



Long-term Safety of Epoetin Alfa-epbx for the Treatment of Anemia in ESKD: Pooled Analyses of Randomized and Open-label Studies

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Rationale & Objective: Epoetin alfa-epbx is a biosimilar to the reference product, epoetin alfa. We compare the safety of epoetin alfa-epbx versus epoetin alfa based on a pooled analysis of findings from 2 randomized, double-blind, comparative clinical studies, and report new data for the long-term safety of epoetin alfa-epbx.

Study Design: Pooled analyses of previously conducted studies.

Setting & Participants: Hemodialysis patients with anemia.

Interventions: Data from patients who received 1 or more subcutaneous or intravenous doses of study drug were integrated across route of administration in combined randomized groups (epoetin alfa-epbx, n = 423; epoetin alfa, n = 426). Data from patients who received 1 or more doses of epoetin alfa-epbx in either open-label extension trial were integrated across route of administration in a combined long-term safety studies group (n = 576).

Outcomes: Adverse events (AEs), immunogenicity, and other outcomes were assessed.

Results: Incidences of treatment-emergent AEs, serious AEs, and discontinuation of study drug treatment because of treatment-emergent AEs were similar between combined randomized epoetin alfa-epbx and epoetin alfa, which had mean treatment durations of 18.1 and 17.7 weeks, respectively. Incidences of treatment-emergent AEs, serious AEs, and discontinuation

of study drug treatment because of treatment-emergent AEs were 86.5%, 39.4%, and 6.6%, respectively, for the combined long-term safety studies group, which had a mean treatment duration of 40.0 weeks. In total, 12 patients across the combined randomized groups (epoetin alfa-epbx, n = 5; epoetin alfa, n = 7) and 9 patients in the combined long-term safety studies group tested anti-recombinant human erythropoietin antibody positive in 1 or more visits during study conduct. No patient in any group developed neutralizing antibodies or pure red blood cell aplasia.

Limitations: Epoetin alfa comparator not included in the long-term safety studies, greater cumulative exposure to study drug for epoetin alfa-epbx, shorter follow-up in the randomized studies, and potential for selection bias among patients in the open-label long-term safety studies.

Conclusions: This analysis reinforces previous conclusions of similar safety profiles between epoetin alfa-epbx and epoetin alfa. Furthermore, epoetin alfa-epbx had no unexpected safety signals during long-term treatment.

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Trial Registration: ClinicalTrials.gov EPOE-10-13 (NCT01473420); EPOE-10-01 (NCT01473407); EPOE-11-04 (NCT01628120); EPOE-11-03 (NCT01628107).

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Anemia is a serious and common complication that often develops during chronic kidney disease (CKD) and worsens with disease progression.¹ Anemia in patients with end-stage kidney disease (ESKD) is frequently severe and may be associated with higher mortality risk.¹⁻³ The primary cause of anemia in CKD is insufficient production of renal erythropoietin, and therefore reduced erythropoiesis.⁴ Epoetin alfa was the first recombinant human erythropoietin (epoetin) to be approved by the US Food and Drug Administration (FDA) for treatment of anemia in patients with CKD.⁵ In patients with CKD and anemia, subcutaneous (SC) or intravenous (IV) administration of epoetin results in clinically significant increases in hemoglobin (Hb) levels and reduces the need for transfusion.⁶⁻⁸

Biosimilars are biologic drugs that are highly similar to a licensed (ie, originator or reference) biologic product,

“notwithstanding minor differences in clinically inactive components,” and for which there are no clinically meaningful differences in safety, purity, and potency from the reference product.⁹ Biosimilarity is established following a stepwise approach to comparative assessments of the proposed biosimilar and reference biologic, beginning with extensive physicochemical and functional characterization of both products, followed by nonclinical testing and, finally, clinical studies (ie, clinical pharmacology and immunogenicity and clinical safety and efficacy).^{9,10} Thus, biosimilarity between a proposed biosimilar and reference biologic is established based on the totality of the evidence obtained at each stage of development.⁹

Availability of epoetin biosimilars could potentially lower the costs of epoetin treatment and provide additional epoetin treatment options.¹¹ Epoetin alfa-epbx (Retacrit;

Hospira Inc, a Pfizer company) was approved by the FDA in May 2018 as a biosimilar of epoetin alfa (Epogen/Procrit; Amgen Inc/Janssen Products LP).¹² Epoetin alfa-epbx has an identical amino acid sequence and similar carbohydrate composition to epoetin alfa.^{13,14} Pharmacokinetic and pharmacodynamic equivalence of single and multiple SC doses of epoetin alfa-epbx to epoetin alfa was established in 2 pharmacokinetic/pharmacodynamic studies conducted in healthy males.^{15,16}

Two comparative, randomized, double-blind, clinical studies, EPOE-10-13¹⁷ and EPOE-10-01,^{18,19} were conducted in hemodialysis (HD) patients with ESKD and anemia to compare the efficacy of epoetin alfa-epbx with epoetin alfa, based on maintenance of Hb levels and study drug dose requirements, and to evaluate safety. Results from these studies demonstrated equivalence in efficacy and similar safety of SC-administered (EPOE-10-13)¹⁷ and IV-administered (EPOE-10-01)^{18,19} epoetin alfa-epbx to epoetin alfa, supporting the demonstration of biosimilarity.^{13,14} Two supportive open-label extension trials for EPOE-10-13 and EPOE-10-01—studies EPOE-11-04²⁰ and EPOE-11-03,²¹ respectively—were conducted to determine the long-term safety in treatment-emergent adverse events (AEs) of epoetin alfa-epbx.

