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Peginesatide in Patients with Anemia Undergoing Hemodialysis

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ABSTRACT

BACKGROUND

Peginesatide, a synthetic peptide-based erythropoiesis-stimulating agent (ESA), is a potential therapy for anemia in patients with advanced chronic kidney disease.

METHODS

We conducted two randomized, controlled, open-label studies (EMERALD 1 and EMERALD 2) involving patients undergoing hemodialysis. Cardiovascular safety was evaluated by analysis of an adjudicated composite safety end point — death from any cause, stroke, myocardial infarction, or serious adverse events of congestive heart failure, unstable angina, or arrhythmia — with the use of pooled data from the two EMERALD studies and two studies involving patients not undergoing dialysis. In the EMERALD studies, 1608 patients received peginesatide once monthly or continued to receive epoetin one to three times a week, with the doses adjusted as necessary to maintain a hemoglobin level between 10.0 and 12.0 g per deciliter for 52 weeks or more. The primary efficacy end point was the mean change from the baseline hemoglobin level to the mean level during the evaluation period; noninferiority was established if the lower limit of the two-sided 95% confidence interval was -1.0 g per deciliter or higher in the comparison of peginesatide with epoetin. The aim of evaluating the composite safety end point in the pooled cohort was to exclude a hazard ratio with peginesatide relative to the comparator ESA of more than 1.3.

RESULTS

In an analysis involving 693 patients from EMERALD 1 and 725 from EMERALD 2, peginesatide was noninferior to epoetin in maintaining hemoglobin levels (mean between-group difference, -0.15 g per deciliter; 95% confidence interval [CI], -0.30 to -0.01 in EMERALD 1; and 0.10 g per deciliter; 95% CI, -0.05 to 0.26 in EMERALD 2). The hazard ratio for the composite safety end point was 1.06 (95% CI, 0.89 to 1.26) with peginesatide relative to the comparator ESA in the four pooled studies (2591 patients) and 0.95 (95% CI, 0.77 to 1.17) in the EMERALD studies. The proportions of patients with adverse and serious adverse events were similar in the treatment groups in the EMERALD studies. The cardiovascular safety of peginesatide was similar to that of the comparator ESA in the pooled cohort.

CONCLUSIONS

Peginesatide, administered monthly, was as effective as epoetin, administered one to three times per week, in maintaining hemoglobin levels in patients undergoing hemodialysis. (Funded by Affymax and Takeda Pharmaceutical; ClinicalTrials.gov numbers, NCT00597753 [EMERALD 1], NCT00597584 [EMERALD 2], NCT00598273 [PEARL 1], and NCT00598442 [PEARL 2].)

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PARTIAL CORRECTION OF ANEMIA WITH erythropoiesis-stimulating agents (ESAs) is a cornerstone of therapy for patients undergoing dialysis, because these agents increase hemoglobin levels, which results in a reduction in blood-transfusion rates.^{1,2} Partial correction of anemia has also been reported to enhance quality of life.³ More intensive treatment with ESAs, targeting near-normal hemoglobin levels, in the Normal Hematocrit Study (NHS),⁴ the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study,⁵ and the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)⁶ further reduced the need for blood transfusions, but an increased risk of adverse events was reported (the composite of death and nonfatal myocardial infarction in the NHS,⁴ the composite of death and cardiovascular events in the CHOIR study,⁵ and stroke in the TREAT⁶). These findings prompted changes in the prescription information for ESAs, including recommendations for lower target hemoglobin levels and the inclusion of boxed warnings about increased risks associated with these agents.

Until recently, the ESAs that were available were erythropoietin analogues manufactured with the use of recombinant DNA technology. Most patients undergoing dialysis receive epoetin alfa up to three times a week, whereas fewer patients receive darbepoetin alfa once a week or every 2 weeks.⁷ A continuous erythropoietin-receptor activator — erythropoietin attached to a polyethylene glycol chain⁸ — is an extended-dose ESA that is marketed outside the United States for initial administration once every 2 weeks, with administration once a month after stabilization of the hemoglobin level.

Peginesatide (Omontys, Affymax) is a synthetic, pegylated, peptide-based ESA that was approved by the Food and Drug Administration in March 2012 for the treatment of anemia due to chronic kidney disease in adults undergoing dialysis. Peginesatide has no sequence homology to,⁹ or immunologic cross-reactivity with,¹⁰ erythropoietin. It stimulates the erythropoietin receptor in vivo, thereby acting as an “epomimetic” agent. Previous studies have suggested that peginesatide administered once a month may be effective in raising and maintaining hemoglobin levels.^{11–13} The current studies were designed to compare peginesatide with epoetin or darbepoetin in a prospective analysis of an independently adjudicated composite end point for cardiovascular safety, with

the use of pooled data from four studies: two involving patients undergoing hemodialysis (the Efficacy and Safety of Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin [EMERALD] 1 and EMERALD 2 studies) and two involving patients not undergoing dialysis (the Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating Agents [PEARL] 1 and PEARL 2 studies). We present the results of the analysis of the efficacy and safety of peginesatide as compared with epoetin in the cohort undergoing hemodialysis (the EMERALD studies cohort) and of the composite safety end point in the pooled cohort from all four studies. Data specific to the cohort that did not undergo dialysis (the PEARL studies cohort) are reported by Macdougall et al. elsewhere in this issue of the *Journal*.¹⁴

METHODS

STUDY OVERSIGHT

We conducted two similarly designed, phase 3, randomized, active-treatment–controlled, open-label, noninferiority studies in the United States (EMERALD 1 and EMERALD 2) and in Europe (EMERALD 2). The protocol was approved by the institutional review board or ethics committee at each study site or by a central institutional review board. All the patients provided written informed consent, and the studies were performed in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice. A data monitoring committee provided independent oversight of patient safety, and a separate, independent event-review committee, whose members were unaware of the treatment assignments and the results of hemoglobin measurements, adjudicated end-point events.

