Supplemental Material

Supplement to:
Locatelli F, Hannedouche T, Fishbane S, et al.
Cardiovascular Safety and All-Cause Mortality of Methoxy Polyethylene Glycol-Epoetin Beta Versus and Other Erythropoiesis-Stimulating Agents in Renal Anemia of Chronic Kidney Disease: A Randomized Trial

Contents

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Supplemental Appendix 2: Cardiovascular end point definitions

A. Primary – APTC/MACE Fatal Events

i. Death due to myocardial infarction: the presence of two of the three following criteria: a) chest pain consistent with angina, b) any abnormal value of cardiac biomarkers (MB fraction of creatine phosphokinase and/or troponin I or T), c) myocardial injury current or the development of Q waves in two contiguous leads of the electrocardiogram. If the clinical diagnosis of myocardial infarction is not possible, autopsy findings with an unequivocal diagnosis of myocardial infarction may be used to confirm the diagnosis.

ii. Death due to stroke: ischemic or hemorrhagic stroke defined as an acute, focal neurological event that occurred within 30 days of death. Confirmation by imaging studies (magnetic resonance imaging or computerised tomography of the brain) or autopsy data will be sought in all cases, but will not be required for adjudication of the event.

iii. Cardiovascular Deaths: deaths that were sudden or unexplained without documentation of myocardial infarction or stroke as follows: Sudden arrhythmic death (observed to have had an arrhythmia)

    i. Sudden death (etiology unspecified)

    ii. Other cardiovascular death: death without documentation of myocardial infarction (A.i) or stroke (A.ii) or that is exclusive of the diagnoses listed in Sections A.iii.i. and A.iii.ii.

B. Noncardiovascular deaths

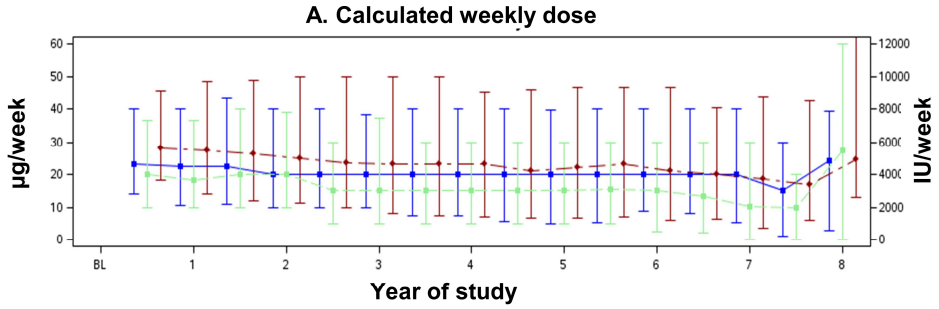
i. Deaths that are exclusive of the diagnoses listed in Section A

C. Death due to discontinuation of dialysis (voluntary)

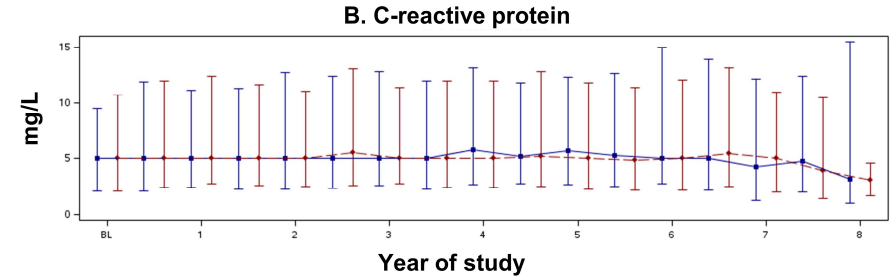
D. Nonfatal Stroke: ischemic or hemorrhagic stroke defined as an acute, focal neurological event that persisted for >24 h. Confirmation by imaging studies (magnetic resonance imaging or computerised tomography of the brain) will be sought in all cases, but will not be required for adjudication of the event. The diagnosis of stroke will be made when an imaging study clearly demonstrates brain injury (ischemic or non-ischemic), despite symptoms resolving in <24 h.