This analysis compares the safety of epoetin alfa-epbx versus epoetin alfa based on a pooled analysis of findings from EPOE-10-13 and EPOE-10-01, with data integrated across the 2 studies and route of administration, and with mean exposure to study drug of approximately 18 weeks. This analysis also provides new data for the long-term safety of epoetin alfa-epbx based on a pooled analysis of findings from the open-label extension trials, with data integrated across the 2 studies and route of administration and with mean exposure to epoetin alfa-epbx of 40.0 weeks.

METHODS

Overview of Studies

An overview of epoetin alfa-epbx clinical development studies is provided in Table 1.^{13,14,17-21} EPOE-10-13 (ClinicalTrials.gov identifier NCT01473420) was a comparative, randomized, double-blind efficacy and safety study of SC-administered epoetin alfa-epbx versus epoetin alfa conducted in HD patients with ESKD and anemia.^{13,14,17} The study consisted of a screening period, 12- to 18-week titration period, 16-week double-blind maintenance period, and follow-up visit.^{13,14,17} Patients who were receiving stable doses of IV or SC epoetin alfa during screening and who met all other eligibility criteria were randomized (1:1) to epoetin alfa-epbx or epoetin alfa in the titration period.^{13,14,17} Patients who were receiving IV epoetin alfa before study initiation were treated with SC study drug through the titration period, and those who demonstrated stable SC dosing were re-randomized (1:1 to SC epoetin alfa-epbx or epoetin alfa) into the maintenance period.^{13,14,17} Stable dosing was

defined as meeting all of the following requirements before entering the maintenance period: change in epoetin dosing of $\leq 10\%$ from the mean, mean Hb level of 9.0 to 11.0 g/dL, no more than 1 Hb level result outside of range from 9.0 to 11.0 g/dL, and no Hb result more than ± 1 g/dL from the mean Hb level. Patients who were already receiving SC epoetin alfa before study initiation were randomized into but not treated in the titration period; they were directly re-randomized (1:1 to SC epoetin alfa-epbx or epoetin alfa) into the maintenance period.^{13,14,17}

EPOE-10-01 (ClinicalTrials.gov identifier NCT01473407) was a comparative, randomized, multicenter, double-blind efficacy and safety study of IV-administered epoetin alfa-epbx versus epoetin alfa conducted in HD patients with ESKD and anemia.^{18,19} The study consisted of a screening period, 24-week treatment period, and follow-up visit.¹⁹ Patients who were receiving stable doses of IV epoetin alfa during screening and who met all other eligibility criteria were randomized (1:1) to receive IV epoetin alfa-epbx or epoetin alfa in the treatment period.¹⁹ EPOE-11-04 and EPOE-11-03 (ClinicalTrials.gov identifiers NCT01628120 and NCT01628107, respectively) were supportive open-label extension trials for EPOE-10-13 and EPOE-10-01, respectively.^{20,21} In both studies, epoetin alfa-epbx was administered to all patients for up to an additional 48 weeks through the same route of administration as in the initial double-blind trial.^{13,14,20,21}

All study protocols and amendments were approved by an independent review board (Quorum Review Institutional Review Board [IRB], Seattle, WA) or local independent ethics committee/IRBs (Table S1). All studies were conducted in compliance with IRB regulations, the Declaration of Helsinki, the International Conference on Harmonization guidelines, Good Clinical Practice guidelines, and all applicable regulatory requirements. Patients provided written informed consent before the performance of any study-specific procedures.

Patients and Treatments

Inclusion and exclusion criteria have been reported previously.^{13,14,17-21} Briefly, EPOE-10-13 and EPOE-10-01 included men and nonpregnant women receiving HD aged 18 to 80 years with ESKD and anemia who, before randomization, had stable Hb levels (mean, 9.0-11.0 g/dL) for 4 or more weeks, were receiving stable adequate HD for 12 or more weeks, had adequate iron stores (plasma ferritin > 100 $\mu\text{g/L}$ and transferrin saturation $> 20\%$), and were receiving stable SC (EPOE-10-13 only) or IV epoetin alfa 1 to 3 times per week and did not require maintenance doses > 600 U/kg/wk of epoetin alfa.^{13,14,17-19} EPOE-11-04 and EPOE-11-03 included patients who previously completed the maintenance period of study EPOE-10-13 and the treatment period of EPOE-10-01, respectively.^{13,14,19-21} In all 4 studies, study drug dosing was individually titrated to maintain Hb levels

