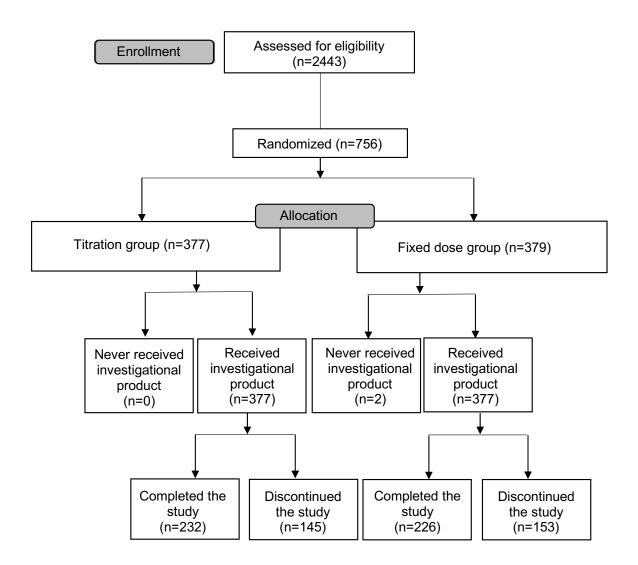
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## **Supplemental Figure S1. Subject Disposition (CONSORT Diagram)**



## Supplemental Figure S2 Forest Plot of Subgroup Analysis of Subject Incidence of Transfusion

#### Subject incidence of RBC transfusion by Subgroups

	oubject mon	delice of RDO trailsta	sion by subgroups	
Subgroup	Titration N1/n (%)	Fixed Dose N1/n (%)		Difference in proportion (%) (95% CI)
Transfusion within 12 months of randomization Yes No	10/32 (31.25) 82/345 (23.77)	10/30 (33.33) 81/347 (23.34)	<del>                                     </del>	2.08 (-21.21,25.37) -0.43 (-6.75,5.9)
Site practice setting Nephrology Non-nephrology	87/354 (24.58) 5/23 (21.74)	87/353 (24.65) 4/24 (16.67)	<del>  • • •</del> •	0.07 (-6.28,6.42) -5.07 (-27.58,17.43)
Age Less than 65 65 to <75 >=75	25/129 (19.38) 21/97 (21.65) 46/151 (30.46)	31/133 (23.31) 21/96 (21.88) 39/148 (26.35)		3.93 (-5.98,13.84) 0.23 (-11.42,11.87) -4.11 (-14.32,6.1)
Gender Male Female	33/154 (21.43) 59/223 (26.46)	40/159 (25.16) 51/218 (23.39)	 	3.73 (-5.62,13.08) -3.06 (-11.13,5.01)
Race White Black Other	60/220 (27.27) 26/125 (20.80) 6/32 (18.75)	58/214 (27.10) 27/133 (20.30) 6/30 (20.00)	<u>                                     </u>	-0.17 (-8.54,8.2) -0.5 (-10.37,9.37) 1.25 (-18.44,20.94)
Baseline hemoglobin (g/dL) <9.0 9.0 to <9.5 9.5 to <10.0	44/173 (25.43) 31/104 (29.81) 17/100 (17.00)	46/172 (26.74) 22/114 (19.30) 23/91 (25.27)		1.31 (-7.96,10.58) -10.51 (-21.9,0.88) 8.27 (-3.3,19.85)
Baseline eGFR (mL/min/1.73m^2) <30.0 >=30.0	86/318 (27.04) 5/58 (8.62)	70/298 (23.49) 21/79 (26.58)	<b>⊢</b> ■	-3.55 (-10.41,3.3) 17.96 (5.83,30.09)
Baseline diabetes Yes No	56/251 (22.31) 36/126 (28.57)	60/250 (24.00) 31/127 (24.41)	 	1.69 (-5.7,9.08) -4.16 (-15.03,6.7)
Initial hemoglobin response quartile (g/dL) Q1: < -0.1 Q2: -0.1 to <0.3 Q3: 0.3 to <0.8 Q4: >=0.8	27/94 (28.72) 20/90 (22.22) 18/84 (21.43) 17/87 (19.54)	29/90 (32.22) 19/92 (20.65) 19/79 (24.05) 10/84 (11.90)		3.5 (-9.8,16.8) -1.57 (-13.49,10.35) 2.62 (-10.26,15.5) -7.64 (-18.47,3.2)
			-30 -20 -10 0 10 20 30 Difference in proportion (%)	

