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Non-Inferiority of Subcutaneous Efepoetin Alfa Compared to Methoxy Polyethylene Glycol-Epoetin Beta in Stage 3 or 4 CKD Patients: Insights From a Phase 3 Trial

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ABSTRACT

Aim: Efepoetin alfa, a novel long-acting erythropoietin (EPO)-hybrid Fc fusion protein, represents a promising erythropoiesis-stimulating agent (ESA) for addressing anaemia in chronic kidney disease (CKD) patients. This Phase 3 trial was to assess the efficacy and tolerability of subcutaneous efepoetin alfa in comparison to subcutaneous methoxy polyethylene glycol-epoetin beta in stage 3 or 4 CKD patients.

Methods: A randomised, multicentre, open-label Phase 3 trial enrolled 391 CKD stage 3 or stage 4 patients. Subjects underwent a 20-week correction period followed by an 8-week evaluation period. Responders continued treatment for an extra 24-week extension to evaluate long-term safety, maintenance effectiveness, and the longer treatment interval.

Results: In the efepoetin alfa Q2W (every 2 weeks) group, the response rate was 75.6%; while in the methoxy polyethylene glycol-epoetin beta Q2W group, the response rate was 69.3%. The difference in the response rate was 6.3% with 95% CI (confidence interval) −3.1% to 15.5%. The lower limit of the 95% CI was above the prespecified non-inferiority margin of −9.0%. Adverse event rates were comparable between the treatment groups.

Conclusion: Efepoetin alfa demonstrated non-inferiority to methoxy polyethylene glycol-epoetin beta in correcting anaemia and maintaining haemoglobin (Hb) levels among stage 3 and 4 CKD patients. Moreover, the safety profile of efepoetin alfa was comparable to methoxy polyethylene glycol-epoetin beta.

1 | Introduction

Chronic kidney disease (CKD) is a growing health issue. The global prevalence of CKD was estimated to be 11%–13% [1]. In 2017, 697.5 million cases of all-stage CKD were recorded and 1.2 million deaths globally due to CKD [2] Furthermore, the incidence of CKD is projected to rise in the coming years, mostly due to an ageing population and increasing prevalence of

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comorbidities, including hypertension and type 2 diabetes mellitus [3].

Anaemia is a common complication of CKD and is a major public health issue because of its prevalent incidence [4], related illnesses and death rates [5, 6], negative impact on quality of life [7], and increased healthcare cost [8, 9]. Approximately 25% of people with stage 3–5 CKD in the United States experience anaemia [4]. Anaemia becomes more common as CKD advances; according to one study, anaemia incidence increased with CKD stage from 18.2% at stage 3a to 72.8% at stage 5 [10].

Currently, short-acting erythropoiesis-stimulating agents (ESAs) are still a very popular therapy for anaemia in CKD. However, these agents often require frequent dosing, which can lead to issues with patient compliance and suboptimal management of anaemia. The development of longer-acting ESAs brings about several advantages for effectively managing anaemia in CKD patients. By allowing for longer dosing intervals, these medications can reduce the variability of haemoglobin (Hb) levels over time, leading to fewer fluctuations and minimising the need for dosage adjustments. Furthermore, the longer intervals between doses save valuable time for healthcare providers, allowing them to dedicate more attention to other essential aspects of CKD management, such as patient education and addressing modifiable risk factors like hypertension and mineral imbalance [11]. Studies have suggested that long-acting ESAs may be associated with a lower risk of all-cause mortality when compared to short-acting ESAs [12, 13]. However, some analyses have had conflicting results [14, 15].

The reduction of endogenous erythropoietin production and iron deficiency (absolute or functional) has been considered to have a leading role in causing symptomatic anaemia [16]. Injectable ESAs are commonly used to treat uraemic anaemia, but there are concerns in available therapies regarding cardiovascular safety and intervals between administrations [17].

Efepoetin alfa represents a novel approach to addressing anaemia in stage 3 or 4 CKD patients. It is a long-acting EPO-hybrid Fc (EPO-hyFc) fusion protein, consisting of a homodimeric EPO fused to the hybridising IgD/IgG4 immunoglobulin domain(hyFc). The CH2-CH3 region of IgG4 is devoid of complement activation reaction and has Fc receptor binding affinity, leading to a prolonged serum half-life. These structural features reduce the overall activities of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity, enabling better safety and lower immunogenicity. The average molecular weight of efepoetin alfa is approximately 120 kD. Efepoetin alfa is almost three times larger than the conventional ESAs in terms of molecular size, significantly reducing its renal clearance. Also, an increase in the sialic acid residues of this product reduces its overall metabolic/clearance rate in the liver. The hyFc region helps EPO remain longer in the body through FcRn recycling [18].