Table 1. Overview of Epoetin alfa-epbx Clinical Development Studies

Study (ClinicalTrials.gov identifier)	Study Design	Study Population	Interventions	Dosing and Treatment Duration	End Points
Subcutaneous Administration					
EPOE-10-13 (NCT01473420) ^{13,14,17}	Randomized, double-blind, parallel-group, active-controlled comparative safety and efficacy trial; 36-42 wk duration ^a	HD patients with ESKD and anemia	Titration period: randomized population (N = 320); maintenance period: randomized population, epoetin alfa-epbx (n = 124); epoetin alfa (n = 122); safety population, epoetin alfa-epbx (n = 122); epoetin alfa (n = 122)	Titration period: 1-3×/wk (starting dose 20%-30% lower than IV epoetin alfa dose received in last wk of screening) for 12-18 wk; maintenance period: 1-3×/wk, at same weekly dose received in last wk of titration or screening period, for 16 wk; 30-d follow-up if not entering long-term safety study	Mean weekly Hb and mean weekly dose/kg body weight during last 4 wk of treatment in maintenance period (co-primary)
EPOE-11-04 (NCT01628120) ^{13,14,20}	Open-label long-term safety study; 48-wk duration	Patients who completed maintenance period wk 16 study assessments during the EPOE-10-13 (core) study	Enrolled population: epoetin alfa-epbx (N = 173); safety population: epoetin alfa-epbx (N = 170)	1-3×/wk, at last dose level administered in study EPOE-10-13, for up to 48 wk	Treatment-emergent adverse events during the treatment period (primary); mean Hb and mean weekly dose/kg body weight during the treatment period (secondary)
IV Administration					
EPOE-10-01 (NCT01473407) ^{18,19}	Randomized, double-blind, parallel-group, active-controlled comparative safety and efficacy trial; 32-wk duration ^a	HD patients with ESKD and anemia	Randomized population: epoetin alfa-epbx (n = 306); epoetin alfa (n = 306); safety population: epoetin alfa-epbx (n = 301); epoetin alfa (n = 304)	1-3×/wk, at same weekly dose administered during last wk of screening, for 24 wk; 30-d follow-up if not entering long-term safety study	Mean weekly Hb and mean weekly dose/kg body weight during last 4 wk of treatment period (co-primary)
EPOE-11-03 (NCT01628107) ^{13,14,21}	Open-label long-term safety study; 48-wk duration	Patients who completed treatment period wk 24 study assessments during the EPOE-10-01 (core) study	Enrolled population: epoetin alfa-epbx (N = 414); safety population: epoetin alfa-epbx (N = 406)	1-3×/wk, at last dose level administered in study EPOE-10-01, for up to 48 wk	Treatment-emergent adverse events during the treatment period (primary); mean Hb and mean weekly dose/kg body weight during the treatment period (secondary)

Abbreviations: ESKD, end-stage kidney disease; Hb, hemoglobin; HD, hemodialysis; IV, intravenous.

^aPatients who enrolled into the long-term safety study were not required to undergo the follow-up assessments.

between 9.0 and 11.0 g/dL,^{13,19} consistent with recommendations in the epoetin alfa US package insert.^{22,23}

Analysis Populations and Assessments

The safety population for the combined randomized treatment groups comprised patients who received 1 or more doses of study drug during the maintenance period in EPOE-10-13 or the treatment period in EPOE-10-01. Data from patients in these core studies were integrated across administration route to create combined randomized epoetin alfa-epbx and epoetin alfa treatment groups. This provided a primary safety overview, allowing for a comparison of safety between study drugs based on the pooled experience in 2 comparative randomized safety and efficacy studies. The safety population for the combined open-label extension trials included all patients who received 1 or more doses of epoetin alfa-epbx in either EPOE-11-04 or EPOE-11-03. Data from patients in these supportive extension trials were integrated across administration route to create a combined open-label long-term safety study group. This provided additional safety data, allowing for evaluation of long-term safety in treatment-emergent AEs with exposure to epoetin alfa-epbx for up to an additional 48 weeks following treatment in the core studies.

Primary safety analyses were conducted on the safety population for the combined randomized treatment groups, and supportive safety analyses were performed on the safety population for the combined open-label long-term safety study group. Safety assessments included AEs, serious AEs (SAEs), clinical laboratory analytes, incidences of out-of-range clinical laboratory analytes, and clinical laboratory screens (ie, Hb < 8.0 or >12.0 g/dL, with ± 2.0 -g/dL change from baseline in Hb level; red blood cell count < $1.5 \times 10^6/\mu\text{L}$ and reticulocyte percentage of total erythrocytes <0.5%; alanine or aspartate transaminase level > 3 times the upper limit of normal and total bilirubin > 1.5 times the upper limit of normal; absolute neutrophil count < 1,000/ μL ; and platelet count < 100,000/ μL and international normalized ratio > 3.5), electrocardiogram findings, and physical examination findings (reported descriptively). Vital signs were collected in the comparative studies. AEs of special interest were myocardial infarction, cerebrovascular events, thromboembolic events, hypertension, seizures, pure red blood cell aplasia (PRCA), and potential allergic reactions.

