<0.0001	
Hb response in all patients who completed the study			Methoxy polyethylene glycol-EPO β Q4W 187/245	Darbepoetin α Q2W 148/245						148 (79%) [91 (62%)]	RR 1.29 (1.11, 1.49)[377]	<0.0005	
Hb response in subset of patients entering 2nd treatment period		26 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q4W 216/245	Darbepoetin α Q2W 222/245						157 (73%) [99 (45%)]	RR 1.63[378] (1.39, 1.93)	<0.0001	
Hb response rate	Roger 2011 UI21505096 Multi	28 wk (20 wk)	C.E.R.A Q4W 153/153	Darbepoetin α QW/Q2W 154/154	CKD Stage 3-4	24%/186 µg/L (23.8%/207 µg/L)	Median 80 µg/4wk (110 µg/4wk)[379]	9.53 g/dL (9.53 g/dL)	11.3 g/dL (11.5 g/dL[380])	144 (94%) [144 (94%)]	RR 1.01 (0.95, 1.07)[381]	NS	Good
Median time to Hb response, days										43 [29]	--	nd	
Stable response										105 (69%) [112 (73%)]	RR 0.94 (0.82, 1.09)[382]	NS	
Hb values exceeding 12 g/dL		8 wk (20 wk)								39 (25%) [72 (48%)]	RR 0.55 (0.40, 0.75)[383]	<0.0001	

[377] Calculated by ERT
[378] Calculated by ERT
[379] Estimated from figure
[380] Estimated from figure
[381] Calculated by ERT
[382] Calculated by ERT
[383] Calculated by ERT

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		CKD Stage	Baseline TSAT/ Ferritin Arm 1 (Arm 2)	Median ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Events No (%) Arm 1 [Arm 2]	RR/OR/HR (95% CI)		
ESA dose													
Required dose change to achieve stable Hb	Roger 2011 UI21505096 Multi	28 wk (20 wk)	C.E.R.A Q4W 153/153	Darbepoetin α QW/Q2W 154/154	CKD Stage 3-4	24%/186 µg/L (23.8%/207 µg/L)	Median 80 µg/4wk (110 µg/4wk)[384]	9.53 g/dL (9.53 g/dL)	11.3 g/dL (11.5 g/dL[385])	65 (62%) [64 (57%)]	RR 1.02 (0.79, 1.33)[386]	NS	Good
Mean number of dose changes per patient										1.12 [1.10]	--	nd	
Multiple dose adjustments										10.7% [21.3%]	--	nd	
C.E.R.A vs. C.E.R.A.													
Mortality													
Death [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	**C.E.R.A. Q2W 73/73**	**C.E.R.A. Q4W 72/72**	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	2 (2%) [1 (1%)]	RR 1.97 (0.18, 21.28)[387]	NS (0.576)	Fair
Transfusion													
Transfusions [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	**C.E.R.A. Q2W 73/73**	**C.E.R.A. Q4W 72/72**	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	2 (3%) [0 (0%)]	nd	nd	Fair
Hb													
Hb levels maintained within ±1 g/dL of the response value [ITT]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	**C.E.R.A. Q2W 73/73**	**C.E.R.A. Q4W 72/72**	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	55 (76%) [50 (70%)]	RR 1.08 (0.89, 1.33)[388]	NS (0.428)	Fair

[384] Estimated from figure
[385] Estimated from figure
[386] Calculated by ERT
[387] Calculated by ERT
[388] Calculated by ERT

Supplemental Table 31. Summary table of RCTs examining ESA vs. ESA in CKD patients with anemia (continuous outcomes)

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Darbepoetin vs. EPO													
Hb													
ΔHb, g/dL	Nissenson 2002 UI12087569 US & Canada	28 wks (28 wks)	IV Darbepoetin α QW + placebo 169/169	IV EPO TIW+ placebo 335/335	5D: HD	32%/411ng/mL (32%/425 ng/mL)	14,177 U/wk (13,576 U/wk)	11.2 (11.2)	11.36 (12.8)	11.2 (11.2)	0.16 (1.6)[389]	nd	Fair
Δ Hb level g/dL	Tolman 2005 UI15788469 UK	9 mo (9 mo)	SC Darbepoetin α QW 99/112	SC EPO β TIW 97/105	5D: HD	478 µg/L (499 µg/L)	Median 91 IU/kg/wk (79 IU/kg/wk)	11.86 (11.73)	11.9 (11.5)	11.86 (11.73)	+0.04 (-0.23)	NS (0.08)	Fair
ΔHb, g/dL	Vanrenterghem 2002 UI12427142 Multi	52 wk (52 wk)	Darbepoetin α 347/347	rHuEPO 175/175	5D: HD, PD	305.8 µg/L (288.7 µg/L)	6000 IU/wk (6000 IU/wk)	11.0 (11.0)	11.5 (11.0)	11.0 (11.0)	0.05 (0.00)	nd	Fair
Difference in ΔHb, g/dL											0.05 (-0.14; 0.24)	Non-inf[390]	Fair
Adjusted ΔHb, g/dL											-0.03 (-0.06)	nd	Fair
Difference in adjusted ΔHb, g/dL											0.03 (-0.16; 0.21)	Non-inf[391]	Fair
ESA dose													
Mean difference in ESA doses	Vanrenterghem 2002 UI12427142 Multi	52 wk (52 wk)	Darbepoetin α 347/347	rHuEPO 175/175	5D: HD, PD	305.8 µg/L (288.7 µg/L)	6000 IU/wk (6000 IU/wk)	11.0 (11.0)	11.5 (11.0)	6000 IU/wk (6000 IU/wk)	-0.04 µg/wk (-5.9; 5.2)	nd	Fair
EPO ζ vs. EPO α													
Hb/Hct													
Hb over the last 4 wk of treatment, g/dL	Krivoshiev 2008 UI18394266 EU	24 wks (24 wks)	EPO ζ 273/305	EPO α 268/304	CKD 5D: HD	---	182.20 IU/kg/wk (166.14 IU/kg/wk)	8.07 (8.04)	11.60 (11.61)	8.07 (8.04)	3.54 (3.59)	Non-inf[392]	Good