In the Phase 2 study (NCT02044653), efficacy and safety of efepoetin alfa were comparable to those of darbepoetin alfa in patients with CKD on haemodialysis and to those of methoxy polyethylene glycol-epoetin beta in patients with CKD on peritoneal dialysis.

This study aimed to evaluate whether subcutaneous administration of efepoetin alfa is as effective and well-tolerated as subcutaneous methoxy polyethylene glycol-epoetin beta in correcting and maintaining Hb levels in CKD patients.

2 | Materials and Methods

2.1 | Study Participants

The study included patients with CKD stage 3 or stage 4 (eGFR ≥ 15 and $< 60\,mL/min/1.73\,m^2$) not undergoing dialysis and presenting with a baseline haemoglobin (Hb) level of 8 g/dL to less than 10 g/dL. Eligible patients were either ESA-naïve or had ceased ESA treatment at least 3 months before screening. The patients were not iron deficient, defined as serum ferritin $\geq 100\,\mu g/L$ and transferrin saturation (TSAT) $\geq 20\%$. Recruitment spanned various centres in Australia, Indonesia, South Korea, Malaysia, Philippines, Taiwan, and Thailand. The trial was conducted during COVID-19, which added to the complexity of the process.

The study adhered to the International Conference on Harmonisation Good Clinical Practice guidelines and applicable national clinical trial regulations. Approval was obtained from local ethics committees before the study began. All patients participating in the study signed the informed consent.

2.2 | Procedures

Eligible patients were randomised 1:1 to treatment (efepoetin alfa) arm and control (methoxy polyethylene glycol-epoetin beta) arm (Figure 1). Efepoetin alfa was administered starting from $4\,\mu g/kg$ body weight Q2W with subsequent titration based on Hb response. The methoxy polyethylene glycol-epoetin beta arm had $0.6\,\mu g/kg$ Q2W as the starting dose. Subjects underwent a 20-week correction period for dosage titration and Hb correction, followed by an 8-week evaluation period for efficacy assessments. Subjects who responded (defined as the change from baseline in mean Hb during the evaluation period ≥ 1 g/dL and the mean Hb of evaluation period (including unscheduled visits if scheduled visit was missed) fell within 10–12 g/dL without RBC transfusion) to efepoetin alfa were eligible to continue treatment. The subjects were further randomised to continue receiving subcutaneous efepoetin alfa Q2W or increase the treatment interval to Q4W for an additional 24-week extension period to assess the long-term safety and maintenance effect. Subjects who were randomised to the Q2W arm received efepoetin alfa Q2W at the dose of response, while a dose equal to twice the Q2W dose was administered to subjects who were randomised to the Q4W arm. Methoxy polyethylene glycol-epoetin beta responders continued the drug during the extension period, receiving it Q4W using a dose equal to twice the previous Q2W dose (Figure 2).

If the Hb response was inadequate, efepoetin alfa dosage could be increased by 25% once every 4 weeks based on scheduled Hb assessments up to the achievement of target Hb response. After the achievement of response, efepoetin alfa dosages were maintained or adjusted up or down (25% increase or decrease once

