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ORIGINAL ARTICLE

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Darbepoetin alfa injection versus epoetin alfa injection for treating anemia of Chinese hemodialysis patients with chronic kidney failure: A randomized, open-label, parallel-group, non-inferiority Phase III trail

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Abstract

Background: Erythropoietin is a glycoprotein that mainly regulates erythropoiesis. In patients with chronic renal failure with anemia, darbepoetin alfa can stimulate erythropoiesis, correct anemia, and maintain hemoglobin levels. This study was designed to demonstrate the efficacy and safety of darbepoetin alfa injections as being not inferior to epoetin alfa injections (Recombinant Human Erythropoietin injection, rHuEPO) when maintaining hemoglobin (Hb) levels within the target range (10.0–12.0 g/dL) for the treatment of renal anemia.

Methods: Ninety-five patients were enrolled in this study from April 15, 2013 to April 10, 2014 at 25 sites. In this study, patients ($n = 95$) aged 18–70 years were randomized into a once per week intravenous darbepoetin alfa group ($n = 56$) and a twice or three times per week intravenous epoetin alfa group ($n = 39$) for 28 weeks, who had anemia with hemoglobin levels between 6 g/dL and 10 g/dL due to chronic kidney disease (CKD) and were undergoing hemodialysis or hemofiltration with ESA-naive (erythropoiesis stimulating agent-naive). The primary efficacy profile was the mean Hb level (the non-inferiority margin was −1.0 g/dL, week 21–28); the secondary efficacy profiles were the Hb increase rate (week 0–4), the target Hb achievement cumulative rate and time, the change trends of the Hb levels, and the target Hb maintenance ratio. Adverse events (AEs) were observed and compared, and the efficacy and safety were analyzed between the two treatment groups. Additionally, the frequencies of dose adjustments between the darbepoetin alfa and epoetin alfa groups were compared during the treatment period. SAS® software version 9.2 was used to perform all statistical analyses. Descriptive statistics were used for all efficacy, safety, and demographic variable analyses, including for the primary efficacy indicators.

Results: The mean Hb level was 11.3 g/dL in the darbepoetin alfa group and 10.7 g/dL in the epoetin alfa group, respectively; the difference of the lower limits of the 95% confidence intervals (CI) between the two groups was 0.1 g/dL (>−1.0 g/dL), and non-inferiority was proven; the Hb levels started to increase in the first four weeks at a similar increase rate; no obvious differences were observed between the groups in the target Hb achievement cumulative rates, and the Hb levels as well as the target Hb level maintenance rate changed over time. The incidence of AEs was 62.5% in the darbepoetin alfa group and 76.9% in the epoetin alfa group. All the adverse events observed in the study were those commonly associated with hemodialysis.

Conclusion: Darbepoetin alfa intravenously once per week can effectively increase Hb levels and maintain the target Hb levels well, which makes it not inferior to epoetin alfa intravenously twice or three times per week. Darbepoetin alfa shows an efficacy and safety comparable to epoetin alfa for the treatment of renal anemia.

KEYWORDS

anemia, chronic renal failure, darbepoetin alfa, hemodialysis, recombinant human erythropoietin

1 | INTRODUCTION

Erythropoietin (EPO) is an erythropoiesis-stimulating glycoprotein. Anemia in patients with chronic kidney disease (CKD) is predominantly caused by insufficient production and circulating levels of EPO due to the failing kidneys.[1] Epoetin alfa (recombinant human erythropoietin, rHuEPO) is a kind of erythropoiesis stimulating agent (ESAs) that is a primary choice for treating anemia in patients with CKD.[2] However, due to its short half-life, its optimal administration route and dose remain controversial.[3]

Darbepoetin alfa, as a second-generation long-acting recombinant erythropoietin preparation, is a new recombinant glycoprotein that is introduced in two *N*-linked glycosylation sites by replacing five amino acid residues in 165 amino acid residues of epoetin alfa.[4] Compared with endogenous erythropoietin and epoetin alfa (rHuEPO), darbepoetin alfa has the characteristics of a prolonged half-life in the blood and increased biological activity *in vivo*.

Clinical studies have shown that darbepoetin alfa with a reduced dose frequency (once a week or biweekly) for treating anemia in CKD patients has similar efficacy and safety as epoetin alfa,[5–8] benefiting both patients and health care staff.[3] This study aimed to verify that the efficacy and safety of darbepoetin alfa are not inferior to epoetin alfa in maintaining Hb levels within the target range (10.0–12.0 g/dL) for the treatment of renal anemia in Chinese hemodialysis patients who are ESA-naive.

2 | METHODS

2.1 | Ethical approval

The implementation of this study strictly followed the protocol requirements, the ethical principles of the *Declaration of Helsinki* and the E6 guidelines of the ICH Clinical Trial Management Code, as well as the local laws and regulations of the various study sites. This study was approved by the Ethics committee of all hospitals. The leading site EC approval number was 2013 (Ethical Review)–08. All patients who participated in this study were provided written informed consent.

2.2 | Study protocol

This was a Phase III, randomized, open-label, parallel-group, multicenter, epoetin alfa positive controlled, noninferiority clinical study carried out from April 15, 2013 to April 10, 2014 at 25 sites. The patients were all CKD anemia patients who had not received ESA administration as inpatients undergoing hemodialysis. Patients were randomized into a darbepoetin alfa group and an epoetin alfa group. The period from week 21 to week 28 was the dose adjustment period to evaluate the efficacy of darbepoetin alfa. In foreign clinical trials,[9] 1 μg darbepoetin alfa has been considered equivalent to 200 IU epoetin alfa through the conversion of the amount of epoetin alfa and darbepoetin alfa administered. During the test period, the dosages of the study drugs were adjusted according to the changes in the patients' Hb concentrations to ensure that the patients' Hb concentrations were maintained within the target range (10.0–12.0 g/dL).

Both of the study drugs were provided by Kyowa Kirin Co., Ltd. The doses were adjusted according to the changes in the Hb concentrations of the subjects. 20 μg darbepoetin alfa (Kyowa Kirin Co.) was established as the initial dose and was administered intravenously once a week. After 4 weeks, if the lower limit of the target Hb concentration (10.0 g/dL) was reached, the dosage was not changed in principle. However, the increase, reduction or withdrawal of darbepoetin alfa could be carried out. Darbepoetin alfa was administered once a week, with maximum doses of 60 μg each time.[10] 3000 IU of epoetin alfa (Kyowa Kirin Co.) was established as the initial dose, and intravenous administration was started three times a week until the lower limit of the target Hb concentration (10.0 g/dL) was reached. In principle, the dosage and frequency of administration should be maintained. However, the increase, reduction, or withdrawal of epoetin alfa could also be carried out within the specified range (3000 IU/week – 9000 IU/week) according to the judgment of the researcher. Epoetin alfa was administered twice or 3 times a week, with a maximum dose of 3000 IU each time.

