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Switching from Epoetin Alfa (Epogen®) to Epoetin Alfa-Epbx (Retacrit™) Using a Specified Dosing Algorithm: A Randomized, Non-Inferiority Study in Adults on Hemodialysis

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Abstract

Background: For patients with anemia undergoing hemodialysis, erythropoiesis-stimulating agents (ESAs) are typically dosed via precise algorithms. Using one such algorithm, we assessed the maintenance of hemoglobin levels in patients switched from epoetin alfa reference product (Epogen®) to epoetin alfa-epbx (Retacrit™; a biosimilar to US-licensed Epogen®/Procrit®). ***Methods:*** This randomized, open-label, non-inferiority study was conducted at Fresenius Medical Care North America (FMCNA) hemodialysis centers. Patients with anemia and chronic kidney disease undergoing maintenance hemodialysis and receiving routine intravenous (IV) Epogen® were randomized 1:1 to switch to IV Retacrit™ or continue standard-of-care (Epogen®) for 24 weeks, using analogous versions of the FMCNA ESA-dosing algorithm. The primary endpoint was the proportion of time patients' hemoglobin was 9–11 g/dL during weeks 17–24. ***Results:*** Of 432 randomized patients, 418 received treatment (Retacrit™, n = 212; standard-of-care, n = 206) and comprised the full analysis set. A similar proportion of patients discontinued from each arm. The proportion of time patients' hemoglobin was within the target range was 61.9% (95% CI 57.5–66.2) in the Retacrit™ arm and 63.3% (95% CI 58.7–67.7) in the standard-of-care arm. The difference in proportions between treatment arms was –1.4% (95% CI –7.6 to 4.9), and the lower bound of the confidence interval was within the pre-specified non-inferiority margin of –12.5%. There was no statistically significant difference between arms in the mean change from baseline in the weekly mean ESA dose during weeks 17–24, and no clinically relevant differences in safety outcomes. ***Conclusions:*** Switching to Retacrit™ was non-inferior to continuing Epogen® in maintaining hemoglobin levels in patients receiving hemodialysis, when both ESAs were dosed using a specified algorithm (ClinicalTrials.gov, NCT02504294).

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Introduction

The introduction of erythropoiesis-stimulating agents (ESAs) represented a major breakthrough in the treatment of anemia in chronic kidney disease (CKD) [1]. Epoetin alfa, a recombinant human erythropoietin, was the first exogenous ESA to receive approval from the US Food and Drug Administration. It is marketed in the United States as Epogen® (Amgen Inc, Thousand Oaks, CA, USA) and Procrit® (Janssen Products, LP, Horsham, PA, USA) [2, 3]. In clinical studies of patients with CKD on dialysis, the administration of epoetin alfa has been shown to result in increases in hemoglobin and a reduced need for red blood cell transfusion [2, 3]. However, expenditure on ESAs in patients with end-stage renal disease is considerable [4].

In Europe, biosimilar epoetins were first authorized more than 10 years ago [5]. Biosimilars are biological products that are highly similar to a licensed reference (i.e., originator) biologic, with no clinically meaningful differences in safety or efficacy [6–8]. Regulatory approval is based on the totality of evidence from analytical, nonclinical, and clinical studies, in which a proposed biosimilar is extensively compared with the originator product to demonstrate biosimilarity [6–8]. Biosimilars provide additional treatment options; they may increase patient access to biologics and have the potential to provide savings for healthcare systems [9, 10].

The first biosimilar ESA to obtain approval in the United States was epoetin alfa-epbx (hereafter referred to as Retacrit™; Hospira Inc, a Pfizer company, Lake Forest, IL, USA) [11, 12]. Retacrit™ was approved by the US Food and Drug Administration in May 2018 as a biosimilar to US-licensed Epogen®/Procrit®, for all indications of the epoetin alfa reference product [11, 12]. Retacrit™ has an identical amino acid sequence and similar carbohydrate composition to Epogen®/Procrit® [13, 14]. In addition to comprehensive analytical and nonclinical studies, the development program that supported regulatory approval in the United States included several comparative clinical studies of Retacrit™ and Epogen®. Similarity in pharmacokinetics and pharmacodynamics was demonstrated in single-dose and multiple-dose studies in healthy male participants [15, 16]; a pilot pharmacokinetics study was also conducted in patients with CKD on hemodialysis (NCT01170078) [13]. Additionally, 2 randomized, double-blind, efficacy and safety studies (one assessing intravenous [IV] administration of Retacrit™ or Epogen® [NCT01473407], and the other subcutaneous administration [NCT01473420]) were conducted in hemodialysis patients [13, 14, 17]. Each comparative efficacy and safety study was followed by a supportive, open-label, long-term safety study (NCT01628107 and NCT01628120, respectively) [13].