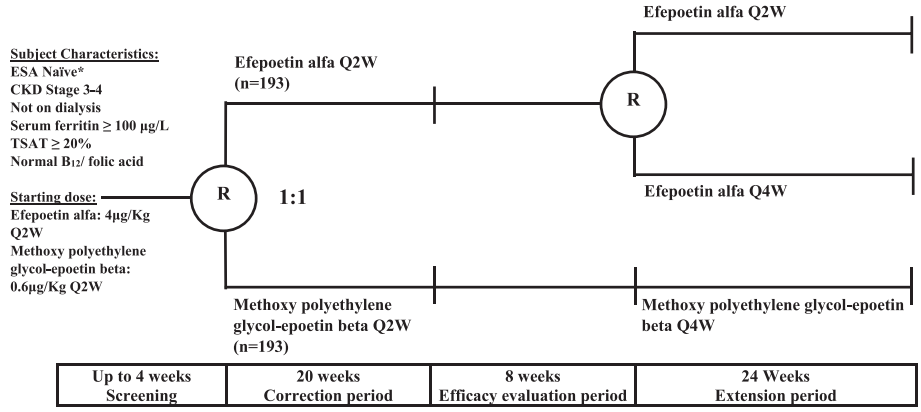

FIGURE 1 | Study design. efepoetin alfa Q2W, twice-monthly continuous efepoetin alfa; methoxy polyethylene glycol-epoetin beta Q2W, twice-monthly methoxy polyethylene glycol-epoetin beta; efepoetin alfa Q4W, once-monthly efepoetin alfa; methoxy polyethylene glycol-epoetin beta Q4W, once-monthly methoxy polyethylene glycol-epoetin beta; R, randomization.

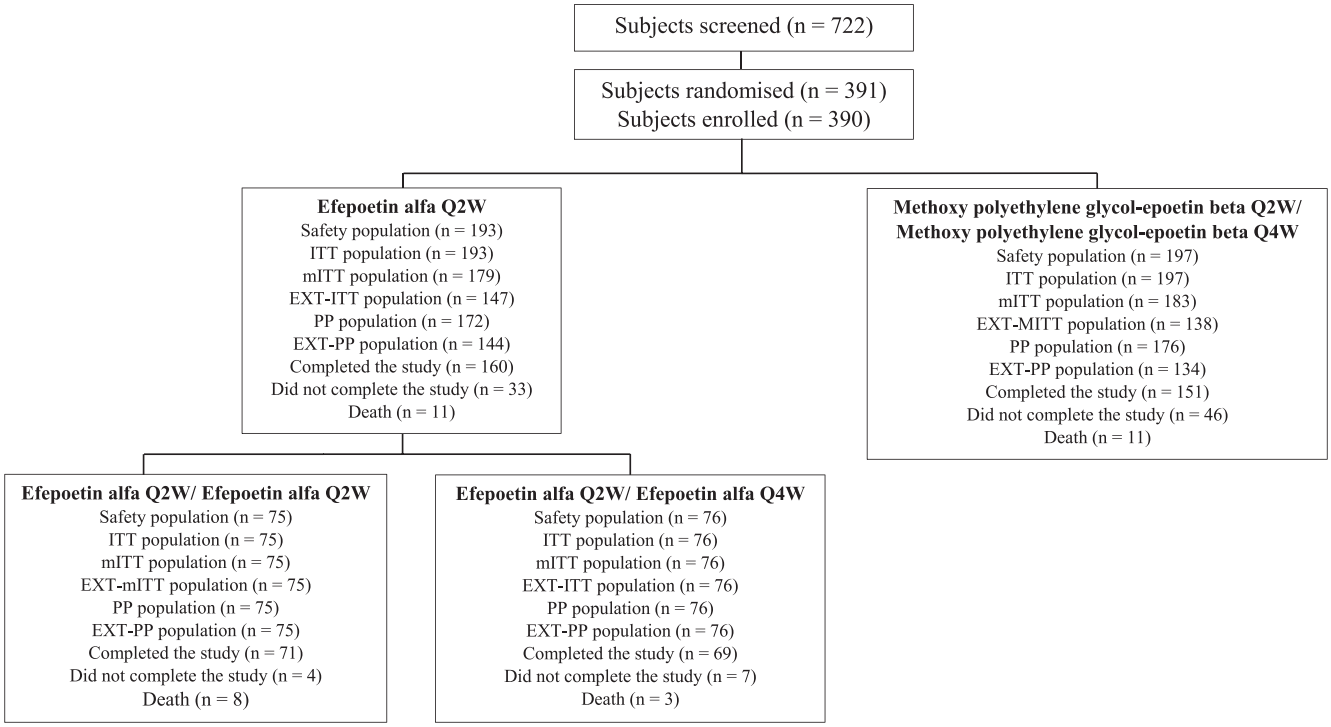

FIGURE 2 | Patient disposition. Q2W, once every 2 weeks; Q4W, once every 4 weeks; ITT, intent-to-treat; mITT, modified intent-to-treat; EXT-mITT, extension modified intent-to-treat; PP, per-protocol; EXT-PP, extension per-protocol.