These studies were funded by Affymax and Takeda Pharmaceutical (Osaka, Japan) and were designed collaboratively by the principal investigators (see the Supplementary Appendix, available with the full text of this article at NEJM.org) and Affymax. Covance (a contract research organization) was responsible for data management; the statistical analyses of efficacy and safety in the individual studies were performed by ICON Clinical Research, the analyses of the composite safety end point were performed by Pacific North-

western Statistical Consulting, and the integrated analyses of efficacy and safety were performed by Affymax. The authors had full access to the data. The first author wrote the introduction and discussion of the manuscript and oversaw all revisions; an employee of Affymax and a medical writer who was contracted by Affymax wrote the preliminary draft of the Methods and Results sections under the direction of the first author. All the authors reviewed and edited the manuscript, vouch for the completeness and accuracy of the data and analyses, and testify to the fidelity of this report to the study protocols, which are available at NEJM.org. The principal investigators made the decision to submit the manuscript for publication. Agreements between Affymax and the investigators stipulated that after the first publication of multicenter data or 36 months after completion of the studies, the investigators would be free to submit the results for publication, and Affymax could review the manuscript before submission.

STUDY POPULATION

The first patient underwent randomization in September 2007, and the last patient completed follow-up in January 2010. Patients 18 years of age or older with chronic kidney disease were eligible if they had been undergoing hemodialysis for at least 3 months and had been receiving continuous epoetin treatment for at least 8 weeks. Other key eligibility criteria included four consecutive screening hemoglobin measurements with a mean value between 10.0 and 12.0 g per deciliter and at least one value for transferrin saturation of 20% or greater and one value for the serum ferritin level of 100 ng or more per milliliter. Key exclusion criteria were bleeding or coagulation disorders, hematologic diseases, or causes of anemia other than chronic kidney disease; a scheduled kidney transplantation; poorly controlled hypertension within the previous 4 weeks; red-cell or whole-blood transfusions within the previous 12 weeks; and active cancer within the previous year (see the Supplementary Appendix).

STUDY PROCEDURES

Each study included a 6-week screening period, a 28-week initial dose-adjustment period, an 8-week evaluation period, and a longer-term follow-up period (≥ 16 additional weeks). Eligible patients were randomly assigned, in a 2:1 ratio, to receive peginesatide once every 4 weeks or to continue to

receive epoetin (epoetin alfa in the United States, and epoetin beta in Europe) one to three times a week, with the frequency and route of administration determined on the basis of the treatment regimen during the screening period; peginesatide and epoetin were administered intravenously in the EMERALD 1 study and intravenously or subcutaneously in the EMERALD 2 study. In both studies, sequential randomization was performed at a central location and was stratified according to the mean screening hemoglobin level (≤ 11.4 g per deciliter vs. ≥ 11.5 g per deciliter), to ensure balance in baseline efficacy variables, and according to the New York Heart Association heart failure class (no heart failure or class I vs. class II, III, or IV), to help ensure balance in baseline cardiovascular risk.¹⁵ In the EMERALD 2 study, randomization was also stratified according to geographic region and according to the route of study-drug administration.

Patients who were randomly assigned to the peginesatide group underwent a 1-week transition period during which they received no epoetin and after which they began receiving peginesatide, with the dose determined according to the last total weekly weight-based dose of epoetin that they had received during the screening period (Table S1 in the Supplementary Appendix). Patients who were assigned to the epoetin group continued to receive epoetin according to their regimen during the screening period. Subsequent doses (not weight-based) of both study medications were adjusted according to prespecified guidelines to maintain the hemoglobin level between 10.0 and 12.0 g per deciliter (Table S2 in the Supplementary Appendix).

Blood chemical measurements were performed at a central laboratory. Hemoglobin measurements were performed at the time of screening, at baseline, and weekly (during the evaluation period and during delays in dosing owing to a high hemoglobin level) or every 2 weeks (during all other periods) thereafter. At each visit, information was obtained on adverse events, transfusions, the need for therapeutic phlebotomies, and the use of concomitant medications.

STUDY END POINTS

The primary efficacy end point was the mean change from the baseline hemoglobin level (with the baseline level calculated as the mean of four consecutive measurements during the screening period and the value on the day of randomiza-

tion) to the mean level during the evaluation period (calculated as the mean of all measurements obtained during weeks 29 through 36) (see the Supplementary Appendix). Secondary efficacy end points were the proportion of patients who received a transfusion during the initial dose-adjustment period and during the evaluation period and the proportion of patients in whom the hemoglobin level was maintained within the target range during the evaluation period. Efficacy was also assessed as the mean change from baseline in hemoglobin levels during 4-week intervals. The analysis of adverse events was performed with pooled data from the two EMERALD studies to provide a larger data set for evaluation (see the Supplementary Appendix). Data on immunogenicity are presented for patients who were receiving peginesatide.