E. Nonfatal myocardial infarction: the presence of two of the three following criteria: a) chest pain consistent with angina, b) any abnormal value of cardiac biomarkers (MB fraction of creatine phosphokinase and/or troponin I or T), c) myocardial injury current or the development of Q waves in two contiguous leads of the electrocardiogram.

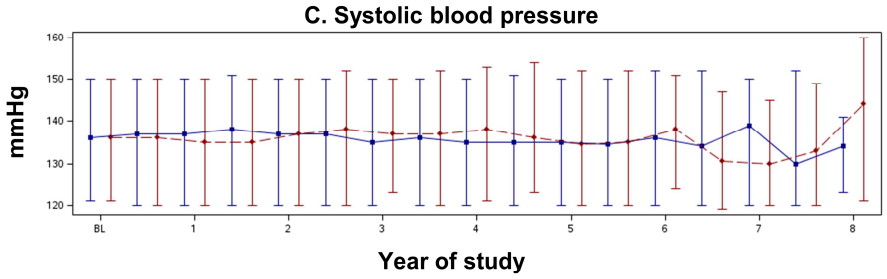
Supplemental Figure 1: **A. Doses of erythropoiesis-stimulating agents during the study. B. C-reactive protein levels during the study. C. Systolic blood pressure during the study. Values shown are median with interquartile ranges**



	BL	1	2	3	4	5	6	7	8
Epoetin alfa/beta	794	719	652	588	535	491	445	383	334	300	263	204	147	101	49	16
Darbepoetin alfa	517	414	445	398	354	316	285	256	230	200	175	131	83	50	25	5
Methoxy polyethylene glycol-epoetin beta	1292	1145	1036	936	834	741	663	600	536	478	423	311	229	161	86	28



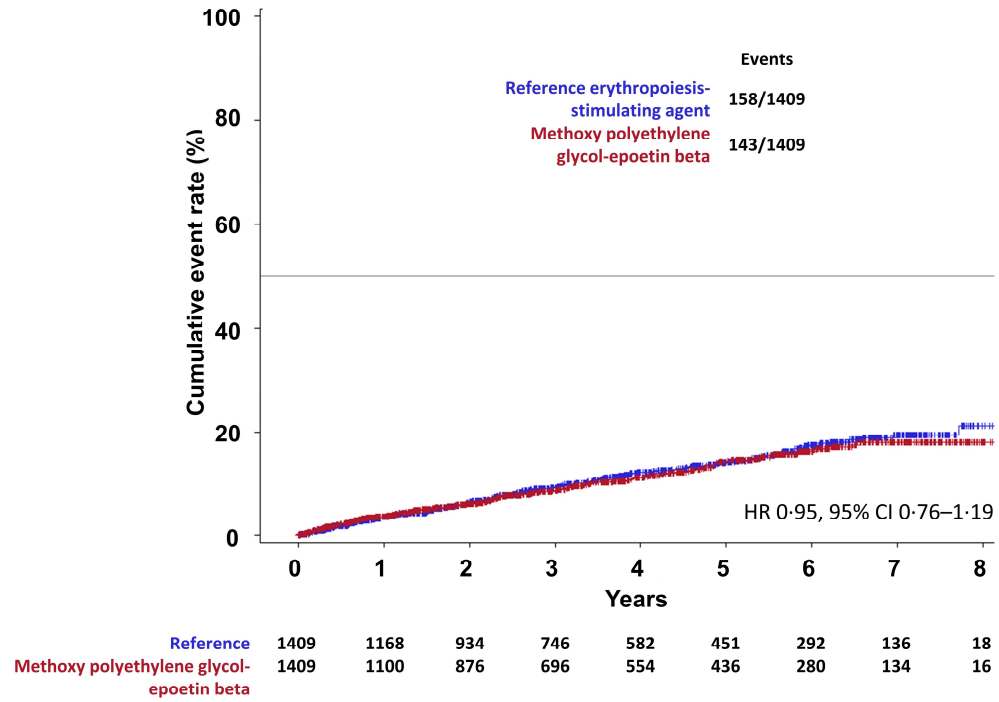
	BL	1	2	3	4	5	6	7	8
Reference	1386	1247	1153	1028	908	826	757	682	592	517	452	399	298	205	129	63	19
Methoxy polyethylene glycol-epoetin beta	1379	1190	1096	963	866	760	688	611	554	496	447	394	294	207	146	77	17