The standard deviation of the Hb concentrations during the evaluation period of the relevant Phase III clinical trials conducted in Japan was approximately 0.5 g/dL. Because the subjects of this study were different from those in related trials carried out in Japan, and considering the possibility of increases in the standard deviation and different Hb means between the two groups, it was assumed that the standard deviation was 1.0 g/dL, the difference in the mean Hb between the two groups (darbepoetin alfa - epoetin alfa) was 0.3 g/dL, α was 0.025 (set according to the bilateral [100 – 2α]% confidence interval) and the noninferiority margin $\delta = 1.0$ g/dL, and to ensure 90% power, there were 57 subjects in the darbepoetin alfa group and 38 subjects in the epoetin alfa group. In the clinical trials carried out in Japan, about 10% of the subjects discontinued before the evaluation period, so as random subjects, there were 60 subjects in the darbepoetin alfa group and 40 subjects in the epoetin alfa group. Therefore, non-inferiority could be verified in this study with a total of 100 subjects. This study was an open trial that was conducted using a central randomization system for dynamic stratified randomization, and it had randomly assigned test (darbepoetin alfa) and control (epoetin alfa) groups according to stratification factors, including the mean hemoglobin concentration at baseline (categorized as <8.0 g/dL and ≥8.0 g/dL). 102 patients were screened, and 95 patients were randomized into groups (56 patients into the darbepoetin alfa group and 39 patients into the epoetin alfa group).

The selected patients were 18–70 years old, had CKD, had received hemodialysis with a frequency of more than twice a week (including hemofiltration), had not received ESA, had Hb concentrations of 6.0–10.0 g/dL, transferrin saturation (TSAT) ≥ 20% or serum Ferritin (SF) ≥ 100 ng/ml; patients with uncontrollable hypertension, congestive heart failure (New York Heart Association heart function Grade III or higher), those who had undergone surgery with massive bleeding, those with

malignant tumors, blood systemic diseases or obvious hemorrhagic diseases, those who had received blood transfusions, anabolic hormones, testosterone enanthate or methanide, those with AST or ALT values >3 times the upper limit of the standard value, those who were allergic to ESA, and pregnant or nursing women were excluded. If a patient's Hb concentration in the trial was <8.0 g/dL four consecutive times, the drug's administration was stopped for more than 4 weeks in accordance with the withdrawal criteria.

2.3 | Efficacy and safety assessments

The primary efficacy endpoint included the mean Hb level during the evaluation period (noninferiority margin −1.0 g/dL, from week 21–28). Secondary efficacy endpoints included the Hb increase rate from week 0 to 4, the target Hb achievement cumulative rate and time, change trends of the Hb level, and a target Hb maintenance ratio from week 0 to 28. Safety endpoints included the incidence and severity of AEs, immunogenicity assessments of darbepoetin alfa antibody, hematologic data, laboratory biochemical data, iron metabolism data, and ECG test results. In addition, the frequencies of dose adjustments between the darbepoetin alfa group and epoetin alfa group were compared during the treatment period.

2.4 | Statistical analysis

SAS® software version 9.2 (SAS Institute Inc.) was used to perform all statistical analyses. For all tests, a p value of ≤ 0.05 was considered statistically significant. The sample size of 100 patients (60 patients in the darbepoetin alfa group and 40 patients in the epoetin alfa group) was derived assuming a dropout rate at 10%. A designated statistician (Tigermed Co., LTD) generated the allocation sequence and assigned the participants to their groups, and investigators at 25 clinical sites enrolled the participants according to this sequence. The efficacy analysis included both the full analysis set (FAS) and the per-protocol set (PPS). The FAS comprised randomized patients who had received at least one dose for a week and who had at least one efficacy assessment available a week later. PPS included patients who completed the study visits as defined in the protocol and who had at least four assessments during the evaluation period (from week 21 to 28), and who had been administered incorrect medication for no longer than 6 weeks. The safety set (SS) comprised all randomized patients who had received at least one dose of the drugs. The two-sided 95% confidence interval (CI) of the difference between the mean Hb for the treatments (the mean Hb level of the darbepoetin alfa group minus that of the epoetin alfa group) was calculated to assess the non-inferiority. If it was above the noninferiority margin of −1.0 g/dL, the non-inferiority was accepted. A logistic regression was carried out to compare the Hb increase rate slope from week 0 to week 4 and assess the proportion of the Hb increase rate of ≥0.5 g/dL per week. The time to the initial achievement of the Hb target (10.0 g/dL) was estimated by the Kaplan-Meier method. The changes in the mean Hb levels from week 0 to week 28 were compared, as were the differences in the target Hb maintenance ratios between the two treatment groups at each evaluation week = (the numbers of the Hb levels within 10.0–12.0 g/dL per week)/total numbers per weeks × 100% for each treatment groups. In addition, descriptive analyses and χ^2 tests were used for subgroup analyses to compare the efficacy in the two groups. Safety analysis: Adverse events were summarized by severity and causality, and their incidence in each group was compared. The incidence of adverse events, adverse reactions, important adverse events, adverse events that led to death, and other serious adverse events that did not cause death were summarized. The basic statistics calculations between the two groups, such as laboratory tests, vital signs, and electrocardiograms, were compared.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

A total of 96 patients who met the eligibility criteria were enrolled and randomized into either the darbepoetin alfa ($n = 57$) or epoetin alfa group ($n = 39$) (Figure 1). Finally, 56 and 39 patients entered the treatment period in the darbepoetin alfa and epoetin alfa groups respectively. Patients' characteristics, primary diseases, and the baseline Hb levels in the PPS population were similar across both treatment groups, with nice proportionality and comparability (Table 1).