Cardiovascular risk was assessed by means of a prospectively planned analysis of a composite safety end point: death from any cause, stroke, myocardial infarction, or a serious adverse event of congestive heart failure, unstable angina, or arrhythmia. The processes of identification and assessment of potential events were prespecified and were designed to ensure that the treatment assignments and hemoglobin levels remained concealed and to minimize bias (see the Supplementary Appendix). The prespecified primary analysis of the composite safety end point assessed the time to the first positively adjudicated event, with the use of data pooled from the EMERALD 1 and EMERALD 2 studies and also from the PEARL 1 and PEARL 2 studies, two parallel studies comparing peginesatide and darbepoetin in patients with chronic kidney disease who were not undergoing dialysis. Prespecified analyses according to population (patients undergoing hemodialysis and patients not undergoing dialysis) were performed; results in the population not undergoing dialysis are reported separately.¹⁴

STATISTICAL ANALYSIS

The primary-analysis population for the assessment of safety comprised all patients who underwent randomization and who received at least one dose of the study drug (i.e., the modified intention-to-treat population). Patient data were summarized according to the assigned study treatment. The primary efficacy analysis included patients in the primary-analysis population who also had at least one hemoglobin measurement during the evaluation period. There was no

imputation of missing data in the primary efficacy analyses.

The primary efficacy end point was analyzed with the use of an analysis-of-variance cell means model to estimate the mean change from the baseline hemoglobin level to the mean level during the evaluation period within each randomization stratum. Estimates of the difference in the primary efficacy end point between the peginesatide group and the epoetin group and corresponding two-sided 95% confidence intervals were calculated with the use of the analysis-of-variance model. Treatment differences were calculated for each of the strata and then these stratum-specific estimates of treatment difference were combined with the use of weights proportional to the total sample size of the stratum. Because there was no imputation of missing data, prespecified per-protocol population analyses and sensitivity analyses with imputation of missing values were performed to address the potential effects of premature withdrawal from the studies (see the Supplementary Appendix).

Each study had at least 99% power to evaluate the noninferiority of peginesatide to epoetin with respect to the primary efficacy end point, assuming an expected mean (\pm SD) between-group difference in hemoglobin level of 0 ± 1.5 g per deciliter. Noninferiority was established if the lower limit of the two-sided 95% confidence intervals for the least-squares mean difference between peginesatide and epoetin was -1.0 g per deciliter or higher. The Cochran–Mantel–Haenszel method was used for the secondary end-point analyses. The efficacy variables for each study are presented separately.

For the primary analysis of the composite safety end point, we estimated that if 553 patients had a positively adjudicated event, the pooled data would provide at least 89% power to exclude a hazard ratio with peginesatide relative to the comparator ESA of more than 1.3, with the use of a one-sided 95% confidence interval (see the Supplementary Appendix).^{4,5,16} The studies were event-driven; patients continued to receive the assigned treatment until the prespecified number of positively adjudicated events across all four studies was reached (with a minimum anticipated follow-up of at least 52 weeks). Patients who discontinued the study drug prematurely remained in the studies and were followed to ensure complete recording of safety events. Hazard ratios were estimated for each study and were combined with the use of

weights inversely proportionate to the variance; a one-sided 95% confidence interval was designated for the primary analysis, and two-sided 95% confidence intervals for the secondary analyses. The Kaplan–Meier method was used to characterize the time to the first event. Analyses of the composite rate of major adverse cardiovascular events (death from any cause, stroke, or myocardial infarction) were also performed.

To determine the influence of events occurring after discontinuation of the study drug, a prespecified sensitivity analysis of the composite safety end point was performed in which data were censored 28 days after a patient received the last dose of the study drug, initiated treatment with a non-study ESA, or underwent renal transplantation, whichever occurred first. A post hoc sensitivity analysis addressed the influence of withdrawals from the studies (see the Supplementary Appendix).

RESULTS

STUDY PATIENTS

In the EMERALD 1 study, 803 patients underwent randomization at 92 sites in the United States, and in the EMERALD 2 study, 823 patients underwent randomization at 39 sites in the United States and 47 sites in Europe. The primary-analysis population comprised 793 patients in the EMERALD 1 study (of whom 524 were assigned to receive peginesatide and 269 were assigned to receive epoetin, with both drugs administered intravenously in all patients) and 815 patients in the EMERALD 2 study (of whom 542 were assigned to receive peginesatide [437 intravenously and 105 subcutaneously] and 273 were assigned to receive epoetin [220 intravenously and 53 subcutaneously]). A total of 225 patients in the EMERALD 1 study (158 [30.2%] in the peginesatide group and 67 [24.9%] in the epoetin group) and 183 patients in the EMERALD 2 study (121 [22.3%] in the peginesatide and 62 [22.7%] in the epoetin group) discontinued the study prematurely; the most common reasons for discontinuation were death and withdrawal of consent; other common reasons included relocation, site closure, and renal transplantation (Fig. 1).

Overall, the groups were well matched at baseline (Table 1, and Table S3 in the Supplementary Appendix). The mean baseline hemoglobin level in both groups was 11.3 g per deciliter in the EMERALD 1 cohort and 11.2 g per deciliter in

the EMERALD 2 cohort. In both studies, the iron status was similar in the two groups. The peginesatide group had higher rates of coronary artery disease (in the EMERALD 1 study) and arrhythmia (in the EMERALD 2 study).

The median duration of follow-up was 67.4 weeks (interquartile range, 60.0 to 77.1) in the peginesatide group and 68.1 weeks (interquartile range, 60.1 to 78.6) in the epoetin group in the EMERALD 1 study and 65.1 weeks (interquartile range, 57.9 to 75.1) in the peginesatide group and 64.1 weeks (interquartile range, 58.3 to 74.9) in the epoetin group in the EMERALD 2 study (see the Supplementary Appendix for information on patient exposure). The median of the mean dose per patient administered during the evaluation period was 5.7 mg of peginesatide per injection and 9900 U of epoetin per week in the EMERALD 1 cohort and 4.8 mg of peginesatide per injection (with both intravenous and subcutaneous injections) and 6805 U of epoetin per week (7100 U per week for intravenous injections and 4625 U per week for subcutaneous injections) in the EMERALD 2 cohort.