	BL	1	2	3	4	5	6	7	8
Reference	1410	1312	1195	1078	908	884	792	708	634	549	483	424	325	235	151	73	21
Methoxy polyethylene glycol-epoetin beta	1379	1190	1096	1026	924	819	727	644	590	525	466	407	301	226	154	89	26

Supplemental Figure 2: **Time-to-event curves for A. Time to myocardial infarction and B. Time to stroke**

A



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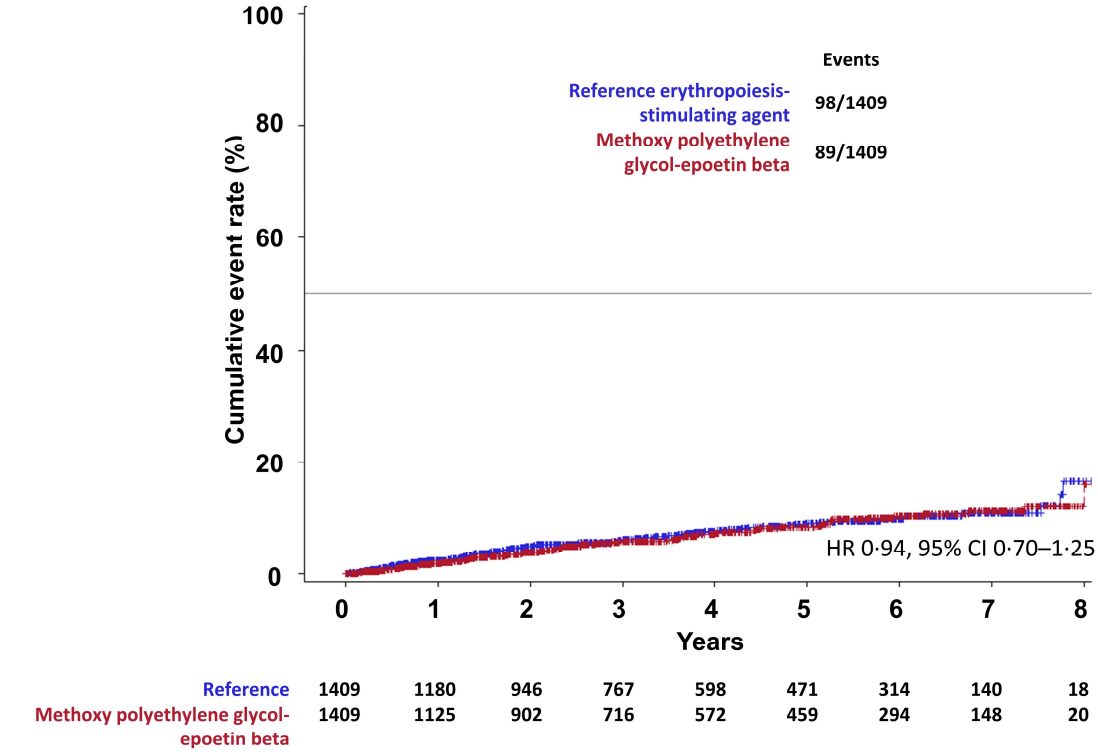