3.2 | Efficacy

There were 35 patients in the PPS. For the primary endpoint (Table 2), the difference in the mean Hb change between the two groups (darbepoetin alfa - epoetin alfa) was 0.6 g/dL (95% CI 0.2–1.1 g/dL). The lower limit of the two-sided 95% CI of the primary endpoint, 0.1 g/dL, was above the noninferiority margin of −1.0 g/dL, and it was shown that darbepoetin alfa had an efficacy equal to that of epoetin alfa. Due to differences in group factors and clinical sites, the data was adjusted with an analysis of the covariance, and the same results were reached. The results for the FAS

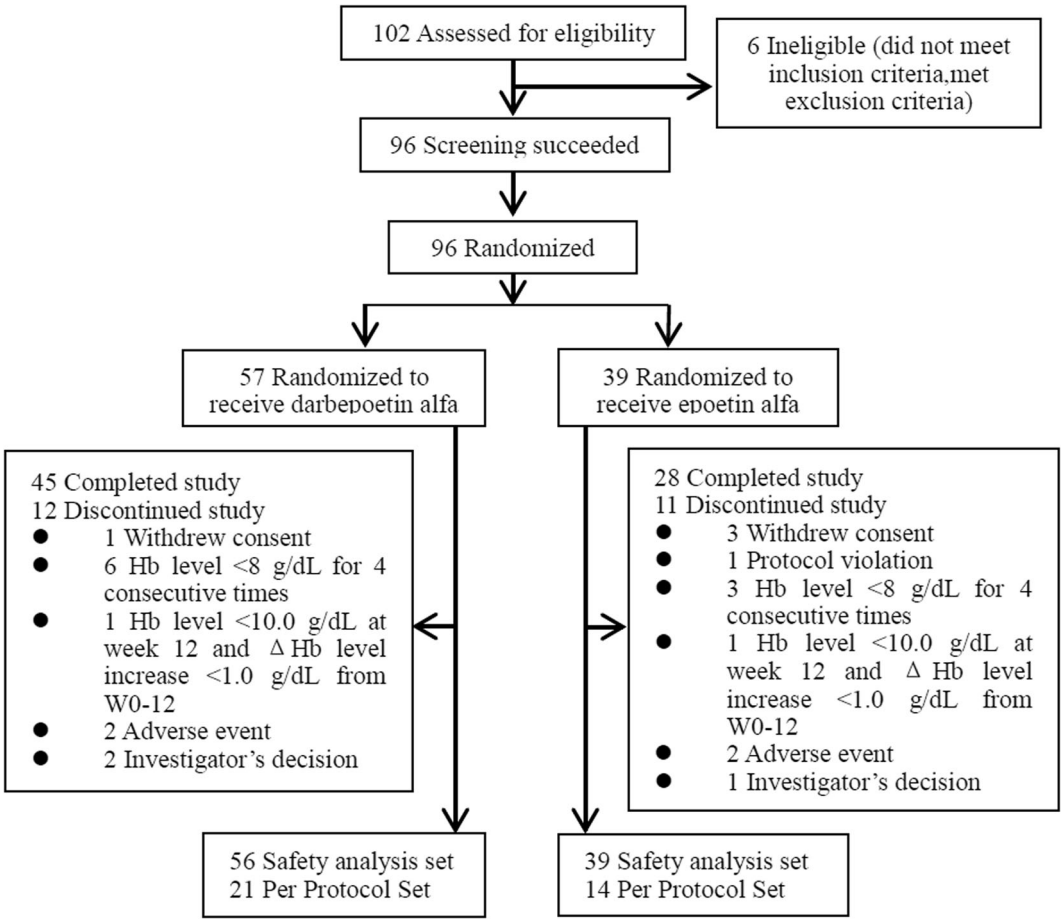

FIGURE 1 Patient disposition

population were not different from those of the PPS population either.

To analyze the relevance of patients' baseline characteristics, including sex, age, BMI, dialysis history, and primary disease, to the mean Hb level, the results were displayed using forest plots (Figure 2). As seen from Table 2 and Figure 2, the darbepoetin alfa group maintained a slightly higher Hb level than that of the epoetin alfa group in the evaluation period, and the baseline factors did not have an obvious influence on it.

3.3 | Secondary efficacy analysis

In PPS, Hb levels increase was observed during the initial 4 weeks. The increase rate of the darbepoetin alfa group and epoetin alfa group were 0.4 ± 0.2 g/dL per week (95% CI 0.3–0.5 g/dL) and 0.5 ± 0.2 g/dL per week (95% CI 0.4–0.6 g/dL), respectively. There were no significant differences in the Hb increase rates between the two groups.

The target Hb achievement cumulative rates (Figure 3) for PPS were 100% in the darbepoetin alfa group and 92.9% in the epoetin alfa group (one patient discontinued). The time of 50% target Hb achievement in the two groups was Week 5. The results were similar in both the FAS and PPS populations. The target Hb concentration achievement rates and achievement times were similar across the two groups.

In PPS, the mean Hb level of patients was 8.3 ± 0.8 g/dL in the darbepoetin alfa group and 8.2 ± 1.0 g/dL in the epoetin alfa group at Week 0. Then, patients in the darbepoetin alfa and epoetin alfa groups achieved the lower limit of target Hb (10.0 g/dL) at Week 7 and Week 5, respectively, and the Hb levels were kept within the target range. At Week 28, the mean Hb level values were 11.3 ± 0.8 g/dL in the darbepoetin alfa group and 10.8 ± 0.7 g/dL in the epoetin alfa group (Figure 4). These results were similar in both the FAS and PPS populations. The variation trends of the concentrations in the two groups were consistent.

3.4 | Target Hb maintenance ratios

In PPS, the proportion of patients with target Hb level is shown in Figure 5. The target Hb maintenance ratio in the darbepoetin alfa group was 4.8% at Week 0, which

TABLE 1 Patient baseline characteristics (per-protocol set)

