Pegmolesatide for the treatment of anemia in patients undergoing dialysis: a randomized clinical trial

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Summary

Background Pegmolesatide, a synthetic peptide-based erythropoietin (EPO) receptor agonist, is being evaluated as an alternative to epoetin alfa for treating anemia of chronic kidney disease (CKD) in Chinese dialysis patients. There is a critical need for a long-acting, cost-effective erythropoiesis-stimulating agent that does not produce EPO antibodies.

Methods A randomized, open-label, active-comparator, non-inferiority phase three trial was conducted at 43 dialysis centers in China between May 17th, 2019, and March 28th, 2022. Eligible patients aged 18–70 years were randomly assigned (2:1) to receive pegmolesatide once every four weeks or epoetin alfa one to three times per week, with doses adjusted to maintain a hemoglobin level between 10.0 and 12.0 g/dL. The primary efficacy endpoint was the mean change in hemoglobin level from baseline to the efficacy evaluation period in the per-protocol set (PPS) population. Non-inferiority of pegmolesatide to epoetin alfa was established if the lower limit of the two-sided 95% confidence interval for the between-group difference was ≥ -1.0 g/dL. Safety assessment included adverse events and potential anaphylaxis reactions. This trial is registered at ClinicalTrials.gov, NCT03902691.

Findings Three hundreds and seventy-two patients were randomly assigned to the pegmolesatide group (248 patients) or the epoetin alfa group (124 patients). A total of 347 patients (233 in the pegmolesatide group and 114 in the epoetin alfa group) were included in the PPS population. In the PPS, the mean change (standard deviation, SD) in hemoglobin level from baseline to the efficacy evaluation period was 0.07 (0.92) g/dL in the pegmolesatide group and −0.22 (0.97) g/dL in the epoetin alfa group. The between-group difference was 0.29 g/dL (95% confidence interval: 0.11–0.47), verifying non-inferiority of pegmolesatide to epoetin alfa. Adverse events occurred in 231 (94%) participants in the pegmolesatide group and in 110 (89%) in the epoetin alfa group. Hypertension was the most common treatment-related adverse event. No fatal cases of anaphylaxis or hypotension were reported.

Interpretation Monthly subcutaneously injection of pegmolesatide was as effective and safe as conventional epoetin alfa administrated one to three times a week in treating anemia in Chinese dialysis patients.

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Keywords: Anemia; Chronic kidney disease; Dialysis; Epoetin alfa; Pegmolesatide

Research in context

Evidence before this study

More than half of dialysis patients with chronic kidney disease (CKD) in China fail to meet the target hemoglobin level recommended by guidelines. Development of continuous, highly selective erythropoietin (EPO) receptor agonists is one way forward for the treatment of renal anemia. The sole EPO-mimetic peptide (EMP), peginesatide, which received FDA approval, was later pulled from the market due to unforeseen severe anaphylaxis and hypotension. Consequently, there is a crucial demand for a long-lasting, economical erythropoiesis-stimulating agent that doesn't generate EPO antibodies.

Added value of this study

This phase three study is the first to assess the efficacy and safety of a novel EMP since the withdrawal of peginesatide from the market. Pegmolesatide learned valuable lessons from peginesatide, and several improvements were made, including the use of consistent preservative-free single-dose vials and exclusive subcutaneous administration. Pegmolesatide showed favorable efficacy and good safety in this phase three study.

Implications of all the available evidence

The study suggests that pegmolesatide can be an alternative treatment to conventional erythropoiesis-stimulating agents for anemia in Chinese dialysis patients. Pegmolesatide was well tolerated, with no reports of severe anaphylaxis. We anticipate that pegmolesatide will demonstrate an improved safety profile compared to its predecessor.

Introduction

Anemia is a common complication of chronic kidney disease (CKD), affecting over 90% of dialysis patients in China.[1,2] Erythropoiesis-stimulating agents (ESAs) are the standard treatment for CKD-associated anemia,[3,4] which can effectively increase hemoglobin level and avoid transfusion dependence.[5] However, in China, more than half of dialysis patients fail to achieve the target hemoglobin level (i.e. between 11.0 and 13.0 g/dL according to the guideline).[4] Several factors may contribute to this low target-achieving rate, including imbalanced economic and medical resources, poor patient compliance with short-acting recombinant human erythropoietin (rHuEPO), iron deficiency, and pure red cell aplasia (PRCA) resulting from anti-EPO antibodies.[6–9]

Continuous development of novel pharmacologic approaches aims to improve anemia management. Oral hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI), such as Roxadustat and Daprodustat, can stimulates endogenous EPO synthesis and improves iron metabolism.[10,11] However, the long-term safety of HIF-PHI in non-dialysis-dependent and dialysis-dependent CKD patients still requires evaluation. Darbepoetin alfa[12] (a hyperglycosylated rHuEPO) and methoxy-polyethylene glycol-epoetin beta[13] (a PEGylated rHuEPO) represent newer generations of longer-acting ESAs, offering extended dosing intervals. Despite these advancements, PRCA secondary to anti-EPO antibodies remains a challenge for rHuEPO but is now quite rare.[9]

EPO-mimetic peptides (EMPs) are synthetic chemical compounds that act as agonists of the EPO receptor. Despite lacking sequence homology with EPO, EMPs can bind to and activate the EPO receptor, stimulating erythropoiesis through the same intracellular signaling pathways.[14,15] Additionally, EMPs have the potential to be administered at longer intervals and theoretically do not induce anti-EPO antibodies. Peginesatide, developed by Affymax, was the only EMP approved by the U.S. Food and Drug Administration (FDA) for treating anemia in CKD patients.[16] However, it was later withdrawn from the market due to unexpected fatal anaphylaxis and hypotension.[17] No other EMPs have been successfully introduced to the market since then. Nevertheless, the clinical demand for long-acting ESAs that are cost-effective and do not induce EPO antibodies persists.