Given the onset of treatment-emergent AEs during the transition of patients from the core study to the long-term safety study, assignment of individual treatment-emergent AEs to the core study or the long-term safety study was made differently in certain instances at the individual study level and for the integrated AE analysis. If the onset of an AE was in the interim period between the core study and the long-term safety study but the AE occurred after the patient received study drug in the core study, the AE was assigned to the core study in the integrated analysis.

Similar assignments were performed in EPOE-10-13 for patients transitioning from the titration period to the maintenance period. This ensured that all treatment-emergent AEs would be assigned most conservatively for the integrated AE analyses.

Immunogenicity was also evaluated throughout the studies.^{13,14,17-21} The presence of anti-recombinant human erythropoietin (anti-rhEPO) antibodies and the potential neutralizing capacity of such antibodies were assessed.

RESULTS

Patients

A total of 430 and 428 patients were randomized to epoetin alfa-epbx and epoetin alfa, respectively, across the 2 comparative safety and efficacy studies (Fig 1). Of these, 423 and 426 patients received epoetin alfa-epbx and epoetin alfa, respectively, and comprised the safety populations for the combined randomized treatment groups. Patient demographics and baseline characteristics were generally well matched between the 2 combined randomized groups (Table 2). Mean duration of treatment was 18.1 (standard deviation [SD], 6.4) and 17.7 (SD, 6.8) weeks for the combined randomized epoetin alfa-epbx and epoetin alfa groups, respectively; median duration of treatment was 22.7 (range, 0.0-24.7) and 21.7 (range, 0.0-25.3) weeks, respectively. Study completion rates were similar between combined randomized epoetin alfa-epbx (83.9%) and epoetin alfa (85.7%; Fig 1). Corresponding rates of study discontinuation due to AEs were 2.4% and 2.3%, respectively. Study drug treatment completion and discontinuation rates were also similar between the combined randomized groups (Table S2).

A total of 587 patients were enrolled across the 2 supportive open-label extension trials (Fig 1). Of these, 576 patients received epoetin alfa-epbx and comprised the safety population for the combined open-label long-term safety study group. Patient demographics and baseline characteristics of the open-label long-term safety study group were generally consistent with the combined randomized groups (Table 2). Diabetes and hypertension were the primary causes of CKD across all groups. Mean and median durations of treatment were 40.0 (SD, 14.1) and 47.0 (range, 0.0-65.3) weeks, respectively, for the combined open-label long-term safety study group. Study completion rate in the combined open-label long-term safety study group was 73.6%, and 7.8% of patients discontinued the study because of AEs (Fig 1).

Adverse Events

Combined Randomized Controlled Trials

Approximately 75% of patients in both combined randomized treatment groups experienced 1 or more treatment-emergent AEs (Table 3). The most common (incidence $\geq 5\%$) treatment-emergent AEs were similar between treatment groups and the most frequently reported treatment-emergent AEs for epoetin alfa-epbx were nausea