[389] The lower limit of the two sided 95% CI (DA -0.06; 0.38 and Epoetin -0.6; 3.8) was well above the protocol-specified non-inferiority margin of -1.0 g/dl (-10 g/L) indicating that DA was as effective as epoetin for maintaining Hb concentrations.

[390] The lower limit of the two-sided 95% CI was therefore above the pre-specified non-inferiority margin of –0.5 g/dL whether adjusted (-0.16) or unadjusted (-0.14) for covariates, demonstrating that darbepoetin alfa was as effective as rHuEPO in maintaining the mean hemoglobin in this group of patients. The lower limit of the 95% CI was similar to the PP analysis set whether adjusted (-0.14) or unadjusted (-0.13) for covariates, and was well above the pre-specified non-inferiority margin of –0.5 g/dL.

[391] The lower limit of the two-sided 95% CI was therefore above the pre-specified non-inferiority margin of –0.5 g/dL whether adjusted (-0.16) or unadjusted (-0.14) for covariates, demonstrating that darbepoetin alfa was as effective as rHuEPO in maintaining the mean hemoglobin in this group of patients. The lower limit of the 95% CI was similar to the PP analysis set whether adjusted (-0.14) or unadjusted (-0.13) for covariates, and was well above the pre-specified non-inferiority margin of –0.5 g/dL.

[392] This was within the predefined equivalence range of ±1.0 g/dL, so both products showed equivalent efficacy in increasing low Hb concentrations to achieve target levels.

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Hb, g/dL	Wizemann 2008 UI18208642 Germany & Poland	24 wk (24 wk)	EPO ζ -EPO α 121/155	EPO α -EPO ζ 118/155	CKD 5D: HD	---	---	11.6 (11.7)	11.35 (11.54)	11.6 (11.7)	-0.25 (-0.16)	---	Good
95% CI of intra-individual difference of Hb										Equivalence range +/-0.6	0.09; 0.28	Non-inf[393]	Good
Hct										34.3 (34.4)	0 (+0.47)	---	Good
Hb, g/dL [PP]	Krivoshiev 2010 UI20369312 Multi	28 wks (28 wks)	EPO ζ 154/232	EPO α 165/230	CKD 5D: HD	nd	97.0 IU/kg/wk (86.0 IU/kg/wk)	10.56 (10.40)	10.94 (11.02)	10.56 (10.40)	+0.38 (+0.62)	nd	Good
ESA dose													
EPO ζ dose over last 4 wks of treatment, IU/kg/wk	Krivoshiev 2008 UI18394266 EU	24 wks (24 wks)	EPO ζ 273/305	EPO α 268/304	CKD 5D: HD	---	182.20 IU/kg/wk (166.14 IU/kg/wk)	8.07 (8.04)	11.60 (11.61)	---	182.20 [166.14]	Non-inf[394]	Good
Weekly EPO dose, IU/kg/wk	Wizemann 2008 UI18208642 Germany & Poland	24 wk (24 wk)	EPO ζ -EPO α 121/155	EPO α -EPO ζ 118/155	CKD 5D: HD	---	---	11.6 (11.7)	11.35 (11.54)	---	92.68 (92.58)	---	Good
95% CI of intra-individual difference of EPO dose										Equivalence range +/-45	-4.67; 4.29	Non-inf[395]	Good
EPO θ vs. EPO β													
Hb, g/dL	Gertz, 2010 UI20812790 Multi	13-24 wk (24 wk)	EPO θ 180/180	EPO β 90/90	CKD 5D: HD	nd	102.5 IU/kg (97.5 IU/kg)	10.87 (10.87)	10.60 (10.66)	10.87 (10.87)	-0.27 (-0.20) [Net: -0.08 (-0.30, 0.14)]	NS (0.46)	Good
HX575 vs. EPO α													
Hb													

[393] Level 1 of the strategy was the calculation of the 95% confidence interval (CI) of the intra-individual difference (epoetin zeta compared with epoetin alfa) of the mean Hb level during double-blind treatment with each study drug, and comparison with the predefined acceptance range (± 0.6 g/dL).

[394] These values were within the range of ±45 IU/kg/wk, which takes into account TIW dosing with the minimum clinically effective dose (15IU/kg)

[395] The statistical tests for dose equivalence assumed that a difference in dose of <15 IU/kg would not be clinically significant. This was based on evidence from epoetin alfa dose–response trials that have shown that a dose of 15 IU/kg, administered three times per week, is close to the no-effect dose. On this basis, the equivalence margin was defined as ±45 IU/kg/wk