Pegmolesatide (R&D code: HS-20039, previously known as pegol-sihematide, EPO-018B) is a novel pegylated EMP developed by Hansoh Pharmaceutical Group Co, Ltd (Shanghai, China). It offers advantages such as reduced immunogenicity and an extended duration of action, demonstrating similar in vivo and in vitro activity to peginesatide.[18] Results from the phase two studies have indicated that subcutaneous administration of pegmolesatide every four weeks effectively achieves and maintains target hemoglobin levels in both dialysis and non-dialysis CKD patients.[19,20] This multicenter, phase three clinical trial aimed to assess the efficacy and safety of pegmolesatide compared to epoetin alfa for treating anemia of CKD in Chinese dialysis patients. Currently, pegmolesatide has been approved in mainland China for the treatment of anemia in both dialysis and non-dialysis CKD patients.

Methods

Study design

This randomized, open-label, active-comparator (epoetin alfa), non-inferiority phase three clinical trial was conducted from May 17th, 2019, to March 28th, 2022, at 43 dialysis centers led by The First Affiliated Hospital, Medical School of Zhejiang University in China. The study consisted of five phases: a screening period (weeks –12 to –9), a run-in period (weeks –8 to –1), a dose-titration period (weeks zero to 16), an efficacy evaluation period (weeks 17–24), and an extended follow-up period (weeks 25–52) (Supplemental Figure S1). The study design was developed by the corresponding author (Jianghua Chen) and sponsored by Hansoh. Data collection was performed by the sponsor, and statistical analyses were conducted by the School of Public Health, Nanjing Medical University. An independent data monitoring committee ensured patient safety throughout the study.

Ethics statement

The study protocol was approved by the ethics committee of each center and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. Written informed consent was obtained from all participants. This trial is registered at ClinicalTrials.gov, NCT03902691.

Participants

Eligible patients with CKD stage five were between the ages of 18 and 70 and had been on maintenance dialysis (hemodialysis or peritoneal dialysis) for at least 12 weeks. They had also received continuous treatment with rHuEPO (<10,000 IU/week) for at least eight weeks prior to enrollment. During the run-in period, eligibility criteria included a hemoglobin level (from the last measurement) in the range of 10.0–13.0 g/dL, a ferritin level of 100 ng/mL or higher, and a transferrin saturation of 20% or higher. A comprehensive list of inclusion and exclusion criteria can be found in Supplement data 1. Written informed consent was obtained from individual participants.

Randomization and masking

We used central randomization that was carried out using IRT system by a third-party vendor, using block permutation (size = six) stratified by type of dialysis

(hemodialysis or peritoneal dialysis). The information such as block size and random seeds were generated and stored by vendor and remained blinded to all researchers until the end of the study. The eligible participants meeting the baseline inclusion criteria were assigned at a 2:1 ratio to receive either pegmolesatide or epoetin alfa in their respective groups. This was operated by the authorized investigator or clinical research coordinator in each site. Since this was an open label study, there was no masking strategy.

Procedures

Potentially eligible patients underwent an 8-week run-in period, during which they were treated with intravenous or subcutaneous administration of epoetin alfa (ESPO, Kyowa Hakko Kirin) one to three times a week. Following the run-in period, eligible patients were randomly assigned in a 2:1 ratio to receive pegmolesatide or epoetin alfa, with stratification based on dialysis method. The initial dose of pegmolesatide was determined by converting the total dose of epoetin alfa received during the last week of the run-in period (Supplemental Table S1). Subsequently, pegmolesatide was administered subcutaneously once every four weeks. Patients assigned to the epoetin alfa group continued to receive the same dose, dosing interval, and administration route as before randomization. Both groups were allowed to adjust subsequent doses based on a predefined algorithm to maintain a hemoglobin level between 10.0 and 12.0 g/dL (Supplemental Table S2).

Outcomes

The primary efficacy endpoint was the mean change in hemoglobin level from baseline (calculated as the mean value measured at week –4, week –2, and week zero) to the efficacy evaluation period (calculated as the mean value measured from weeks 17 to 24). Secondary efficacy endpoints included the proportion of patients with a change in hemoglobin level from baseline within ±1.0 g/dL on at least three of the four measurements during the efficacy evaluation period, the proportion of patients with hemoglobin levels within the target range (10.0–12.0 g/dL) on at least three of the four measurements during the efficacy evaluation period, and the mean change in hemoglobin level from baseline at each post-randomized study visit. Other secondary efficacy endpoints also included the change and variability of reticulocytes from baseline at each post-randomized visit and drug exposure of patients with hemoglobin fluctuation ±1.0 g/dL during the efficacy evaluation period.