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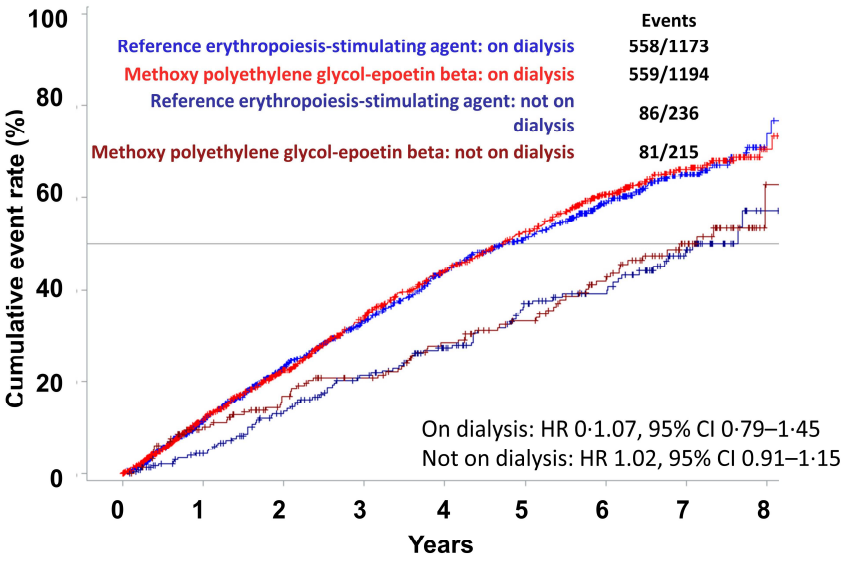
***Supplemental Figure 3*: Time-to-event curves for death from any cause, nonfatal stroke or nonfatal myocardial infarction, for patients on dialysis or not on dialysis**



On dialysis									
Reference	1173	944	729	567	431	335	206	91	10
Methoxy polyethylene glycol-epoetin beta	1194	918	716	553	429	333	200	94	11
Not on dialysis									
Reference	236	207	175	147	121	94	76	39	7
Methoxy polyethylene glycol-epoetin beta	215	173	145	128	109	91	67	35	4

Supplemental Table 1: **Inclusion and exclusion criteria**

Inclusion criteria	Exclusion criteria
Written informed consent	Uncontrolled hypertension
Adult patients (≥18 years old) with symptomatic anemia associated with chronic kidney disease (renal anemia)	Hypersensitivity to the active substance or any of the excipients of methoxy polyethylene glycol-epoetin beta and other ESAs
Patients with renal anemia who are not treated with an ESA:	Any other contraindication to ESA therapy

Anemia defined as hemoglobin concentration <11 g/dL (mean of two screening values with at least 1 day and a maximum of 2 weeks between measurements) with a clinical indication for ESA treatment	Conditions known to cause inadequate response to ESA treatment or anemia other than symptomatic anemia associated with chronic kidney disease, including:
	• Hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types)
	• Anemia due to hemolysis
	• Pure red cell aplasia
	• Other:
	  • High likelihood of early withdrawal (e.g. within 1 year) or interruption of the study
	  • Pregnancy or breast-feeding
	Women of childbearing potential without effective contraception
	  • Administration of another investigational drug within 1 month before screening or planned during the study period

or	
Patients with renal anemia who are on maintenance ESA therapy	
If on dialysis: regular long-term hemodialysis or peritoneal dialysis therapy with the same mode of dialysis for at least 3 months before screening	
Continuous intravenous or subcutaneous maintenance ESA therapy: darbepoetin afa (Aranesp®, Nespo®, Aranest®), epoetin alfa (Eprex®, Epogen®, Epopen®, Erypo®) or epoetin beta (NeoRecormon®, Recormon®) administered according to approved label of the same agent and route of administration for at least 2 months before screening	
Hemoglobin concentration between 10 and 12 g/dL (mean of two screening values with at least 1 day and a maximum of 2 weeks between measurements)	
Patients with adequate iron status defined as: serum ferritin above or equal to 100 ng/mL or transferrin saturation above or equal to 20%	

ESA=erythropoiesis-stimulating agent.

