Supporting material

Supporting Table 1. Outcome definition and source of information. Mortality Information System (MIS) Hospital Information System (HIS).

Outcome	Definition	Source
All-cause mortality	Yes/No	MIS
Blood transfusion	ICD9 (Procedure Codes): 99.0	HIS
Major Cardiovascular Events (MACE)	Acute myocardial infarction or cerebrovascular diseases or thrombosis. ICD9 (Diagnosis Codes): 410 or 430-438 or (444; 445; 451-453).	HIS
Blood Dyscrasias	Haemolytic anaemia or aplastic anaemia or other and unspecified anaemia. ICD9 (Diagnosis Codes): 283 or 284 or 285	HIS
Hypersensitivity reactions	ICD9 (Diagnosis Codes): 995.0; 995.2; 995.3.	HIS
Composite outcome	All-cause mortality or Blood transfusion or Acute myocardial infarction or cerebrovascular diseases or thrombosis.	MIS or HIS

Supporting Table 2. Definition of confounders and source of information.

Outcome	Definition	Source^	Confounding categories^^
Age	Age at prescription of ETP (mean, age-classes)	ETP	D
Gender		ETP	D
Baseline Hb levels	Expressed as g/dl and grouped in 4 classes (<8; 8-<10; 10-<11; ≥11)	ETP	RF
Special nutrition program	Yes/No	ETP	RF
Diabetes	ICD9: 250 or ATC=A10 or Allowance code=13	HIS, D&I	C
Hypertension	ICD9: 401-405	HIS	C
Heart diseases	ICD9: 420-429	HIS	C
Arrythmia	ICD9: 426-427	HIS	C
Heart failure	ICD9: 428	HIS	C
Cerebrovascular Disease	ICD9: 430-438	HIS	C
Arterial and venousThrombosis	ICD9: 444; 445; 451-453	HIS	C
Hospital admissions	Number of hospitalizations in the previous 2 years	HIS	HC
EPT duration	Mean ETP duration in months	ETP	HC
ESA packages dispensed	Mean number of ESA packages dispensed per ETP	ETP	HC
DDD (Defined Daily Dose)	Mean DDD of ESA per ETP	ETP	HC

^ Source of data: Electronic Therapeutic Plan (ETP); Hospital Information System (HIS); Drug Prescription & Clinical Investigation Databases (D&I). Medical history was retrieved up to 2 year before the ESA prescription (index date).

^^ Confounding categories: Demographics (D); Risk Factor (RF); Comorbidity (C); Health care utilization (HC).

Supporting Table 3..Descriptive analysis of considered outcome events by setting and ESAs (biosimilars, epoetin alpha originator or other originators).

	Chronic kidney disease setting (n= 8161)				Oncology setting (n=5309)			
	Biosimilars epoetin alpha (n=154)	Originator epoetin alpha (n=1614)	Other orignators (n=6393)		Biosimilars epoetin alpha (n=453)	Originator epoetin alpha (n=1617)	Other orignators (n=3239)	
	No. of events			Total	No. of events			Total
Composite outcome	61	633	2198	2892	229	898	1620	2747
All-cause mortality	40	454	1517	2011	176	733	1223	2132
Blood transfusion	13	153	525	691	81	287	593	961
MACE	11	132	414	557	15	62	135	212
Blood dyscrasia	19	174	625	818	63	272	527	862
Haemolytic anaemia	1	1	2	4	2	2	6	10
Aplastic anaemia	1	11	32	44	10	41	80	131
Other anaemia	17	162	591	770	51	229	441	721
Hypersensitivity reactions	0	1	14	15	3	4	8	15

Supporting table 4. Descriptive analysis of considered outcome events in the CKD setting by ESAs (biosimilars, epoetin alpha originator or other originators), mean follow up, and incidence rate.