Characteristics	Darbepoetin alfa $n = 21$	Epoetin alfa $n = 14$	Total $n = 35$
Sex, *n* (%)	21 (100.0%)	14 (100.0%)	35 (100.0%)
Male	15 (71.4%)	10 (71.4%)	25 (71.4%)
Female	6 (28.6%)	4 (28.6%)	10 (28.6%)
Age (years) mean ± *SD*	50.4 ± 13.0	56.0 ± 9.8	52.7 ± 12.0
<65, *n* (%)	18 (85.7%)	11 (78.6%)	29 (82.9%)
≧65, *n* (%)	3 (14.3%)	3 (21.4%)	6 (17.1%)
Height (cm) mean ± *SD*	167.7 ± 6.4	168.4 ± 8.5	168.0 ± 7.2
Dry weight (kg) mean ± *SD*	64.2 ± 12.0	65.5 ± 14.0	64.7 ± 12.6
Primary diseases, *n* (%)			
Chronic glomerulonephritis	11 (52.4%)	6 (42.9%)	17 (48.6%)
Diabetic kidney disease	3 (14.3%)	2 (14.3%)	5 (14.3%)
Polycystic kidney disease	2 (9.5%)	1 (7.1%)	3 (8.6%)
Others	5 (23.8%)	5 (35.7%)	10 (28.6%)
Duration of dialysis (months) mean ± *SD*	1.3 ± 2.4	8.3 ± 28.1	4.1 ± 17.8
Complication *n* (%)	21 (100.0%)	14 (100.0%)	35 (100.0%)
Hb level (g/dL) mean ± *SD*	8.3 ± 0.8	8.2 ± 1.0	8.3 ± 0.9
SF (ng/ml) mean ± *SD*	445.5 ± 456.5	321.9 ± 232.2	396.1 ± 383.3
TSAT (%) mean ± *SD*	25.5 ± 11.1	23.9 ± 6.2	24.8 ± 9.3

Note: Fisher's test was used to compare categorical variables. Wilcoxon's rank-sum test was used to compare measurement data between groups.
Abbreviations: *SD*, standard deviation; SF, serum ferritin; TSAT, transferrin saturation.

TABLE 2 The mean Hb level (g/dL) in the evaluation period (per-protocol set)

				Adjusted by the difference of groups factors and clinical sites (ANCOVA)	
Items	*n*	Mean	95% CI	Mean	95% CI
Darbepoetin alfa	21	11.3	11.0–11.6	11.3	11.0–11.7
Epoetin alfa	14	10.7	10.2–11.1	10.6	10.2–11.0
Difference (darbepoetin alfa subtract epoetin alfa)		0.6	0.1–1.1	0.7	0.2–1.2

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; *SD*, standard deviation.

then increased to 19.0% at Week 2, exceeded 50% from Week 8, and stayed between 61.9% and 95.2% during the evaluation period (Week 21–28); comparatively, that of the epoetin alfa group was 14.3% at Week 0, which then increased to 23.1% at Week 2, exceeded 50% from Week 9 (except being 46.2% at Week 19), and stayed between 76.9% and 85.7% from Week 21–28; the Hb maintenance rates look similar between two groups, while the darbepoetin alfa group once reached 100% temporarily at Week 19. A majority of the patients in the two groups were observed to maintain their target Hb levels well during the evaluation period. The results in the FAS population were similar to those of the PPS population.

3.5 | Safety assessment

The incidences of adverse events were 62.5% (35/56) in darbepoetin alfa group and 76.9% (30/39) in the epoetin alfa group ($p = 0.1795$), respectively. Incidence frequencies (≥ 5%) of AEs in either of the groups are shown in Table S1. Most of the AEs were mild or moderate in severity. Serious adverse events accounted for 24.2%

Subgroup	N	NESP group n (mean) [SD]	ESPO group n (mean) [SD]	Difference(95% CI)	Treatment *P-value*	Subgroup *P-value*
Sex					*0.0161*	*0.2965*
male	*25*	15 (11.34) [0.539]	10 (10.79) [0.796]	0.5530 (0.0025, 1.1035)		
female	*10*	6 (11.13) [0.770]	4 (10.42) [0.832]	0.7073 (-0.4742, 1.8888)		
Age					*0.0193*	*0.0349*
<65 years	*29*	18 (11.39) [0.539]	11 (10.79) [0.755]	0.6032 (0.1102, 1.0963)		
≥65 years	*6*	3 (10.61) [0.599]	3 (10.30) [0.972]	0.3150 (-1.5144, 2.1444)		
BMI					*0.0245*	*0.2214*
<24kg/m^2	*23*	15 (11.30) [0.609]	8 (10.93) [0.563]	0.3658 (-0.1748, 0.9065)		
≥24kg/m^2	*11*	6 (11.24) [0.634]	5 (10.26) [1.065]	0.9779 (-0.1904, 2.1462)		
Dialysis history					*0.0083*	*0.1659*
<60 months	*34*	21 (11.28) [0.601]	13 (10.61) [0.777]	0.6678 (0.1844, 1.1511)		
≥60 months	*1*	0	1 (11.60) [NC]			
Chronic glomerulo-nephritis					*0.0128*	*0.2750*
yes	*17*	11 (11.15) [0.574]	6 (10.54) [0.913]	0.6074 (-0.1556, 1.3704)		
no	*18*	10 (11.42) [0.628]	8 (10.78) [0.736]	0.6339 (-0.0473, 1.3151)		

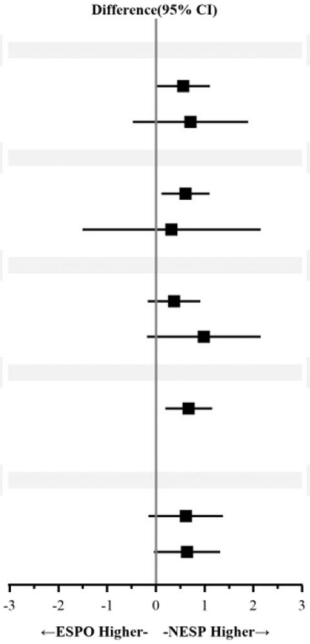

FIGURE 2 Subgroup analysis of the main efficacy indicators (per-protocol set)