Supplemental Table 2: **Starting dose of methoxy polyethylene glycol-epoetin beta according to previous ESA treatment when switching from another ESA**

Previous darbepoetin alfa dose (μg/week)	Previous epoetin dose (IU/week)	Methoxy polyethylene glycol-epoetin beta dose (μg/once monthly)
<40	<8000	120
40 –80	8000–16000	200
>80	>16000	360

ESA=erythropoiesis-stimulating agent; IU=international unit.

Supplemental Table 3: **Schedule of assessments**

The following laboratory assessments were to be performed during the randomized treatment period:

Test	Frequency
Hemoglobin	At study visit 1, at monthly visits and at the final visit. In correction patients' hemoglobin was assessed twice monthly until stabilized.
Platelet count	At study visit 1 and at monthly visits.
Total white blood cell count	At study visit 1 and every 3 months
C-reactive protein	Every 3 months
Serum albumin, calcium, phosphorus, potassium	At study visit 1 and every 3 months
Serum ferritin, serum iron, serum transferrin or total iron-binding capacity, transferrin or percentage of hypochromic red blood cells	Every 3 months
Cholesterol, triglycerides, HbA_{1c}, glucose	At study visit 1 and once a year
Anti-erythropoietin antibody determination	At study visit 1, once a year and at the final visit
Dialysis quantification indexes and renal function: • Patients on hemodialysis: Kt/V or urea reduction ratio • Patients on peritoneal dialysis: the weekly Kt/V • Patients not on dialysis: serum creatinine, creatinine clearance/estimated GFR	• At study visit 1 and every 6 months
12-lead ECG recording	At study visit 1 before dose administration.

Supplemental Table 4: **Additional baseline characteristics**

	Reference ESA	Methoxy polyethylene glycol-epoetin beta
Pre-dialysis systolic blood pressure (mmHg), n (%)	n=1091	n=1104
<140	569 (52)	597 (54)
140–160	359 (33)	384 (35)
>160	163 (15)	123 (11)
HbA_{1c} (%)	n=1221	n=1248
Mean±SD	5.8±3.3	5.9±4.1
Median (IQR)	5.6 (5.1–6.3)	5.6 (5.1 – 6.3)
Albumin (g/dL)	n=1308	n=1318
Categories, n (%)		
<3.5	261 (20)	261 (20)
3.5–4.0	583 (45)	607 (46)
>4.0	464 (35)	450 (34)
Triglycerides [mmol/L]	n=1291	n=1320
Mean ±SD	1.96±3.61	1.91±1.29
Median (IQR)	1.59 (1.10–2.30)	1.58 (1.10–2.33)
HD Vascular Access, n (%)	n=1092	n=1103
Arteriovenous fistula	889 (81)	900 (82)
Arteriovenous graft	61 (6)	56 (5)
Central venous catheter	142 (13)	147 (13)
eGFR (mL/min/1.73m^2)	n=229	n=207
Categories, n (%)		
<30	178 (78)	171 (83)
30–44	39 (17)	28 (14)
≥45	12 (5)	8 (4)
Smoking Status at Screening, n (%)	n=1406	n=1409
Smoker	156 (11)	137 (10)
Non-Smoker	1250 (89)	1272 (90)

ESA=erythropoiesis-stimulating agent; HbA_{1c}=hemoglobin A_{1c}; eGFR=estimated glomerular filtration rate; HD=hemodialysis; IQR=interquartile range; SD=standard deviation.