every 4 weeks based on previous dose) to maintain Hb levels within the 10–12 g/dL range. Increases and decreases in dose were not made more than once in 4 weeks, unless considered necessary by the investigator. If the Hb increased to ≥ 11.5 g/dL, the dose was reduced by approximately 25%. If the Hb continued to increase to ≥ 12 g/dL, dosing was temporarily withheld until the Hb began to decrease, and dosing was restarted when the Hb level fell back to the predetermined Hb level for restarting (i.e., ≤ 11.5 g/dL) based on the next scheduled Hb result. At this point, therapy was reinitiated at a dose approximately 25% below the previous dose or maintained at the previous dose based on the investigator's judgement and the Hb level measured at that current visit. If the rate of rise in Hb is greater than 2 g/dL in 1 month or the Hb increased by more than 1.0 g/dL in a 2-week period, the dose was decreased by approximately 25%. If the increase in Hb was less than 1.0 g/dL over 4 weeks and iron stores and availability were adequate, the dose was increased by approximately 25% of the previous dose. Further increases or decreases were made at 4-week intervals until the Hb was in the specified target Hb range. During the maintenance period, dosage of efepoetin alfa was adjusted to maintain target Hb ≤ 12 g/dL. If the Hb was ≥ 12 g/dL, the dose was adjusted as described above. Doses were individualised to ensure that Hb was maintained at an appropriate level for each patient. Methoxy polyethylene glycol-epoetin beta dose adjustments were made in accordance with the approved package insert [19] and the Institution's standard of care. To accommodate most of the study population based on body weight, initial doses of 50 µg and 100 µg were provided. Additional dosages were provided if requested from the study site ($n = 9$ requests, from Korea).

2.3 | Study Endpoints

The primary endpoint was the percentage of subjects achieving and maintaining Hb response (response rate) during the evaluation period. Response is defined as an increase in Hb ≥ 1 g/dL compared with baseline and a Hb concentration within the range of 10 to 12 g/dL inclusive without transfusion. This study has several secondary endpoints. The first secondary endpoint evaluated the mean change in Hb levels between the baseline and evaluation period. The second secondary endpoint evaluated the mean change in Hb levels between the evaluation period and the end of the extension period. The adverse events data were collected to compare the safety profiles of the two treatment arms. To monitor the immunogenicity of efepoetin alfa, anti-drug antibodies were tested until the end of the study.

TABLE 1 | Baseline characteristics.

Parameters	Efepoetin alfa ($n = 193$)	Methoxy polyethylene glycol-epoetin beta ($n = 197$)
Age (mean ± SD), years	65.3 ± 12	66.3 ± 12.1
Male	82 (42.5%)	124 (62.9%)
Female	111 (57.5%)	73 (37.1%)
Body weight (mean ± SD), kg	63.9 ± 11.7	61.1 ± 13.4
Hb (mean ± SD), g/dL	9.3 ± 6.8	9.3 ± 6.1

2.4 | Statistical Analysis

This study aimed to establish non-inferiority of efepoetin alfa compared to the active control (methoxy polyethylene glycol-epoetin beta). Considering a difference of response rate < 9% is not clinically significant, the non-inferiority margin of the response rate in this study was selected to be −9%. The required sample size with equal allocation to achieve a 90% power at a one-sided significance level of 0.025 can be determined by 154 participants in each treatment group. Therefore, a total of 386 subjects (193 subjects in each group) were planned to be enrolled. Hence the study would have more than 98% power to demonstrate that efepoetin alfa is as effective as methoxy polyethylene glycol-epoetin beta based on the Hb level change from baseline during the evaluation period, assuming a non-inferiority limit of −0.75 g/dL, a common standard deviation of 1.5 g/dL, and a one-sided significance level of 0.025.

3 | Results

3.1 | Study Population

Patients were screened at 55 sites in 7 countries/regions. The study began in August 2020 and was completed in June 2023. A total of 722 subjects were screened, and 391 subjects were randomised in a 1:1 ratio to receive either efepoetin alfa or methoxy polyethylene glycol-epoetin beta. One subject in the efepoetin alfa group was not treated; hence, they are not included in the safety population. Patient baseline characteristics were well balanced in age, body weight, and the Hb level. Sex was slightly unbalanced (Table 1). Therefore, we had sub-group analyses to show the response rate was comparable in both males and females.

