Changes in Iron Availability with Roxadustat in Non-Dialysis-Dependent and Dialysis-Dependent Patients with Anemia of CKD

Supplemental Material

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Rescue therapy criteria

Red blood cell (RBC) transfusion

RBC transfusion was allowed in all studies for all patients who needed rapid correction of anemia due to acute or severe blood loss, for patients who had moderate to severe symptoms from their anemia, or if the investigator was of the opinion that the RBC transfusion was a medical necessity.

Erythropoiesis-stimulating agent (ESA) use

ESA use was allowed for patients who met all the following criteria:

- Their hemoglobin (Hb) level had not sufficiently responded to ≥2 dose increases or the maximum dose limit of the study drug had been reached
- Their Hb was <8.0 g/dl (non-dialysis-dependent [NDD]-chronic kidney disease [CKD]), <8.5 g/dl, (ROCKIES and SIERRAS), or <9.0 g/dl (HIMALAYAS) on two consecutive measurements
- Clinical judgement did not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in Hb
- To reduce the risk of alloimmunization in transplant eligible patients and/or to reduce other transfusion-related risk

Patients receiving ESA rescue therapy were to hold study treatment until rescue ESA was stopped.

Intravenous iron supplementation

Intravenous iron supplementation was permitted as rescue therapy if a patient's Hb had not responded to ≥2 dose increases of the study drug while taking oral iron, the patient was unresponsive to or did not tolerate oral iron, and Hb was <8.5 g/dl and ferritin was <100 ng/ml and/or transferrin saturation was <20%.

Table S1. Roxadustat dosing during the studies

	NDD-CKD (*N*=4277)			DD-CKD (*N*=3917)		
	OLYMPUS (*n*=2761)	**ALPS (*n*=594)**	**ANDES (*n*=922)**	**ROCKIES (*n*=2133)**	**SIERRAS (*n*=741)**	**HIMALAYAS (*n*=1043)**
Starting dose	70 mg TIW	≤70 kg: 70 mg TIW; >70 kg: 100 mg TIW	<70 kg: 70 mg TIW; ≥70 kg: 100 mg TIW	ESA-naive: <70 kg: 70 mg TIW; ≥70 kg: 100 mg TIW Prior ESA use: dose conversion algorithm	ESA-naive: <70 kg: 70 mg TIW; ≥70 kg: 100 mg TIW Prior ESA use: dose conversion algorithm	<70 kg: 70 mg TIW; ≥70 kg: 100 mg TIW
Dose adjustment	Dose titrated every 4 weeks to maintain Hb 11.0±1 g/dl	Dose titrated every 4 weeks to maintain Hb 11.0±1 g/dl with initial correction period		Dose titrated every 4 weeks to maintain Hb 11.0±1 g/dl with initial correction period if ESA-naive		

CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; NDD, non-dialysis-dependent; TIW, three times weekly.

Table S2. Starting dose of roxadustat for patients stable on ESA prior to randomization

Roxadustat (mg/dose TIW)	Epoetin alfa or beta (IU/week)	Darbepoetin alfa (µg/week)	Mircera (µg/month)
70	<5000	<25	<80
100	5000 to <8000	25 to <40	80 to <120
150	8000 to <16,000	40 to <80	120 to <200
200	≥16,000	≥80	≥200

ESA, erythropoiesis-stimulating agent; TIW, three times weekly.

Table S3. Patient disposition in the NDD-CKD and DD-CKD populations

NDD-CKD		
	Roxadustat	**Placebo**
ITT population, *n*	2391	1886
Patients treated, *n* (%)	2386 (99.8)	1884 (99.9)
Completed treatment, *n* (%)	1485 (62.2)	769 (40.8)
Discontinued treatment early, *n* (%)	901 (37.8)	1115 (59.2)
Reasons for discontinuation, *n* (%)		
Withdrawal by subject	393 (16.5)	533 (28.3)
Adverse event	150 (6.3)	83 (4.4)
Death	81 (3.4)	30 (1.6)
Development of study specific discontinuation criteria	76 (3.2)	252 (13.4)
Physician decision	49 (2.1)	67 (3.6)
Lost to follow-up	33 (1.4)	8 (0.4)
Kidney transplant	24 (1.0)	9 (0.5)
Dialysis initiation	23 (1.0)	11 (0.6)
Non-compliance to protocol	23 (1.0)	20 (1.1)
Other	49 (2.0)	102 (5.4)
DD-CKD		
	Roxadustat	**Epoetin alfa**
ITT population, *n*	1943	1947
Subjects treated, *n* (%)	1940 (99.8)	1940 (99.6)
Completed treatment, *n* (%)	1135 (58.5)	1287 (66.3)
Discontinued treatment early, *n* (%)	805 (41.5)	653 (33.7)
Reasons for discontinuation, *n* (%)		