Supplemental Table 5. **Concomitant iron supplementation**

	Reference ESA	Methoxy polyethylene glycol-epoetin beta
Patients with at least 1 treatment during the study, n (%)	1315 (93)	1289 (92)
Top treatments:		
Iron sucrose	666 (47)	661(47)
Ferrous gluconate	428 (30)	390 (28)
Iron polymaltose	99 (7)	111 (8)
Ferrous sulfate	101 (7)	101 (7)
Iron dextran	85 (6)	102 (7)
Route		
IV or IV infusion	1244 (85)	1212 (85)
Oral	211 (14)	208 (15)

Supplemental Table 6: **Selected baseline parameters by withdrawal in the first year**

	Censored in first year		Remained on study past 1 year	
Parameter, mean (SD) unless stated	Reference ESA (*n*=129)	Methoxy polyethylene glycol-epoetin beta (*n*=172)	Reference ESA (*n*=1148)	Methoxy polyethylene glycol-epoetin beta (*n*=1090)
Hemoglobin, g/dL	10.8 (1.02)	10.88 (0.93)	10.76 (1.03)	10.75 (0.99)
Transferrin saturation, %	27 (13)	29 (15)	31 (23)	30 (20)
Ferritin, ng/mL	464 (561)	497 (353)	488 (391)	481 (415)
ESA type at screening, n (%)	*n* = 107	*n* = 148	*n* = 910	*n* = 865
Darbepoetin alfa	52 (49)	51 (34)	397 (44)	373 (43)
Epoetin alfa	23 (21)	46 (31)	182 (20)	193 (22)
Epoetin beta	32 (30)	51 (34)	331 (36)	299 (35)
Dialysis at screening	*n* = 129	*n* = 172	*n* = 1148	*n* = 1090
Hemodialysis	99 (77)	138 (80)	875 (76)	847 (78)
Peritoneal dialysis	9 (7)	12 (7)	67 (6)	70 (6)
None	21 (16)	22 (13)	206 (18)	173 (16)

Supplemental Table 7: **Adjudicated causes of death**

	Reference ESA n=1409	Methoxy polyethylene glycol-epoetin beta n=1409
All deaths	**557**	**558**
Death due to myocardial infarction	37	37
Death due to stroke	26	28
Other cardiovascular death	53	39
Death sudden due to arrhythmia	14	21
Death sudden etiology unknown	136	185
Noncardiovascular death	264	223
Death due to discontinuation of dialysis	27	25

ESA=erythropoiesis-stimulating agent.

Supplemental Table 8: **Time-dependent Cox regression models for hemoglobin level and dose prior to the event: Safety population, without baseline factors included (individual covariates Cox model) or with baseline factors included (multivariable Cox model)**

INDIVIDUAL COVARIATES COX MODEL*		
Mean hemoglobin concentration in 3 months before event (*vs* reference 10–11 g/dL)		
g/dL	HR (95% CI)	p value[†]
<10	2.76 (2.41–3.17)	<0.001
11–<12	0.72 (0.62–0.83)	<0.001
≥12	0.66 (0.53–0.81)	<0.001
Mean ESA dose quartile in 3 months prior to event (*vs* reference first quartile)		
	HR (95% CI)	p value
Second quartile	1.26 (1.06–1.48)	0.007
Third quartile	1.37 (1.16–1.62)	<0.001
Fourth quartile	2.44 (2.10–2.83)	<0.001
MULTIVARIABLE COX MODEL[‡]		
Mean hemoglobin concentration in 3 months before event (*vs* reference 10–11 g/dL)		
g/dL	HR (95% CI)	p value
<10	2.79 (2.43; 3.21)	<0.001
11–<12	0.71 (0.61; 0.82)	<0.001
≥12	0.68 (0.55; 0.83)	<0.001
Mean ESA dose quartile in 3 months prior to event (*vs* reference first quartile)		
	HR (95% CI)	p value
Second quartile	1.28 (1.08–1.51)	0.004
Third quartile	1.39 (1.17–1.65)	<0.001
Fourth quartile	2.52 (2.16–2.94)	<0.001

* Model containing on treatment hemoglobin or dose categories and treatment only.