PRIMARY EFFICACY END POINT

The primary efficacy analysis (which included data only from patients who had at least one hemoglobin measurement during the evaluation period) included data from 693 patients (87.4% of the patients in the primary-analysis population) in the EMERALD 1 study (445 [84.9%] in the peginesatide group and 248 [92.2%] in the epoetin group) and 725 patients (89.0% of the patients in the primary-analysis population) in the EMERALD 2 study (488 [90.0%] in the peginesatide group and 237 [86.8%] in the epoetin group). The mean changes from the baseline hemoglobin level to the mean level during the evaluation period were -0.24 ± 0.96 g per deciliter in the peginesatide group and -0.09 ± 0.92 g per deciliter in the epoetin group in the EMERALD 1 study and -0.07 ± 1.01 g per deciliter in the peginesatide group and -0.17 ± 1.00 g per deciliter in the epoetin group in the EMERALD 2 study. In both studies, the prespecified noninferiority criterion was met: the least-squares mean difference between the groups was -0.15 g per deciliter (95% confidence interval [CI], -0.30 to -0.01) in the EMERALD 1 study and 0.10 g per deciliter (95% CI, -0.05 to 0.26) in the EMERALD 2 study. The results of all per-protocol and sensitivity analyses were consistent with the primary efficacy results.

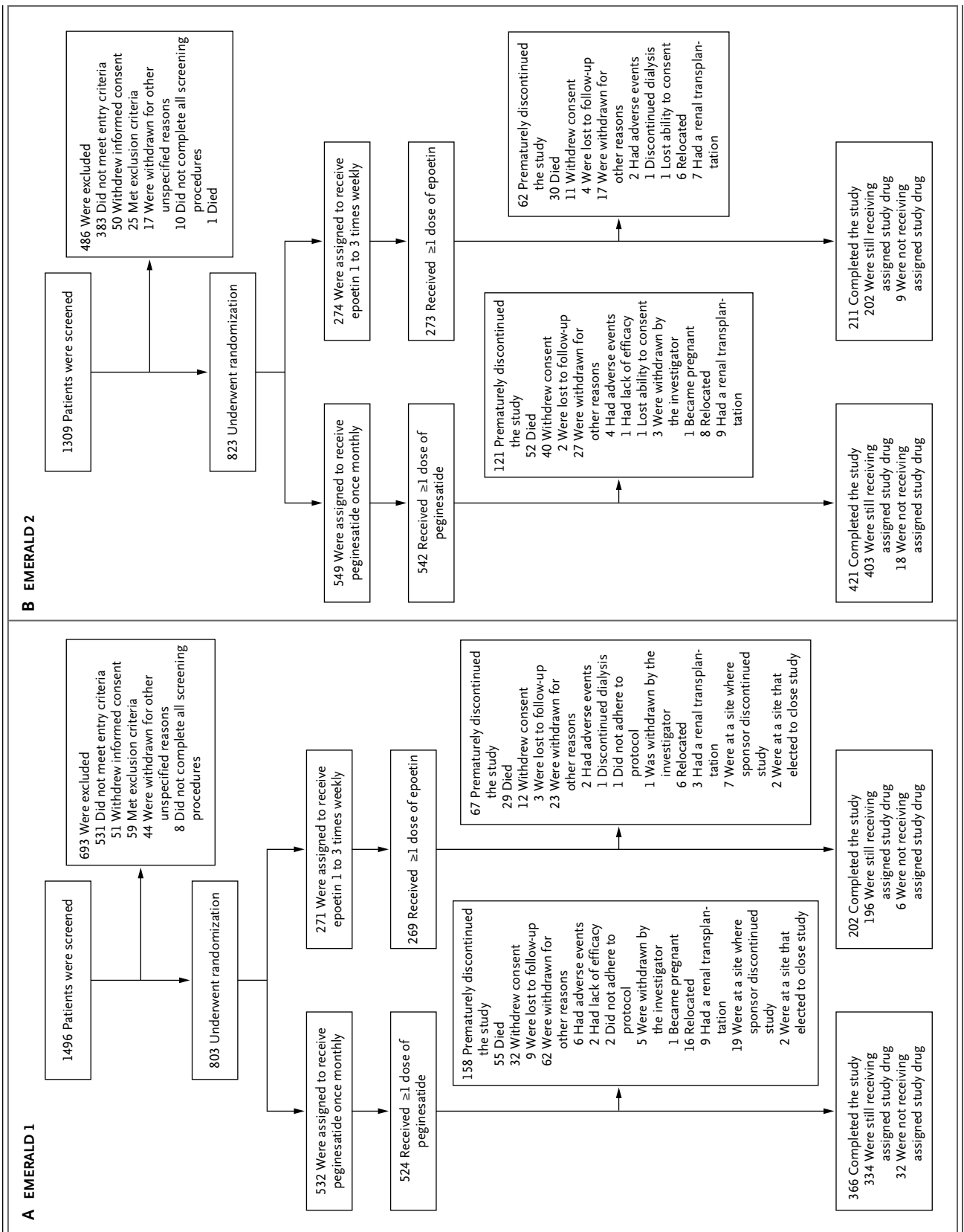


Figure 1 (facing page). Screening, Randomization, and Follow-up.