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Absolute ΔHb, g/dL (PP)	HaagWeber 2009 UI19863881 Germany & Austria	24-28 wk (≥24 wk)	HX575 207/314	EPO α 118/164	CKD 5D: HD	25%/677 ng/mL (26%/672.2 ng/mL)	6649 IU/wk (6236 IU/wk)	11.7 (12.0)	11.8 (12.0)	11.7 (12.0)	0.147 (0.063) Point estimate of difference 0.084 (-0.170; 0.338)	Non-inf[396]	Fair
Absolute ΔHb, g/dL (ITT)										11.7 (12.0)	0.003 (-0.187) Point estimate of difference 0.189 (-0.039; 0.418)	Non-inf[397]	Fair
Range of mean Hb values in Part II		29-56 wk (≥24 wk)	HX575-HX575 304/314	EPO α-HX575 161/164						11.7 (12.0)	11.6-11.9 (11.5-12.1)	---	Fair
C.E.R.A. vs. EPO													
Hb													
Mean ΔHb, g/dL [PP]	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 154/190	EPO QW-TIW 167/191	CKD 5D: HD & PD	30%/418 ng/mL (31%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	11.70 (11.65)	0.032 (-0.109)	---	Good
			C.E.R.A. Q4W 153/191	EPO QW-TIW 167/191		28%/427 ng/mL (31%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	11.66 (11.65)	-0.131 (-0.109)	---	
Difference in mean Δ Hb between			C.E.R.A. Q2W 154/190	EPO QW-TIW 167/191		30%/418 ng/mL (31%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	11.70 (11.65)	0.141 (-0.098; 0.380)	Non-inf[398]	

[396] Therapeutic equivalence of HX575 to the comparator epoetin-α was considered to be demonstrated if the 95% confidence interval (CI) of the difference in mean changes in Hb levels between treatment groups lay within the interval of ± 0.5 g/dL.

[397] Therapeutic equivalence of HX575 to the comparator epoetin-α was considered to be demonstrated if the 95% confidence interval (CI) of the difference in mean changes in Hb levels between treatment groups lay within the interval of ± 0.5 g/dL.

[398] The lower limit of the 97.5% CI was therefore well above the prespecified margin of -0.75 g/dL in both groups, demonstrating that once-monthly or twice-monthly C.E.R.A. (both p <0.0001; Figure 4) is as effective as epoetin in maintaining anemia control among these patients who randomly converted directly from epoetin (one to three times a week).

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
groups			C.E.R.A. Q4W 153/191	EPO QW-TIW 167/191		28%/427 ng/mL (31%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	11.66 (11.65)	-0.022 (-0.262; 0.217)	Non-inf[399]	
Mean ΔHb, g/dL [PP]	Levin 2007 UI17950856 Multi	29-36 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q2W 118/223	EPO QW-TIW 180/226	CKD 5D: HD & PD	27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	100 µg/2wk (9600 IU/wk)	-0..071 (-0.075)	Non-inf[400]	Good
			Methoxy polyethylene glycol-EPO β Q4W 172/224	EPO QW-TIW 180/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	200 µg/4wk (9600 IU/wk)	-0.025 (-0.075)	Non-inf[401]	
ESA dose													
Median ESA dose	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 154/190	EPO QW-TIW 167/191	CKD 5D: HD & PD	30.45%/417.75 ng/mL (30.50%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	60 µg/2wk (6000 IU/wk)	-4 µg/2wk (-500 IU/wk)	---	Good
			C.E.R.A. Q4W 153/191	EPO QW-TIW 167/191		27.55%/426.50 ng/mL (30.50%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	120 µg/4wk (6000 IU/wk)	+30 µg/4wk (-500 IU/wk)	---	
Median ESA dose	Levin 2007 UI17950856 Multi	29-36 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q2W 196/223	EPO QW-TIW 205/226	CKD 5D: HD & PD	27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	100 µg/2wk (9600 IU/wk)	-43 µg/2wk (+1200 IU/wk)	--	Good
			Methoxy polyethylene glycol-EPO β Q4W 188/224	EPO QW-TIW 205/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	200 µg/4wk (9600 IU/wk)	-25 µg/4wk (+1200 IU/wk)	--	
C.E.R.A. vs. Darbepoetin α													
QoL													

[399] The lower limit of the 97.5% CI was therefore well above the prespecified margin of -0.75 g/dL in both groups, demonstrating that once-monthly or twice-monthly C.E.R.A. (both p <0.0001; Figure 4) is as effective as epoetin in maintaining anemia control among these patients who randomly converted directly from epoetin (one to three times a week).

[400] The lower limit of the 97.5% CI was above the prespecifi ed concentration of –0.75 g/dL for both groups given methoxy polyethylene glycol-epoetin beta, indicating that this treatment was as effective as conventional epoetin treament for maintenance of haemoglobin in this population (p<0·0001 for both comparisons). This analysis was robust for the intention-to-treat and per-protocol populations (p<0·0001 for both comparisons).

[401] The lower limit of the 97.5% CI was above the prespecifi ed concentration of –0.75 g/dL for both groups given methoxy polyethylene glycol-epoetin beta, indicating that this treatment was as effective as conventional epoetin treament for maintenance of haemoglobin in this population (p<0·0001 for both comparisons). This analysis was robust for the intention-to-treat and per-protocol populations (p<0·0001 for both comparisons).