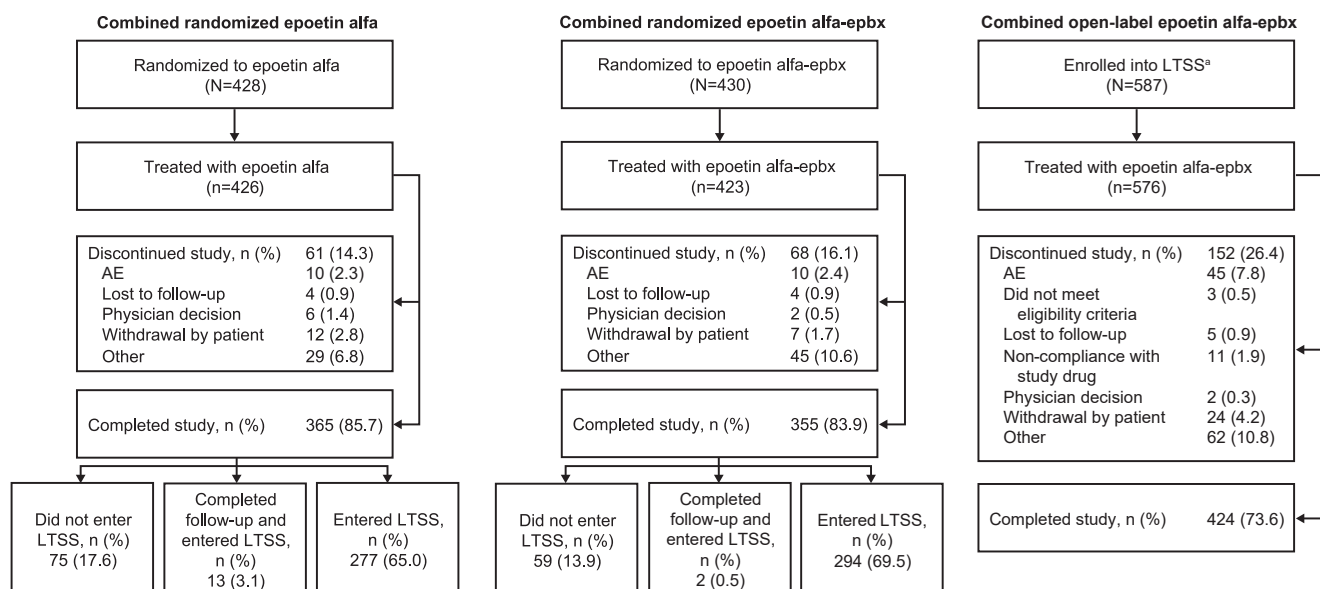


Figure 1. Patient disposition. Study completion and study discontinuation rates for the combined randomized and combined open-label long-term safety study (LTSS) groups. ^aPatients were eligible for the open-label LTSSs, EPOE-11-04 and EPOE-11-03, if they received treatment and completed the required study assessments during the respective core studies: EPOE-10-13 maintenance period, up to and including week 16 study assessments; and EPOE-10-01 treatment period, up to and including week 24 study assessments. Patients who discontinued treatment before week 16 of the maintenance period in EPOE-10-13 and before week 24 of the treatment period in EPOE-10-01 were offered treatment with standard-of-care erythropoiesis-stimulating agents (ESAs) for the rest of the maintenance and treatment periods and were to complete the required week 16 (EPOE-10-13) or week 24 (EPOE-10-01) study assessments to be eligible for enrollment in the LTSS. Enrollment in the LTSS occurred within 28 days after completion of the maintenance period week 16 study assessments for the EPOE-10-13 core study and after completion of the treatment period week 24 study assessments for the EPOE-10-01 core study. Abbreviation: AE, adverse event.

(9.5% vs 7.7% for epoetin alfa), arteriovenous fistula-site complication (7.6% and 7.0%, respectively), and vomiting (7.6% and 4.9%, respectively; Table 3).

Similarly, the incidence of SAEs (23.9% vs 27.2% and treatment-emergent SAEs resulting in death ($n = 9$ [2.1%] in each group) were similar between combined randomized epoetin alfa-epbx and epoetin alfa (Table 3). Incidences of the 8 most common SAEs (congestive heart failure, noncardiac chest pain, cellulitis, osteomyelitis, pneumonia, fluid overload, hyperkalemia, and dyspnea) were similar between the 2 combined randomized groups, and the 3 most frequently reported SAEs for epoetin alfa-epbx were pneumonia (1.7% vs 2.3% for epoetin alfa), congestive heart failure (1.2% in each group), and osteomyelitis (1.2% and 0.2%, respectively).

Of the 18 deaths reported for the combined randomized groups, 8 ($n = 1$, epoetin alfa-epbx; $n = 7$, epoetin alfa) were the result of cardiovascular disease. The remaining causes of death for the combined randomized epoetin alfa-epbx group were azotemia associated with discontinuation of dialysis treatment ($n = 3$), sepsis, gastrointestinal hemorrhage, sudden death (unknown cause), infectious peritonitis, and metabolic encephalopathy ($n = 1$ each); and for the combined randomized epoetin alfa group, they were aortic stenosis and metastatic lung cancer ($n = 1$ each).

The incidences of treatment-emergent AEs leading to discontinuation of study drug treatment were similar between combined randomized epoetin alfa-epbx (3.1%) and epoetin alfa (3.5%). The incidences of AEs of special interest were generally low and similar between the 2 combined randomized groups. Furthermore, there were no reported cases of PRCA (Table 4).

Combined Open-label Long-term Safety Study of Epoetin Alfa-epbx

In the combined open-label long-term safety study group, 498 (86.5%) patients experienced 1 or more treatment-emergent AEs. The most common (incidence $\geq 5\%$) treatment-emergent AEs were anemia, arteriovenous fistula-site complication, back pain, cough, diarrhea, dizziness, dyspnea, headache, hypotension, hyperkalemia, hypertension, muscle spasms, nausea, pain in extremity, peripheral edema, pneumonia, pyrexia, upper respiratory tract infection, and vomiting.

One or more SAEs were reported by 227 (39.4%) patients in the combined open-label long-term safety study group, the 5 most common being pneumonia (3.6%), sepsis (3.3%), congestive cardiac failure (2.8%), hyperkalemia (2.6%), and acute myocardial infarction (2.3%). In total, 43 (7.5%) patients in the combined open-label

Table 2. Patient Demographics and Baseline Characteristics (Safety Population)