	Chronic kidney disease setting (n= 8161)											
	Biosimilars epoetin alpha				Originator epoetin alpha				Other originators			
	n	Time of follow-up (days)	Mean Time of follow-up (months)	rate*100 person-year	n	Time of follow-up (days)	Mean Time of follow-up (months)	rate*100 person-year	n	Time of follow-up (days)	Mean Time of follow-up (months)	rate*100 person-year
	154	23809	4,2		**1614**	242319	4,1		**6393**	999519	4,3	
Composite outcome	61	21005	3,7	106	633	214353	3,6	108	2198	905675	3,9	89
All-cause mortality	40	23809	4,2	61	454	242319	4,1	68	1517	999519	4,3	55
Blood transfusion	13	22644	4,0	21	153	229593	3,9	24	525	956110	4,1	20
MACE	11	22634	4,0	18	132	232172	3,9	21	414	972267	4,2	16
Blood dyscrasia	19	21975	3,9	32	174	226803	3,8	28	625	944918	4,0	24
Hypersensitivity reactions	0	23809	4,2	0	1	242307	4,1	0	14	998169	4,3	1

Supporting table 5.Descriptive analysis of considered outcome events in the oncology setting by ESAs (biosimilars, epoetin alpha originator or other originators), mean follow up, and incidence rate.

Oncology setting (n=5309)												
	Biosimilars epoetin alpha				Originator epoetin alpha				Other originators			
	n	Time of follow-up (days)	mean Time of follow-up (months)	rate*100 person-year	n	Time of follow-up (days)	mean Time of follow-up (months)	rate*100 person-year	n	Time of follow-up (days)	mean Time of follow-up (months)	rate*100 person-year
	453	65018	3,9		**1617**	222860	3,8		**3239**	472891	4,0	
Composite outcome	229	55250	3,3	151	898	191002	3,2	172	1620	402294	3,4	147
All-cause mortality	176	65018	3,9	99	733	222860	3,8	120	1223	472891	4,0	94
Blood transfusion	81	58841	3,6	50	287	200464	3,4	52	593	425941	3,6	51
MACE	15	63744	3,9	9	62	219056	3,7	10	135	463378	3,9	11
Blood dyscrasia	63	58951	3,6	39	272	200889	3,4	49	527	428845	3,6	45
Hypersensitivity reactions	3	64714	3,9	2	4	222432	3,8	1	8	472045	4,0	1

Supplementary table 6.Descriptive analysis of considered outcome events in the oncology sub-setting by ESAs (biosimilars, epoetin alpha originator or other originators).The sub-setting included all the patients of the oncology cohort enrolled up to 30 June 2014 (n=4415), for which the causes of death were available.

Biosimilars epoetin alpha vs Originator epoetin alpha

Death	Biosimilars epoetin alpha (N=315)	Originator epoetin alpha (N=1339)	Total
Death from tumours	113 (35.85%)	561 (41.90%)	674
Death from other causes	3 (0.95%)	18 (1.34%)	21
Total deaths	116	579	695

Biosimilars epoetin alpha vs Other originators

Death	Biosimilars epoetin alpha (N=315)	Other originators (N=2761)	Total
Death from tumours	113 (35.85%)	940 (35.05%)	1053
Death from other causes	3 (0.95%)	46 (1.66%)	49
Total deaths	116	986	1102

Supplementary table 7.Comparison between the hazard ratios for the effectiveness and safety outcomes in the oncology overall cohort versus the sub-setting obtained through multivariate Cox proportional hazards regression analysis.