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
ΔPhysical functioning	Macdougall 2008 UI18287255 Multi	28 wks (28 wks)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD 3-4	24%/175 µg/L (24%/186 µg/L)	0.34 µg/kg (0.19 µg/kg)	10.2 (10.2)	12.18 (12.01)	---	4.0 (3.0)[402]	---	Fair
ΔPhysical role										---	3.5 (9.5)[403]	---	Fair
ΔBody pain										---	1.0 (2.0)[404]	---	Fair
ΔGeneral health										---	6.0[405] (4.0)[406]	---	Fair
ΔPhysical component score										---	0.5 (1.0)[407]	---	Fair
ΔVitality										---	7.0[408] (11.0)[409]	---	Fair
ΔEmotional role										---	5.5[410] (7.0)[411]	---	Fair
ΔSocial functioning										---	5.0[412] (4.0)[413]	---	Fair
ΔMental health										---	2.0 (4.0)[414]	---	Fair
ΔMental component score										---	2.0 (3.0)[415]	---	Fair
Hb													
ΔHb, g/dL [PP]	Canaud 2008 UI18586762	52 wk (52 wk)	C.E.R.A. 157/157	Darbepoetin α 156/156	CKD 5D	28%/nd (28%/nd)	0.35 µg/kg/wk (0.44 µg/kg/wk)	12.0 (11.9)	12.1 (11.8)	12.0 (11.9)	0.06 (-0.12)	---	Fair

[402] Estimated from graph
[403] Clinically meaningful improvement in DA arm from baseline to weeks 29 (an increase of ≥5 points)
[404] Estimated from graph
[405] Clinically meaningful improvement in C.E.R.A. arm from baseline to weeks 29 (an increase of ≥5 points)
[406] Estimated from graph
[407] Estimated from graph
[408] Clinically meaningful improvement in C.E.R.A. arm from baseline to weeks 29 (n increase of ≥5 points)
[409] Clinically meaningful improvement in DA arm from baseline to weeks 29 (n increase of ≥5 points)
[410] Clinically meaningful improvement in C.E.R.A. arm from baseline to weeks 29 (n increase of ≥5 points)
[411] Clinically meaningful improvement in DA arm from baseline to weeks 29 (n increase of ≥5 points)
[412] Clinically meaningful improvement in C.E.R.A. arm from baseline to weeks 29 (n increase of ≥5 points)
[413] Estimated from graph
[414] Estimated from graph
[415] Estimated from graph

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Mean difference in ΔHb, g/dL [PP]	Multi									12.0 (11.9)	0.18 (-0.05; 0.41)	Non-inf[416]	Fair
Mean difference in ΔHb, g/dL [ITT]										12.0 (11.9)	0.29 (0.02; 0.55)	Non-inf[417]	Fair
ΔHb, g/dL	Macdougall 2008 UI18287255 Multi	28 wks (28 wks)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD 3-4	24%/175 µg/L (24%/186 µg/L)	0.34 µg/kg (0.19 µg/kg)	10.2 (10.2)	12.18 (12.01)	10.2 (10.2)	2.12l (2.02)	---	Good
Adjusted[418] ΔHb, g/dL										10.2 (10.2)	2.15 (2.00)	---	Good
Difference in adjusted ΔHb between the 2 groups, g/dL										10.2 (10.2)	0.16 (-0.05; 0.35)	Non-inf[419]	Good
Hb, g/dL	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	nd	8-11 g/dL (8-11g/dL)	12.2 (12.1)	8-11 g/dL (8-11g/dL)	+1.2 to +4.2 (+1.1; +4.1)[420]	nd	Fair
Hb, g/dL [ITT]			C.E.R.A. Q2W 73/73	Darbepoetin α QW/Q2W 151/151			Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)		11.92 (11.89)	8-11 g/dL (8-11g/dL)	+0.92 to +3.92 (+0.89 to +3.89)[421]	nd	Fair
Hb, g/dL [ITT]			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	8-11 g/Dl (8-11g/Dl)	+0.7 to 3.7 (+0.89; +3.89)[422]	nd	Fair

[416] The lower limit of 95% CI was greater than the predefined -0.75g/dL non-inferiority threshold demonstrating that C.E.R.A. was non-inferior to DA (p<0001)
[417] The lower limit of 95% CI was greater than the pre-defined -0.75g/dL non-inferiority threshold demonstrating that C.E.R.A. was non-inferior to DA (p<0.0001)
[418] Adjusted for baseline Hb and geographic region
[419] The lower limit of the 95% CI was well above the prespecified level of -0.75 g/dL, demonstrating that C.E.R.A. once Q2W is as effective as DA QW for anemia correction (p<0.0001)
[420] The Hb was given in a range at baseline (taken from the inclusion criteria). Therefore the achieved Hb is also given in a range of what the difference could be.
[421] The Hb was given in a range at baseline (taken from the inclusion criteria). Therefore the achieved Hb is also given in a range of what the difference could be.
[422] The Hb was given in a range at baseline (taken from the inclusion criteria). Therefore the achieved Hb is also given in a range of what the difference could be.