Withdrawal by subject	213 (11.0)	166 (8.5)
Death	141 (7.3)	129 (6.6)
Kidney transplant	115 (5.9)	147 (7.6)
Adverse event	110 (5.7)	54 (2.8)
Physician decision	68 (3.5)	32 (1.6)
Patient relocated/moved (or lost to follow-up)	54 (2.8)	65 (3.4)
Development of study specific discontinuation criteria	32 (1.6)	0 (0.0)
Other	72 (3.7)	60 (3.1)

CKD, chronic kidney disease; DD, dialysis-dependent; ITT, intention-to-treat; NDD, non-dialysis-dependent.

Table S4. Baseline IV iron use by country

	NDD-CKD				DD-CKD			
	Roxadustat (*N*=2319)		Placebo (*N*=1886)		Roxadustat (*N*=1943)		Placebo (*N*=1947)	
Country	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)
Dominican Republic	8	2 (25.0)	4	0	NA	NA	NA	NA
Guatemala	21	0	6	0	NA	NA	NA	NA
Mexico	75	0	56	0	56	4 (7.1)	57	3 (5.3)
Panama	6	0	6	0	NA	NA	NA	NA
Canada	26	0	24	2 (8.3)	27	5 (18.5)	28	6 (21.4)
United States of America	552	1 (0.2)	441	2 (0.5)	882	355 (40.2)	887	345 (38.9)
Argentina	68	4 (5.9)	52	1 (1.9)	31	11 (35.5)	22	8 (36.4)
Brazil	43	2 (4.7)	42	1 (2.4)	14	6 (42.9)	16	2 (12.5)
Chile	7	1 (14.3)	4	0	3	1 (33.3)	3	0
Colombia	20	0	10	0	0	NA	1	0
Peru	90	4 (4.4)	85	6 (7.1)	41	12 (29.3)	41	10 (24.4)
Bulgaria	63	10 (15.9)	50	9 (18.0)	113	32 (28.3)	122	22 (18.0)
Belarus	7	0	5	0	0	NA	3	0

Czech Republic	10	1 (10.0)	10	0	13	1 (7.7)	13	1 (7.7)
Hungary	33	2 (6.1)	29	4 (13.8)	32	8 (25.0)	31	5 (16.1)
Poland	52	2 (3.8)	34	2 (5.9)	31	8 (25.8)	27	8 (29.6)
Romania	32	9 (28.1)	17	4 (23.5)	13	6 (46.2)	8	2 (25.0)
Russian Federation	116	2 (1.7)	84	3 (3.6)	217	85 (39.2)	214	75 (35.0)
Slovakia	4	1 (25.0)	5	0	16	9 (56.3)	16	6 (37.5)
Ukraine	172	28 (16.3)	148	33 (22.3)	191	49 (25.7)	192	55 (28.6)
Estonia	0	0	1	1 (100.0)	NA	NA	NA	NA
Latvia	NA	NA	NA	NA	2	0	4	0
Sweden	NA	NA	NA	NA	4	0	5	1 (20.0)
United Kingdom	8	2 (25.0)	4	1 (25.0)	NA	NA	NA	NA
Greece	4	0	2	0	NA	NA	NA	NA
Italy	4	2 (50.0)	2	0	NA	NA	NA	NA
Serbia	56	9 (16.1)	29	3 (10.3)	NA	NA	NA	NA
Spain	18	1 (5.6)	14	1 (7.1)	20	5 (25.0)	19	2 (10.5)
Belgium	5	0	4	1 (25.0)	NA	NA	NA	NA
Germany	3	0	2	0	NA	NA	NA	NA
South Africa	12	1 (8.3)	4	1 (25.0)	NA	NA	NA	NA