Multivariate Cox proportional hazards regression analysis								
Oncology setting								
	Biosimilars epoetin alpha vs Originator epoetin alpha							
	Cohort enrollment period 1/1/2012 - 31/12/14 N=2070 (Biosimilars=453)				**Cohort enrollment period 1/1/2012 - 30/06/14 N= 1654 (Biosimilars=315)**			
	N	**HR adj**	**LCI95%**	**UCI95%**	**N**	**HR adj**	**LCI95%**	**UCI95%**
Composite outcome	1127	0,91	0,79	1,06	912	0,92	0,78	1,09
All-cause mortality	909	**0,82**	**0,70**	**0,97**	743	**0,81**	**0,67**	**0,98**
Blood transfusion	368	1,06	0,82	1,35	293	1,14	0,86	1,52
MACE	77	0,84	0,48	1,47	64	0,75	0,38	1,47
Blood dyscrasia	335	0,86	0,66	1,14	270	1,04	0,76	1,42
	Biosimilars epoetin alpha vs Other orignators							
	Cohort enrollment period 1/1/2012 - 31/12/14 N=3692 (Biosimilars=453)				**Cohort enrollment period 1/1/2012 - 30/06/14 N= 3076 (Biosimilars=315)**			
	N	**HR adj**	**LCI95%**	**UCI95%**	**N**	**HR adj**	**LCI95%**	**UCI95%**
Composite outcome	1849	1,01	0,88	1,16	1569	0,99	0,84	1,16
All-cause mortality	1399	1,01	0,86	1,18	1186	0,98	0,82	1,18
Blood transfusion	674	0,98	0,77	1,23	581	0,97	0,74	1,27
MACE	150	0,79	0,46	1,35	119	0,78	0,41	1,50
Blood dyscrasia	590	0,86	0,66	1,12	517	0,93	0,69	1,24

Supplementary table 8.Crude and adjusted HRs for the effectiveness and safety outcomes obtained by the multivariate analysis by settings.

	Chronic kidney disease setting (n= 8161)							Oncology setting (n=5309)					
	HR_crude	**LCI95%**	**UCI95%**	**HR_adj**	**LCI95%**	**UCI95%**		**HR_crude**	**LCI95%**	**UCI95%**	**HR_adj**	**LCI95%**	**UCI95%**
Composite outcome													
Epoetin alpha originator	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	0,98	0,75	1,27	1,02	0,78	1,33		0,89	0,77	1,03	0,91	0,79	1,06
All-cause mortality													
Epoetin alpha originator	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	0,90	0,65	1,24	0,92	0,67	1,28		0,82	0,70	0,97	0,82	0,70	0,97
Blood transfusion													
Epoetin alpha originator	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	0,86	0,49	1,52	0,95	0,54	1,69		0,97	0,76	1,24	1,06	0,82	1,35
MACE													
Epoetin alpha originator	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	0,85	0,46	1,58	0,92	0,49	1,70		0,84	0,48	1,47	0,84	0,48	1,47
Blood dyscrasia													
Epoetin alpha originator	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	1,12	0,70	1,80	1,19	0,74	1,92		0,81	0,61	1,06	0,86	0,66	1,14
	HR_crude	**LCI95%**	**UCI95%**	**HR_adj**	**LCI95%**	**UCI95%**		**HR_crude**	**LCI95%**	**UCI95%**	**HR_adj**	**LCI95%**	**UCI95%**
Composite outcome													
Other originators	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	1,18	0,91	1,52	1,09	0,85	1,41		1,03	0,89	1,18	1,01	0,88	1,16
All-cause mortality													
Other originators	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	1,10	0,81	1,51	1,00	0,73	1,38		1,05	0,90	1,23	1,01	0,86	1,18
Blood transfusion													
Other originators	1,00	-	-	1,00	-	-		1,00	-	-	1,00	-	-
Epoetin alpha biosimilars	1,04	0,60	1,80	0,99	0,57	1,71		0,98	0,78	1,24	0,98	0,77	1,23
MACE													

Other originators	1,00	-	-		1,00	-	-		1,00	-	-		1,00	-	-
Epoetin alpha biosimilars	1,13	0,62	2,06		1,08	0,60	1,97		0,81	0,47	1,37		0,79	0,46	1,35
Blood dyscrasia															
Other originators	1,00	-	-		1,00	-	-		1,00	-	-		1,00	-	-
Epoetin alpha biosimilars	1,29	0,82	2,03		1,26	0,80	1,99		0,86	0,67	1,12		0,86	0,66	1,12

Supplementary table 9a.CKD setting: predefined subgroup analyses for effectiveness and safety outcomes — Epoetin alpha biosimilars versus Epoetin alpha originator.