Two similarly designed studies involving patients undergoing hemodialysis were conducted: the Efficacy and Safety of Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin (EMERALD) 1 study (Panel A) and the EMERALD 2 study (Panel B). Patients who discontinued the study drug remained in the study for the collection of data relevant to the composite safety end point. Thus, discontinuing the study drug was distinct from discontinuing the study, and separate reasons for each were recorded and summarized. In the EMERALD 1 study, the study drug was not administered to 8 patients randomly assigned to the peginesatide group and 2 patients assigned to the epoetin group. The reasons for premature discontinuation of the study drug in the peginesatide group were adverse events (20 patients), lack of efficacy (1), renal transplantation (3), withdrawal of consent for study treatment (2), change to peritoneal dialysis (2), nonadherence to the protocol (1), investigator's decision (1), and relocation (2). The reasons for premature discontinuation of the study drug in the epoetin group were renal transplantation (5 patients) and withdrawal of consent for study treatment (1). In the EMERALD 2 study, the study drug was not administered to 7 patients randomly assigned to the peginesatide group and 1 patient assigned to the epoetin group. The reasons for premature discontinuation of the study drug in the peginesatide group were adverse events (2 patients), lack of efficacy (1), renal transplantation (6), withdrawal of consent for study treatment (4), investigator's decision (1), and relocation (4). The reasons for premature discontinuation of the study drug in the epoetin group were renal transplantation (3 patients), withdrawal of consent for study treatment (1), and relocation (5).

SECONDARY AND OTHER EFFICACY END POINTS

The proportion of patients who received at least one transfusion during the initial dose-adjustment period and the evaluation period was similar in the two treatment groups: 10.3% in the peginesatide group and 8.6% in the epoetin group in the EMERALD 1 study (relative risk with peginesatide, 1.21; 95% CI, 0.76 to 1.92) and 7.7% and 9.9% in the two groups, respectively, in the EMERALD 2 study (relative risk, 0.79; 95% CI, 0.50 to 1.24). The proportion of patients in whom the mean hemoglobin concentration was maintained within the target range during the evaluation period was 63.0% in the peginesatide group and 71.7% in the epoetin group in the EMERALD 1 study (relative response rate with peginesatide, 0.88; 95% CI, 0.79 to 0.97) and 63.5% and 65.9% in the EMERALD 2 study (relative response rate with

peginesatide, 0.96; 95% CI, 0.87 to 1.07) (see the Supplementary Appendix for more details regarding the analysis of response rate). In both studies, the iron status at the end of the evaluation period and the percentage of patients receiving iron supplementation during the study were generally similar in the two groups (Table S4 in the Supplementary Appendix). The mean hemoglobin values in 4-week intervals were similar in the two groups and were within the target range in the two groups in both studies (Fig. 2).

ADVERSE EVENTS

In the EMERALD studies, the proportion of patients in whom an adverse event was reported was similar in the peginesatide group and the epoetin group (94.6% and 93.0%, respectively), with no major between-group differences (i.e., differences of ≥ 5 percentage points in the rates of individual events [Table S5 in the Supplementary Appendix]). Serious adverse events were reported in 572 patients (53.7%) in the peginesatide group and 309 (57.0%) in the epoetin group; the serious adverse events that occurred in at least 3% of the patients in either group are shown in Table 2. There were no clinically relevant between-group differences in the incidence of adverse events associated with the ESA class of drugs, including hypertension-related and thromboembolic events (Table 2). There was no evidence of drug-induced hepatotoxic effects with either drug, and other data on clinical laboratory results and vital signs suggested no major differences between the groups.

Across the two EMERALD studies, 22.2% of the patients in the peginesatide group and 19.6% of those in the epoetin group had confirmed (i.e., two consecutive) hemoglobin measurements that were higher than 13 g per deciliter through the end of treatment (Table S6 in the Supplementary Appendix). Ten patients — seven (0.7%) in the peginesatide group and three (0.6%) in the epoetin group — underwent at least one therapeutic phlebotomy.

IMMUNOGENICITY OF PEGINESATIDE

Drug-specific binding antibodies developed in 12 patients (1.1%) in the peginesatide groups (6 in each study); in 8 patients, the antibodies were neutralizing in an in vitro assay. Ten of the 12 patients (including the 8 patients with neutralizing antibodies) had at least two clinical signs of

Table 1. Baseline Demographic and Clinical Characteristics in the EMERALD 1 and EMERALD 2 Studies.*

Characteristic	EMERALD 1			EMERALD 2		
	Peginesatide (N=524)	Epoetin (N=269)	P Value†	Peginesatide (N=542)	Epoetin (N=273)	P Value†
Age — yr	57.3±14.0	57.5±13.7	0.86	58.8±14.5	58.6±13.7	0.83
Male sex — no. (%)	293 (55.9)	144 (53.5)	0.52	331 (61.1)	153 (56.0)	0.18
Race — no. (%)‡			0.15			0.37
White	263 (50.2)	116 (43.1)		354 (65.3)	183 (67.0)	
Black	234 (44.7)	136 (50.6)		165 (30.4)	75 (27.5)	
Hemoglobin — g/dl	11.3±0.5	11.3±0.5	NA§	11.2±0.6	11.2±0.6	NA§
Primary cause of chronic kidney disease — no. (%)			0.82			0.15
Diabetes	222 (42.4)	118 (43.9)		174 (32.1)	96 (35.2)	
Hypertension	184 (35.1)	97 (36.1)		155 (28.6)	57 (20.9)	
Undergoing hemodialysis >1 yr — no. (%)	475 (90.6)	237 (88.1)	0.27	460 (84.9)	233 (85.3)	0.87
NYHA class — no. (%)			NA§			NA§
No heart failure or class I	426 (81.3)	217 (80.7)		438 (80.8)	223 (81.7)	
Class II, III, or IV	98 (18.7)	52 (19.3)		104 (19.2)	50 (18.3)	
History of cardiovascular risk factors — no. (%)						
Diabetes	298 (56.9)	151 (56.1)	0.84	238 (43.9)	124 (45.4)	0.67
Coronary artery disease	238 (45.4)	100 (37.2)	0.02	209 (38.6)	91 (33.3)	0.13
Peripheral vascular disease	145 (27.7)	70 (26.0)	0.59	112 (20.7)	49 (17.9)	0.36
Arrhythmia	102 (19.5)	65 (24.2)	0.12	122 (22.5)	40 (14.7)	0.007

* Plus-minus values are means ±SD. A more detailed listing of baseline variables is provided in Table S3 in the Supplementary Appendix; none of the additional variables listed in Table S3 differed significantly between treatment groups in either study. EMERALD denotes Efficacy and Safety of Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin, NA not available, and NYHA New York Heart Association.