Safety assessment included the collection of adverse events (AEs), serious adverse events (SAEs), clinical laboratory measurements, vital signs, physical examination findings, and electrocardiographic results from enrollment to 28 days after discontinuation of study drugs. A composite safety endpoint (consisting of all-cause death, stroke or myocardial infarction) and other cardiovascular events (hospitalization for congestive heart failure or hospitalization for unstable angina) were evaluated by an independent clinical endpoint committee (CEC) in a blinded manner to provide additional information on cardiovascular safety. The incidence and proportion of patients developing anti-drug antibodies and neutralizing antibodies in the pegmolesatide group were also reported.

Statistical analysis

A total of 141 participants were projected to be an adequate sample size to substantiate the non-inferiority of pegmolesatide compared to epoetin alfa. This estimation was based on 90% statistical power at a one-sided α level of 0.025, assuming no difference between groups, a standard deviation of 1.7 per deciliter (based on the unpublished data from a phase two study[19]), and a non-inferiority margin of –1.0 per deciliter for the primary efficacy outcome. Allowing for a 15% dropout rate would provide an insufficient size to gather sufficient safety data, and therefore the study aimed to recruit 330 participants.

The demographic baseline analysis and efficacy analyses were performed on both the full analysis set (FAS), which included all patients who received randomization and at least one dose of the treatment regimen, and the per-protocol set (PPS), which included patients who completed at least three hemoglobin measurements during the efficacy evaluation period and had no major protocol violations. The results from the PPS population were reported unless otherwise specified. Safety analysis was conducted on the safety set (SS), which included patients who received at least one dose of the treatment regimen and had records of safety endpoints.

The primary efficacy endpoint was analyzed using an analysis-of-covariance (ANCOVA) model, which estimated the mean change in hemoglobin level from baseline to the efficacy evaluation period. The model included treatment group (pegmolesatide vs. epoetin alfa) as a fixed effect and baseline hemoglobin level ($\leq$11.4 g/dL or $\geq$ 11.5 g/dL) and dialysis mode (hemodialysis or peritoneal dialysis) as covariates. The between-group difference in Least-Square Means (LSM) and its corresponding two-sided 95% CI were calculated. Non-inferiority for pegmolesatide was established if the lower limit of the two-sided 95% CI was $\geq$ –1.0 g/dL. Additional analyses, such as the FAS and sensitivity analyses with imputation of missing values, were conducted to provide supportive information. Prespecified subgroup analysis stratified by dialysis mode, baseline hemoglobin level, New York Heart Association (NYHA) functional class, age, and sex were also performed to assess the robustness of the study finding.

The secondary efficacy endpoints of binary variables were analyzed using the Cochran-Mantel-Haenszel (CMH) method, with baseline hemoglobin level (≤11.4 g/dL or ≥ 11.5 g/dL) and dialysis method as stratification factors. The analysis calculated the baseline stratum-weighted difference in proportions between the treatment groups and their corresponding 95% CI.

For the analyses of safety endpoints, the effects of treatment on cardiovascular risks, including composited safety events and other cardiovascular events, were analyzed using a Cox proportional hazards regression model. Baseline hemoglobin level, dialysis mode and NYHA class were included as covariates. A detailed statistical analysis can be found in Supplemental Data. Statistical analyses were performed using SAS 9.4 software.

Role of the funding source

The study was funded by Hansoh Pharmaceutical Group Co, Ltd (Shanghai, China). The study funder provided study drugs and participated in study design, data collection, data analysis, data interpretation, and the writing of the report. All authors had full access to all data in the study and provided final approval to submit the manuscript. Jianghua Chen had final responsibility for the decision to submit for publication.

Results

A total of 372 patients were randomly assigned to the pegmolesatide group (248 patients) or the epoetin alfa group (124 patients) across 43 centers in China from May 17th, 2019, to March 28th, 2022. Among them, 370 patients (99.5%) were included in both FAS and SS populations. Twenty-five patients were excluded from the PPS, primarily due to the withdrawal of consent and adverse events, which left the PPS population of 347 patients (233 in the pegmolesatide group and 114 in the epoetin alfa group). A total of 315 patients (214 in the pegmolesatide group and 101 in the epoetin alfa group) completed the 52-week study (Fig. 1), with a mean (standard deviation, SD) duration of exposure of 48.6 (9.9) weeks in the pegmolesatide group and 45.6 (12.7) weeks in the epoetin alfa group. The median dose per patient administered during the study was 3.0 (1.7, 4.2) mg of pegmolesatide per injection and 4975.9 (3735.3, 6860.0) IU of epoetin alfa per week.

The baseline characteristics of the patients were comparable between the pegmolesatide and epoetin alfa groups, as shown in Table 1. The mean age of the patients was 49.2 (10.6) years, with 62.4% (231 patients) being male. The majority of patients (67.6%, 250 patients) underwent hemodialysis. The mean baseline hemoglobin levels were 11.11 (0.75) g/dL in the pegmolesatide group and 11.11 (0.68) g/dL in the epoetin alfa group. The iron status and heart function class were similar between the two groups.