Epoetin alpha biosimilars versus Epoetin alpha originator	Composite outcome				All-cause mortality				Blood transfusion				MACE				Blood dyscrasia			
	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value
	1,02	**0,78**	**1,33**	**0,8859**	**0,92**	**0,67**	**1,28**	**0,6227**	**0,95**	**0,54**	**1,69**	**0,8715**	**0,92**	**0,49**	**1,70**	**0,7774**	**1,19**	**0,74**	**1,92**	**0,4646**
Sex																				
Male	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Female	1,12	0,96	1,30	0,1588	1,18	0,99	1,41	0,0719	1,15	0,85	1,57	0,3708	0,85	0,60	1,19	0,3368	1,11	0,84	1,48	0,4667
Age (years)																				
<45	0,30	0,14	0,64	0,0017	0,15	0,05	0,47	0,0012	0,92	0,37	2,28	0,8559	0,37	0,05	2,67	0,3234	0,79	0,29	2,16	0,6477
45-64	0,78	0,59	1,04	0,0893	0,38	0,25	0,57	0,0000	1,16	0,69	1,94	0,5869	1,84	1,09	3,08	0,0219	1,44	0,91	2,28	0,1152
64-84	0,80	0,67	0,95	0,0107	0,59	0,48	0,73	0,0000	1,15	0,82	1,62	0,4289	1,05	0,72	1,54	0,7902	1,31	0,96	1,79	0,0911
>84	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Baseline Hb levels (g/dl)																				
< 8	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
8-10	0,79	0,61	1,04	0,0898	0,97	0,69	1,36	0,8423	0,38	0,25	0,59	0,0000					0,78	0,48	1,27	0,3192
10-11	0,55	0,40	0,75	0,0002	0,75	0,51	1,10	0,1463	0,18	0,10	0,32	0,0000					0,35	0,19	0,64	0,0006
≥*11*	0,31	0,15	0,64	0,0017	0,49	0,22	1,09	0,0806	0,24	0,07	0,78	0,0177					0,35	0,10	1,18	0,0893
Number of hospitalizations in the previous 2 years																				
0	0,52	0,39	0,68	0,0000	0,45	0,32	0,62	0,0000	0,57	0,35	0,94	0,0267								
1	0,65	0,52	0,81	0,0002	0,59	0,45	0,77	0,0001	0,54	0,35	0,85	0,0074								
2-3	0,80	0,65	0,98	0,0276	0,79	0,62	1,00	0,0485	0,77	0,52	1,15	0,1968								
>3	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Other ETP active																				
specialnutritionprogram	1,58	1,01	2,47	0,0448	4,65	1,93	11,23	0,0006												
Comorbidities																				
Diabetes					0,81	0,68	0,97	0,0228												
Hypertension	0,77	0,65	0,91	0,0021	0,72	0,59	0,87	0,0009												
Heartdiseases									1,59	1,12	2,24	0,0087								

Arrythmia																				
Heartfailure																				
CerebrovascularDisease									2,61	1,83	3,70	0,0000								
Arterial and venousThrombosis																				

Supplementary table 9b. CKD setting: predefined subgroup analyses for effectiveness and safety outcomes — Epoetin alpha biosimilars versus Other originators.

