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**Original Research Article**

# Effectiveness of pegylated erythropoietin in renal anaemia patients on dialysis-a multicentre, cross-sectional, observational outcome study

**E. Mahesh[1]*, C. M. Thiagarajan[2], Mahendra M. Mulani[3], Mukesh M. Shete[4], Krishna V. Patil[5], K. Sravan Kumar[6], Babu Francis[7], Shriniwas M. Ambike[8], Kanai Lal Karmakar[9], Shashi Kumar[10], Javed M. Vakil[11], Sanjay Rampure[12], Ashok Kumar Panda[13], N. Venkatesh[14], Ajay Goyal[15], V. Dhanalakshmi[16], Amit Pasari[17], Manish R. Balwani[17], Manish Kumar Singla[18]**

[1]Ramaiah Memorial Hospital, Bangalore, Karnataka, India
[2]Fortis Malar Hospital, Chennai, Tamil Nadu, India
[3]Aadhya Women's and Kidney Hospital, Ahmedabad, Gujarat, India
[4]Kimaya Kidney Care, Mumbai, Maharashtra, India
[5]Sunshine Hospital, Hyderabad, Telangana, India
[6]Varma Hospital, Bhimavaram, Andhra Pradesh, India
[7]Lisie Hospital, Kochi, Kerala, India
[8]Jehangir Hospital, Pune, Maharashtra, India
[9]RG Kar Medical College and Hospital, Kolkata, West Bengal, India
[10]Paras HMRI Hospital, Patna, Bihar, India
[11]Vakil Kidney Care, Ahmedabad, Gujarat, India
[12]Malathi Manipal Hospital, Bangalore, Karnataka, India
[13]Care Hospital, Bhubaneswar, Odisha, India
[14]Annai Arul Hospital, Chennai, Tamil Nadu, India
[15]Kidney Care Centre, Panchkula, Haryana, India
[16]Virinchi Hospital, Hyderabad, Telangana, India
[17]Saraswati Kidney Care Hospital, Nagpur, Maharashtra, India
[18]Max Super Speciality Hospital, Mohali, Punjab, India

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***Correspondence:**
Dr. E. Mahesh,
E-mail: manasnephro2002@yahoo.co.in



## ABSTRACT

**Background:** Low dose of pegylated erythropoietin (PegEPO) is better than conventional erythropoietin stimulating agents (ESAs) in improving hyporesponsiveness and maintaining stable haemoglobin (Hb) levels in renal anaemic patients undergoing hemodialysis. This real-world study aimed to assess effectiveness and safety of low-dose PegEPO (30 µg/0.3 mL), administered at different time-points in renal anaemia patients on dialysis.
**Methods:** HEMEPEG (HEMoglobin outcomE with PegEPO) was a multicentre, retrospective, cross-sectional, observational study of renal anaemia patients receiving PegEPO up to 3 months. The study assessed an increase in Hb, patients achieving Hb 10-12 g/dl, and Hb increase by ≥1 and ≥2 g/dl.
**Results:** Data from 223 out of 273 patients from 19 Indian centers were analyzed. PegEPO was administered weekly to 132 patients (59.19%), with 38.64% being diabetic and 77.27% previously treated with ESAs. Ten day dosing was given to 91 patients (40.81%), including 46.15% diabetic patients and 72.53% previously treated with ESAs. A Significant ($p<0.0001$) increase in mean Hb levels from baseline to day 30, 60 and 90 were observed for both studied groups, with a target Hb of 10-12 g/dl achieved in 51.08% and 52.85% of patients in the respective groups after 3 months. An increase in Hb by ≥1 and ≥2 g/dl were observed in weekly (68.67% and 45.78%) and 10-day group (77.14% and 50.00%) patients, respectively.
**Conclusions:** PegEPO (30 µg/0.3 mL) was effective treatment of renal anaemia and diabetic chronic kidney disease (CKD) patients on dialysis when administered weekly or every 10 days over a 3-month treatment period.

**Keywords:** PegEPO, Anaemia, CKD, Dialysis, Outcome

## INTRODUCTION

In patients with CKD, anaemia remains a major and frequent complication diminishing patients' quality of life with increased morbidity and mortality.[1,2] The deficiency of endogenous erythropoietin (EPO), decreased iron intake, and increased hepcidin levels are major factors associated with anaemia in CKD patients.[2-4] Kidneys synthesize EPO. There is loss of kidney mass in CKD patients leading to impaired EPO production resulting in anemia.[4] ESAs are major tools for the management of anaemia in CKD patients.[3,5,6] The therapeutic target in anaemia patients with CKD remains the correction and maintenance of target Hb levels without fluctuations, with the least possible ESA dose.[3] In CKD patients on dialysis with Hb <10 g/dl, the kidney disease: improving global outcomes (KDIGO) and European renal best practice guidelines recommend treatment with ESA with a target Hb of 10-11.5 g/dl.[7-9]