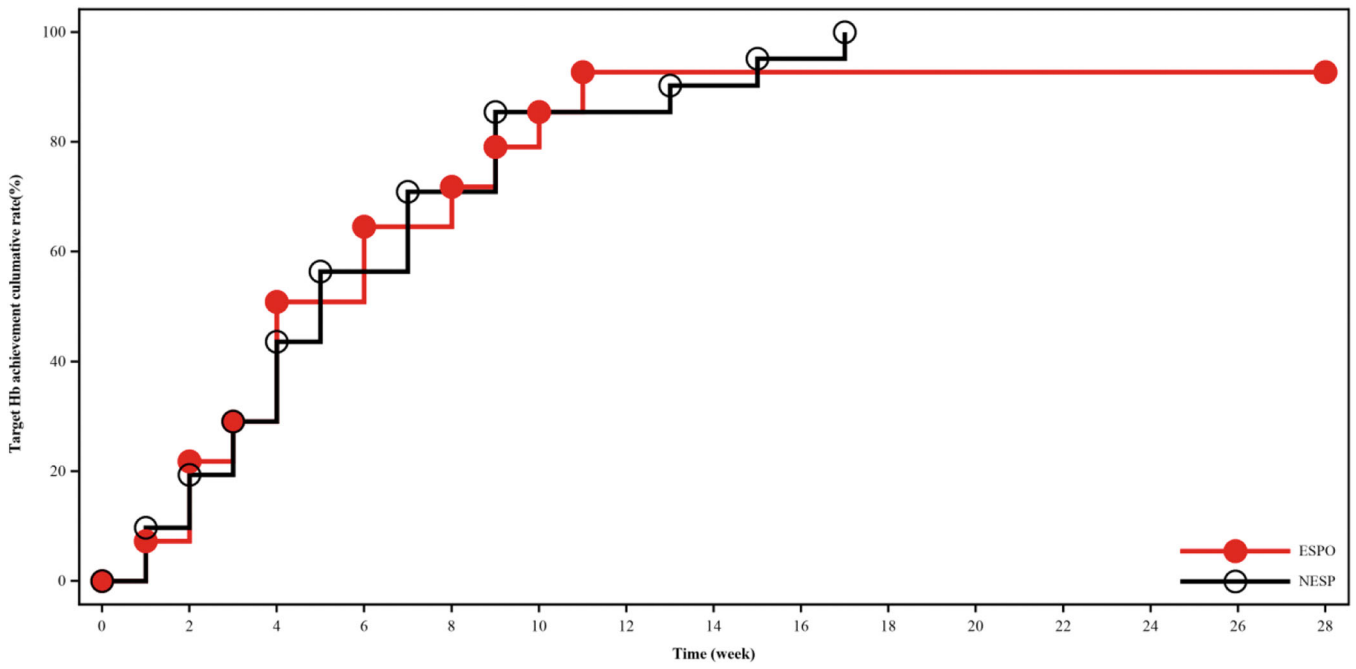

FIGURE 3 Target Hb achievement cumulative rate (%) and time (week) of the two groups (per-protocol set)

(23/95), of which 26.8% (15/56) were from the darbepoetin alfa group and 20.5% (8/39) were from the epoetin alfa group ($p = 0.6274$). Serious adverse events in the darbepoetin alfa included pulmonary infection (7.1%, $n = 4$), cerebral hemorrhage (3.6%, $n = 2$) and cataracts (1.8%, $n = 1$), abdominal distention (1.8%, $n = 1$), hematochezia (1.8%, $n = 1$), chest pain (1.8%, $n = 1$), back pain (1.8%, $n = 1$), bronchitis (1.8%, $n = 1$), upper respiratory tract infection (1.8%, $n = 1$), urinary tract infection (1.8%, $n = 1$), herpes zoster (1.8%, $n = 1$), arteriovenous fistula (AVF) obturation (1.8%, $n = 1$), arteriovenous fistula (1.8%, $n = 1$), sudden death (1.8%, $n = 1$), and those of the epoetin alfa group were arteriovenous fistula (AVF) obturation (5.1%, $n = 2$),