Outcome	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value	Quality
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Δ (95% CI) Arm 1 (Arm 2)		
Hb, g/dL	Carrera 2010 UI20522670 Multi	14 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q4W 245/245	Darbepoetin α QW 245/245	CKD Stage 5D: HD	27%/427 µg/L (27%/446 µg/L)	Median 30.0 µg/wk (20.0 µg/wk)	12.09 g/dL (12.07 g/dL)	11.8 (10.7)	12.09 (12.07)	-0.99 (-0.87)	nd	Good
ΔHb over time	Roger 2011 UI21505096 Multi	28 wk (20 wk)	C.E.R.A Q4W 153/153	Darbepoetin α QW/Q2W 154/154	CKD Stage 3-4	24%/186 µg/L (23.8%/207 µg/L)	Median 80 µg/4wk (110 µg/4wk)[423]	9.53 g/dL (9.53 g/dL)	11.3 g/dL (11.5 g/dL[424])	9.53 (9.53)	1.62 (1.66)[425]	Non-inf [426]	Good
Mean increase in Hb, g/dL/wk											0.20 (0.27)	nd	
ESA dose													
Δ Mean monthly dose, %	Carrera 2010 UI20522670 Multi	52 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q4W 211/245	Darbepoetin α QW 219/245	CKD Stage 5D: HD	27%/427 µg/L (27%/446 µg/L)	Median 30.0 µg/wk (20.0 µg/wk)	12.09 g/dL (12.07 g/dL)	11.8 (10.7)	159.38 (64.85)	6.8 (58.8)	nd	Good
ΔMedian dose from baseline to evaluation	Roger 2011 UI21505096 Multi	28 wk (20 wk)	C.E.R.A Q4W 153/153	Darbepoetin α QW/Q2W 154/154	CKD Stage 3-4	24%/186 µg/L (23.8%/207 µg/L)	Median 80 µg/4wk (110 µg/4wk)[427]	9.53 g/dL (9.53 g/dL)	11.3 g/dL (11.5 g/dL[428])	80 (110)	6.6% (35.6%)	nd	Good
C.E.R.A vs. C.E.R.A.													
Hb													
Hb, g/dL [ITT]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	C.E.R.A. Q4W 72/72	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	8-11 g/dL (8-11g/dL)	+0.92 to +3.92 (+0.7; 3.7)[429]	nd	Fair

[423] Estimated from figure
[424] Estimated from figure
[425] Between-group treatment difference of -0.036 g/dL
[426] The lower limit of the 95% CI for the group difference was -0.25 g/dL, which was above the protocol-specified non-inferiority limit of -0.75, demonstrating that C.E.R.A. was statistically non-inferior to darbepoetin alfa (P < 0.0001).
[427] Estimated from figure
[428] Estimated from figure
[429] The Hb was given in a range at baseline (taken from the inclusion criteria). Therefore the achieved Hb is also given in a range of what the difference could be.

Supplemental Table 32. Summary table of adverse events in RCTs examining ESA vs. ESA in CKD patients with anemia (categorical outcomes)

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Darbepoetin vs. EPO												
AEs	Nissenson 2002 UI12087569 US & Canada	28 wks (28 wks)	IV Darbepoetin α QW + placebo 169/169	IV EPO TIW+ placebo 335/335	5D: HD	32%/411ng/mL (32%/425 ng/mL)	14,177 U/wk (13,576 U/wk)	11.2 (11.2)	11.36 (12.8)	AE occurring in at 10% of the patients	158 (94%) [332 (99%)]	0.005
HTN										nd	48 (28%) [80 (24%)]	NS
Drug D/C										Did not complete the study	48 (28%) [94 (28%)]	NS
Thrombosis, vascular access										nd	27 (16%) [59 (18%)]	NS
Drug D/C	Tolman 2005 UI15788469 UK	9 mo (9 mo)	SC Darbepoetin α QW 87/112	SC EPO β TIW 82/105	5D: HD	478 **µg/L** (499 **µg/L**)	Median 91 IU/kg/wk (79 IU/kg/wk)	11.86 (11.73)	11.9 (11.5)	Withdrawal	1 (1%) [4 (5%)]	NS
Hypertension										Intercurrent hypertension	6 (7%) [7 (9%)]	NS
At last one AE	Vanrenterghem 2002 UI12427142 Multi	52 wk (52 wk)	Darbepoetin α 347/347	rHuEPO 175/175	5D: HD, PD	305.8 µg/L (288.7 µg/L)	6000 IU/wk (6000 IU/wk)	11.0 (11.0)	11.5 (11.0)	nd	96% (95%)	nd
Hypotension										nd	39% (38%)	nd
Myalgia										nd	34% (36%)	nd
HTN										nd	30% (28%)	nd
Pruritus										nd	14% (5%)	nd
Back pain										nd	10% (16%)	nd
EPO ζ vs. EPO α												
Total AE	Krivoshiev 2008 UI18394266 EU	24 wks (24 wks)	EPO ζ 300/305	EPO α 298/304	CKD 5D: HD	---	182.20 IU/kg/wk (166.14 IU/kg/wk)	8.07 (8.04)	11.61 (11.63)	Emergent AE's that occurred in ≥5% of the patients.	123 (40%) [114 (38%)]	NS
AE leading to withdrawal										Withdrew because of AE	21 (7%) [15 (5%)]	NS[430]
SAEs										SAEs	54 (18%) [53 (17%)]	NS[431]

[430] Calculated by ERT
[431] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Infections and infestations										Most commonly reported	38 (13%) [39 (13%)]	NS[432]
Nervous systems disorder										---	17 (6%) [10 (3%)]	NS[433]
Vascular disorders										---	26 (9%) [27 (9%)]	NS[434]
HTN										---	20 (7%) [13 (4%)]	NS[435]
GI disorders										---	16 (5%) [13 (4%)]	NS[436]
Cardiac disorders	Wizemann 2008 UI18208642 Germany & Poland	24 wk (24 wk)	EPO ζ -EPO α 121/155	EPO α-EPO ζ 118/155	CKD 5D: HD	---	---	11.6 (11.7)	11.35 (11.54)	---	19 (6) [17 (5%)]	---
Total AE [safety]	Krivoshiev 2010 UI20369312 Multi	28 wks (28 wks)	EPO ζ 232/232	EPO α 230/230	CKD 5D: HD	nd	97.0 IU/kg/wk (86.0 IU/kg/wk)	10.56 (10.40)	10.94 (11.02)	All AEs that occurred in >5% of the patients	91 (39%) [92 (40%)]	NS (0.865[437])
AE related to study drug [safety]										A relationship between study drug and event could not be ruled out	5 (2%) [3 (1%)]	NS (0.488[438])
SAEs [safety]										SAEs belonging mainly to system organ classes of surgical and medical procedures	38 (16%) [30 (13%)]	NS (0.313[439])