† P values were calculated with the use of analysis of variance for continuous variables and the Mantel–Haenszel chi-square test for categorical variables, with adjustment for stratification factors.

‡ Race was determined from information in the case-report form.

§ Statistical tests were not performed on stratification factors.

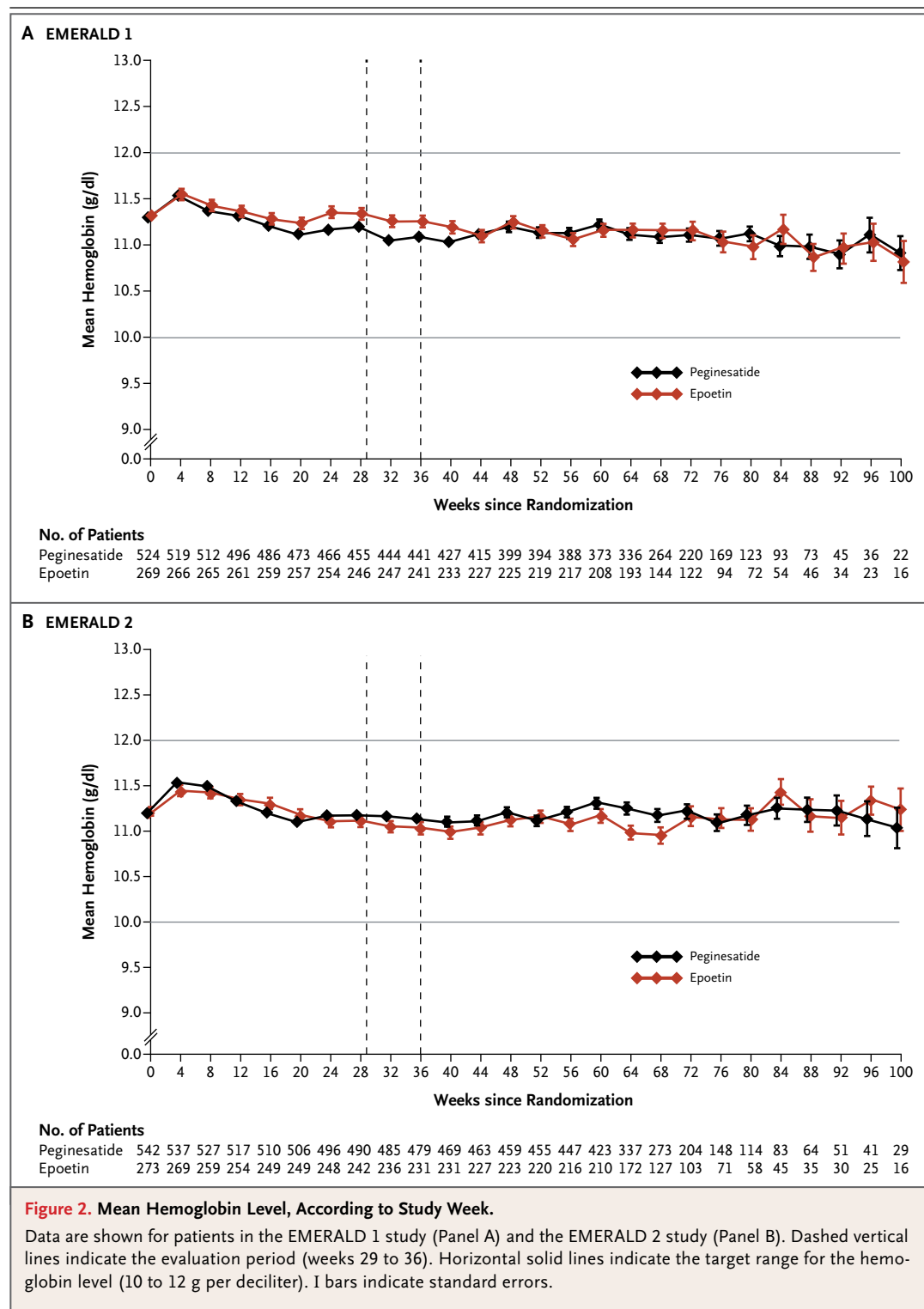
possible reduced efficacy (declining hemoglobin levels, the need for increased doses to maintain hemoglobin levels, or the need for transfusion that was not explained by a concurrent acute medical event). No cases of pure red-cell aplasia were reported, and antierythropoietin antibodies did not develop in any patient. No patient had an allergic drug reaction, including anaphylaxis, associated with the formation of antibodies.

COMPOSITE SAFETY END POINT

In the combined phase 3 studies (EMERALD 1, EMERALD 2, PEARL 1, and PEARL 2), a total of 1737 patients were randomly assigned to receive peginesatide and 872 to receive the comparator ESA. Of these patients, 1722 and 869 in the two

groups, respectively, received at least one dose of the study drug and were included in the pooled analysis of the composite safety end point. The proportion of patients with unknown vital status was low overall (4.1%) and was similar in the two groups (see the Supplementary Appendix).