Hong Kong	13	0	8	0	NA	NA	NA	NA
Republic of Korea	269	9 (3.3)	198	9 (4.5)	16	2 (12.5)	18	4 (22.2)
Taiwan	134	1 (0.7)	101	2 (2.0)	1	1 (100.0)	4	1 (25.0)
Malaysia	39	0	17	0	11	0	12	0
Philippines	54	0	54	0	43	0	42	0
Singapore	2	0	2	0	NA	NA	NA	NA
Thailand	68	2 (2.9)	50	1 (2.0)	30	6 (30.0)	26	0
Vietnam	132	1 (0.8)	131	1 (0.8)	76	24 (31.6)	76	19 (25.0)
India	103	1 (1.0)	102	2 (2.0)	43	1 (2.3)	43	2 (4.7)
Georgia	10	0	7	0	0	0	0	0
Turkey	31	2 (6.5)	20	0	0	0	0	0
Australia	14	0	11	0	17	3 (17.6)	17	0
New Zealand	7	0	11	0	NA	NA	NA	NA

CKD, chronic kidney disease; DD, dialysis-dependent; IV, intravenous; NA, not applicable; NDD, non-dialysis dependent.

Intention-to-treat analysis set. Geographic regions are assigned using the United Nations MP4 standard for geographic regions.

Table S5. Baseline oral iron use by country

	NDD-CKD				DD-CKD			
	Roxadustat (*N*=2319)		Placebo (*N*=1886)		Roxadustat (*N*=1943)		Placebo (*N*=1947)	
Country	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)
Dominican Republic	8	3 (37.5)	4	3 (75.0)	NA	NA	NA	NA
Guatemala	21	9 (42.9)	6	4 (66.7)	NA	NA	NA	NA
Mexico	75	14 (18.7)	56	7 (12.5)	56	1 (1.8)	57	5 (8.8)
Panama	6	4 (66.7)	6	3 (50.0)	NA	NA	NA	NA
Canada	26	3 (11.5)	24	1 (4.2)	27	0	28	0
United States of America	552	98 (17.8)	441	60 (13.6)	882	55 (6.2)	887	64 (7.2)
Argentina	68	8 (11.8)	52	3 (5.8)	31	15 (48.4)	22	7 (31.8)
Brazil	43	2 (4.7)	42	1 (2.4)	14	3 (21.4)	16	5 (31.3)
Chile	7	3 (42.9)	4	0	3	1 (33.3)	3	0
Colombia	20	8 (40.0)	10	5 (50.0)	0	NA	1	1 (100.0)
Peru	90	19 (21.1)	85	13 (15.3)	41	3 (7.3)	41	2 (4.9)
Bulgaria	63	12 (19.0)	50	5 (10.0)	113	16 (14.2)	122	16 (13.1)
Belarus	7	4 (57.1)	5	3 (60.0)	0	NA	3	2 (66.7)