In the 2 pivotal comparative efficacy and safety studies in patients on hemodialysis, adjustments to the dose of Retacrit™ and Epogen® were permitted in accordance with recommendations in the United States prescribing information for Epogen® [3, 13, 17]. However, in clinical practice, owing to the complexities of maintaining hemoglobin levels within a narrow target range and the desire to use ESAs judiciously, many dialysis centers utilize algorithms to adjust ESA doses in a precise manner [18–21]. Therefore, studies examining the dosing of biosimilar epoetins according to such algorithms will be of clear relevance to dialysis providers.

We conducted the PIEDA study (A Phase 3b Investigation of Erythropoietin Drugs Using a Specified Dosing Algorithm) with the primary objective of investigating how switching from Epogen® reference product (the standard-of-care treatment) to Retacrit™ affects the maintenance of hemoglobin levels in patients on hemodialysis when using a specified ESA-dosing algorithm. The computerized algorithm used in the study was originally developed for Epogen® and has been utilized with this product in real-world practice at Fresenius Medical Care North America (FMCNA) dialysis centers. A non-inferiority design was employed to assess whether Retacrit™ is at least as effective as Epogen® for hemoglobin maintenance. The secondary objective was to evaluate how switching from Epogen® to Retacrit™ affects the dosing of ESAs, again using the specified ESA-dosing algorithm.

Methods

Study Design

This was a multicenter, prospective, randomized, open-label, 24-week, non-inferiority study with one Retacrit™ arm and one standard-of-care arm ("standard-of-care" is equivalent to Epogen®). The study was registered at ClinicalTrials.gov (NCT02504294; first posted July 21, 2015) and conducted with 18 investigators at 46 facilities at FMCNA outpatient hemodialysis centers in the United States and Puerto Rico. A single network of dialysis centers was chosen to ensure consistent use of the proprietary dosing algorithm across study sites. Medical and clinical monitoring was conducted by the sponsor or Frenova Renal Research (Waltham, MA, USA).

Patient Population

Patients were adults (≥18 years old) with anemia and CKD who had been receiving in-center hemodialysis for ≥120 days. Patients needed to be stable on treatment with Epogen®, defined as having

received routine IV Epogen® for treatment of anemia for ≥16 weeks and not having missed more than 3 prescribed doses within the 12 weeks before randomization. Patients had to be currently using the IV Epogen® version of the FMCNA ESA-dosing algorithm for anemia management and be receiving hemodialysis at a clinic using the FMCNA dosing algorithm for IV iron.

Female patients were excluded if they were pregnant or lactating, or were of childbearing potential but did not agree to use a highly effective method of contraception as determined by the investigator. Patients were also excluded if they had any concurrent condition that could lead to greater-than-normal loss of blood, as were those with a history of transfusion of any blood product in the past 3 months, with 2 or more transfusions in the past year, or who had donated or lost >475 mL blood volume (including plasmapheresis) in the past 3 months. Patients who were receiving a long-acting ESA or who had received a long-acting ESA in the 16 weeks before study randomization were also excluded. After the commencement of the study, the exclusion criteria were revised to provide clarity on permitted anti-platelet therapy and the use of heparin during hemodialysis, as well as criteria for management of patients on warfarin therapy.

Randomization and Treatments

Following a 30-day period for screening procedures, eligible patients were randomized 1:1 to continue Epogen® or to switch to Retacrit™, both administered by IV injection for 24 weeks. The computer-generated randomization schedule was produced by Edetek Inc. (Princeton, NJ, USA) and concealed until treatment allocation. Randomization was performed by investigators using an interactive response system and was stratified by 3 groups of average hemoglobin values over the 8-week baseline period: <9.0 g/dL (below target), ≥9.0 to ≤11.0 g/dL (at target), and >11.0 g/dL (over target). Patients were randomized in blocks per strata, per study site, with a block size of six. Retacrit™ was supplied by the sponsor in aqueous form, packaged in single-dose vials of multiple concentrations (2,000, 3,000, 4,000, and 10,000 units/vial); Epogen® was provided by the study sites.

At the randomization visit for patients assigned to the Retacrit™ arm, participants had their Epogen® prescription discontinued and Retacrit™ initiated using the identical ESA dose and frequency as was prescribed for Epogen® before randomization. Retacrit™ was administered during hemodialysis treatment, as per routine ESA-dosing practices; dosing was scheduled for 1–3 times per week, and the prescribed dose was required to be a multiple of 200 units. For patients assigned to the standard-of-care arm, Epogen® was continued using the same dose and frequency that was prescribed before randomization. Throughout the 24-week treatment period, the dose of Retacrit™ and Epogen® was adjusted using the most recent analogous versions of the FMCNA ESA-dosing algorithm. The Retacrit™ version of the algorithm effective at the time of the study (known as "Epoetin Hospira cMAB [Corporate Medical Advisory Board] version 1.1") was identical to the corresponding Epogen® version of the algorithm ("Epogen cMAB version 5.1") with respect to dose computations and decision-planning; the key difference between the analogous versions of the algorithm was the specified ESA (i.e., Retacrit™ or Epogen®). The algorithm-assigned dose of both ESAs was permitted to be overridden at the discretion of the investigator or physician if determined medically appropriate, as per the usual clinical practice.