Characteristic ^a	Combined Randomized Epoetin alfa (n = 426)	Combined Randomized Epoetin alfa-epbx (n = 423)	Combined Open-label Long-term Safety Study Epoetin alfa-epbx (n = 576)
Men	230 (54.0%)	219 (51.8%)	312 (54.2%)
Age, years	57 (12)	56 (13)	57 (12)
Race			
White	208 (48.8%)	210 (49.6%)	286 (49.7%)
Black or African American	185 (43.4%)	194 (45.9%)	252 (43.8%)
Native Hawaiian or other Pacific Islander	5 (1.2%)	2 (0.5%)	3 (0.5%)
Asian	15 (3.5%)	8 (1.9%)	18 (3.1%)
American Indian or Alaska Native	2 (0.5%)	1 (0.2%)	2 (0.3%)
Other	10 (2.3%)	8 (1.9%)	15 (2.6%)
Missing	1 (0.2%)	0 (0%)	0 (0%)
Primary cause of CKD			
Diabetes	192 (45.1%)	197 (46.6%)	260 (45.1%)
Hypertension	142 (33.3%)	146 (34.5%)	203 (35.2%)
Nephropathies	60 (14.1%)	49 (11.6%)	70 (12.2%)
Congenital renal disease	13 (3.1%)	11 (2.6%)	14 (2.4%)
Other	16 (3.8%)	17 (4.0%)	25 (4.3%)
Unknown	3 (0.7%)	3 (0.7%)	4 (0.7%)
Frequency of HD, ×/wk			
2	3 (0.7%)	1 (0.2%)	1 (0.2%)
3	423 (99.3%)	422 (99.8%)	575 (99.8%)
Dosing frequency, ×/wk			
1	167 (39.2%)	159 (37.6%)	236 (41.0%)
2	64 (15.0%)	62 (14.7%)	76 (13.2%)
3	195 (45.8%)	201 (47.5%)	263 (45.7%)
Missing	0 (0%)	1 (0.2%)	1 (0.2%)
Hb, g/dL	10.4 (0.7)	10.4 (0.8) ^b	10.4 (0.7)
Hematocrit, %	32.9 (2.7)	33.0 (2.7) ^b	32.9 (2.7)
Ferritin, ng/mL	934 (412)	941 (431)	946 (410)
TSAT, %	33.6 (12.0)	34.8 (12.2)	34.7 (12.4)
Medical history of comorbid conditions present at baseline			
Hypertension	419 (98.4%)	415 (98.1%)	568 (98.6%)
Diabetes	273 (64.1%)	267 (63.1%)	362 (62.8%)
Thromboembolism including myocardial infarction and cerebrovascular accident	176 (41.3%)	150 (35.5%)	213 (37.0%)
Vascular access thrombosis	41 (9.6%)	37 (8.7%)	48 (8.3%)
Use of iron supplementation			
At baseline	214 (50.2%)	212 (50.1%)	294 (51.0%)
During treatment	325 (76.3%)	333 (78.7%)	499 (86.6%)

Note: Values expressed as number (percent) or mean (standard deviation).

Abbreviations: CKD, chronic kidney disease; Hb, hemoglobin; HD, hemodialysis; TSAT, transferrin saturation.

^aPercentages for Race may not sum to 100 because patients could select multiple races and because of rounding. Percentages for other characteristics also may not sum to 100 because of rounding.

^bMean (standard deviation) Hb and hematocrit based on data for 422 patients treated with epoetin alfa-epbx.

long-term safety study group experienced a treatment-emergent SAE resulting in death. The most common cause of death in the combined open-label long-term safety study group was cardiovascular disease (n = 17). Other causes of death were nervous system disorders (n = 8), renal disorders, sepsis (n = 5 each), hemorrhage (n = 3), acute respiratory failure (n = 2), pulmonary embolism, hypoglycemia, and unknown cause (n = 1

each). Forty of the 43 treatment-emergent SAEs resulting in death were considered by the investigators to be probably not related or not related to study drug; 3 (intracerebral hemorrhage, myocardial infarction, and cardiorespiratory arrest) were considered by the investigators to be possibly related to study drug.

In the combined open-label long-term safety study group, 38 (6.6%) patients experienced an AE leading

Table 3. Overview of AEs (safety population)

AEs	Combined Randomized Epoetin alfa (n = 426)	Combined Randomized Epoetin alfa-epbx (n = 423)
No. of events	1,556	1,419
Patients with event		
≥1 AE	318 (74.6%)	321 (75.9%)
≥1 treatment-related AE ^a	18 (4.2%)	14 (3.3%)
≥1 severe AE ^b	67 (15.7%)	64 (15.1%)
≥1 SAE	116 (27.2%)	101 (23.9%)
Discontinuation of study drug treatment due to an AE	15 (3.5%)	13 (3.1%)
Discontinuation from study due to an AE	10 (2.3%)	10 (2.4%)
AE resulting in death ^c	9 (2.1%)	9 (2.1%)
Medical intervention due to an AE ^d	255 (59.9%)	268 (63.4%)
≥1 AE of special interest	50 (11.7%)	64 (15.1%)
Treatment-emergent AE in ≥5% of patients in either treatment group ^e		
Diarrhea	33 (7.7%)	26 (6.1%)
Nausea	33 (7.7%)	40 (9.5%)
Arteriovenous fistula-site complication	30 (7.0%)	32 (7.6%)
Hypotension	29 (6.8%)	15 (3.5%)
Muscle spasm	28 (6.6%)	31 (7.3%)
Dyspnea	26 (6.1%)	25 (5.9%)
Cough	25 (5.9%)	21 (5.0%)
Dizziness	25 (5.9%)	23 (5.4%)
Pain in extremity	22 (5.2%)	17 (4.0%)
Vomiting	21 (4.9%)	32 (7.6%)
Headache	19 (4.5%)	29 (6.9%)
Hypertension	19 (4.5%)	24 (5.7%)
Fall	16 (3.8%)	22 (5.2%)

Note: Values expressed as number (percent).