[†] p value for a difference in the hazard ratio from 1; p values are exploratory and for illustration only.

[‡] Model containing hemoglobin or dose categories, treatment, and baseline factors: age, body mass index, sex, region, dialysis treatment, presence of risk factors and treatment setting.

Supplemental Table 9: **Adverse events**

MedDRA System Organ Class MedDRA Preferred Term Patients, n (%)	**Reference n=1409**	**Methoxy polyethylene glycol-epoetin beta n=1409**
Any adverse event		
Total number of patients with at least one adverse event	1340 (95)	1351 (96)
Overall total number of events	21270	20549
Adverse events experienced by ≥5% of patients		
Infections and infestations		
Pneumonia	239 (17)	243 (17)
Urinary tract infection	217 (15)	217 (15)
Bronchitis	208 (15)	201 (14)
Nasopharyngitis	171 (12)	187 (13)
Upper respiratory tract infection	160 (11)	138 (10)
Gastroenteritis	115 (8)	134 (10)
Sepsis	92 (7)	82 (6)
Respiratory tract infection	92 (7)	77 (5)
Influenza	87 (6)	75 (5)
Lower respiratory tract infection	70 (5)	84 (6)
Device related infection	82 (6)	62 (4)
Peritonitis	69 (5)	73 (5)
Gastrointestinal disorders		
Diarrhea	274 (19)	280 (20)
Constipation	179 (13)	149 (11)
Vomiting	149 (11)	124 (9)
Abdominal pain	102 (7)	111 (8)
Nausea	99 (7)	104 (7)
Abdominal pain upper	76 (5)	85 (6)
Dyspepsia	81 (6)	60 (4)
Vascular disorders		
Hypertension	446 (32)	462 (33)
Hypotension	156 (11)	136 (10)
Musculoskeletal and connective tissue disorders		
Muscle spasms	211 (15)	199 (14)
Back pain	166 (12)	120 (9)
Pain in extremity	133 (9)	125 (9)
Arthralgia	116 (8)	125 (9)
Osteoarthritis	119 (8)	99 (7)
Musculoskeletal pain	79 (6)	72 (5)
Injury, poisoning and procedural complications		
Procedural hypotension	231 (16)	236 (17)
Arteriovenous fistula site complication	209 (15)	187 (13)
Arteriovenous fistula thrombosis	178 (13)	151 (11)
Arteriovenous fistula site hemorrhage	79 (6)	88 (6)
Metabolism and nutrition disorders		
Fluid overload	168 (12)	144 (10)
Hyperkalemia	154 (11)	147 (10)
Hyperphosphatemia	142 (10)	136 (10)
Respiratory, thoracic and mediastinal disorders		
Cough	194 (14)	163 (12)
Dyspnea	120 (9)	122 (9)
General disorders and administration site conditions		
Pyrexia	119 (8)	111 (8)
Eedema due to renal disease	81 (6)	80 (6)
Asthenia	64 (5)	87 (6)
Cardiac disorders		
Atrial fibrillation	166 (12)	151 (11)
Angina pectoris	79 (6)	71 (5)
Nervous system disorders		
Headache	130 (9)	144 (10)
Dizziness	82 (6)	89 (6)
Blood and lymphatic system disorders		
Anemia	158 (11)	195 (14)
Psychiatric disorders		
Insomnia	116 (8)	104 (7)
Depression	67 (5)	77 (5)
Endocrine disorders		
Hyperparathyroidism secondary	167 (12)	169 (12)
Skin and subcutaneous tissue disorders		
Pruritus	118 (8)	114 (8)
Eye disorders		
Cataract	81 (6)	84 (6)

MedDRA, Medical Dictionary for Regulatory Activities.