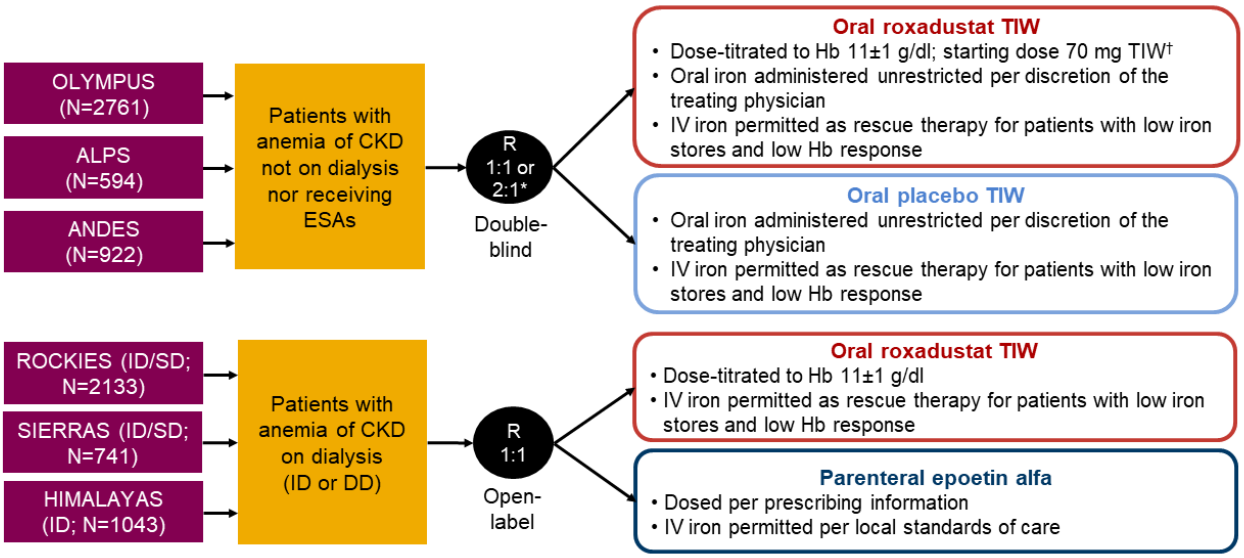
Czech Republic	10	0	10	2 (20.0)	13	0	13	0
Hungary	33	5 (15.2)	29	2 (6.9)	32	0	31	0
Poland	52	15 (28.8)	34	12 (35.3)	31	5 (16.1)	27	1 (3.7)
Romania	32	10 (31.3)	17	5 (29.4)	13	8 (61.5)	8	0
Russian Federation	116	41 (35.3)	84	21 (25.0)	217	55 (25.3)	214	43 (20.1)
Slovakia	4	0	5	0	16	0	16	0
Ukraine	172	45 (26.2)	148	31 (20.9)	191	56 (29.3)	192	59 (30.7)
Estonia	0	NA	1	0	NA	NA	NA	NA
Latvia	NA	NA	NA	NA	2	1 (50.0)	4	1 (25.0)
Sweden	NA	NA	NA	NA	4	0	5	0
United Kingdom	8	1 (12.5)	4	1 (25.0)	NA	NA	NA	NA
Greece	4	0	2	0	NA	NA	NA	NA
Italy	4	3 (75.0)	2	0	NA	NA	NA	NA
Serbia	56	34 (60.7)	29	19 (65.5)	NA	NA	NA	NA
Spain	18	8 (44.4)	14	3 (21.4)	20	0	19	0
Belgium	5	3 (60.0)	4	1 (25.0)	NA	NA	NA	NA
Germany	3	0	2	0	NA	NA	NA	NA
South Africa	12	3 (25.0)	4	1 (25.0)	NA	NA	NA	NA

Hong Kong	13	0	8	3 (37.5)	NA	NA	NA	NA
Republic of Korea	269	107 (39.8)	198	56 (28.3)	16	14 (87.5)	18	15 (83.3)
Taiwan	134	5 (3.7)	101	4 (4.0)	1	0	4	1 (25.0)
Malaysia	39	18 (46.2)	17	8 (47.1)	11	11 (100.0)	12	12 (100.0)
Philippines	54	3 (5.6)	54	4 (7.4)	43	0	42	0
Singapore	2	1 (50.0)	2	2 (100.0)	NA	NA	NA	NA
Thailand	68	12 (17.6)	50	4 (8.0)	30	4 (13.3)	26	4 (15.4)
Vietnam	132	52 (39.4)	131	49 (37.4)	76	20 (26.3)	76	18 (23.7)
India	103	3 (2.9)	102	8 (7.8)	43	0	43	0
Georgia	10	2 (20.0)	7	2 (28.6)	NA	NA	NA	NA
Turkey	31	9 (29.0)	20	1 (5.0)	NA	NA	NA	NA
Australia	14	1 (7.1)	11	1 (9.1)	17	0	17	0
New Zealand	7	0	11	1 (9.1)	NA	NA	NA	NA

CKD, chronic kidney disease; DD, dialysis-dependent; NA, not applicable; NDD, non-dialysis dependent.

Intention-to-treat analysis set. Geographic regions are assigned using the United Nations MP4 standard for geographic regions.

Figure S1. Overview of the roxadustat pivotal, phase 3 NDD-CKD and DD-CKD trial designs.



CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ID, incident dialysis; IV, intravenous; NDD, non-dialysis dependent; R, randomization; SD, standard deviation;TIW, three times weekly.

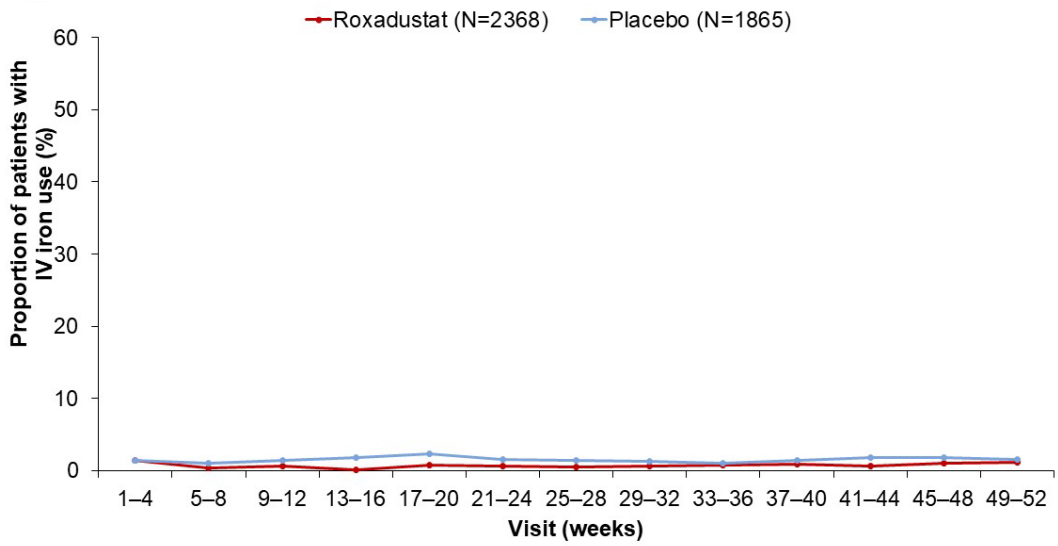
*1:1 randomization in OLYMPUS, 2:1 randomization in ALPS and ANDES.

†100 mg TIW for patients with bodyweight ≥70 kg in ANDES and ALPS.

‡IV iron was permitted per local standard of care in the epoetin alfa arm of the ROCKIES study.

Figure S2. A) IV and B) oral iron use in the NDD-CKD population.

A)