N1 = Number of subject with any transfusion; n = Number of subject in subgroup; Q1 = 1<sup>st</sup> quartile; Q2 = 2<sup>nd</sup> quartile; Q3 = 3<sup>rd</sup> quartile; Q4 = 4<sup>th</sup> quartile

# Supplemental Table S1. Subject Disposition with Discontinuation Reason

	Darbepoetin alfa		
	Titration	Fixed Dose	Total
	(N = 377)	(N = 379)	(N = 756)
	n (%)	n (%)	n (%)
Investigational product accounting			
Subjects who never received investigational product	0 (0.0)	2 (0.5)	2 (0.3)
Subjects who received investigational product	377 (100.0)	377 (99.5)	754 (99.7)
Subjects who completed investigational product	174 (46.2)	174 (45.9)	348 (46.0)
Subjects who discontinued investigational product	203 (53.8)	203 (53.6)	406 (53.7)
Adverse event	19 (5.0)	16 (4.2)	35 (4.6)
Subject request	40 (10.6)	42 (11.1)	82 (10.8)
Decision by sponsor	15 (4.0)	19 (5.0)	34 (4.5)
Lost to follow-up	15 (4.0)	5 (1.3)	20 (2.6)
Death	20 (5.3)	22 (5.8)	42 (5.6)
Protocol-specified criteria	93 (24.7)	97 (25.6)	190 (25.1)
Kidney transplantation	0 (0.0)	2 (0.5)	2 (0.3)
Initiation of dialysis	90 (23.9)	90 (23.7)	180 (23.8)
Lack of efficacy	2 (0.5)	5 (1.3)	7 (0.9)
Missing	1 (0.3)	0 (0.0)	1 (0.1)
Pregnancy	0 (0.0)	1 (0.3)	1 (0.1)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Study completion accounting			
Subjects who completed study	232 (61.5)	226 (59.6)	458 (60.6)
Subjects who discontinued study	145 (38.5)	153 (40.4)	298 (39.4)
Full consent withdrawn	76 (20.2)	84 (22.2)	160 (21.2)
Decision by sponsor	5 (1.3)	7 (1.8)	12 (1.6)
Lost to follow-up	28 (7.4)	23 (6.1)	51 (6.7)
Death	36 (9.5)	39 (10.3)	75 (9.9)

N = number of subjects randomized. Percentages are based on N.

### Supplemental Table S2 Subgroup of Cumulative Dose by Initial Hemoglobin Response

	Darbe	_	
Subgroup of initial Hemoglobin response	Titration (N = 355)	Fixed Dose (N = 345)	Median Difference <sup>b</sup> (95% CI) <sup>c</sup>
1: Initial Hemoglobin response < -0.1 g/dL Cumulative dose (μg)  n Mean <sup>a</sup> SD Median Q1, Q3	94 824.5 1432.5 1185.0 360.0, 2270.0	90 389.0 298.1 450.0 270.0, 720.0	-610.0 (-940.0, -280.0)
2: Initial Hemoglobin response ≥ -0.1 -< 0.3 g/dL Cumulative dose (µg) n Mean <sup>a</sup> SD Median Q1, Q3	90 802.0 1337.3 860.0 390.0, 1920.0	92 395.3 350.1 500.0 210.0, 750.0	-410.0 (-610.0, -210.0)
3: Initial Hemoglobin response ≥ 0.3 -< 0.8 g/dL Cumulative dose (μg) N Mean <sup>a</sup> SD Median Q1, Q3	84 692.9 1252.8 685.0 265.0, 1705.0	79 431.2 317.4 480.0 300.0, 750.0	-275.0 (-490.0, -60.0)
4: Initial Hemoglobin response ≥ 0.8 g/dL Cumulative dose (μg) N Mean <sup>a</sup> SD Median Q1, Q3	87 458.7 1067.9 560.0 210.0, 1240.0	84 434.5 313.1 500.0 330.0, 750.0	-85.0 (-230.0, 60.0)

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N = number of subjects randomized who have hemoglobin measurement and first dose at day 1 and have hemoglobin measurement at week 5. n = the number of subjects who had darbepoetin administered. CI = Confidence Interval. SD = standard deviation

The cumulative dose is the sum of all darbepoetin doses received from all study visits.