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

^aTreatment-related AEs include those considered as definitely, probably, or possibly related to study drug, as well as those for which a causal relationship was missing.

^bSAEs also include those for whom severity was missing.

^cExcludes patients who reported an AE resulting in death during the titration period of EPOE-10-13.

^dIncludes patients for whom treatment was required or other action was taken.

^eAll investigator AE terms were coded using MedDRA version 14.1. Patients are counted once within each system organ class for each preferred term and may have had more than 1 AE.

to discontinuation of study drug treatment, the most common being cardiac arrest, congestive heart failure (0.7% each), cardiorespiratory arrest, cerebral hemorrhage (0.5% each), acute myocardial infarction, myocardial infarction, nausea, sepsis, and septic shock (0.3% each).

Table 4. AEs of Special Interest (safety population)

AEs	Combined Randomized Epoetin alfa (n = 426)	Combined Randomized Epoetin alfa-epbx (n = 423)
No. of events	77	86
Patients with ≥1 event ^a	50 (11.7%)	64 (15.1%)
Thromboembolic events	26 (6.1%)	33 (7.8%)
Hypertension	21 (4.9%)	28 (6.6%)
Thrombosis of vascular access ^b	18 (4.2%)	28 (6.6%)
Cerebrovascular events	6 (1.4%)	4 (0.9%)
Potential allergic reactions	6 (1.4%)	10 (2.4%)
Myocardial infarction	3 (0.7%)	4 (0.9%)
Seizures	1 (0.2%)	1 (0.2%)
Pure red blood cell aplasia	0 (0%)	0 (0%)

Note: Values expressed as number (percent). All investigator AE terms were coded using MedDRA version 14.1.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

^aPatients were counted once within each category for each preferred term and may have had more than 1 AE.

^bThe AEs of special interest in the Thrombosis of vascular access category are a subset of those in the Thromboembolic events category.

Two of the 38 patients had AEs leading to discontinuation of study drug treatment that were considered by the investigators to be possibly related to study drug. The most common AEs of special interest in the combined open-label long-term safety study group were thromboembolic events (13.2%), thrombosis of vascular access (8.5%), and hypertension (7.5%). Furthermore, there were no reported cases of PRCA.

Clinical Laboratory, Vital Signs, and Other Safety Assessments

Mean change from baseline to each assessment visit for Hb level was minimal and similar between the combined randomized groups (Table S3). Most patients had Hb levels that remained within the target range, and the incidence of patients who experienced an Hb excursion (<8.0 or >12.0 g/dL) was generally similar between the combined randomized groups. Additionally, there were no clinically significant changes in other hematology parameters or chemistry parameters during the randomized studies. Furthermore, vital signs were similar between combined randomized epoetin alfa-epbx and epoetin alfa.

Mean change from baseline to each assessment visit for Hb level was minimal for the combined open-label long-term safety study group. Additionally, there were no clinically significant changes in other hematology parameters or chemistry parameters during the open-label long-term safety study.

Immunogenicity

A total of 12 patients across the combined randomized groups (epoetin alfa-epbx, $n = 5$; epoetin alfa, $n = 7$) were confirmed anti-rhEPO antibody positive at 1 or more visits during study conduct (ie, baseline, at any time during treatment period, or end of treatment/follow-up/withdrawal). Nine patients in the combined open-label long-term safety study group were confirmed anti-rhEPO antibody positive at 1 or more visits during study conduct. Of these, only 2 did not test positive during the randomized core studies. A summary of patients who tested positive for anti-rhEPO antibodies at each visit is provided in Table S4. No patient in any group developed neutralizing antibodies. Overall, an evaluation of reported events did not identify events of hypersensitivity consistent with an immune response to epoetin.

DISCUSSION

This analysis compares the safety of epoetin alfa-epbx and epoetin alfa based on a pooled analysis of findings from 2 randomized double-blind clinical trials (EPOE-10-13 and EPOE-10-01) conducted in HD patients with anemia.^{13,14,17-19} This analysis also reports new data for the long-term safety of epoetin alfa-epbx based on a pooled analysis of findings from 2 open-label extension trials (EPOE-11-04 and EPOE-11-03) for studies EPOE-10-13 and EPOE-10-01. These analyses provide the largest and longest-duration clinical safety summary to date for epoetin alfa-epbx, with more than 800 patients treated with epoetin alfa-epbx or epoetin alfa (mean exposure, ~ 18 weeks) across 2 randomized double-blind studies and 576 patients treated with epoetin alfa-epbx (mean exposure, 40.0 weeks) across 2 open-label long-term safety studies.