The recombinant human erythropoietin (epoetin alpha) was the first ESA approved for renal anaemia. Subsequently, second-generation darbepoetin and third-generation PegEPO derivative, which is also known as continuous EPO receptor activator (CERA), were developed.[4,10,11] The CERA agent is a modified recombinant human EPO and its efficacy and safety for anaemia in CKD patients have been demonstrated in several clinical studies.[9,12-14] CERA is administered biweekly or monthly for the treatment of anaemia associated with CKD.[15] Studies have demonstrated a target Hb range of 10 to 11.5 g/dl with biweekly or monthly CERA administration.[16] In addition, few reports has been indicated that the weekly CERA administration is effective in the renal anaemia patients undergoing the hemodialysis.[17]

Pegylated erythropoietin (methoxy polyethylene glycol-epoetin β) under the CERA category has been approved for the treatment of anaemia in CKD by the US food and drug administration.[15] Intas Pharmaceuticals Ltd. has developed a biosimilar pegylated recombinant human erythropoietin (PegEPO) formulation. A chemical bond between an amino group present in erythropoietin and monomethoxy polyethylene glycol is present in PegEPO.[18] Biosimilar PegEPO demonstrated similar efficacy and safety in renal anaemic patients as compared with the reference innovator product in phase III randomized clinical study,[19] and has been approved by the drugs controller general of India (DCGI) for the treatment of anaemia associated with chronic renal failure in adults, including patients undergoing dialysis.[20] Besides randomized clinical trials, real-world data complement and help expand therapeutic evidence in clinical practice.[21] There is a lack of data on PegEPO in real-world clinical settings. Hence, this study was conducted to evaluate the real-world effectiveness and safety of biosimilar PegEPO in renal anaemia patients on dialysis. We also evaluated the effectiveness and safety of PegEPO administered as a weekly or 10-day dosing schedule in these patients along with gender-wise comparison.

## METHODS

### *Study design and population*

The HEMEPEG (HEMoglobin outcomE with PegEPO in dialysis patients) was a multicentre, retrospective, cross-sectional, observational study. Ethics committee approval was taken from the institutional ethics committee of Ramaiah medical college with number DRP/IFP1019/2023. A total of 273 patients with renal anaemia on were included administered PegEPO 30 µg/0.3 mL for ≥3 months between December 2020 and May 2021. Patients administered with PegEPO injection (intravenous or subcutaneous) at an interval of 7/10 days were included in the analysis. All the enrolled patients fulfilled all the above inclusion and none of the exclusion criterion. Retrospective data was collected in the data capture form at baseline and days 30, 60, and 90.

### *Patient assessment and outcomes*

Patient's baseline demographics and characteristics including age, gender diagnosis, history of comorbidities, duration of disease, treatment and improvement in Hb levels, and safety profile were captured. The study assessments included the mean improvement in Hb levels at 1, 2, and 3 months. At 3 months, the proportion of patients achieving target Hb levels of 10-12 g/dl and with an increase in Hb by ≥1 and ≥2 g/dl were evaluated. Besides gender-wise comparison for the effectiveness of PegEPO, the safety profile was also assessed. This study is reported as per the strengthening the reporting of observational studies in epidemiology (STROBE) guideline (Table 1 for entire Checklist).

### *Statistical analysis*

The qualitative variables were expressed in proportion and percentage and the quantitative variables are expressed in mean and standard deviation (SD) including 95% confidence interval (CI). Descriptive statistics are presented for the demographic characteristics, comorbidities, treatment history, and summarized with frequency and proportions (percentages). Comparison between different parameters was done using the unpaired t test; a $p<0.05$ was considered statistically significant. The statistical analysis was performed using GraphPad Prism version 9.

## RESULTS

### *Demographics and clinical characteristics*

Data of 273 patients from 19 different centres across India were captured. Of these, 223 patients were considered in the analysis, while the remaining 50 patients were lost to follow-up. Patients received a

weekly (n=132) or 10-day (n=91) administration of PegEPO. Figure 1 details the patient distribution in this study. The mean (SD) age of patients was 49.34 (13.67) years for the weekly dose group and 48.48 (13.08) years for the 10-day dose group. A majority of the patients were males in both groups (weekly: 62.88%; 10-day: 60.44%). The mean (SD) duration of CKD was 2.83 (2.39) years for the weekly and 3.23 (2.55) years for the 10-day dose groups. A majority of the patients had a history of previous treatment with ESA viz. EPO and darbepoetin (weekly: 77.27%; 10-day: 72.53%). Associated comorbidities in the majority of patients included hypertension, diabetes, and dyslipidaemia. The demographics and baseline characteristics of the study population are presented in Table 2.