Patients also received IV iron during the 24-week period, per the FMCNA IV iron-dosing algorithm. Upon completion of the trial or early termination, patients in the Retacrit™ arm discontinued Retacrit™ and resumed routine medical care with Epogen®.

Assessments

Baseline data for patients in both arms consisted of clinical information obtained at screening and randomization, as well as information obtained retrospectively for the 12-week period immediately before randomization. Information on concomitant medications was captured from patient records for the 16 weeks before randomization and throughout the trial, and included ESA and IV iron therapies.

Clinical laboratory assessments were performed by Spectra Laboratories (Rockleigh, NJ, USA). The majority of the laboratory tests utilized for this protocol were performed per the standard clinical management of hemodialysis patients. Historical standard-of-care laboratory reports for weekly hemoglobin levels, monthly transferrin saturation (TSAT) levels, and 3-monthly ferritin levels, which had been performed within 12 weeks before randomization, were recorded during the screening and end-of-baseline period. During weeks 1–24, per routine care, patients in both arms had blood drawn for measurement of serum hemoglobin, TSAT, and ferritin. At the 4-weekly study visits, there was recording of patients' weekly hemoglobin levels (including all values between visits), monthly TSAT levels, and 3-monthly ferritin levels, as applicable, since their previous study visit.

In addition, during the screening period, serum pregnancy tests (only in females of childbearing potential) and testing for anti-epoetin antibodies (all patients) were performed. Serum anti-drug antibody samples were analyzed for the presence or absence of anti-epoetin antibodies at IPM Biotech (Hamburg, Germany) following a tiered approach. Samples that screened positive for anti-epoetin were tested in a confirmatory assay conducted in the presence and absence of epoetin. Enrolled patients who were confirmed as antibody-positive were to be informed of their antibody status and withdrawn from the study. Additionally, confirmed positive samples were characterized for antibody titer and for neutralizing activity.

Furthermore, at the week 24 end-of-treatment visit (or at early termination), a second serum pregnancy test was performed (for females of childbearing potential), and a second serum sample was drawn from all patients for potential future testing for anti-epoetin antibodies. Per protocol, these samples were to be frozen and stored for 48 months from the last patient visit. If any participant in the future develops clinical signs or symptoms for which the treating physician would wish to test for anti-epoetin antibodies, then these historical end-of-trial blood samples may, at that time, be analyzed to retrospectively determine whether the patient had anti-epoetin antibody at the end of the study (i.e., to establish the patient's post-trial "baseline" immunogenicity status). Otherwise, end-of-trial immunogenicity samples were not to be analyzed.

The safety variables assessed were the number of deaths and the number (and mean frequency) of hospital admissions. Additionally, investigators monitored patients for clinical and laboratory evidence of adverse events (AEs) throughout the study. AEs were coded using the Medical Dictionary for Regulatory Activities version 19.0. An AE was considered to be treatment-emergent if the event started or worsened in severity after the start of the study drug until 30 days after the last dose of study

medication. AEs of special interest (identified prospectively based on the safety information for the Epogen® reference product) included myocardial infarction, cerebrovascular events, thromboembolic events, hypertension, seizures, pure red cell aplasia, and potential allergic reactions. Serious AEs (SAEs) included those that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in a congenital abnormality, or a persistent or significant disability or incapacity.

Other safety evaluations included laboratory tests, vital signs, changes in electrocardiograms, and investigator-reported tolerability.

Protocol-defined withdrawal criteria, which were assessed at the 4-weekly and end-of-treatment study visits, are listed in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000492621).

Endpoints

The primary efficacy endpoint was the proportion of time patients' hemoglobin levels were 9–11 g/dL during the final 8 weeks of the study (weeks 17–24). This endpoint was introduced in a protocol amendment in December 2015, after the commencement of the study; the original primary endpoint was the proportion of patients who maintained a mean hemoglobin level within the target range during the final 8 weeks of the study. The modification was introduced to allow continuous rather than categorical assessment of data, and hence provide similar statistical power to the initial design but with a smaller sample size. Accordingly, the planned statistical analysis of the primary endpoint (detailed below) was also updated.

The secondary efficacy endpoint was the change from baseline in the mean ESA dose per patient per week over the final 8 weeks of the study, with baseline defined as the mean ESA dose per patient per week during the 8 weeks prior to randomization.