[432] Calculated by ERT
[433] Calculated by ERT
[434] Calculated by ERT
[435] Calculated by ERT
[436] Calculated by ERT
[437] Calculated by ERT
[438] Calculated by ERT
[439] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
SAEs related to study medication [safety]										Possibly related to study drug administration	3 (3%) [1 (2%)]	NS (0.344[440])
HTN [safety]										Hypertensive crisis	6 (3%) [13 (6%)]	NS (0.107[441])
Thrombolic event [safety]										nd	9 (4%) [4 (2%)]	NS (0.177[442])
Stroke [safety]										nd	9 (4%) [9 (4%)]	NS (0.985[443])
MI [safety]										nd	5 (2%) [9 (4%)]	NS (0.278[444])
EPO θ vs. EPO β												
Withdrawal 2º AE	Gertz, 2010 UI20812790 Multi	24 wk (24 wk)	EPO θ 180/180	EPO β 90/90	CKD 5D: HD	nd	102.5 IU/kg (97.5 IU/kg)	10.87 (10.87)	10.60 (10.66)	nd	9 (5%) [6 (7%)]	NS
Total										nd	136 (76%) [73 (81%)]	NS
Headache										nd	21 (12%) [11 (12%)]	NS
Muscle spasms										nd	20 (11%) [15 (17%)]	NS
Procedural hypotension										nd	17 (9%) 14 (16%)]	NS
Severe intensity AE										nd	17 (9%) [10 (11%)]	NS
Cardiac disorders										nd	8 (4%) [5 (6%)	NS
Adverse drug reactions										nd[445]	39 (22%) [20 (22%)	NS
Serious AE										nd	36 (20%) [20 (22%)]	NS
Serious AE "related to study medication"										nd[446]	9 (5.0%) [5 (5.6%)]	NS

[440] Calculated by ERT
[441] Calculated by ERT
[442] Calculated by ERT
[443] Calculated by ERT
[444] Calculated by ERT
[445] Most common: hypertension, headache, arteriovenous fistula thrombosis
[446] Most common: arteriovenous fistula thrombosis, cardiac failure, "worsening of disease," myocardial infarction, pneumonia, extremity necrosis

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR	Baseline TSAT / Ferritin	Mean ESA dose	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)	Arm 1 (Arm 2) [CKD Stage]	Arm 1 (Arm 2)	Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
HX575 vs. EPO α												
Vascular hypotensive disorders	HaagWeber 2009 UI19863881 Germany & Austria	56 wk (≥24 wk)	HX575 451	EPO α 164	CKD 5D: HD	25%/677 ng/mL (26%/672.2 ng/mL)	6906 IU/wk (6477 IU/wk)	11.7 (12.0)	11.7 (11.9)	Incidence (Events/pt-y)	23.1 (0.95) [12.8 (0.33)]	---
Vascular hypertensive disorders not elsewhere classified										Incidence (Events/pt-y)	12.2 (0.34) [6.1 (0.22)]	---
C.E.R.A. vs. EPO												
Any AE	Spinowitz 2009 UI18004064 Multi	36 wks (36 wks)	C.E.R.A. Q2W 165/168	EPO QW-TIW 168/168	CKD 5D: HD & PD	29%/515 ng/mL (30%/482 ng/mL)	60 µg/2weeks (7,310 IU/week)	11.85 (11.83)	11.99 (11.82)	Blood loss, infection, osteomyelitis, aneamia, acute MI, congestive cardiac failure	156 (95%) [159 (95%)]	NS[447]
SAEs										---	66[448] (31%) [69 (41%)]	NS[449]
HTN	Sulowicz 2007 UI17699476 Multi	36 wk (36 wk)	C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191	CKD 5D: HD & PD	30.45%/417.75 ng/mL (30.50%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	---	27 (14%) [25 (13%)]]	---
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		27.55%/426.50 ng/mL (30.50%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	---	30 (16%) [25 (13%)]	---
Procedural hypotension			C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191		30.45%/417.75 ng/mL (30.50%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	---	17 (9%) [20 (10%)]	---
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		27.55%/426.50 ng/mL (30.50%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	---	29 (15%) [20 (10%)]	---

[447] Calculated by ERT
[448] Calculated by ERT
[449] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Any AE			C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191		30.45%/417.75 ng/mL (30.50%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	---	171 (90%) [167 (87%)]	---
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		27.55%/426.50 ng/mL (30.50%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	---	177 (93%) [167 (87%)]	---
SAEs			C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191		30.45%/417.75 ng/mL (30.50%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	---	70 (37%) [85 (45%)]	---
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		27.55%/426.50 ng/mL (30.50%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	---	73 (38%) [85 (45%)]	---
AE leading to withdrawal			C.E.R.A. Q2W 190/190	EPO QW-TIW 191/191		30.45%/417.75 ng/mL (30.50%/435 ng/mL)	56 µg/2wk (5500 IU/wk)	11.70 (11.65)	11.70 (11.52)	---	1 (1%) [2 (1%)]	---
			C.E.R.A. Q4W 191/191	EPO QW-TIW 191/191		27.55%/426.50 ng/mL (30.50%/435 ng/mL)	150 µg/4wk (5500IU/wk)	11.66 (11.65)	11.46 (11.52)	---	0 (0%) [1 (1%)]	---
Any AE	Levin 2007 UI17950856 Multi	52 wk (52 wk)	Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226	CKD 5D: HD & PD	27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	203 (92%) [214 (95%)]	RR 0.97[450] (0.92; 1.01)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	202 (92%) [214(95%)]	RR 0.97[451] (0.92; 1.01)	NS