A total of 391 subjects were randomised, and 390 (efepoetin alfa 193 and methoxy polyethylene glycol-epoetin beta 197) of them received at least one dose of the study drug during the correction and evaluation periods (one of the randomised subjects was not treated). Of these, 362 subjects remained in the study until Week 20 and started the evaluation period. The main reasons for subjects being excluded were inability to follow the study visits and procedures (due to COVID-related lockdowns), adverse events, deaths, and protocol deviations. This was comparable across treatment groups (179 [92.7%] in the efepoetin alfa group and 183 [92.9%] in the methoxy polyethylene glycol-epoetin beta group). A total of 348 subjects were included in the per-protocol (PP) population; this was comparable across treatment groups (172 [89.1%] in the efepoetin group and 176 [89.3%] in the methoxy polyethylene glycol-epoetin beta group).

3.2 | Efficacy

The analysis of primary and secondary efficacy endpoints demonstrated non-inferiority of efepoetin alfa to methoxy polyethylene glycol–epoetin beta.

The primary endpoint was to compare the response rate in two treatment arms in the per-protocol population. The non-inferiority was confirmed as the response rate of efepoetin alfa Q2W was 75.6%, while the methoxy polyethylene glycol-epoetin beta Q2W was 69.3%. The difference was 6.3% (95% CI: −3.1, 15.5%), and the lower limit of the 95% CI was above the prespecified non-inferiority margin of −9.0%.

The first secondary endpoint was to compare the mean change in Hb levels between the baseline and evaluation period. The non-inferiority was confirmed as the LS mean difference was −0.15 g/dL (95% CI: −0.33 to 0.02), and the lower limit of 95% CI was above the prespecified non-inferiority margin of −0.75 g/dL. The second secondary endpoint was to evaluate the group difference in the mean change in Hb levels between the evaluation period and the end of the extension period. The comparison of efepoetin alfa Q2W versus methoxy polyethylene glycol-epoetin beta Q4W and efepoetin alfa Q4W versus methoxy polyethylene glycol-epoetin beta Q4W was performed separately. The non-inferiority was confirmed in both comparisons as the lower limit of 95% CI was above the prespecified non-inferiority margin of −0.75 g/dL (Table 2).

Analysis of the secondary endpoints of the study showed that the patients treated with efepoetin alfa had a stable rise in Hb levels (Figure 3). The percentage of the patients who had overshoot (at least once the Hb was > 12 g/dL) was much lower

TABLE 2 | Secondary endpoints.

No.	Parameters	Efepoetin alfa Q2W ($n=172$)	Methoxy polyethylene glycol-epoetin beta Q2W ($n=176$)	LS mean difference	95% confidence interval
1	LS mean change in Hb levels between the baseline and evaluation period	1.59 g/dL	1.75 g/dL	−0.15 g/dL	−0.33, 0.02
2	LS mean change in Hb levels between the evaluation period and the end of extension period	Efepoetin alfa Q2W ($n=75$)	Methoxy polyethylene glycol-epoetin beta Q4W ($n=134$)	LS mean difference	95% Confidence interval
		−0.22 g/dL	−0.41 g/dL	0.19 g/dL	−0.10, 0.48
		Efepoetin alfa Q4W ($n=69$)	Methoxy polyethylene glycol-epoetin beta Q4W ($n=134$)	LS mean difference	95% Confidence interval
		−0.61 g/dL	−0.41 g/dL	−0.20 g/dL	−0.50, 0.11