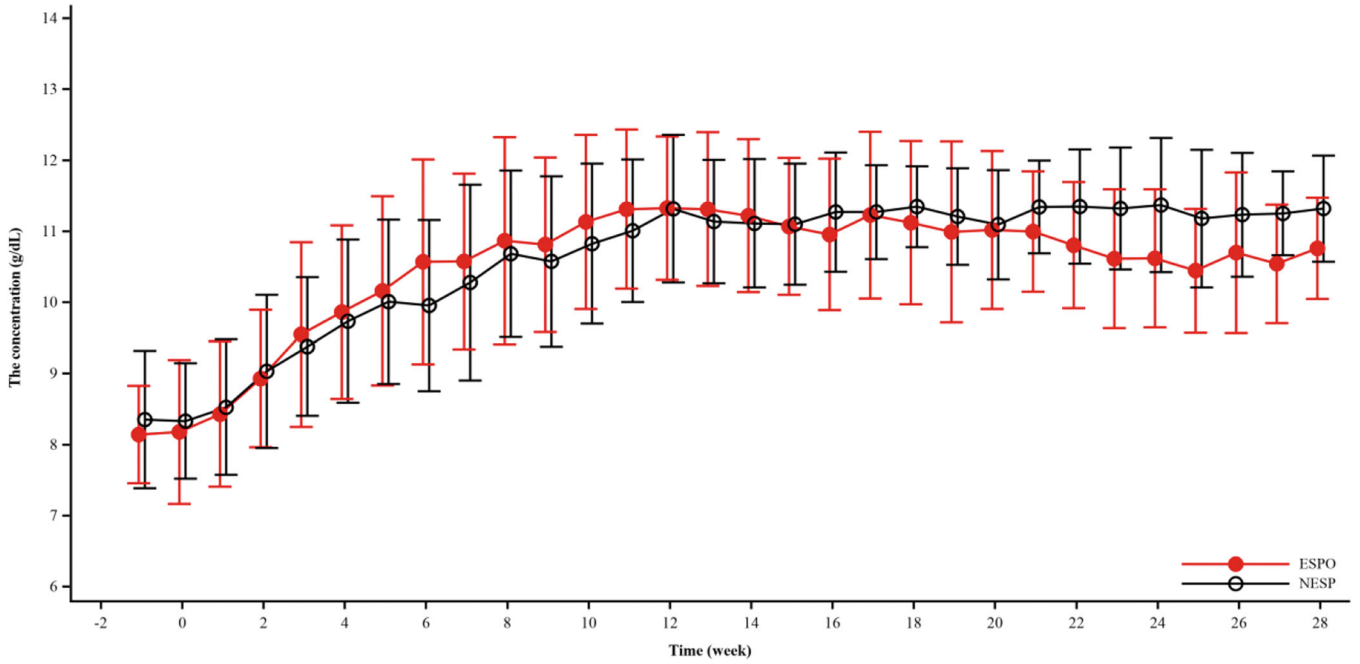

FIGURE 4 Changes of the mean Hb level from baseline to the end of the study

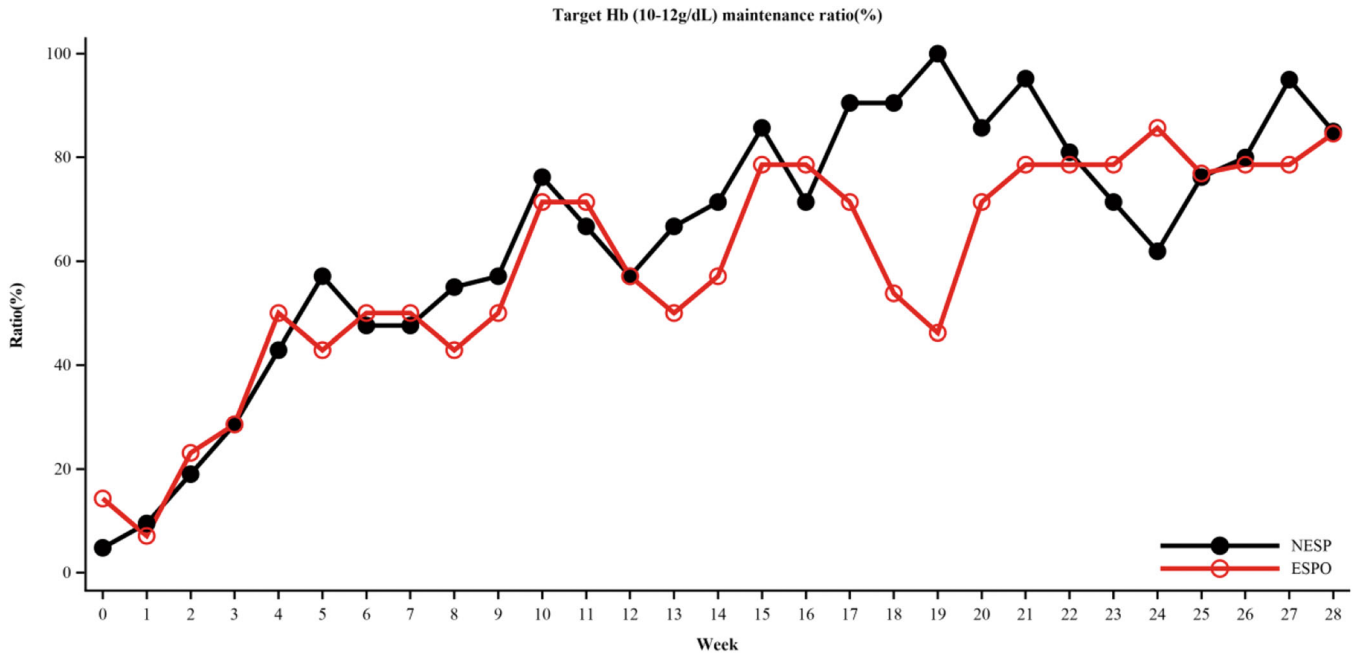

FIGURE 5 Target Hb maintenance ratios from Week 0 to Week 28 (per-protocol set)

device-related infection (2.6%, $n = 1$), gouty arthritis (2.6%, $n = 1$), cerebral hemorrhage (2.6%, $n = 1$), hypertensive encephalopathy (2.6%, $n = 1$), lacunar infarction (2.6%, $n = 1$), and hypotension (2.6%, $n = 1$).

The incidence of ADRs was 21.1% (20/95) in total, which included 26.8% (15/56) in the darbepoetin alfa group and 12.8% (5/39) in the epoetin alfa group. Almost all ADRs were mild or moderate in intensity. Serious ADRs accounted for 5.3% (5/95) of the total, which included 5.4% (3/56) (cerebral hemorrhage, chest pain, and unknown death) in the darbepoetin alfa group, and 5.1% (2/39) (cerebral hemorrhage and hypertension encephalopathy) in the epoetin alfa group. Serious adverse reactions in the darbepoetin alfa group: cerebral hemorrhage, chest pain, and sudden death occurred in 1 case (1.8%); serious adverse reactions in the epoetin alfa group: cerebral

hemorrhage and hypertensive encephalopathy occurred in 1 case (2.6%). With the exception of death, the other ADRs were relieved or disappeared in the end.

Death ($n = 3$, 3.2%) were considered to have a correlation with the study drugs in the darbepoetin alfa group and 1 (2.6%) in the epoetin alfa group.

Multifactor stratification of the sexes, ages, BMIs, duration of dialysis histories, and primary disease histories of the patients at the baseline period was conducted to analyze the correlations between adverse drug reactions, and the following meta-analysis was obtained through statistical methods (Figure 6). It can be seen from the forest map that there was no significant correlation between the incidence of adverse events and the subjects' sex, age, BMI, duration of dialysis histories, and different factors of primary disease. There was no significant difference in the incidence of adverse events between the two groups.

Laboratory tests such as blood routine, blood biochemistry, and iron metabolism showed no obvious abnormalities. There were no obvious changes in blood pressures, dry weights, or electrocardiograms in both groups. All patients tested negative for antiepoetin α antibody.

3.6 | Comparison of dose adjustment times between groups

For 0–28 weeks, the times of dose adjustments in the darbepoetin alfa group and epoetin alfa group were 4.8 ± 2.9 and 10.8 ± 9.9, respectively.

From the weekly dose distribution diagram (FAS), it can be seen that the weekly dose level of the darbepoetin alfa group reached a relatively stable state in 12–14 weeks (Figure 7). In the same epoetin alfa group, the weekly dose reached a steady-state level at about 14 weeks (Figure 7). The times of reaching stable periods were basically the same. It can be seen from the darbepoetin alfa dose distribution diagram that 20 μg was the dose at the median level, so 20 μg as the starting dose is relatively reasonable for the Chinese population, and the time and safety of reaching the target hemoglobin were in line with expectations.

4 | DISCUSSION

The main curative effect index of this trial was to evaluate the average Hb concentrations during the evaluation period for the darbepoetin alfa group and epoetin alfa group. The average Hb concentration difference in PPS (darbepoetin alfa - epoetin alfa) was 0.6 g/dL, for which the lower limit of the 95% confidence interval was 0.1 > –1.0 g/dL, so the efficacy of darbepoetin alfa once a week is not inferior to that of epoetin alfa 2–3 times a week. The target Hb cumulative achievement rate and the target Hb maintenance rate look similar between the two groups.