Regarding past medical histories that are known risk factors for cardiovascular events, the pegmolesatide group had higher rates of heart failure, cerebrovascular disease, and thromboembolism disease, while the epoetin alfa group had a higher rate of arrhythmia. Six patients in each group (2.4% in the pegmolesatide group and 4.8% in the epoetin alfa group) had a documented medical history of drug allergy.

In the PPS population, the mean change in hemoglobin level from baseline to the efficacy evaluation period was 0.07 (0.92) g/dL in the pegmolesatide group and −0.22 (0.97) g/dL in the epoetin alfa group. The between-group difference was 0.29 g/dL [95% confidence interval (CI): 0.11–0.47]. These results indicated that pegmolesatide was non-inferior to epoetin alfa in terms of the primary efficacy endpoint (Table 2). Further, the lower confidence limit was above zero, suggesting a superior efficacy of pegmolesatide. Similar findings were observed in the FAS population and a sensitivity analysis (Supplemental Table S3). The non-inferiority of pegmolesatide was consistent across all prespecified subgroups (Supplemental Figure S2). Interestingly, male participants appeared to show a stronger efficacy. Of note, female had a smaller sample size thus this finding is warranted for further investigation.

In the study, the proportion of patients in the PPS population who maintained a mean change in hemoglobin level from baseline within ±1.0 g/dL during the efficacy evaluation period was 64.0% (149 patients) in the pegmolesatide group and 59.7% (68 patients) in the epoetin alfa group. The between-group proportion difference was 4.2% (95% CI −6.6 to 15.1, Table 2). Additionally, the proportion of patients in whom the mean hemoglobin level stayed within the target range of 10.0–12.0 g/dL during the efficacy evaluation period was 67.8% (158 patients) in the pegmolesatide group and 71.9% (82 patients) in the epoetin alfa group. The between-group proportion difference was −4.0% (95% CI −14.2 to 6.3, Table 2). Similar results were observed in the FAS population (Supplemental Table S3).

During the 52-week study period, both the pegmolesatide group and the epoetin alfa group showed mean hemoglobin levels that remained within the target range, and the mean change in hemoglobin from baseline was maintained within ±1.0 g/dL. In the pegmolesatide group, there was a slight increase in hemoglobin levels at the start of the dose-titration period, peaking at 0.62 g/dL in week six. Following subsequent dose adjustments, the mean hemoglobin gradually decreased and stabilized around the baseline level (Fig. 2). The change and variability of reticulocyte was described in Supplemental Figure S3 and S4. Drug exposure of patients whose hemoglobin fluctuation was ±1.0 g/dL during the efficacy evaluation period was presented in Supplemental Table S8.

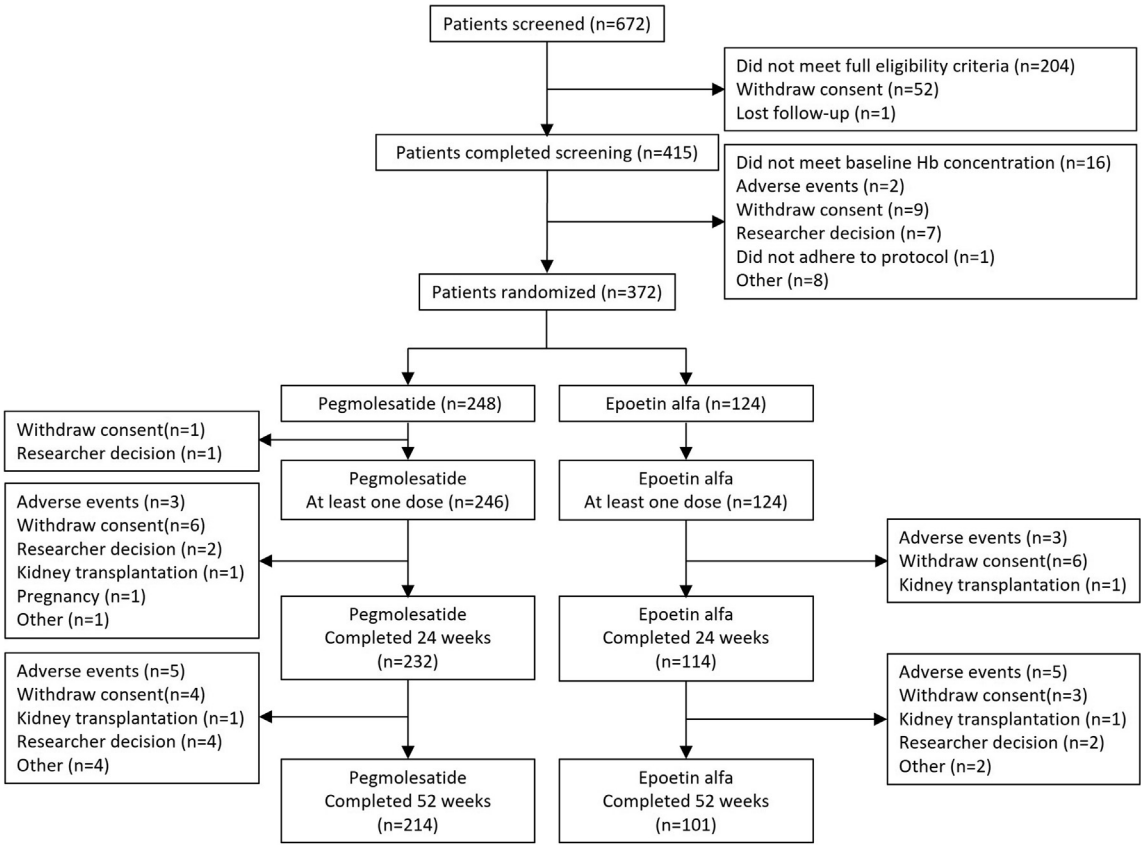

Fig. 1: Patient disposition.