Epoetin alpha biosimilars versus Other originators	Composite outcome				All-cause mortality				Blood transfusion				MACE				Blood dyscrasia			
	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value
	1,09	**0,85**	**1,41**	**0,4911**	**1,00**	**0,73**	**1,38**	**0,9827**	**0,99**	**0,57**	**1,71**	**0,9576**	**1,08**	**0,60**	**1,97**	**0,7922**	**1,26**	**0,80**	**1,99**	**0,3253**
Sex																				
Male	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Female	0,82	0,75	0,89	0,0000	0,80	0,72	0,88	0,0000	0,80	0,67	0,95	0,0118	0,98	0,81	1,19	0,8567	0,90	0,77	1,06	0,1995
Age (years)																				
<45	0,51	0,37	0,72	0,0001	0,14	0,07	0,28	0,0000	1,06	0,62	1,81	0,8405	0,18	0,05	0,72	0,0157	1,07	0,67	1,72	0,7809
45-64	0,51	0,43	0,61	0,0000	0,27	0,21	0,35	0,0000	0,96	0,72	1,28	0,7662	0,58	0,39	0,86	0,0073	0,94	0,72	1,23	0,6405
64-84	0,64	0,58	0,71	0,0000	0,49	0,43	0,55	0,0000	1,00	0,83	1,21	0,9916	0,68	0,54	0,85	0,0007	1,04	0,87	1,24	0,6487
>84	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Baseline Hb levels (g/dl)																				
< 8	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
8-10	0,79	0,66	0,94	0,0075	0,85	0,69	1,05	0,1266	0,53	0,40	0,72	0,0000					0,80	0,58	1,11	0,1826
10-11	0,55	0,45	0,66	0,0000	0,59	0,47	0,74	0,0000	0,27	0,19	0,38	0,0000					0,52	0,37	0,74	0,0003
≥*11*	0,516	0,372	0,715	0,0001	0,639	0,437	0,936	0,0213	0,221	0,104	0,467	0,0001					0,433	0,226	0,829	0,0115
Number of hospitalizations in the previous 2 years																				
0	0,50	0,43	0,59	0,0000	0,44	0,36	0,52	0,0000	0,68	0,53	0,89	0,0046					0,59	0,46	0,76	0,0001
1	0,66	0,57	0,75	0,0000	0,58	0,49	0,68	0,0000	0,60	0,46	0,78	0,0002					0,81	0,64	1,03	0,0901
2-3	0,77	0,68	0,87	0,0000	0,70	0,60	0,81	0,0000	0,84	0,65	1,07	0,1596					0,93	0,74	1,18	0,5648
>3	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Other ETP active																				
specialnutritionprogram	2,52	2,01	3,15	0,0000	6,20	4,03	9,55	0,0000	2,15	1,40	3,30	0,0005					1,70	1,20	2,41	0,0028
Comorbidities																				
Diabetes					0,89	0,80	0,98	0,0202									0,83	0,70	0,97	0,0193
Hypertension	0,86	0,78	0,94	0,0015	0,75	0,67	0,84	0,0000												

Heartdiseases									1,30	1,07	1,59	0,0086								
Arrythmia																				
Heartfailure	1,11	1,00	1,23	0,0490	1,22	1,09	1,38	0,0010												
CerebrovascularDisease	1,17	1,04	1,31	0,0116					2,66	2,14	3,31	0,0000								
Arterial and venousThrombosis																				

Supplementary table 10a.Oncology setting: predefined subgroup analyses for effectiveness and safety outcomes — Epoetin alpha biosimilars versus Epoetin alpha originator.