Our pooled analysis of studies EPOE-10-13 and EPOE-10-01 demonstrated similar safety between epoetin alfa-epbx and epoetin alfa. Furthermore, pooled analysis of open-label extension trials (EPOE-11-04 and EPOE-11-03) for studies EPOE-10-13 and EPOE-10-01 demonstrated that epoetin alfa-epbx was well tolerated, with no unexpected safety or immunogenicity signals with long-term treatment. These findings add to the body of literature demonstrating the safety of epoetin alfa biosimilars, such as a study describing the safety and efficacy of the epoetin alfa biosimilar, HX575.²⁴

The AEs, including SAEs, observed in the safety population for the combined randomized studies were generally similar between epoetin alfa-epbx and epoetin alfa and were concordant with the type and incidences of AEs described for epoetin alfa.^{22,23} These findings reinforce previous conclusions of similar safety of epoetin alfa-epbx to epoetin alfa.^{13,14,19} The open-label extension trials provide new safety data, allowing for evaluation of long-term safety with prolonged exposure to epoetin alfa-epbx. The incidence of AEs (86.5%) and SAEs (39.4%) for the combined open-label long-term safety study group is likely attributable to the longer duration of treatment

(mean exposure, 40.0 vs ~ 18 weeks). Nonetheless, in the long-term safety study, no new safety signals were identified. Types of AEs observed for the combined open-label long-term safety study group were consistent with those historically described for the reference product, epoetin alfa. Additionally, there were no clinically significant changes in hematology or chemistry parameters during the randomized studies and the open-label long-term safety study. Furthermore, Hb levels were stable throughout the duration of the studies and remained within target range for most patients.

ESKD is associated with higher mortality risk.^{25,26} Furthermore, the leading cause of death among patients with ESKD is cardiovascular disease^{25,26}; therefore, the cardiovascular events observed during this analysis of the epoetin alfa-epbx clinical development program are consistent with expectations for an HD population. Infection, bacteremia, and sepsis are also major sources of morbidity and mortality in patients with ESKD receiving maintenance HD therapy.²⁷⁻²⁹ Therefore, the 2 deaths due to sepsis and 1 death due to infectious peritonitis, which occurred in patients receiving epoetin alfa-epbx and were considered not related or probably not related to the study drug, are also consistent with expectations for an HD population.

PRCA is a rare hematologic disorder that may develop after treatment with erythropoiesis-stimulating agents (ESAs) due to the production of anti-erythropoietin neutralizing antibodies.³⁰ Previously described cases of ESA-induced antibody-mediated PRCA predominantly occurred in patients who received a particular formulation of an epoetin alfa product (Eprex/Erypo; Janssen-Cilag GmbH, Neuss, Germany) marketed outside of the United States, and only when the drug was administered SC.³¹⁻³³ However, in our studies, route of administration did not detectably influence the risk for developing antibody-mediated PRCA with erythropoietin products because there were no reported events of PRCA in the epoetin alfa-epbx clinical development program.

As a continuation of initial treatment in the randomized studies, the open-label extension trials provided safety data for epoetin alfa-epbx when administered either SC for up to 64 weeks (16.0 months) or IV for up to 72 weeks (18.0 months). Accordingly, these studies are helpful in the evaluation of AEs that may develop with long-term epoetin treatment. The latency period for PRCA may be longer, though, because previously described cases of ESA-induced PRCA were diagnosed after a median treatment duration of 9.1 months for patients receiving Eprex/Erypo, 18.0 months for patients receiving epoetin beta, and 24.8 months for patients receiving Epogen.³¹ However, anti-erythropoietin antibodies are likely to develop earlier and may be present after 3 months of treatment.³⁰ No patient in the epoetin alfa-epbx clinical development program developed neutralizing antibodies. Furthermore, reported events within the category of potential allergic reactions were generally identified as having an alternative etiology or pertinent medical history that excluded true epoetin-

related hypersensitivity reactions. Overall, these findings suggest that there is no impact of immunogenicity on the safety of epoetin alfa-epbx.

Based on intended design features of trials included in this analysis, the long-term safety study did not include epoetin alfa as a comparator, and cumulative exposure to study drug in the overall program was greater for epoetin alfa-epbx than for epoetin alfa. These factors may limit the ability to draw comparisons between treatment arms when the long-term safety study data are included in the analysis. However, no new safety signals were identified in the open-label extension trials; the types of AEs observed for the combined open-label long-term safety study group were consistent with those historically described for the reference product. This analysis may also be limited by the short duration of follow-up in the randomized studies and the potential for selection bias among patients included in the open-label extension trials. Nonetheless, one strength of this analysis is the inclusion of data from 2 randomized controlled trials, which minimizes the potential for confounding.

In conclusion, this analysis reinforces previous conclusions of similar safety of epoetin alfa-epbx to the reference product, epoetin alfa, based on a pooled analysis of the experience in 2 randomized double-blind clinical studies.^{13,14,19} Furthermore, pooled analysis of new data from 2 supportive open-label extension trials demonstrated that epoetin alfa-epbx was well tolerated and had no unexpected safety or immunogenicity signals during long-term treatment in HD patients with anemia.

SUPPLEMENTARY MATERIAL

Supplementary File 1 (PDF)

Table S1: Local IECs/IRBs used in studies EPOE-10-13, EPOE-10-01, EPOE-11-04 and EPOE-11-03.

Table S2: Patient disposition: study drug treatment completion and discontinuation rates.

Table S3: Mean baseline and mean change from baseline in Hb (safety population).

Table S4: Immunogenicity results (safety population).

ARTICLE INFORMATION

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