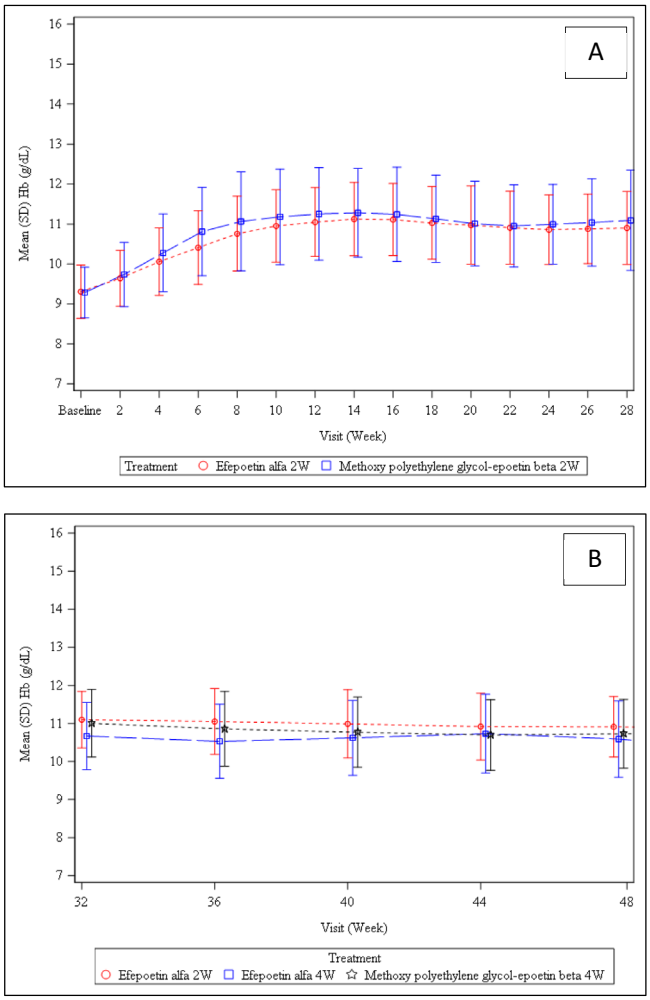

FIGURE 3 | Mean haemoglobin (SD) values during correction and evaluation period (A) and extension period (B) with efepoetin alfa and methoxy polyethylene glycol-epoetin beta. 2 W, once every 2 weeks; 4 W, once every 4 weeks; SD, standard deviation.

in the efepoetin alfa arm than in the methoxy polyethylene glycol-epoetin beta arm (Figure 4). In subgroup analyses, there was no difference according to sex, age, and baseline Hb level. The drug is effective over the population who were enrolled (Figure S1).

3.3 | Safety and Tolerability

The safety evaluation was based on the Safety Population, which comprised 390 subjects who received at least one dose of the study drug. Overall, a comparable safety profile was observed between efepoetin alfa and methoxy polyethylene glycol-epoetin beta (Tables 3 and 4).

A total of 15 (3.8%) subjects died due to AEs in the Correction and Evaluation Phase. Of the 15 subjects, 8 (4.1%) subjects were in the efepoetin alfa Q2W group and 7 (3.6%) subjects were in the methoxy polyethylene glycol-epoetin beta Q2W group. A total of 7 (2.5%) subjects died in the Extension Phase. Of the 7 subjects, 2 (2.7%) subjects were in the efepoetin alfa Q2W group, 1 (1.4%) subject was in the efepoetin alfa Q4W group, and 4 (2.9%) subjects were in the methoxy polyethylene glycol-epoetin beta Q4W group.

The fatal events reported in 11 subjects in the efepoetin alfa group (both phases included) were septic pulmonary embolism, upper gastrointestinal haemorrhage, cardiac arrest (4 subjects), coronavirus infection (2 subjects), pneumonia, myocardial infarction, and death from unknown causes. The fatal events reported in 11 subjects in the methoxy polyethylene glycol-epoetin beta group (both phases included) were cerebral infarction, pneumonia (2 subjects), rectal haemorrhage, cardiac arrest (2 subjects), aspiration pneumonia, acute kidney injury, coronavirus infection, acute myocardial infarction, and septic shock. The fatal events were primarily reported in subjects with multiple pre-existing medical conditions. All events were considered not