Epoetin alpha biosimilars versus Epoetin alpha originator	Composite outcome				All-cause mortality				Blood transfusion				MACE				Blood dyscrasia			
	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value	HR_adj	LCI95%	UCI95%	p-value
	0,91	**0,79**	**1,06**	**0,2242**	**0,82**	**0,70**	**0,97**	**0,0209**	**1,06**	**0,82**	**1,35**	**0,6686**	**0,84**	**0,48**	**1,47**	**0,5335**	**0,86**	**0,66**	**1,14**	**0,2944**
Sex																				
Male	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Female	0,83	0,74	0,93	0,0019	0,75	0,66	0,86	0,0000	0,99	0,80	1,21	0,8971	0,71	0,45	1,12	0,1415	1,08	0,87	1,34	0,5049
Age (years)																				
<45	0,81	0,59	1,09	0,1645	0,55	0,38	0,79	0,0014	1,33	0,79	2,26	0,2836	0,40	0,13	1,17	0,0925	1,48	0,89	2,47	0,1351
45-64	0,86	0,72	1,04	0,1223	0,78	0,64	0,96	0,0176	1,57	1,10	2,24	0,0123	0,35	0,19	0,67	0,0013	1,30	0,90	1,88	0,1618
64-84	0,88	0,74	1,04	0,1400	0,80	0,67	0,96	0,0182	1,18	0,84	1,66	0,3436	0,39	0,22	0,66	0,0006	1,13	0,80	1,61	0,4906
>84	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Baseline Hb levels (g/dl)																				
< 8	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
8-10	0,73	0,59	0,91	0,0046	0,76	0,60	0,96	0,0205	0,53	0,39	0,73	0,0001					0,61	0,43	0,86	0,0054
10-11	0,42	0,24	0,72	0,0018	0,47	0,26	0,85	0,0119	0,13	0,03	0,52	0,0041					0,27	0,08	0,88	0,0302
≥*11*	0,53	0,21	1,30	0,1640	0,62	0,23	1,71	0,3583	0,23	0,03	1,68	0,1475					0,33	0,05	2,44	0,2788
Number of hospitalizations in the previous 2 years																				
0	0,47	0,39	0,57	0,0000	0,54	0,44	0,67	0,0000	0,53	0,38	0,73	0,0001	0,30	0,14	0,67	0,0030	0,38	0,26	0,54	0,0000
1	0,66	0,56	0,78	0,0000	0,72	0,60	0,87	0,0006	0,71	0,54	0,94	0,0156	0,55	0,30	0,99	0,0479	0,55	0,41	0,74	0,0001
2-3	0,78	0,67	0,92	0,0024	0,92	0,77	1,09	0,3216	0,66	0,50	0,87	0,0029	0,63	0,36	1,13	0,1204	0,62	0,47	0,82	0,0008
>3	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Comorbidities																				
Diabetes																				
Hypertension																				
Heartdiseases									2,19	1,46	3,29	0,0002								

Arrythmia									0,57	0,32	1,02	0,0601							
Heartfailure	1,55	1,07	2,24	0,0204	1,55	1,04	2,31	0,0298									2,59	1,52	4,39	0,0005
CerebrovascularDisease	1,27	0,97	1,66	0,0879															
Arterial and venousThrombosis	1,45	1,05	2,00	0,0234									3,65	1,67	7,99	0,0012			

Supplementary table 10b. Oncology setting: predefined subgroup analyses for effectiveness and safety outcomes — Epoetin alpha biosimilars versus Other originators.