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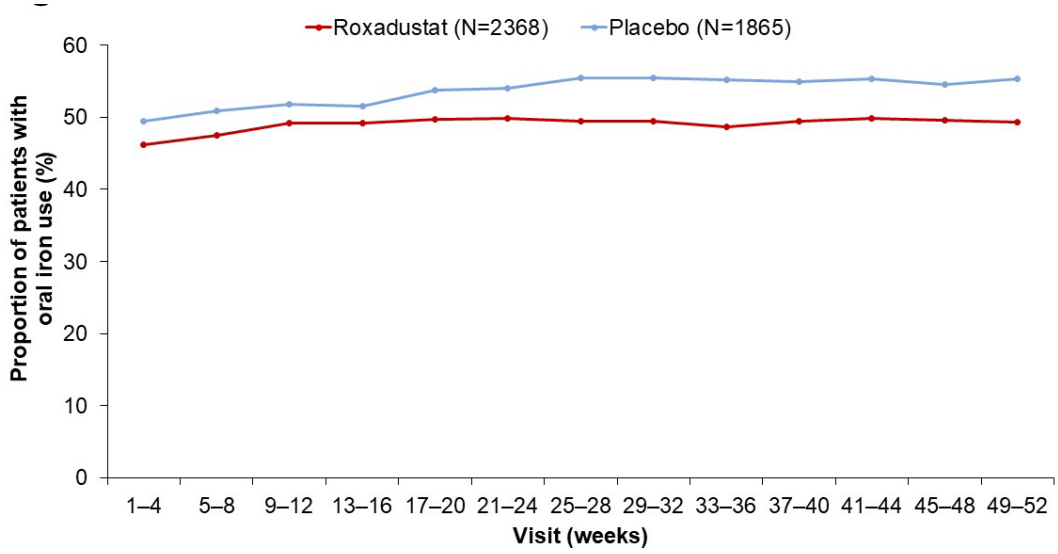
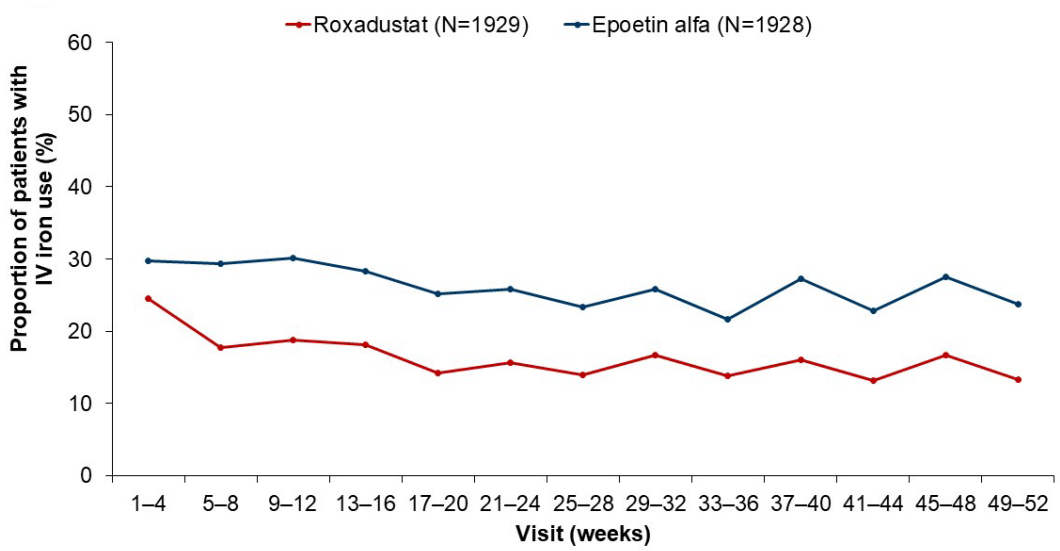


CKD, chronic kidney disease; IV, intravenous; NDD, non-dialysis-dependent.

Full analysis set.

Figure S3. A) IV and B) oral iron use in the DD-CKD population.

A)



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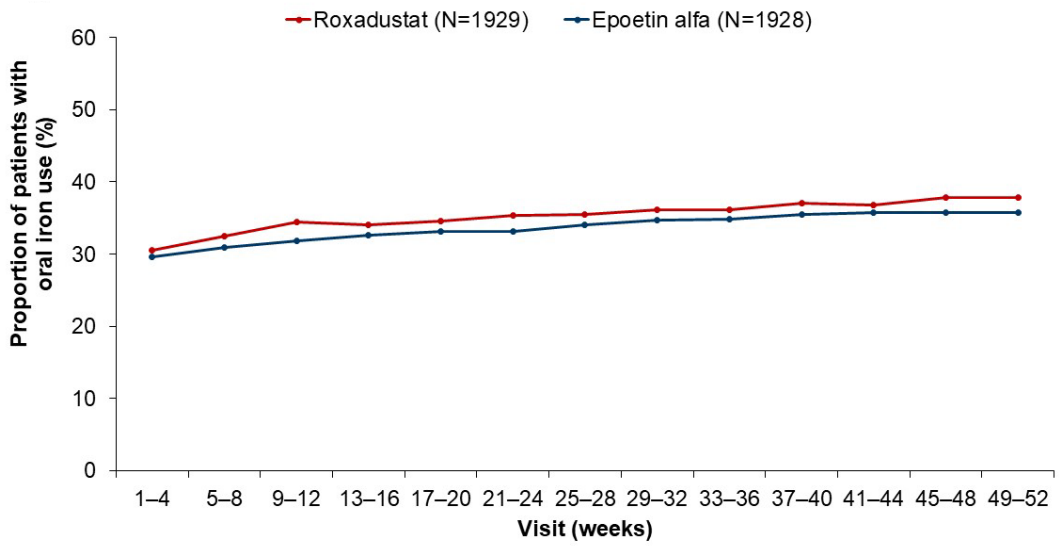

CKD, chronic kidney disease; DD, dialysis-dependent; IV, intravenous.

Full analysis set.