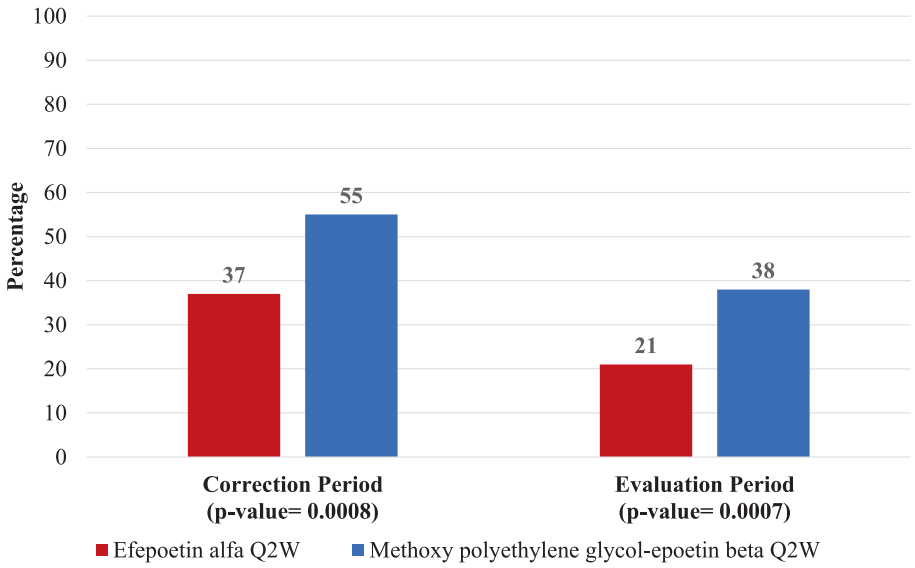

FIGURE 4 | The percentage of the patients who had a Hb overshoot (Hb > 12 g/dL). Q2W, once every 2 weeks.

TABLE 3 | Adverse events in the correction and evaluation period.

Adverse events, subject (%)	Efepoetin alfa Q2W (*N* = 193)	Methoxy polyethylene glycol-epoetin beta Q2W (*N* = 197)
Treatment-emergent adverse event/TEAE[a]	124 (64.2%)	123 (62.4%)
TEAE related to study drug[b]	13 (6.7%)	16 (8.1%)
SAE[c]	30 (15.5%)	35 (17.8%)
Death due to AEs[d]	8 (4.1%)	7 (3.6%)

[a]Most frequently reported TEAEs were coronavirus infection, hyperkalaemia, hypertension, urinary tract infection, dyspepsia, and peripheral oedema.
[b]The most frequently reported TEAEs were hypertension and a decrease in TSAT saturation.
[c]Most frequently reported SAE by SOCs are infections and infestations, cardiac disorders, metabolic and nutritional disorders, and renal and urinary disorders.
[d]All events were considered not related to the study drug.

related to the study drug by the Investigator except four subjects for which no relationship to the study drug could be assessed since the patients died outside the site and no autopsy could be done.

A total of 44 SAEs were reported in 30 (15.5%) subjects in the efepoetin alfa Q2W group and 65 SAEs in 35 (17.8%) subjects in the methoxy polyethylene glycol-epoetin beta Q2W group. SOCs with ≥2.5% subjects having SAEs in either of the treatment groups were infections and infestations (7.8% efepoetin alfa Q2W, 9.6% methoxy polyethylene glycol-epoetin beta Q2W), renal and urinary disorders (1.6%, 4.1%), cardiac disorders (3.6%, 2.5%), and metabolism and nutrition disorders (2.1%, 2.5%).

Anti-efepoetin alfa antibodies were not detected in any of the 800 samples tested across 5 visits over the entire study.

4 | Discussion

Anaemia is common in CKD patients not on dialysis and the percentage increases with CKD stage, confirmed by previous

TABLE 4 | Adverse events in extension period.

Adverse events, subject (%)	Efepoetin alfa Q2W (*N* = 75)	Efepoetin alfa Q4W (*N* = 72)	Methoxy polyethylene glycol-epoetin beta Q4W (*N* = 138)
Treatment-emergent adverse event/TEAE[a]	32 (42.7%)	32 (44.4%)	56 (40.6%)
TEAE related to study drug[b]	2 (2.7%)	4 (5.6%)	1 (0.7%)
SAE[c]	8 (10.7%)	10 (13.9%)	23 (16.7%)
Death due to AEs[d]	2 (2.7%)	1 (1.4%)	4 (2.9%)

[a]Most frequently reported TEAEs were coronavirus infection, hyperkalaemia, and hypertension.
[b]None of the related TEAEs were reported in > 4 subjects overall.
[c]Most frequently reported SAE by SOCs is infections and infestations, cardiac disorders, metabolic and nutritional disorders, and renal and urinary disorders.
[d]All events were considered not related to the study drug.

reports [10]. Treatment with short-acting ESAs in this population may require frequent dosing, which can affect medication compliance. It has been demonstrated that most of the CKD patients not on dialysis (86%) prefer a monthly regimen over a weekly ESA dosing [20]. As well, patients who were surveyed, nearly three-quarters (72.5%) of renal anaemic patients would prefer fewer injections and the number of patients missing ESA doses appears lower with weekly administration than with twice weekly epoetin [21]. Efepoetin alfa's long-acting profile can help to improve anaemia management.