[450] Calculated by ERT
[451] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Diarrhea			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	38 (17%) [30 (13%)]	RR 1.29[452] (0.83; 2.00)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	26 (12%) [30 (13%)]	RR 0.89[453] (0.54; 1.45)	NS
Nasopharyngitis			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	28 (13%) [24 (11%)]	RR 1.19[454] (0.71; 1.98)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	39 (18%) [24 (11%)]	RR 1.66[455] (1.04; 2.67)	NS
Hypertension			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	23 (10%) [35 (16%)]	RR 0.67[456] (0.41; 1.09)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	29 (13%) [35 (16%)]	RR 0.85[457] (0.54; 1.34)	NS

[452] Calculated by ERT
[453] Calculated by ERT
[454] Calculated by ERT
[455] Calculated by ERT
[456] Calculated by ERT
[457] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Ateriovenous graft thrombosis			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	25 (11%) [32 (14%)]	RR 0.80[458] (0.49; 1.30)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	26 (12%) [32 (14%)]	RR 0.83[459] (0.51; 1.35)	NS
Upper respiratory tract infection			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	20 (9%) [25 (11%)]	RR 0.81[460] (0.47; 1.42)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	30 (14%) [25 (11%)]	RR 1.23[461] (0.75; 2.02)	NS
Headache			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	30 (14%) [24 (11%)]	RR 1.27[462] (0.77; 2.11)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	17 (18%) [24 (11%)]	RR 0.72[463] (0.40; 1.31)	NS

[458] Calculated by ERT
[459] Calculated by ERT
[460] Calculated by ERT
[461] Calculated by ERT
[462] Calculated by ERT
[463] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Fluid overload			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	27 (12%) [17 (8%)]	RR 1.62[464] (0.91; 2.88)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	22 (10%) [17 (8%)]	RR 1.32[465] (0.72; 2.42)	NS
Muscle spasms			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	19 (9%) [24 (10%)]	RR 0.81[466] (0.45; 1.43)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	19 (9%) [24 (10%)]	RR 0.81[467] (0.46; 1.44)	NS
SAE			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	101 (46%) [99 (44%)]	RR 1.04[468] (0.85; 1.28)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	87 (40%) [99 (44%)]	RR 0.90[469] (0.72; 1.12)	NS

[464] Calculated by ERT
[465] Calculated by ERT
[466] Calculated by ERT
[467] Calculated by ERT
[468] Calculated by ERT
[469] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Sepsis			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	5 (2%) [9 (4%)]	RR 0.57[470] (0.19; 1.66)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	6 (3%) [9 (4%)]	RR 0.68[471] (0.25; 1.88)	NS
Pneumonia			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	9 (4%) [5 (2%)]	RR 1.83[472] (0.62; 5.38)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	5 (2%) [5 (2%)]	RR 1.02[473] (0.30; 3.48)	NS
Serious arteriovenous graft thrombosis			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	2 (12%) [7 (8%)]	RR 0.29[474] (0.06; 1.38)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	8 (4%) [7 (8%)]	RR 1.17[475] (0.43; 3.17)	NS

[470] Calculated by ERT
[471] Calculated by ERT
[472] Calculated by ERT
[473] Calculated by ERT
[474] Calculated by ERT
[475] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR	Baseline TSAT / Ferritin	Mean ESA dose	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)	Arm 1 (Arm 2) [CKD Stage]	Arm 1 (Arm 2)	Arm 1 (Arm 2)	Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
AE leading to withdrawal			Methoxy polyethylene glycol-EPO β Q2W 221/223	EPO QW-TIW 225/226		27%/453 µg/L (31%/ 505 µg/L)	100 µg/2wk (9600 IU/wk)	11.97 (11.91)	11.80 (11.82)	9 (4%) [1 (0.4%)]	RR 9.16[476] (1.17; 71.72)	NS
			Methoxy polyethylene glycol-EPO β Q4W 220/224	EPO QW-TIW 225/226		28%/522 µg/L (31%/ 505 µg/L)	200 µg/4wk (9600 IU/wk)	11.85 (11.91)	11.61 (11.82)	6 (3%) [1 (0.4%)]	RR 6.14[477] (0.74; 50.56)	NS
C.E.R.A. vs. Darbepoetin α												
Any AE	Canaud 2008 UI18586762 Multi	52 wk (52 wk)	C.E.R.A. 157/157	Darbepoetin α 156/156	CKD 5D	28.4%/nd (28.0%/nd)	0.35 µg/kg/wk (0.44 µg/kg/wk)	12.0 (11.9)	12.1 (11.8)	---	135 (88%) [143 (92%)]	NS[478]
SAEs										---	71 (46%) [75 (48%)][479]	NS[480]
AE leading to withdrawal										---	1 (1%) [1 (1%)]	NS[481]
Treatment related AE	Macdougall 2008 UI18287255 Multi	28 wks (28 wks)	C.E.R.A. Q2W 162/162	Darbepoetin α QW 162/162	CKD 3-4	24%/175 µg/L (24%/186 µg/L)	0.34 µg/kg (0.19 µg/kg)	10.2 (10.2)	12.18 (12.01)	---	13[482] (8%) [9[483] (6%)	NS
SAEs										---	49[484] (30%) [58[485] (36%)	NS
SAEs related to study medication										Maculopapular rash, angioneirotic adema HTN	10[486] (1%) [2[487] (1%)	NS