According to the recommendations of the *Chinese Experts' Consensus on the Diagnosis and Treatment of Renal Anemia* in 2018, the initial rate of Hb growth for ESAs in the treatment of renal anemia should be

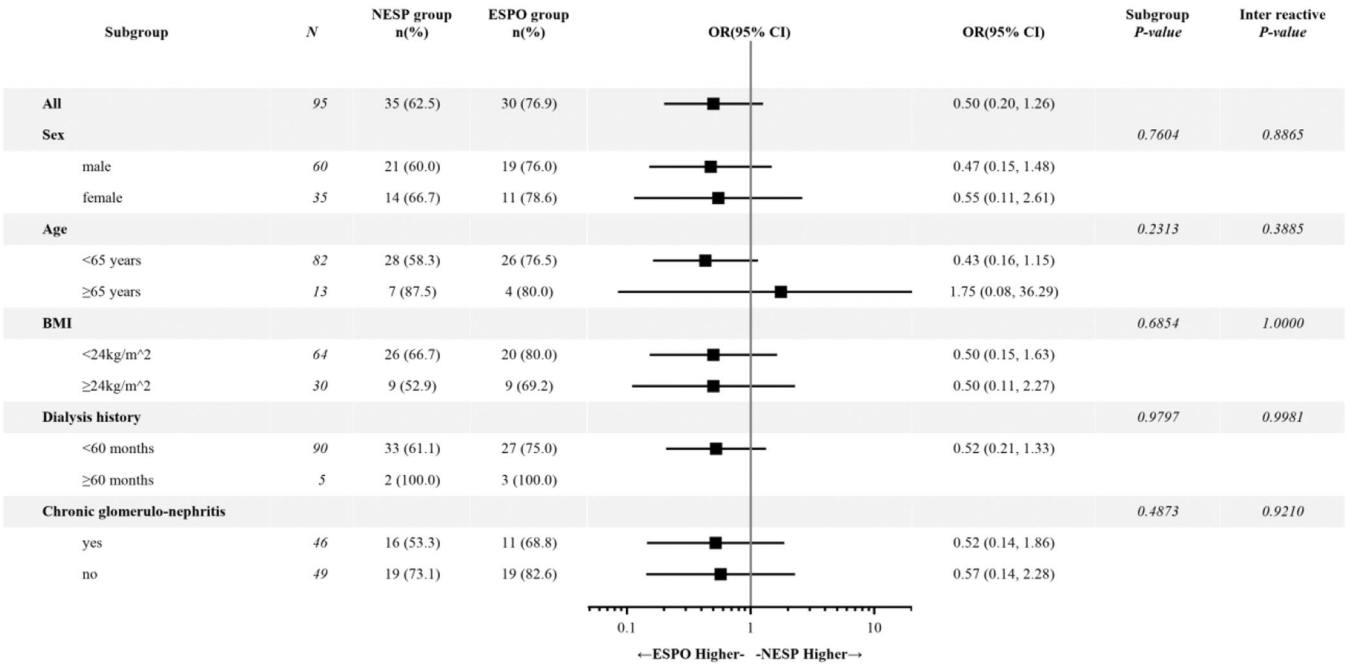

FIGURE 6 Subgroup analysis of incidence of adverse events (safety set). BMI, body mass index; CI, confidence interval; NESP, novel erythropoiesis stimulating protein

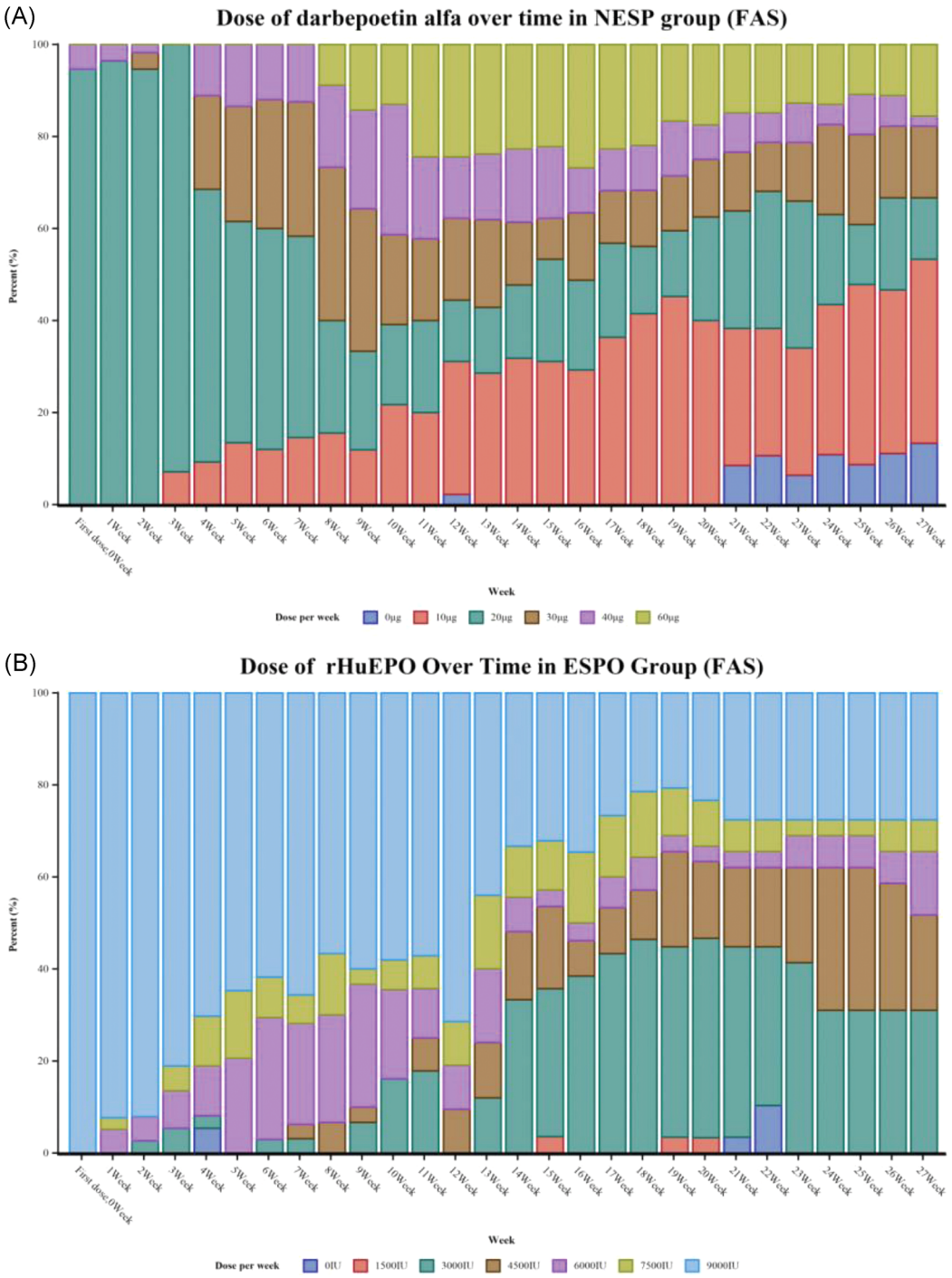

FIGURE 7 The weekly dose level of darbepoetin alfa and epoetin alfa group (full analysis set)