Among the patients treated with pegmolesatide, a total of 1605 episodes of adverse events (AEs) occurred in 231 patients (93.9%), while in the epoetin alfa group, 812 AEs occurred in 110 patients (88.7%) (Table 3 and Supplemental Table S4). AEs that were observed in at least five percent of patients in either group are listed in Supplemental Table S5, with upper respiratory tract infection (24.8%, 61 patients vs. 19.4%, 24 patients) and hypotension during dialysis (13.4%, 33 patients vs. 4.0%, five patients) being more frequent in the pegmolesatide group. The proportion of patients with treatment-related AEs was similar between the pegmolesatide group (23.2%, 57 patients) and the epoetin alfa group (21.0%, 26 patients) (Table 3), and the majority of events were classified as mild or moderate (grade 1–2). Hypertension was the most commonly reported treatment-related AE, occurring in 26 patients (10.6%) in the pegmolesatide group and in 12 patients (9.7%) in the epoetin alfa group.

In the pegmolesatide group, serious adverse events (SAEs) were reported in 59 patients (24.0%), while in the epoetin alfa group, SAEs occurred in 27 patients (21.8%). The most common SAE was arteriovenous fistula site complication, which occurred in nine patients (3.7%) in the pegmolesatide group and three patients (2.4%) in the epoetin alfa group. During the study, a total of eight participants died, with four deaths (1.6%) in the pegmolesatide group and four deaths (3.2%) in the epoetin alfa group. None of these deaths were considered to be related to the treatment (Supplemental Table S6).

The composite cardiovascular events were adjudicated in six patients (2.4%) treated with pegmolesatide and five patients (4.0%) treated with epoetin alfa. The hazard ratio for the occurrence of composite cardiovascular events with pegmolesatide compared to epoetin alfa was 0.47 (95% CI 0.14–1.59). Additionally, other cardiovascular events were adjudicated in three patients (1.2%) with pegmolesatide and five patients (4.0%) with epoetin alfa, with a hazard ratio of 0.28 (95% CI 0.07–1.17) for pegmolesatide compared to epoetin alfa (Table 3).

AEs related to potential hypersensitivity reactions were observed in 31 patients (12.6%) in the pegmolesatide group and 25 patients (20.2%) in the epoetin alfa group (Supplemental Table S7). Most of these events were of mild or moderate intensity and resolved quickly with appropriate treatment. Specifically, treatment-related hypersensitivity reactions were adjudicated in

Characteristics	Pegmolesatide (N = 246)	Epoetin alfa (N = 124)
Age–yr	49.0 (10.2)[a]	49.5 (11.4)[a]
Distribution–no. (%)		
<65 yr	233 (94.7)	111 (89.5)
≥65 yr	13 (5.3)	13 (10.5)
Male sex–no. (%)	153 (62.2)	78 (62.9)
Dialysis methods–no. (%)		
Hemodialysis	166 (67.5)	84 (67.7)
Peritoneal dialysis	80 (32.5)	40 (32.3)
Duration of stage 5 CKD–mo.	58.9 (51.9)[a]	61.6 (56.5)[a]
Transferrin saturation–%, median (Q1, Q3)	33.0 (26.5, 42.1)	32.6 (26.2, 40.8)
Ferritin–μg/L	405 (403)[a]	367 (326)[a]
Baseline hemoglobin level		
Mean value—g/dL	11.1 (0.8)[a]	11.1 (0.7)[a]
Distribution–no. (%)		
<11.4 g/dL	166 (67.5)	82 (66.1)
≥11.5 g/dL	80 (32.5)	42 (33.9)
NYHA class–no. (%)		
Class 0–I	192 (78.0)	106 (85.5)
Class II	53 (21.5)	18 (14.5)
History of cardiovascular risk factors–no. (%)		
Hypertension	239 (97.2)	119 (96.0)
Diabetes	45 (18.3)	24 (19.4)
Hyperlipidemia	91 (37.0)	46 (37.1)
Coronary heart disease	34 (13.8)	19 (15.3)
Cerebrovascular disease	42 (17.1)	15 (12.1)
Heart failure	43 (17.5)	14 (11.3)
Arrhythmia	15 (6.1)	15 (12.1)
Peripheral vascular disease	27 (11.0)	15 (12.1)
Thromboembolic disease	8 (3.3)	1 (0.8)
History of allergy — no. (%)	6 (2.4)	6 (4.8)

The full analysis set (FAS) comprised all patients who underwent randomization and received at least one dose of the study drug. [a]Mean (SD).