[476] Calculated by ERT
[477] Calculated by ERT
[478] Calculated by ERT
[479] Serious adverse events were considered to be related to study treatment in one patient in CERA group (arteriovenous graft thrombosis) and three patients in DA group (arteriovenous graft thrombosis, AVF site hemorrhage and cerebral infarction)
[480] Calculated by ERT
[481] Calculated by ERT
[482] Calculated by ERT
[483] Calculated by ERT
[484] Calculated by ERT
[485] Calculated by ERT
[486] Calculated by ERT
[487] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
AE leading to study withdrawal										Withdrawn as a result of AE	5[488] (3%) [10[489] (6%)	NS
Any AE										Most common: HTN, peripheral edema, diarrhea, nasopharyngitis	146[490] (90%) [147[491] (91%)	NS
AV thromboembolic events										Limb venothrombosis, pulmonary embolism, MI, stroke	5[492] (3%) [2[493] (1%)	NS
SAE [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	Darbepoetin α QW/Q2W 151/151	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.89)	None considered to be treatment related	11[494] (15%) [30 (20%)]	NS (0.391)
			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	None considered to be treatment related	11[495] (15%) [30 (20%)]	NS (0.415)
AE related to study medication [safety]			C.E.R.A. Q2W 73/73				Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)		11.92 (11.89)	Related to study medication	1 (1%) [0 (0%)][496]	nd
			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	Related to study medication	0 (0%) [0 (0%)]	nd

[488] Calculated by ERT
[489] Calculated by ERT
[490] Calculated by ERT
[491] Calculated by ERT
[492] Calculated by ERT
[493] Calculated by ERT
[494] Event rate calculated by ERT
[495] Event rate calculated by ERT
[496] Calculated by ERT

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Any AE [safety]			C.E.R.A. Q2W 73/73				Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)		11.92 (11.89)	At least 1 AE mild or moderate in intensity	48 (67%) [99 (66%)][497]	NS (0.978)
			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	At least 1 AE mild or moderate in intensity	46 (64%) [99 (66%)][498]	NS (0.808)
HTN [safety]			C.E.R.A. Q2W 73/73				Median IQR range 0.17 µg/kg/wk (0.17 µg/kg/wk)		11.92 (11.89)	nd	1 (1%) [5 (3%)][499]	NS (0.416)
			C.E.R.A. Q4W 72/72				Median IQR range 0.22 µg/kg/wk (0.17 µg/kg/wk)		11.70 (11.89)	nd	3 (4%) [5 (3%)][500]	NS (0.748)
Hypertension	Roger 2011 UI21505096 Multi	28 wk (20 wk)	C.E.R.A Q4W 153/153	Darbepoetin α QW/Q2W 154/154	CKD Stage 3-4	24%/186 µg/L (23.8%/207 µg/L)	Median 80 µg/4wk (110 µg/4wk)[501]	9.53 g/dL (9.53 g/dL)	11.3 g/dL (11.5 g/dL[502])	nd	24 (16%) [37 (24%)]	nd
Renal impairment											9 (6%) [16 (10%)]	
Hyperkalemia											13 (9%) [8 (5%)]	
Upper respiratory tract infection											9 (6%) [11 (7%)]	
Constipation											5 (3%) [12 (8%)]	
Diarrhea											10 (7%) [6 (4%)]	
Urinary tract infection											6 (4%) [8 (5%)]	
Hypotension											5 (3%) [8 (5%)]	

[497] Calculated by ERT
[498] Calculated by ERT
[499] Calculated by ERT
[500] Calculated by ERT
[501] Estimated from figure
[502] Estimated from figure

Adverse Event	Author, Year, Country	Outcome Assessment Time (Treatment Duration)	Treatments (Number Analyzed / Enrolled)		Baseline GFR Arm 1 (Arm 2) [CKD Stage]	Baseline TSAT / Ferritin Arm 1 (Arm 2)	Mean ESA dose Arm 1 (Arm 2)	Hemoglobin (g/dL)		Results		P-value
			Arm 1 (Intervention)	Arm 2 (Comparator)				Baseline Arm 1 (Arm 2)	Achieved Arm 1 (Arm 2)	Definition	Events No (%) Arm 1 [Arm 2]	
Nasopharyngitis											5 (3%) [8 (5%)]	
Pneumonia											2 (1%) [8 (5%)]	
C.E.R.A vs. C.E.R.A.												
SAE [safety]	Kessler 2010 UI19888948 Multi	53 wk (53 wk)	C.E.R.A. Q2W 73/73	C.E.R.A. Q4W 72/72	CKD Stage 3-4	≥20%/≥100 ng/mL (≥20%/≥100 ng/mL)	Median IQR range 0.17 µg/kg/wk (0.22 µg/kg/wk)	8-11 g/dL (8-11g/dL)	11.92 (11.70)	None considered to be treatment related	11[503] (15%) [11 (15%)]	NS (0.972)
AE related to study medication [safety]										Related to study medication	1 (1%) [0 (0%)][504]	nd
Any AE [safety]										At least 1 AE mild or moderate in intensity	48 (67%) [46 (64%)][505]	NS (0.814)
HTN [safety]										nd	1 (1%) [3 (4%)][506]	NS (0.330)

[503] Event rate calculated by ERT
[504] Calculated by ERT
[505] Calculated by ERT
[506] Calculated by ERT