Epoetin alpha biosimilars versus Other originators	Composite outcome				All-cause mortality				Blood transfusion				MACE				Blood dyscrasia			
	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value	HR_adj	LCI95 %	UCI95 %	p-value
	1,01	**0,88**	**1,16**	**0,9252**	**1,01**	**0,86**	**1,18**	**0,9536**	**0,98**	**0,77**	**1,23**	**0,8328**	**0,79**	**0,46**	**1,35**	**0,3901**	**0,86**	**0,66**	**1,12**	**0,2676**
Sex																				
Male	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Female	0,67	0,61	0,74	0,0000	0,67	0,60	0,75	0,0000	0,66	0,57	0,77	0,0000	0,83	0,60	1,15	0,2561	0,76	0,65	0,90	0,0012
Age (years)																				
<45	0,74	0,58	0,95	0,0178	0,46	0,34	0,64	0,0000	1,40	0,96	2,04	0,0778	0,54	0,22	1,30	0,1683	0,72	0,45	1,14	0,1602
45-64	0,88	0,76	1,01	0,0688	0,73	0,62	0,87	0,0002	1,33	1,03	1,71	0,0268	0,46	0,27	0,77	0,0032	1,13	0,86	1,46	0,3811
64-84	0,83	0,72	0,94	0,0043	0,82	0,71	0,95	0,0072	1,01	0,79	1,28	0,9627	0,82	0,54	1,25	0,3535	0,95	0,74	1,22	0,7017
>84	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Baseline Hb levels (g/dl)																				
< 8	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
8-10					0,87	0,69	1,10	0,2368												
10-11					0,54	0,33	0,89	0,0147												
≥11					1,80	0,78	4,14	0,1675												
Number of hospitalizations in the previous 2 years																	0,486	0,374	0,633	0
0	0,63	0,54	0,73	0,0000	0,76	0,64	0,90	0,0013	0,65	0,51	0,83	0,0006								
1	0,62	0,54	0,71	0,0000	0,69	0,59	0,81	0,0000	0,64	0,52	0,80	0,0001					0,48	0,38	0,61	0,0000
2-3	0,83	0,73	0,94	0,0037	0,88	0,76	1,02	0,0925	0,85	0,69	1,04	0,1145					0,83	0,68	1,03	0,0869
>3	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-	1,00	-	-	-
Comorbidities																				
Diabetes																				
Hypertension																				
Heartdiseases																				
Arrythmia																				

Heartfailure	1,37	1,02	1,84	0,0340					1,79	1,15	2,79	0,0098					1,72	1,09	2,70	0,0200
Cerebrovascular Disease	1,37	1,11	1,68	0,0029	1,34	1,06	1,70	0,0132					2,54	1,46	4,42	0,0010				
Arterial and venousThrombosis	1,46	1,14	1,87	0,0027	1,61	1,22	2,13	0,0008	1,43	0,95	2,16	0,0868	2,36	1,15	4,83	0,0188				

Supplementary table 11.Patients characteristics after genetic matching by settings and ESAs (biosimilars, epoetin alpha originator or other originators).

	Genetic matched chronic kidney disease setting (n= 462)						Genetic matched oncology setting (n=1359)				
	Biosimilars epoetin alpha	**Originator epoetin alpha**	**Other orignators**	**p value Biosimilar vs originator epoetin alpha**	**p value Biosimilars vs other originators**		**Biosimilars epoetin alpha**	**Originator epoetin alpha**	**Other orignators**	**p value Biosimilar vs originator epoetin alpha**	**p value Biosimilars vs other originators**
	N	**N**	**N**				**N**	**N**	**N**		
	154	**154**	**154**				**453**	**453**	**453**		
Sex				0,8192	1,0000					1,0000	0,9470
Male	84	82	84				233	233	232		
Female	70	72	70				220	220	221		
Age* (years)				0,9995	1,0000						
<45	2	2	2				20	20	21	0,9999	0,9979
45-64	9	9	9				126	125	126		
64-84	54	53	54				226	227	224		
>84	89	90	89				81	81	82		
Mean (SD)	79.2 (10.2)	79.5 (11.6)	79.6 (12.6)	0,7944	0,7428		68.5 (11.9)	68.3 (12.2)	68.0(12.5)	0,7529	0,4612
Baseline Hb levels (g/dl)*				0,9702	1,0000					1,0000	1,0000
< 8	10	8	10				29	29	29		
8-10	92	94	92				409	409	409		
10-11	50	50	50				12	12	12		
≥11	2	2	2				3	3	3		
Mean (SD)	9.3 (1.3)	9.3 (0.9)	9.3 (1.1)	0,8799	0,8803		9.0 (0.8)	9.0 (0.8)	9.0 (0.7)	0,8629	0,8513
Other ETP active*											
Special nutrition program	9	8	9	0,8030	1,0000						
Comorbidities in the previous 2 y.											
Diabetes	69	68	69	0,9087	1,0000		101	99	102	0,8727	0,9365
Hypertension	50	51	50	0,9034	1,0000		82	82	82	1,0000	1,0000
Heart diseases	75	75	74	1,0000	0,9092		33	33	33	1,0000	1,0000
Arrythmia	39	39	40	1,0000	0,8962		20	20	20	1,0000	1,0000