Additionally, pre-specified exploratory analyses were performed to compare variables such as TSAT levels, ferritin levels, and IV iron dosing requirements associated with use of Retacrit™ and Epogen®, in addition to other hemoglobin-level comparisons. With the exception of the percentage of patients with mean hemoglobin levels in specific ranges over the final 8 weeks of the study, exploratory endpoints are not reported here.

Statistical Considerations

For the primary endpoint, the proportion of time a patient's hemoglobin level was 9–11 g/dL over the final 8 weeks of the study was calculated using the number of hemoglobin measurements that were within the target range during weeks 17–24 as the numerator and the total number of hemoglobin measurements during weeks 17–24 as the denominator. A clustered binomial analysis using the logistic regression method was performed on binary response data to compare the proportions of time hemoglobin levels were within the target range in each treatment arm. Patients' baseline hemoglobin levels were included as a covariate. The generalized estimating equation method was used to construct 95% CIs of the proportions and of the difference in proportions. Non-inferiority was considered demonstrated if the lower bound of the 95% CI for the difference in proportions was greater than the non-inferiority margin of –12.5%. This margin was selected as it was considered by the study team to represent a clinically meaningful difference between the groups. Assuming an SD of 28%, a true difference between the groups of 0, and a 70% evaluable rate, 378 randomized patients were required to provide approximately 90% power to demonstrate non-inferiority.

The secondary endpoint was evaluated using an analysis of covariance model with treatment as a factor and mean ESA dose per week over the 8-week period before randomization as a covariate. The least-squares mean, SE, and least-squares mean difference between the treatment arms, along with the 95% CI of the difference between them, were obtained.

Missing assessments and missing data were not imputed. For the Retacrit™ and standard-of-care arms, the full analysis set (FAS) comprised all patients who received at least one dose of Retacrit™ or Epogen® after randomization, respectively. For analysis of a particular variable, a patient had to have at least one measurement in the defined visit to be included. The primary analysis of the primary endpoint was performed on the FAS; for this endpoint, a patient was required to have at least one valid value during the final 8 weeks of the study to be included. The per protocol set comprised patients who completed the final 8 weeks of treatment and did not miss more than 3 defined and scheduled doses of the ESA to which they were randomized during the final 8-week period. Patients who received a dose of the treatment other than that to which they were randomized during the final 8 weeks were excluded from per protocol set. Patients who were scheduled to have their ESA dose(s) held or interrupted according to the dosing algorithm were not considered to have missed doses.

Efficacy and safety summaries and analyses were performed on FAS data. Additional efficacy analyses were performed in the per protocol set. In the efficacy analysis, patients were analyzed in the group according to the treatment assigned at randomization. In the safety analysis, patients were analyzed in the group according to the treatment received.

Results

Patient Dispositions, Demographics, and Baseline Characteristics

Of 501 patients screened, a total of 432 patients were randomized to the Retacrit™ arm (n = 221) or the standard-of-care arm (n = 211) between July 13, 2015 and January 18, 2016 (Fig. 1). The FAS population comprised 212 patients (95.9%) in the Retacrit™ arm and 206 patients (97.6%) in the standard-of-care arm. The per protocol set included 137 patients (62.0%) in the Retacrit™ arm and 130 patients (61.6%) in the standard-of-care arm. A similar proportion of patients discontinued from the study in both treatment arms (Retacrit™: n = 56/221, 25.3%; standard of care: n = 48/211, 22.7%). The most common reason for discontinuation was meeting one or more protocol withdrawal criteria (Retacrit™: n = 27/221, 12.2%; standard of care: n = 26/211, 12.3%). The final study visit occurred on July 16, 2016.

