Peginesatide and Epoetin Doses in Patients on Dialysis

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BACKGROUND

- Peginesatide (OMONTYS®) is a peptide-based erythropoiesis-stimulating agent (ESA) approved in the U.S. for the once-monthly treatment of anemia due to CKD in adult patients on dialysis.
- High ESA doses may be associated with higher cardiovascular-related mortality[1]; a risk likely complicated by patient factors such as health status.[2]

OBJECTIVE

- Post-hoc analysis to evaluate the relative dose of peginesatide compared with epoetin in patients on dialysis.

METHODOLOGY

- Data were pooled from two Phase 3, randomized, active-controlled, open-label trials. Patients were randomized in a 2:1 ratio to assess the safety and efficacy of peginesatide once monthly (n = 1066) compared with epoetin 1-3 times weekly (n = 542) in hemodialysis (HD) patients (EMERALD 1 and 2).
- Key inclusion criteria
  - HD ≥3 months.
  - Intravenous (IV) or subcutaneous (SC) epoetin ≥8 weeks (stable dose ≥4 weeks) before randomization.
  - Mean hemoglobin (Hb) ≥10.0 g/dL and ≤12.0 g/dL during screening.
  - Transferrin saturation (TSAT) ≥20% and ferritin ≥100 ng/mL.
- Patients received treatment for ≥52 weeks:
  - Peginesatide starting dose based on total weekly epoetin dose during the last week of the screening period.
  - Doses titrated to maintain target Hb levels of 10-12 g/dL, consistent with dosing guidelines in effect when the studies were conducted.
- Relationship between baseline epoetin dose and mean ESA dose during the evaluation period (weeks 29-36) assessed:
  1) Baseline epoetin dose during the week before randomization determined for each patient and divided into "low" and "high" baseline epoetin dose groups (representing the bottom and top 25% of patients).
  2) Dose ratio (baseline epoetin dose to mean evaluation period peginesatide) calculated for each patient.

RESULTS

- Groups were similar with respect to baseline demographics (Table 1).

Table 1. Baseline Demographics

	Low Baseline Dose (Epoetin ≤4800 U/week)		High Baseline Dose (Epoetin ≥16,400 U/week)		All Patients	
Characteristic	Peginesatide (n = 265)	Epoetin (n = 137)	Peginesatide (n = 247)	Epoetin (n = 155)	Peginesatide (n = 1066)	Epoetin (n = 542)
Age, mean (SD), y	59 (13.9)	60 (14.4)	55 (13.3)	55 (12.7)	58 (14.2)	58 (13.7)
Race, n (%)						
White	176 (66)	91 (66)	118 (48)	59 (38)	617 (58)	299 (55)
Black	70 (26)	37 (27)	123 (50)	81 (52)	399 (37)	211 (39)

SD, standard deviation.

- Median duration of patient exposure to study treatment was similar in the peginesatide and epoetin groups, respectively: 64 and 67 weeks (EMERALD 1); 64 and 63 weeks (EMERALD 2).
- Hb levels were similar at baseline and during the evaluation period (Table 2).

Table 2. Hemoglobin and Other Key Parameters at Baseline and During the Evaluation Period

Parameter	Low Baseline Dose (Epoetin ≤4800 U/week)				High Baseline Dose (Epoetin ≥16,400 U/week)			
	Peginesatide		Epoetin		Peginesatide		Epoetin	
	BL*	EP	BL*	EP	BL*	EP	BL*	EP
Hb, g/dL, mean (SE)	11.3 (0.03)	11.4 (0.06)	11.3 (0.04)	11.2 (0.07)	11.2 (0.04)	10.9 (0.06)	11.3 (0.04)	11.3 (0.08)
TSAT, %, mean (SD)	33.5 (12.8)	36.3 (15.0)	33.2 (12.8)	29.8 (13.2)	26.8 (9.4)	30.9 (12.5)	27.0 (8.9)	32.5 (12.9)
≥1 dose of iron, n, %	156 (59)	157 (65)	74 (54)	79 (62)	138 (56)	153 (71)	96 (62)	100 (70)

BL, baseline; EP, evaluation period; Hb, hemoglobin; SD, standard deviation; SE, standard error; TSAT, transferrin saturation.
*For iron, values refer to the screening period.

- Median dose ratios in the low- and high-baseline epoetin dose groups are shown in Table 3.
  - The relative dose of peginesatide for patients receiving high epoetin doses at baseline was less than half that for patients receiving low epoetin doses at baseline.

Table 3. Dose Ratios

	Mean Baseline Epoetin Dose[1] (U/week)	Mean Peginesatide Dose[1] (mg/month)	Median Dose Ratio[2] Baseline Epoetin: Peginesatide
Low	2900	3	1040:1
High	32000	15	2150:1

[1]Mean dose given to top ("high"; ≥16,400 U/wk) or bottom ("low"; ≤4800 U/wk) 25% of patients based on baseline epoetin doses across all patients in study. [2]Calculated as median of ratios for each patient within low- or high-dose groups.

- The relationship between epoetin and peginesatide dose was nonlinear (Figure 1).

Figure 1. Dose Relationship Curve

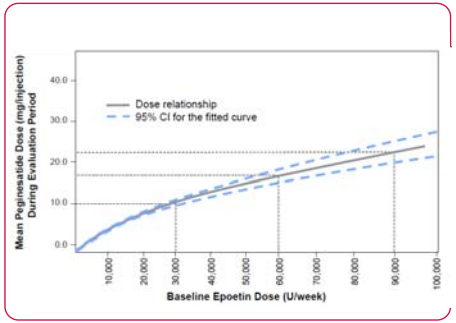

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Table 4. Estimated Peginesatide Starting Doses for Patients Based on Previous Weekly ESA Dose

Previous Total Weekly Epoetin Alfa Dose (U/week)	Peginesatide Dose Once Monthly (mg/month)
<2,500	2
2,500 to <4,300	3
4,300 to <6,500	4
6,500 to <8,900	5
8,900 to <13,000	6
13,000 to <19,000	8
19,000 to <33,000	10
33,000 to <68,000	15
≥68,000	20

- Dose conversion from epoetin to peginesatide in the prescribing information (Table 4) was developed based on a log-linear relationship between epoetin and peginesatide (Figure 1).

CONCLUSIONS/DISCUSSION

- Results of this post-hoc analysis from two Phase 3 trials suggest:
  - Those patients requiring more epoetin at baseline tend to require relatively less peginesatide to achieve similar Hb levels (ie, nonlinear dose relationship).
  - The nonlinear dose relationship between baseline epoetin doses and peginesatide doses is reflected in the dose-conversion table (Table 4).
- Availability of a once-monthly ESA may provide another treatment option for anemia due to CKD in patients on dialysis.

References
1. Regidor DL et al. *J Am Soc Nephrol.* 2006;17:1181-1191.
2. Besarab A. *Adv Chronic Kidney Dis.* 2009;16:131-142.

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