Table 1: **Baseline and demographic characteristics (FAS).**

Outcome	Pegmolesatide	Epoetion alfa	Difference (95% CI)	P value
	Value	Value		
Primary efficacy endpoint–dL				
Mean change in Hb level from baseline to wk 17–24	0.07 (0.92)[a]	−0.22 (0.97)[a]	0.29 (0.11, 0.47)	0.0018
Secondary efficacy endpoint–no. (%)				
Proportion of patients with ΔHb maintained within ±1.0 dL during wk 17–24	149 (64.0)	68 (59.7)	4.2 (−6.6, 15.1)	0.45
Proportion of patients with Hb stayed within 10.0–12.0 dL during wk 17–24	158 (67.8)	82 (71.9)	−4.0 (−14.2, 6.3)	0.45

PPS population included patients who completed at least three hemoglobin measurements during efficacy evaluation period and had no major violation of study protocol. For the primary efficacy endpoint, difference was analyzed with least square mean. ΔHb was defined as the mean change in hemoglobin values from baseline to the efficacy evaluation period. Abbreviation: Hb, hemoglobin. [a]Mean (SD).

Table 2: **Primary and secondary efficacy endpoint (PPS population).**

two patients (0.8%) in the pegmolesatide group, both manifesting as pruritus without rash, redness or purpura. One reaction occurred two days after the first dose of pegmolesatide and was resolved after oral administration of anti-allergic drugs. The other reaction occurred ten days after the second dose and resolved spontaneously without any treatment. No fatal cases of anaphylaxis or hypotension were reported.

Twenty patients (8.1%) in the pegmolesatide group developed pegmolesatide-specific antibodies. Among them, five patients (2.0%) had positive antibody results at a single visit, while 15 patients (6.1%) had positive

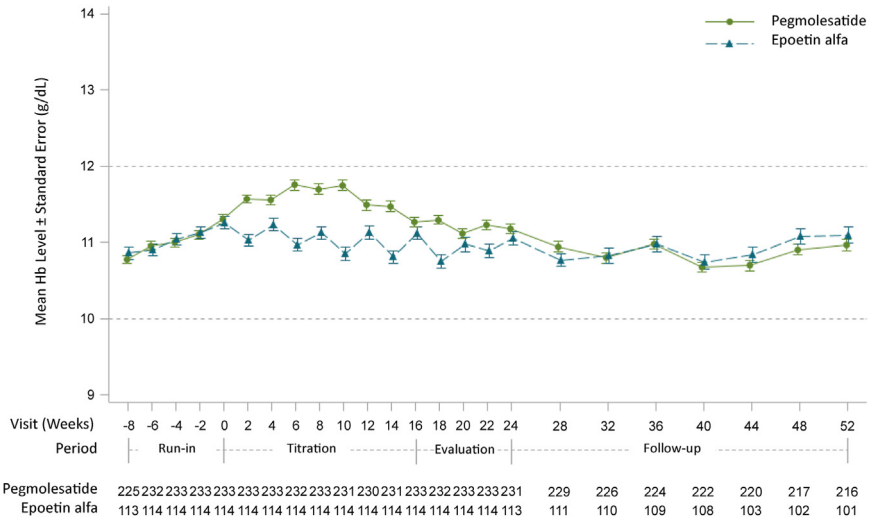

Fig. 2: Mean hemoglobin level of the two groups during the study (PPS). Horizontal dashed lines indicate the target range for the hemoglobin level (10.0–12.0 dL). I bars indicate standard errors.

results at two or more visits. Additionally, three patients (1.2%) tested positive for neutralizing antibodies in an in vitro assay. Four patients (1.6%) experienced a decrease in efficacy associated with the development of antibodies but responded well to treatment with currently approved rHuEPO after withdrawal from the study. Notably, no allergic reactions related to the production of pegmolesatide-specific antibodies were reported, and there were no suspected cases of PRCA.

Discussion

In this 52-week, phase three study conducted in China, pegmolesatide demonstrated comparable effectiveness and safety to epoetin alfa in treating anemia in patients with CKD undergoing dialysis. Pegmolesatide was found to be non-inferior to epoetin alfa, with consistent results observed across all predefined subgroups. Additionally, the mean hemoglobin level in the pegmolesatide group remained within the target range, and the change in hemoglobin level was within ±1.0 g/dL of baseline throughout the study period, indicating sustained efficacy.

During the dose-titration period, there was a slight difference in hemoglobin variability between the pegmolesatide and epoetin alfa groups. Similar observations have been reported in other studies that involved switching from conventional erythropoietin (EPO) to comparator ESAs.[10,21,22] This discrepancy may be attributed to the well-established drug dosage and interval in the epoetin alfa group during the run-in period. Additionally, the dosing adjustment for epoetin alfa was more frequent and timely (every two weeks) compared to pegmolesatide (once a month).

In the pegmolesatide group, there was a transient increase in mean hemoglobin levels after conversion from epoetin alfa, followed by a gradual return to baseline through subsequent dose titration based on the predetermined algorithm. The transient increase in hemoglobin levels could be influenced by factors such as the drug's target, individual patient response to treatment, target hemoglobin level, and dose adjustment algorithm.