The cumulative dose is the sum of all darbepoetin doses received from all study visits. Differences are fixed dose - titration.

<sup>&</sup>lt;sup>a</sup> Geometric mean

<sup>&</sup>lt;sup>b</sup> The median of the difference in cumulative dose between treatment groups is obtained using Hodges-Lehmann estimate.

<sup>&</sup>lt;sup>c</sup> The 2-sided 95% CI is obtained using a nonparametric Wilcoxon rank-sum statistic.

# Supplemental Table S3. Primary and Sensitivity Analysis of the Primary Endpoint of Subject Incidence of Red Blood Cell Transfusion

	Titration	Fixed Dose	Treatment			
Drimon	(N = 377) / analysis: On-treatr	(N = 379)	Effect			
Any RBC Transfusion <sup>a</sup>	/ analysis. On-lieali	пент арргоаст				
Yes -n (%) (95% CI) Stratified Risk <sup>c,d</sup> (95% CI)	92 (24.40) (20.07, 28.74)	91 (24.14) (19.82, 28.46)	-0.27 <sup>b</sup> (-6.39, 5.85) 0.998 <sup>d</sup> (0.776, 1.285)			
Exposure-adjusted Subject Incidence Rate per 100 subj-yre	17.7	17.6	-0.1 <sup>g</sup>			
(95% CI)	(14.3, 21.7) <sup>f</sup>	(14.2, 21.6) <sup>f</sup>	(-11.3, 11.2) <sup>g</sup>			
Sensit	Sensitivity analysis: On-study approach					
Any RBC Transfusion <sup>a</sup>	, ,	<b>7</b> 11				
Yes -n (%) (95% CI) Stratified Risk <sup>c,d</sup> (95% CI)	100 (26.53) (22.07, 30.98)	99 (26.12) (21.70, 30.54)	-0.40 <sup>b</sup> (-6.68, 5.87) 0.996 <sup>d</sup> (0.785, 1.264)			
Exposure-adjusted Subject Incidence Rate per 100 subj-yre	16.8	16.8	0.1 <sup>g</sup>			
(95% CI)	(13.6, 20.4) <sup>f</sup>	(13.7, 20.5) <sup>f</sup>	(-10.2, 10.3) <sup>g</sup>			
Sensitivity analysis: Completer analysis set						
Any RBC Transfusion <sup>a</sup> Yes -n (%) (95% CI) Stratified Risk <sup>c,d</sup> (95% CI)	38 (19.59) (14.00, 25.17)	36 (18.37) (12.95, 23.79)	-1.22 <sup>b</sup> (-9.00, 6.56) 0.986 <sup>d</sup> (0.651, 1.494)			
Exposure-adjusted Subject Incidence Rate per 100 subj-yre (95% CI)	10.8 (7.7, 14.9) <sup>f</sup>	10.1 (7.1, 14.0) <sup>f</sup>	-0.7 <sup>g</sup> (-11.2, 9.8) <sup>g</sup>			

N = number of subjects in full analysis set. Percentages are based on N. CI = Confidence Interval.

<sup>&</sup>lt;sup>a</sup> Subject incidence of receiving at least one RBC transfusion.

<sup>&</sup>lt;sup>b</sup> Difference in proportions between treatment groups.

 $<sup>^{\</sup>rm c}$  Stratification factors are: RBC Transfusion within 12 months of randomization and site practice setting.

<sup>&</sup>lt;sup>d</sup> The relative risk ratio and CI are obtained using the Cochran-Mantel-Haenszel method. A risk ratio < 1.0 indicates a lower event rate for the fixed dose arm relative to titration arm. Exposure time in subject-years on-treatment approach is defined as (Date of the last dose of IP received + 3 months or the end of study date, whichever is earlier - the randomization date + 1) / 365.25 days.

<sup>&</sup>lt;sup>e</sup> Exposure-adjusted subject incidence rate is calculated as the number of subjects with event per 100 subject-years of exposure.

<sup>&</sup>lt;sup>f</sup> The 95% CI is obtained using Chi-squared approximation to Poisson distribution.

<sup>&</sup>lt;sup>9</sup> The treatment effect and 95% CI are obtained using a Poisson model. The treatment effect is calculated as the incidence rate difference between two treatment groups.