steadily increased within a range of 1–2 g/dL per month. The Hb concentration level is positively correlated with the systolic and diastolic blood pressure.[11,12] Excessively high and fast Hb incrementing may increase the risk of worsening hypertension and related adverse reactions. Although our study showed a slightly higher mean Hb level in the darbepoetin alfa group during the evaluation period, the Hb elevation rate in the first 4 weeks was comparable between two groups (0.4 ± 0.2 g/dL per week in the darbepoetin alfa group vs. 0.5 ± 0.2 g/dL per week in the epoetin alfa group). The slightly higher mean Hb level in the darbepoetin alfa group may have been a result of the protocol setting of the maximum weekly dose for the two products (60 μg for darbepoetin alfa vs. 9000 IU for epoetin alfa), considering the reported conversion ratio of 1:200 (darbepoetin alfa: epoetin alfa).[9] Higher maximum dose setting may better satisfy

individualized weekly dose adjustments and may correlate with the highest transient target Hb achievement rate of 100% that occurred in the darbepoetin alfa group at Week 19. As shown in Figure 7, some patients in the darbepoetin alfa group accepted the maximum dose of 60 μg.

The efficacy results in this study show that for hemodialysis patients who have not received ESA preparation treatments after hemodialysis introduction, the intravenous administration of DA-α once a week can effectively increase the Hb concentration, and stabilize the Hb levels within the target range, and it has the same anemia-correction effect as epoetin alfa 2–3 times a week.

In addition, patients undergoing hemodialysis who are currently using short-acting rHuEPO agents need to be administered the treatment two or three times a week for years. Darbepoetin alfa is administered intravenously once a week to reduce the frequency of administration and the number of dose adjustments (Table 3). According to the calculations (epoetin alfa three times a week), epoetin alfa needs to be used 156 times per year to maintain dialysis patients. If it is replaced with DA-α once a week, the number of doses can be reduced to 52, so as to improve patients' compliance and reduce the risk of medical accidents associated with drug administration. For medical personnel, it can also reduce the workload associated with drug preparation and administration, medical equipment use and waste, as well as the number of drug storage places. The consumption of medical resources is consistent with the results of articles published abroad in recent years,[13–17] and the use of prefilled syringes for darbepoetin alfa reduces the use of syringes by medical staff for pipetting operations, which facilitates its use by medical staff.[17]

The adverse events and adverse reactions that occurred during the trial were almost always reported by patients on hemodialysis. During the study period, the adverse reactions in both groups were mainly mild to moderate. Studies domestically and abroad have shown that,[9,18–20] hypertension and elevated blood pressure are the most common adverse reactions of epoetin alfa. The anemia is improved with epoetin alfa administration, and hypertension often develops or worsens, especially when the anemia improvement rate is faster, or when the anemia improvement target is set higher. As darbepoetin alfa has the same mechanism of action as epoetin alfa, special care should be taken when administering darbepoetin alfa to patients with high blood pressure or those with high blood pressure risks. The rate of improvement in anemia should be gradual, and attention should be paid to blood pressure elevation. In addition, the Hb concentration should be prevented from rising too fast or too much. Once this occurs, appropriate treatment should be given. The darbepoetin alfa group and epoetin alfa group had similar incidences and compositions of adverse events, but the darbepoetin alfa group had a higher incidence of adverse reactions. Since this trial was an open design study, investigators tend to be more conservative in their judgment of AE causality for unlisted new drugs. The higher incidence of adverse reactions in the darbepoetin alfa group may not mean it poses a higher safety risk.

TABLE 3 Comparison of 0–28 weeks dose adjustment times in two groups (full analysis set)

Groups	*n*	Mean ± *SD*	Median	Q1–Q3	Min–Max
Darbepoetin alfa	56	4.8 ± 2.9	5.0	3.0–7.0	0.0–11.0
Epoetin alfa	39	10.8 ± 9.9	9.0	3.0–18.0	0.0–33.0

Abbreviation: *SD*, standard deviation.

The mortality rate in this trial is not higher than that reported in Japanese clinical trials and related literature.[21–23] Sakaguchi et al. reported that among patients undergoing hemodialysis, use of long-acting ESAs might be associated with a higher risk of death than use of short-acting ESAs.[24] But many KOLs think it should be further explored. Norio Hanafusa and Ken Tsuchiya commented that the article by Sakaguchi et al. raised important issues in clinical practice.[25] They consider that the title of the article is misleading, and that it was in fact a higher dose of long-acting ESAs that was associated with worse survival. Elucidating the true association between ESA type and mortality is reserved for future prospective studies with between-group adjustments for doses of ESA. The Editorial by Tilman B. Drüeke states that for now, the observation by Sakaguchi et al. is more of a challenge than final proof.[26] It needs to be confirmed or invalidated in CKD populations in other geographic regions, ideally in prospective studies with large sample sizes. And the Japanese Society for Dialysis Therapy (JSDT) also commented that Sakaguchi's study is an observational study and does not directly show the causal relationship between the use of long-acting ESA and the increased risk of death. In the future, further studies including intervention studies will be required, and there is room for further discussion on the methodology (drug selection) to achieve the target Hb value specified in the guidelines.[27]

In conclusion, For hemodialysis patients who have not been treated with ESA preparations after hemodialysis introduction, intravenous administration of darbepoetin alfa once a week can effectively increase the hemoglobin levels, correct anemia, and maintain hemoglobin concentrations within the target range. The curative effect is not inferior to that of epoetin alfa administered intravenously 2–3 times a week. The adverse events and adverse reactions that occurred in the trial were almost always reported events in hemodialysis patients. The efficacy and safety of darbepoetin alfa in treating Chinese ESA-naive hemodialysis patients are well-supported by

the current work, with reduction dosing frequency and dose adjustment.

CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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