In the pooled analysis of data from the four studies, a composite safety end-point event occurred in 384 patients (22.3%) who received peginesatide and in 188 patients (21.6%) who received the comparator ESA (hazard ratio with peginesatide, 1.06; 95% CI, 0.89 to 1.26) (Fig. 3A). The results in the cohort that was undergoing hemodialysis (patients in the EMERALD studies) indicated a similar cardiovascular safety profile: a hazard ratio with peginesatide relative to epo-



etin of 0.95 (95% CI, 0.77 to 1.17) (Fig. 3B). There were no apparent between-group differences in the proportion of patients with events of the individual components of the safety end point (including death), either in the pooled cohort from all four studies (Table S7 and Fig. S1 in the Supplementary Appendix) or in the cohort that was undergoing hemodialysis (Table 2, and

Table 2. Component Events of the Composite Safety End Point, Most Common Serious Adverse Events, and Adverse Events Associated with the Erythropoiesis-Stimulating Agent (ESA) Class of Drugs.*

Event	Peginesatide (N = 1066)	Epoetin (N = 542)
no. of patients (%)		
Component event of the composite safety end point†		
Death	115 (10.8)	64 (11.8)
Cardiovascular	31 (2.9)	14 (2.6)
Noncardiovascular	43 (4.0)	24 (4.4)
Sudden‡	26 (2.4)	12 (2.2)
Unknown cause§	15 (1.4)	14 (2.6)
Stroke	26 (2.4)	20 (3.7)
Myocardial infarction	49 (4.6)	29 (5.4)
Congestive heart failure	103 (9.7)	49 (9.0)
Unstable angina	24 (2.3)	12 (2.2)
Arrhythmia	63 (5.9)	35 (6.5)
Serious adverse event occurring in ≥3% of patients in either group¶		
Congestive cardiac failure	61 (5.7)	37 (6.8)
Acute myocardial infarction	30 (2.8)	18 (3.3)
Pneumonia	67 (6.3)	31 (5.7)
Sepsis	35 (3.3)	26 (4.8)
Cellulitis	34 (3.2)	15 (2.8)
Fluid overload	41 (3.8)	27 (5.0)
Hyperkalemia	49 (4.6)	23 (4.2)
Respiratory failure	32 (3.0)	12 (2.2)
Adverse-event category associated with the ESA class of drugs		
Hypertension-related events	208 (19.5)	101 (18.6)
Thromboembolic events		
Arterial event	71 (6.7)	48 (8.9)
Venous event	21 (2.0)	9 (1.7)
Complication related to vascular access	193 (18.1)	107 (19.7)
Convulsions	23 (2.2)	11 (2.0)
Infusion or injection-related reactions	32 (3.0)	11 (2.0)
Cancer	41 (3.8)	23 (4.2)

* Data are pooled from the EMERALD 1 and EMERALD 2 studies.

† Component events of the composite safety end point were adjudicated by an independent event-review committee whose members were unaware of the treatment assignments and hemoglobin levels; patients could have more than one event.

‡ Sudden death was defined as nontraumatic or unexpected death within 1 hour after the onset of symptoms or unWitnessed death.

§ The cause of death was classified as unknown if the primary cause could not be determined, including those cases in which there was insufficient information.

¶ There were no major differences (i.e., differences of ≥2 percentage points) between the pooled peginesatide and epoetin groups with respect to serious adverse events, including those that were reported at a frequency of less than 3% in either group.

|| Categories of adverse events associated with the ESA class of drugs were identified from the *Medical Dictionary for Regulatory Activities* (MedDRA) with the use of the Standardized MedDRA Query (SMQ); however, in the case of infusion or injection-related reactions and complications related to vascular access, for which there are no suitable SMQs in MedDRA, the categories were identified according to sponsor-defined groups of preferred terms. This approach enabled the grouping of similar or related events that embodied similar clinical concepts. The proportion of patients reporting adverse events was similar in the pooled peginesatide and epoetin groups (94.6% and 93.0%, respectively), with no major between-group differences (≥5 percentage points) in any individual event.

Fig. S1 in the Supplementary Appendix). Mortality among the patients undergoing hemodialysis was similar in the peginesatide and epoetin groups (hazard ratio for death, 0.90; 95% CI, 0.67 to 1.23). Results for the composite safety end point in subgroups defined according to baseline variables (e.g., black vs. nonblack race and presence vs. absence of diabetes) were consistent with those in the overall population undergoing hemodialysis (Fig. S2 in the Supplementary Appendix). The sensitivity analysis addressing the potential effect of withdrawals from the studies showed results similar to those of the primary analysis (see the Supplementary Appendix). Hazard ratios for major adverse cardiovascular events among patients still in the studies (“on-study” analysis) and among patients still receiving the study drug (“on-drug” analysis), as estimated in sensitivity analyses, are shown in Figure S3 in the Supplementary Appendix. The hazard ratio for death with peginesatide relative to epoetin in the on-drug analysis was 0.57 (95% CI, 0.38 to 0.85).