Heart failure	55	54	54	0,9051	0,9051		7	7	7	1,0000	1,0000
Cerebrovascular Disease	21	19	21	0,7346	1,0000		14	13	14	0,8451	1,0000
Arterial and venous Thrombosis	1	1	1	1,0000	1,0000		8	8	8	1,0000	1,0000
Number of hospitalizations in the previous 2 years				0,9951	0,9983					1,0000	0,9997
0	42	40	41				102	102	102		
1	43	44	43				134	134	134		
2-3	48	49	48				144	144	145		
>3	21	21	22				73	73	72		

Supporting table 12. Determinants of prescription for biosimilars in CDK and oncology settings.

	Chronic kidney disease setting (n= 8161)									Oncology setting (n=5309)								
Variables	**Biosimilars vs originator epoetin alpha**					**Biosimilars vs other originators**				**Biosimilars vs originator epoetin alpha**					**Biosimilars vs other originators**			
	OR	LCI95%	UCI95%	p-value		OR	LCI95%	UCI95%	p-value	OR	LCI95%	UCI95%	p-value		OR	LCI95%	UCI95%	p-value
Sex																		
Male	1,00	-	-	-		1,00	-	-	-	1,00	-	-	-		1,00	-	-	-
Female	0,93	0,67	1,31	0,6957		0,95	0,69	1,32	0,7811	0,96	0,78	1,19	0,7070		0,73	0,60	0,90	**0,0026**
Age years)																		
<45	0,68	0,16	2,89	0,5996		0,72	0,17	2,99	0,65122	0,64	0,37	1,11	0,11174		0,71	0,42	1,21	0,2106
45-64	0,74	0,36	1,52	0,4148		0,72	0,36	1,45	0,3540	0,77	0,55	1,06	0,1073		0,74	0,54	1,00	0,0510
64-84	1,34	0,93	1,93	0,1164		1,27	0,90	1,81	0,17319	0,81	0,61	1,09	0,17057		0,79	0,60	1,05	0,1022
>84	1,00	-	-	-		1,00	-	-	-	1,00	-	-	-		1,00	-	-	-
Baseline Hb levels (g/dl)																		
< 8	1,00	-	-	-		1,00	-	-	-	1,00	-	-	-		1,00	-	-	-
8-10	0,94	0,47	1,87	0,8507		0,63	0,32	1,23	0,1783	1,13	0,74	1,72	0,5717		0,77	0,51	1,16	0,2176
10-11	1,55	0,75	3,20	0,2314		0,64	0,32	1,28	0,2093	1,49	0,68	3,26	0,3136		1,02	0,49	2,11	0,9665
≥*11*	0,44	0,09	2,09	0,2990		0,27	0,06	1,24	0,0930	1,80	0,44	7,43	0,41733		2,97	0,70	12,65	0,1403
Number of hospitalizations in the previous 2 years																		
0	3,12	1,69	5,75	**0,0003**		1,60	0,86	2,97	0,1339	1,28	0,91	1,80	0,1610		1,17	0,85	1,62	0,3349
1	1,71	0,97	3,03	0,0648		1,34	0,77	2,32	0,29668	1,27	0,92	1,75	0,1470		1,12	0,83	1,53	0,4537
2-3	1,37	0,80	2,36	0,2491		1,24	0,74	2,10	0,4178	1,26	0,92	1,73	0,1516		1,14	0,84	1,54	0,4072
>3	1,00	-	-	-		1,00	-	-	-	1,00	-	-	-		1,00	-	-	-
Comorbidities																		
Heart failure	1,82	1,22	2,71	**0,0036**														
Heart diseases						2,21	1,49	3,28	**0,0001**									