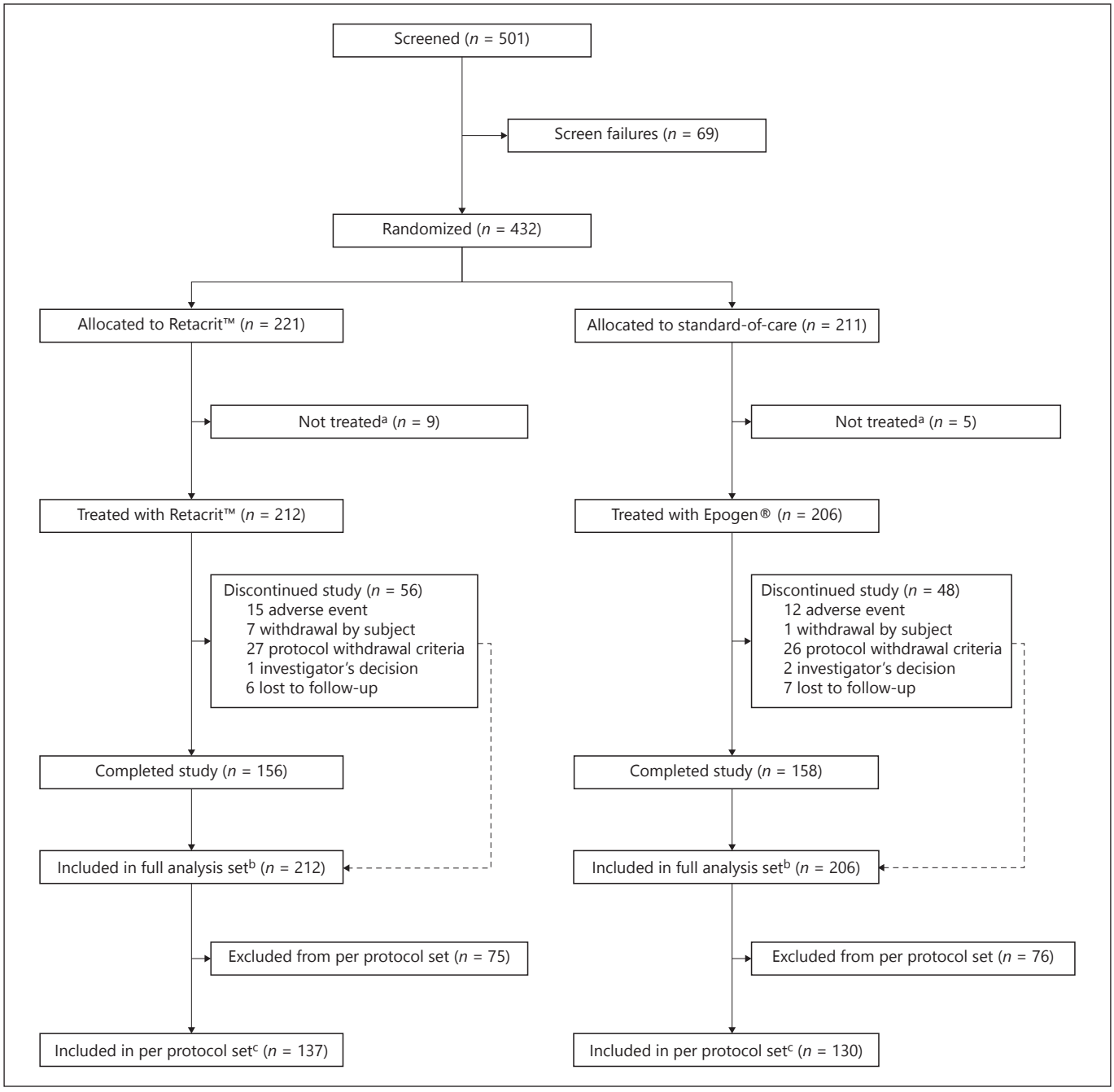

Fig. 1. Study profile. [a] Of the 9 patients randomized to the Retacrit™ arm but not treated, 2 completed the study with doses held throughout and 7 discontinued (2 due to protocol deviation, 2 due to withdrawal by subject, 1 due to an adverse event, 1 due to investigator decision, and 1 lost to follow-up). Of the 5 patients randomized to the standard-of-care arm but not treated, 4 completed the study with doses held throughout and 1 discontinued due to an adverse event. [b] For the Retacrit™ and standard-of-care arms, the full analysis set comprised all patients who received at least one dose of Retacrit™ or Epogen® after randomization, respectively. For analysis of a particular variable, a patient was required to have at least one measurement in the defined visit to be included. For the primary endpoint, a patient had to have at least one valid value during the final 8 weeks of the study to be included. For the primary endpoint, the numbers of patients analyzed were 178 in the Retacrit™ arm and 173 in the standard-of-care arm. [c] The per protocol set comprised patients who completed the final 8 weeks of treatment and did not miss more than the 3 defined and scheduled doses of the ESA to which they were randomized during the final 8-week period.

Table 1. Patient demographics and baseline characteristics (full analysis set)