To optimize the dosage regimen, close monitoring of hemoglobin levels in the early stages after drug conversion is recommended, with monthly frequency. Two strategies that can be explored further include reducing the initial dose and adopting a more stringent target hemoglobin level and dosing adjustment regimen. These strategies can be investigated using clinical pharmacology models and validated in post-marketing studies.

The safety profiles of pegmolesatide and epoetin alfa were generally comparable. The most frequently reported AEs in the pegmolesatide group included upper respiratory tract infection, hyperkalemia, and hypertension, which are commonly observed in the dialysis population.[23,24] Assessment of cardiovascular risks was of particular interest in this study, considering that it is a common complication of CKD and treatment with ESAs. The PEARL studies previously reported a higher proportion of composite safety endpoint events and sudden death in CKD patients not on dialysis treated with peginesatide.[25] However, the two EMERALD studies demonstrated similar incidence rates of composite safety endpoint events between the two treatment groups in patients undergoing hemodialysis.[16] In our study, there were no significant between-group

Event	Pegmolesatide (N = 246)					Epoetin alfa (N = 124)				
	No. of patients (%)	CTCAE				No. of patients (%)	CTCAE			
		Grade 1∼2	Grade 3	Grade 4	Grade 5		Grade 1∼2	Grade 3	Grade 4	Grade 5
Any adverse event	231 (93.9)	144 (58.5)	73 (29.7)	10 (4.1)	4 (1.6)	110 (88.7)	59 (47.6)	42 (33.9)	5 (4.0)	4 (3.2)
Any treatment-related adverse event[b]	57 (23.2)	35 (14.2)	21 (8.5)	1 (0.4)	0	26 (21.0)	16 (12.9)	10 (8.1)	0	0
Treatment-related adverse events occurring in ≥1% of patients in either group										
Hypertension[c]	26 (10.6)	13 (5.3)	13 (5.3)	0	0	12 (9.7)	5 (4.0)	7 (5.6)	0	0
Hyperkalemia	6 (2.4)	1 (0.4)	4 (1.6)	1 (0.4)	0	7 (5.6)	5 (4.0)	2 (1.6)	0	0
Prolonged QT interval on ECG	5 (2.0)	4 (1.6)	1 (0.4)	0	0	1 (0.8)	1 (0.8)	0	0	0
Elevated alanine aminotransferase	1 (0.4)	1 (0.4)	0	0	0	2 (1.6)	2 (1.6)	0	0	0
Any serious adverse event	59 (24.0)	10 (4.1)	40 (16.3)	5 (2.0)	4 (1.6)	27 (21.8)	4 (3.2)	15 (12.1)	4 (3.2)	4 (3.2)
Serious adverse events occurring in ≥1% of patients in either group										
Arteriovenous fistula site complications	9 (3.7)	3 (1.2)	6 (2.4)	0	0	3 (2.4)	1 (0.8)	2 (1.6)	0	0
Infectious pneumonia	4 (1.6)	0	3 (1.2)	1 (0.4)	0	3 (2.4)	0	2 (1.6)	1 (0.8)	0
Peripheral edema	5 (2.0)	1 (0.4)	4 (1.6)	0	0	1 (0.8)	1 (0.8)	0	0	0
Heart failure	2 (0.8)	0	2 (0.8)	0	0	4 (3.2)	0	3 (2.4)	1 (0.8)	0
Cerebral hemorrhage	4 (1.6)	0	0	1 (0.4)	3 (1.2)	1 (0.8)	0	0	0	1 (0.8)
Arteriovenous fistula thrombosis	4 (1.6)	2 (0.8)	2 (0.8)	0	0	0	0	0	0	0
Peritoneal dialysis complications	3 (1.2)	0	3 (1.2)	0	0	1 (0.8)	0	1 (0.8)	0	0
Acute myocardial infarction	1 (0.4)	0	1 (0.4)	0	0	2 (1.6)	0	0	1 (0.8)	1 (0.8)
Uremic encephalopathy	0	0	0	0	0	2 (1.6)	0	2 (1.6)	0	0
Chest discomfort	0	0	0	0	0	2 (1.6)	0	2 (1.6)	0	0
Composite safety events	6 (2.4)					5 (4.0)				
All-cause death	4 (1.6)	0	0	0	4 (1.6)	4 (3.2)	0	0	0	4 (3.2)
Stroke	4 (1.6)	0	1 (0.4)	0	3 (1.2)	2 (1.6)	0	0	0	2 (1.6)
Myocardial infarction	1 (0.4)	0	1 (0.4)	0	0	2 (1.6)	0	0	1 (0.8)	1 (0.8)
Other cardiovascular events										
Heart failure requiring hospitalization	1 (0.4)	0	1 (0.4)	0	0	5 (4.0)	0	4 (3.2)	1 (0.8)	0
Unstable angina requiring hospitalization	2 (0.8)	1 (0.4)	1 (0.4)	0	0	0	0	0	0	0

[a]SS population included patients who had been received at least one dose of treatment regimen and had records of safety endpoints. Safety events were recorded from enrollment to 28 days after discontinuation of study drugs. [b]Related to the study drug was defined as definitely related, possibly related, and undeterminable. [c]Hypertension including preferred terms of "elevated blood pressure" and "high blood pressure".