This is the first phase 3 clinical trial publication to compare efepoetin alfa and methoxy polyethylene glycol-epoetin beta. The primary endpoint and all the important secondary endpoints were met. This study demonstrates that efepoetin alfa is non-inferior to methoxy polyethylene glycol-epoetin beta in the management of anaemia in patients with stage 3 or 4 CKD. It was the COVID-19 pandemic during the enrolment and treatment period of the trial. The lockdown and COVID-19 infections significantly affected the enrolment and increased the dropout rate. The most common AEs reported in both treatment groups are characteristic of the population under study and reflect the pandemic.

Both in the correction and evaluation periods (Figure 4) there were significantly fewer overshoots of Hb > 12 g/dL in the efepoetin alfa arm than in the methoxy polyethylene glycol-epoetin beta arm, which may suggest a lower risk of cardiovascular thromboembolic complications (*p*-value: 0.0008 in correction, 0.0007 in evaluation). Commercially, methoxy polyethylene glycol-epoetin beta has been approved in multiple countries and comes in fixed-dose prefilled syringes with varied strengths. However, it can be difficult to precisely provide the dose that has been estimated based on body weight and dose adjustment guidelines, especially in hospitals where not all strengths are easily accessible (e.g., pharmacies in Taiwan and Malaysia usually stock only two or three strengths). To address this, based on feedback from investigators, our clinical trial offered 50 and 100 μg strengths, which covered most patients. An additional strength (75 μg) was provided upon request by individual sites. Investigators were directed to administer methoxy polyethylene glycol-epoetin beta according to local product information recommendations. On the other hand, efepoetin alfa came with a prefilled syringe that had a graduated scale, which made dosage administration more accurate. This design might be advantageous for treating anaemic patients more effectively, especially in situations when accurate dosage is essential. Poor clinical outcomes are associated with changes in Hb [22–25]. However, to demonstrate a superior cardiovascular-related safety profile, more real-world patient data is needed.

ESAs have been well-established as efficacious in correcting and maintaining haemoglobin levels in patients with chronic kidney disease (CKD), with a recognised and manageable side effect profile. Recent publications of trials investigating the use of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) in non-dialysis CKD patients have demonstrated efficacy but raised concerns regarding their safety profiles [26, 27]. For instance, the phase 3 trials conducted by Yamamoto et al. with molidustat in both ESA- naïve and previously treated non-dialysis patients confirmed its efficacy but highlighted the uncertainty of its long-term safety [26]. Similarly, the study using roxadustat in non-dialysis CKD by Coyne et al. echoed these findings, noting potential class-specific side effects of HIF-PHIs [28]. Given these safety concerns, further studies are needed. The ideal agent for treating uraemic anaemia should maintain stable haemoglobin levels, have a reassuring safety profile, and be cost-effective. However, the optimal route of administration may depend on patient preferences, lifestyle considerations, health care setting constraints, and specific clinical parameters.

The limitations of this study were it being open-label, allowing potential assessment biases and the absence of blinded assessment of clinical endpoints. In addition, the choice of dosages for methoxy polyethylene glycol-epoetin beta was somewhat limited when compared to, for example, Europe. This study's strength lies in its multi-country and multi-site design, which enhances the generalisability and external validity of its findings across diverse populations and healthcare systems. Furthermore, by directly comparing a novel treatment (efepoetin alfa) to a well-established standard of care, the study offers a comprehensive evaluation of both the efficacy and long-term safety of the novel treatment in a real-world clinical setting.

5 | Conclusion

The primary endpoint for the study was met. Based on final analysis, efepoetin alfa was demonstrated to be non-inferior to methoxy polyethylene glycol-epoetin beta. Efepoetin alfa also had a comparable safety profile to methoxy polyethylene glycol-epoetin beta in anaemia stage 3 and 4 CKD patients.

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Conflicts of Interest

Simon Roger has received speaker's fee and consultancy fees from Kalbe Genexine Biologics, and I-Wen Wu has received consultancy from Innogene Kalbiotech Pte Ltd.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.