	Retacrit™ (*n* = 212)	Standard-of-care (*n* = 206)
Age, years		
Mean (SD)	60.5 (13.96)	59.3 (14.23)
Median (min–max)	62.0 (26–94)	60.5 (21–90)
Gender, *n* (%)		
Male	130 (61.3)	104 (50.5)
Female	82 (38.7)	102 (49.5)
Race, *n* (%)		
American Indian or Alaska native	0 (0.0)	0 (0.0)
Asian	11 (5.2)	9 (4.4)
Black	60 (28.3)	47 (22.8)
Native Hawaiian or other Pacific Islander	1 (0.5)	0 (0.0)
White	137 (64.6)	146 (70.9)
Other	3 (1.4)	4 (1.9)
Ethnicity, *n* (%)		
Hispanic or Latino	81 (38.2)	90 (43.7)
Not Hispanic or Latino	130 (61.3)	116 (56.3)
Missing	1 (0.5)	0 (0.0)
Pre-dialysis weight, kg		
Mean (SD)	87.46 (24.963)	83.04 (23.210)
Median (min–max)	84.30 (40.3–169.2)	78.40 (42.2–187.5)
Height, cm		
Mean (SD)	167.18 (10.88)	166.7 (11.3)
Median (min–max)	166.0 (139.0–198.0)	166.0 (139.0–198.0)
BMI, kg/m^2		
Mean (SD)	31.23 (8.34)	29.79 (7.560)
Median (min–max)	29.85 (15.7–66.1)	28.15 (17.2–73.2)
Epogen® dose, U/week		
Mean (SD)	11,848.8 (12,967.19)	11,383.4 (11,504.32)
Median (min–max)	7,900 (0–62,625)	7,775 (0–71,875)
ESA dosing frequency, *n* (%)		
1/week	21 (9.9)	14 (6.8)
2/week	7 (3.3)	13 (6.3)
3/week	183 (86.3)	179 (86.9)
Other	1 (0.5)	0 (0.0)
Baseline hemoglobin, g/dL		
Mean (SD)	10.58 (0.67)	10.64 (0.59)
Median (min–max)	10.68 (7.95–12.60)	10.68 (8.64–12.61)
Dialysis vintage, days		
Mean (SD)	1,253.4 (1,101.16)	1,405.0 (1,287.27)
Median (min–max)	957.0 (3–6,127)	1,056.0 (120–9,568)

Pre-dialysis weight used for BMI calculation.
Standard-of-care is equivalent to Epogen®.
BMI, body mass index; ESA, erythropoiesis-stimulating agent; max, maximum; min, minimum; U, unit.

Patient demographics and baseline characteristics are presented in Table 1. In the FAS, the mean (SD) age for all participants was 59.9 (14.1) years. The majority were male (*n* = 234/418, 56.0%) and identified as white (*n* = 283/418, 67.7%), black (*n* = 107/418, 25.6%), or Asian (*n* = 20/418, 4.8%).

Treatment Exposure

For the FAS population, drug exposure was similar for both treatment arms. In the Retacrit™ arm, mean (SD) exposure was 135.8 (45.99) days and the median exposure was 160.0 days. In the standard-of-care arm, mean (SD) exposure was 138.6 (48.53) days and the

Table 2. Proportion of time (%) that patients' hemoglobin levels were 9–11 g/dL over the final 8 weeks of the study (full analysis set)

	Retacrit™ (*n* = 212)	Standard-of-care (*n* = 206)
n	178	173
Mean (SD)	62.6 (30.2)	62.8 (30.8)
Estimated proportion	61.9	63.3
95% CI of the proportions	57.5 to 66.2	58.7 to 67.7
Estimated difference vs. standard-of-care	−1.4	
95% CI of the difference	−7.6 to 4.9	

A clustered binomial analysis using the logistic regression method was performed with centered version of baseline hemoglobin levels included as a covariate. The generalized estimating equation method was used to construct 95% 2-sided CIs.

Standard-of-care is equivalent to Epogen®.

median exposure was 161.0 days. In both arms, the majority of patients had exposure of ≥20 weeks (Retacrit™: *n* = 140/212, 66.0%; standard-of-care: *n* = 150/206, 72.8%).

Primary Endpoint

Data from 178 patients in the Retacrit™ arm and 173 patients in the standard-of-care arm were included in the analysis of the primary endpoint carried out within the FAS. During the final 8 weeks of the study, the estimated proportion of time that patients had hemoglobin levels in the target range was 61.9% (95% CI 57.5–66.2) for the Retacrit™ arm and 63.3% (95% CI 58.7–67.7) for the standard-of-care arm (Table 2). The estimated difference in proportions between the treatment arms (Retacrit™ arm minus standard-of-care arm) was –1.4%, with a 95% CI of (–7.6 to 4.9). The –7.6% lower bound of the 95% CI was greater than the pre-specified non-inferiority margin of –12.5%, thereby demonstrating the non-inferiority of Retacrit™ to standard-of-care in the maintenance of patients' hemoglobin levels; similar results were observed in the per protocol set, supporting the conclusion of non-inferiority (online suppl. Fig. S1).

Secondary Endpoint

Within the FAS, analysis of the change from baseline in the weekly mean ESA dose over the final 8 weeks of the study was based on data from 180 patients in the Retacrit™ arm and 174 patients in the standard-of-care arm. The least-squares mean (SE) change from baseline was –1,861.8 (563.5) units/week for the Retacrit™ arm and –799.8 (573.1) units/week for the standard-of-care arm (online suppl. Table S1). The analysis of covariance model revealed no statistically significant difference between treatment arms (p = 0.19). Results were similar in the per protocol set (data not shown).