Table 3: **Treatment-related AEs and SAEs occurring in ≥1% of patients (SS population).**[a]

differences in the incidence of composite safety endpoint events and other cardiovascular events. Nevertheless, it is important to further confirm the cardiovascular safety of pegmolesatide through post-marketing studies with long-term follow-up.

This phase three study is the first to assess the efficacy and safety of a novel EMP since the withdrawal of peginesatide from the market. Pegmolesatide underwent a rigorous drug development process, incorporating valuable lessons learned from peginesatide. Severe allergic reactions of peginesatide that resulted in fatal anaphylactic events occurred within 30 min (median time of 3.5 min) of the first intravenous dose that was administered in multiple use vials.[17] The exact cause of this severe anaphylaxis is still unclear. The changed formulation, post-approval multi-dose vials with preservatives containing phenols and subvisible particles, which was different from pre-approval preservative-free single-dose vials, may be a possible reason.[17] Several improvements were made in the manufacture of pegmolesatide, including simplified excipient formulation, the use of consistent single-use vials for both pre-marketing and post-marketing phases, and exclusive subcutaneous administration.

To address potential hypersensitivity reactions, careful monitoring was implemented, and appropriate measures to manage potential anaphylactic events were readily available throughout the study. Notably, the hypersensitivity reactions observed in our study significantly differed in severity and nature compared to those associated with peginesatide occurring after marketing. No severe anaphylactic reactions were reported. Among patients receiving pegmolesatide, treatment-related hypersensitivity reactions were adjudicated in only two patients (0.8%), presenting as mild pruritus that resolved quickly with proper treatment. Through these concerted efforts, we anticipate that pegmolesatide will demonstrate an improved safety profile compared to its predecessor.

The incidence of drug-specific antibodies (8.1%) and neutralizing antibodies (1.2%) against pegmolesatide observed in our study was slightly higher than what was reported for peginesatide in previous studies.[16,25–27] This discrepancy could be attributed, at least in part, to differences in the sensitivity and specificity of the screening and confirmatory assays used. The FDA has implemented a lower cutoff for assay sensitivity since 2016,[28] resulting in a higher number of positive cases. Additionally, the more frequent detection of anti-drug antibodies (up to 15 tests) in our study may have contributed to the higher positivity rate. It is important to note that no suspected cases of PRCA or allergic reactions associated with the production of pegmolesatide-specific antibodies were reported in our study. Since pegmolesatide does not exhibit immunological cross-reactivity with erythropoietin, the decrease in efficacy observed in four patients (1.6%) due to antibody production was effectively managed by switching to other ESAs, as anticipated.

Our study has several limitations. Firstly, although the sample size and follow-up duration provided sufficient information on efficacy and safety endpoints, the relatively small number of reported cardiovascular events in the study limits the ability to draw definitive conclusions regarding long-term outcomes. Post market surveillance study is warranted to monitor the long-term cardiovascular safety. Secondly, the open-label design of the study introduces the possibility of biases from both patients and physicians. However, to mitigate this, we established independent data monitoring and clinical endpoint committees to assess safety and cardiovascular events in a blinded manner, reducing potential bias. Thirdly, it is important to note that this multicenter study was conducted exclusively in the Chinese population, and generalizability to other ethnic groups remains unknown.

In conclusion, our findings demonstrate that subcutaneous injection of pegmolesatide once a month is noninferior to conventional epoetin alfa administered one to three times a week for the treatment of anemia in Chinese patients on dialysis. Pegmolesatide was well tolerated, with no reports of severe anaphylaxis.

Contributors

Jianghua Chen and Ping Zhang contributed to supervision of the study. Jianghua Chen, Ping Zhang, and Yan Jiang contributed to the validation of the study. Jianghua Chen, Ping Zhang, Yan Jiang, Chunping Xu, Linghui Zhou, Hongguang Zheng, Deqiong Xie, Minghao Guo, Xiangyang Huang, Guoyuan Lu, Hongli Jiang, Hongyu Qiu, Bicheng Liu, Shaomei Li, Qinkai Chen, Yu'ou Xia, Bengui Sun, Xiao Yang, Shiying Zhang, Shutong Du, Mindan Sun, Menghua Chen, Aimin Zhong, Xiaoling Wang, Zhanzheng Zhao, Hua Zhou, Guisen Li, Yueqin Ren, Qun Luo, Aicheng Yang, Ping Luo, Shuifu Tang, Chengyun Xu, Qin Wang, Xiaoxia Wang, Tiekun Yan, Wei He, Shuguang Qin, Weili Zhang, Lu Lv, Cheng Wang, Hong Liu, and Jing Li contributed to the investigation of the study. Liangliang He was involved in data collection. Chuan Li was involved in data analysis. Chao Pan accessed and verified the data in the manuscript. Qiong Wu was involved in the conception or design of the study. All authors verified that this study was done according to the protocol and was attested for data accuracy and completeness. All authors were involved in the interpretation of the data. All authors contributed to the writing and review of the manuscript.

Data sharing statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request (Jianghua Chen, chenjianghua@zju.edu.cn).

Declaration of interests

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102273.

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