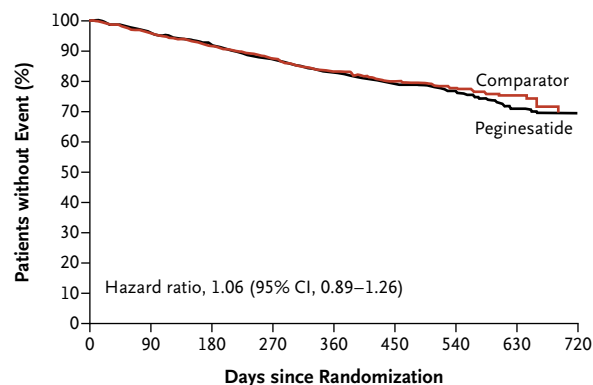
DISCUSSION

We studied the efficacy and cardiovascular safety of peginesatide as compared with other ESAs, using the target hemoglobin level (10 to 12 g per deciliter in the EMERALD studies) that was the standard when the trials were conducted. For the assessment of cardiovascular safety, composite safety end-point events were adjudicated by an independent event-review committee whose members were unaware of the group assignments and hemoglobin levels.

Among patients undergoing hemodialysis (those in the EMERALD 1 and EMERALD 2 studies), peginesatide administered once a month was as effective as epoetin administered one to three times a week in maintaining hemoglobin levels. Rates of confirmed hemoglobin excursions and transfusions were similar in the two groups.

Adverse (including serious adverse) events in the EMERALD studies were similar in the peginesatide and epoetin groups and were consistent with expected adverse events in patients undergoing hemodialysis. No between-group differences were observed in the rate of events associated with the ESA class of drugs, including venous thromboembolic events, complications related to hemodialysis access, hypertension-related events, and cancer.

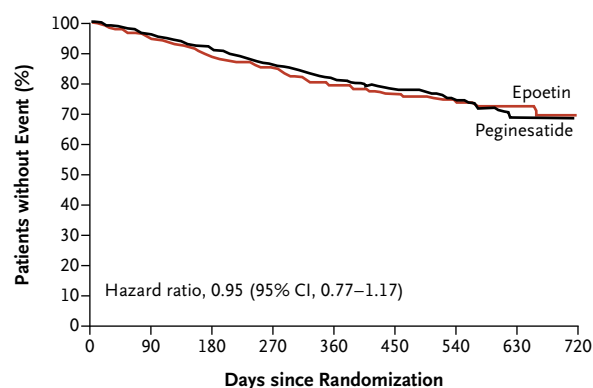
A Pooled EMERALD 1 and 2 and PEARL 1 and 2 Cohorts



No. at Risk

Peginesatide	1722	1608	1497	1388	1288	919	473	187	28
Comparator	869	812	767	716	665	459	254	111	16

B EMERALD 1 and 2 Cohorts



No. at Risk

Peginesatide	1066	991	914	845	776	519	201	78	16
Epoetin	542	502	466	429	392	241	112	57	12

Figure 3. Kaplan–Meier Curves for the Event-free Rate of the Composite Safety End Point.

The curves illustrate the proportion of patients at each time point who had not had any of the following events: death from any cause, stroke, myocardial infarction, or a serious adverse event of congestive heart failure, unstable angina, or arrhythmia (all of which are components of the composite safety end point). Panel A shows data for this end point in the pooled analysis of four phase 3 studies: EMERALD 1 and EMERALD 2 plus the Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating Agents (PEARL) 1 and PEARL 2 studies, which involved patients who were not undergoing dialysis. Panel B shows data for the composite safety end point in the analysis of data only from patients undergoing hemodialysis (the EMERALD 1 and EMERALD 2 studies).

In the analysis of the composite safety end point with the use of data pooled from the two EMERALD studies and the two PEARL studies, the incidence of events was similar in the group receiving peginesatide and the group receiving

the comparator ESAs. Among the patients undergoing hemodialysis (patients in the EMERALD studies), the occurrence of the composite safety end point was similar in the two groups; the point estimate was approximately 1 and was consistent across patient subgroups.

Peginesatide-specific neutralizing antibodies developed in eight patients; antierythropoietin antibodies did not develop in any patients, and no pure red-cell aplasia cases were reported. According to a previous report of an ongoing study, peginesatide was used to treat a small cohort of patients with chronic kidney disease who had pure red-cell aplasia and antierythropoietin antibodies, most of whom were transfusion-dependent.¹⁷ Longer-term follow-up of patients is warranted to further evaluate the immunogenicity profile of peginesatide, including the incidence of antibody formation and potential clinical consequences.

There are several limitations of these studies. First, in the composite safety end point that was used to assess cardiovascular risk, we included “softer” end points such as arrhythmia, congestive heart failure, and unstable angina. Although end points were adjudicated by an event-review committee whose members were unaware of the group assignments and who used criteria widely used in other trials with cardiovascular outcomes, including trials of ESAs, adjudicating events such as congestive heart failure in a population with anuria that is prone to frequent episodes of volume overload and flash pulmonary edema is difficult. The results of an evaluation of the more definite end points of death (including sudden death), myocardial infarction, and stroke were consistent with the overall hemodialysis findings.

A second limitation of the studies was the open-label design. However, efforts were made to minimize potential bias, including concealing the group assignments and the hemoglobin concentrations from the members of the event-review committee and prospectively defining an investigator-independent process for identifying potential events for adjudication. Third, the number of premature withdrawals may have influenced the results. However, analyses of the per-protocol population (for efficacy) and sensitivity analyses (for efficacy and safety) showed

results consistent with those of the primary analyses. Fourth, the EMERALD studies used a hemoglobin target (10 to 12 g per deciliter) that was consistent with clinical practice guidelines at the time the studies were conducted. Current U.S. labels on ESAs recommend reducing or interrupting ESA treatment if the hemoglobin level approaches or exceeds 11 g per deciliter. However, since the dose of peginesatide can be adjusted,^{12,13} it seems unlikely that lower targets would have led to clinically relevant differences between the agents.

In conclusion, peginesatide, administered once a month, was similar to epoetin, administered one to three times a week, for the treatment of anemia in patients receiving hemodialysis.

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