Mean Hemoglobin Levels

The percentages of patients in the FAS with mean hemoglobin levels within specified ranges at baseline and during the final 8 weeks of the study treatment period are presented in online supplemental Table S2. A majority of patients demonstrated baseline hemoglobin levels of 10–11 g/dL in both the Retacrit™ (*n* = 105/178, 59.0%) and standard-of-care (*n* = 106/173, 61.3%) arms. During the final 8 weeks of treatment, the majority of patients also had hemoglobin levels in the range 10–11 g/dL in both the Retacrit™ (*n* = 101/178, 56.7%) and standard-of-care (*n* = 92/173, 53.2%) arms.

Safety

In the FAS, 257 of 418 patients (61.5%) reported at least one treatment-emergent AE: 135 of 212 patients (63.7%) in the Retacrit™ arm and 122 of 206 patients (59.2%) in the standard-of-care (i.e., Epogen®) arm (Table 3). Of these, 3 patients (1.4%) in the Retacrit™ arm and 1 patient (0.5%) in the standard-of-care arm reported AEs that were considered related to study drug. The treatment-emergent AEs reported most frequently (≥5% of patients in either arm) were dyspnea (Retacrit™, *n* = 9/212, 4.2%; standard-of-care, *n* = 11/206, 5.3%), fall (Retacrit™, *n* = 8/212, 3.8%; standard-of-care, *n* = 11/206, 5.3%), and nausea (Retacrit™, *n* = 4/212, 1.9%; standard-of-care, *n* = 14/206, 6.8%).

Table 3. Treatment-emergent AEs of all causalities (full analysis set)

Category	Retacrit™ (n = 212)	Standard-of-care (n = 206)
Total number of AEs	494	532
Patients with events, n (%)		
AEs	135 (63.7)	122 (59.2)
AEs related to the study drug	3 (1.4)	1 (0.5)
Discontinued due to an AE	13 (6.1)	9 (4.4)
Severe AEs	34 (16.0)	32 (15.5)
Serious and treatment-related AEs	1 (0.5)	0 (0.0)
AEs resulting in death	10 (4.7)	9 (4.4)
Serious AEs	66 (31.1)	64 (31.1)

An AE was considered to be treatment-emergent if the event started or worsened in severity after the start of the study drug until 30 days after the last dose of study drug.

Standard-of-care is equivalent to Epogen®.

AE, adverse event.

The proportion of patients with SAEs was identical in the Retacrit™ arm (n = 66/212, 31.1%) and the standard-of-care arm (n = 64/206, 31.1%). Furthermore, the number of patients reporting severe AEs was similar between the Retacrit™ arm (n = 34/212, 16.0%) and the standard-of-care arm (n = 32/206, 15.5%).

There were 24 deaths reported in the FAS: 12 of 212 patients (5.7%) in the Retacrit™ arm and 12 of 206 patients (5.8%) in the standard-of-care arm. In total, 131 patients were hospitalized: 68 of 212 (32.1%) in the Retacrit™ arm and 63 of 206 (30.6%) in the standard-of-care arm.

Overall, the distribution of AEs of special interest was similar between the 2 treatment arms. The incidence of AEs was aligned with that expected based on the Epogen® package insert [3].

Analysis of changes from baseline in laboratory parameters and vital signs demonstrated no notable changes within or between arms. For the FAS, mean changes from baseline to the final 8 weeks of the study for hemoglobin levels and TSAT were minimal for both arms. The mean change from baseline to the final 12 weeks of the study for ferritin was an increase of 108.26 ng/mL for the Retacrit™ arm (n = 145), and an increase of 55.84 ng/mL for the standard-of-care arm (n = 140).

Two randomized patients tested positive for anti-epoetin antibodies at screening. Samples from both patients were low titer and negative for neutralizing antibody. In addition to the immunogenicity sampling conducted at screening, a serum sample was collected for all patients at the week 24 end-of-treatment visit (or at early termination). These samples were to be stored for potential future analysis for anti-epoetin antibodies, should a patient develop signs or symptoms during normal clinical care after the study that would warrant such testing; routine analysis of the end-of-trial blood draws was not planned as part of the study. Nonetheless, samples for 2 patients (one from each treatment arm, and neither of whom had signs or symptoms suggestive of immunogenicity) were tested for antibodies unnecessarily. Both these samples were antibody-negative.

In summary, comparative safety data did not suggest any clinically relevant differences between the Retacrit™ and standard-of-care arms.

Discussion

Prior to this study, Retacrit™ was confirmed to have comparable safety and efficacy to US-licensed Epogen® in 2 randomized, double-blind, comparative clinical studies that enrolled patients with CKD on hemodialysis who were receiving Epogen® maintenance therapy [13, 14, 17]. Those studies were conducted to support regulatory approval and used ESA dose adjustments consistent with recommendations in the United States prescribing information for Epogen® [13, 17]. As a result, the primary objective of the PIEDA study was to evaluate switching from Epogen® to Retacrit™, as compared with continued Epogen® treatment, for the maintenance of hemoglobin levels in patients on hemodialysis when using a specified computerized ESA-dosing algo-

rithm that has been utilized in real-world clinical practice. Non-inferiority of Retacrit™ to Epogen® treatment in the maintenance of hemoglobin levels was demonstrated, and no notable differences in the rates of AEs, SAEs, or deaths were observed between the arms. Moreover, given that ESA dose is an important consideration with regards to both treatment cost and the possibility of adverse outcomes [22–24], it is notable that there was no statistically significant difference between arms in terms of the change from baseline in the weekly mean ESA dose.

As many dialysis centers in the United States utilize specific algorithms for ESA treatment decisions and dose adjustments, data on the dosing of an epoetin alfa biosimilar via such an algorithm will be of relevance to many practitioners. The algorithm used in the PIEDA study, while proprietary to FMCNA, is comparable to computerized protocols used by other dialysis centers across the United States, and we anticipate that our conclusions can be applied to algorithms utilized by other dialysis providers. Therefore, our findings build on the results of the registration studies by confirming that, in a real-world scenario, switching from Epogen® to Retacrit™, with precise dose adjustments performed according to an algorithm designed for Epogen®, is not associated with a worsening of efficacy or safety, or significant differences in dosing, compared with continuing standard-of-care treatment.

The PIEDA cohort was racially diverse, and the study design was broadly similar to that of other notable non-inferiority studies of ESAs in patients undergoing hemodialysis, such as MAXIMA [25] and EMERALD 1 and 2 [26]. Although those studies used the change from baseline in hemoglobin levels as the primary efficacy endpoint, we based our assessment on the proportion of time patients' hemoglobin levels were at target. As the goal of ESA therapy is to maintain hemoglobin levels within a desired target range, with dose adjustments often required to achieve this, the primary and secondary endpoints used in PIEDA, which respectively assessed these 2 parameters, were considered appropriate for characterizing the effects of switching from Epogen® to Retacrit™. Moreover, these endpoints were considered to be of particular relevance to dialysis providers seeking to evaluate this biosimilar ESA. The examination of mortality, hospitalizations, AEs, and discontinuation rates enhanced the robustness of the study.

Two limitations should be noted. First, the open-label nature of the study represents a source of potential bias. It should, however, be considered that the primary endpoint was based on an objective laboratory measure and ESA-dosing decisions were determined by algorithm, rather than investigator discretion. A second potential weakness is that the original design of the study was changed after recruitment commenced, most notably with the modification of the primary endpoint; however, this alteration was made in the interests of sample size and took place before study completion and data analysis.

Overall, we believe our findings will help dialysis providers and clinicians in making informed clinical and economic decisions about the possible utility of Retacrit™. Biosimilars of epoetin alfa have the potential to play an important part in controlling US healthcare costs for patients with end-stage renal disease, while maintaining high-quality anemia therapy [9]. In Europe, based on publicly available list-price data across >20 countries, the price per treatment day for epoetin (considering biosimilar and referenced originator products combined) was, overall, 31% lower in 2016 than in the year before epoetin biosimilars were introduced [10]. Such cost savings could be used in a variety of ways, including the treatment of additional patients. Indeed, the same European analysis estimated that the overall utilization of biosimilar and originator epoetin had increased by 66% over the same time period [10]. It should be noted, however, that the magnitude of the changes in price and utilization varied substantially among the different countries included in the analysis, as did the uptake of epoetin biosimilars as measured by market share versus the originator product [10]. This heterogeneity likely reflects country-specific factors such as market characteristics, payer archetypes, and policies on pharmacy-mediated substitution, among others [27]. How such factors may influence the development of the nascent market for biosimilar ESAs in the United States will be of significant interest.

In conclusion, in the current study, switching to the epoetin alfa biosimilar Retacrit™ was found to be non-inferior to continued treatment with Epogen® reference product in maintaining hemoglobin levels in patients with anemia and CKD managed on hemodialysis, when both treatments were dosed using a specified algorithm.

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Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and all local regulatory requirements. Patients were required to give informed consent before any screening procedures were carried out. The final protocol, its amendments, and informed consent documentation were reviewed and approved by the central and local institutional review boards at each of the participating centers.

Disclosure Statement

R.T. is a consultant to FMCNA and has received honoraria from Pfizer for participating in advisory boards. R.G. is an employee of Pfizer. J.H. and F.W.M. are employed by Fresenius Medical Care. A.A. was an employee of Pfizer at the time of study conduct.

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Author Contribution

R.T., F.W.M., and A.A. contributed to study design. All authors contributed to the acquisition, analysis, or interpretation of data for the work. All authors participated in drafting or revising the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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