**Table 1: STROBE statement-checklist of items that should be included in reports of cross-sectional studies.**

| Variables | Item no. | Recommendation | Reported in (headings) |
|---|---|---|---|
| **Title and abstract** | 1 | (a) Indicate the study's design with a commonly used term in title or the abstract | Title page |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract section |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for investigation being reported | Introduction, paragraphs 1-2 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction, para. 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in paper | Methods: Study designs and populations section |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods: Study designs and populations section |
| Participants | 6 | (a) Give the eligibility criteria, and sources and methods of selection of participants. | Methods: Study designs and populations section |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Methods: Patient assessment and outcomes section |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than 1 group | We analyzed the medical charts of Renal anaemic patients |
| Bias | 9 | Describe any efforts to address potential sources of bias | Statistical analysis |
| Study size | 10 | Explain how the study size was arrived at | Methods: Study designs and populations and Figure 1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in analyses. If applicable, describe which groupings were chosen and why | Methods: Patient assessment and outcomes section |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | Statistical analysis |
| | | (b) Describe any methods used to examine subgroups and interactions | |
| | | (c) Explain how missing data were addressed | |
| | | (d) If applicable, explain how loss to follow-up was addressed | |
| | | (e) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study-e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Methods: Study designs and populations and Figure 1 |
| | | (b) Give reasons for non-participation at each stage | Loss of follow-up |

Continued.

| Variables | Item no. | Recommendation | Reported in (headings) |
|---|---|---|---|
| | | (c) Consider use of a flow diagram | Included, Figure-1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders | Results: Demographics and clinical characteristics section, Table 2 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 50 patients due to loss of follow-up |
| Outcome data | 15* | Report numbers of outcome events or summary measures | Figure 3 and 4 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders adjusted for and why they included | Results: Table 2, Table 3 and figure 2A and 2B |
| | | (b) Report category boundaries when continuous variables were categorized | |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done-e.g., analyses of sub groups and interactions, and sensitivity analyses | Not Available |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | Discussion: Paragraph 1, Conclusion |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | Limitations section |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | Discussion section |
| Generalisability | 21 | Discuss generalisability (external validity) of study results | Discussion: Paragraph 3 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for present study and, if applicable, for the original study on which the present article is based | No funding available for from govt or non-govt organization, funding section |

*Give information separately for exposed and unexposed groups.

**Table 2: Demographics and baseline characteristics of study patients.**

| Variables | Weekly dose group, (n=132) | 10-day dose group, (n=91) |
|---|---|---|
| **Gender, n (%)** | | |
| Male | 83 (62.88) | 55 (60.44) |
| Female | 49 (37.12) | 36 (39.56) |
| **Age (In years), mean (SD)** | 49.34 (13.67) | 48.48 (13.08) |
| **Duration of CKD (In years), mean (SD)** | 2.83 (2.39) | 3.23 (2.55) |
| **Previous ESA use, n (%)** | 102 (77.27) | 66 (72.53) |
| EPO | 62 (46.97) | 50 (54.95) |
| Darbepoetin | 35 (26.52) | 15 (16.48) |
| **Comorbidity, n (%)** | | |
| Hypertension | 103 (78.03) | 79 (86.81) |
| Diabetes | 51 (38.64) | 42 (46.15) |
| Dyslipidaemia | 17 (12.88) | 7 (7.69) |
| Coronary artery disease | 4 (3.03) | 2 (2.2) |
| Others | 11 (8.33) | 4 (4.4) |

**Table 3: Mean (SD) improvement in Hb level from baseline at days 30, 60 and 90 with PegEPO.**

| Parameters | Weekly dose group, (n=132) | | 10-day dose group, (n=91) | |
|---|---|---|---|---|
| | Hb g/dl | 95% CI | Hb g/dl | 95% CI |
| **Baseline** | 8.16 (1.11) | - | 8.00 (1.28) | - |
| **Day 30** | 9.03 (1.28)* | -13.14, -8.9 | 8.62 (1.38)* | -11.63, -5.56 |
| **Day 60** | 9.42 (1.58)* | -23.71, -18.18 | 9.61 (1.46)* | -24.31, -16.86 |
| **Day 90** | 9.98 (1.33)* | -27.92, -21.43 | 10.21 (1.32)* | -31.16, -23.07 |

Values are expressed as mean (SD) with 95% CI. *p<0.0001, p was calculated for increase in Hb from baseline at every time point.

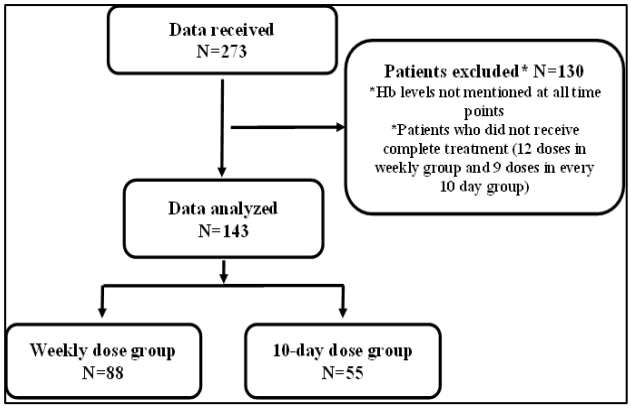


**Figure 1: Study patient distribution.**

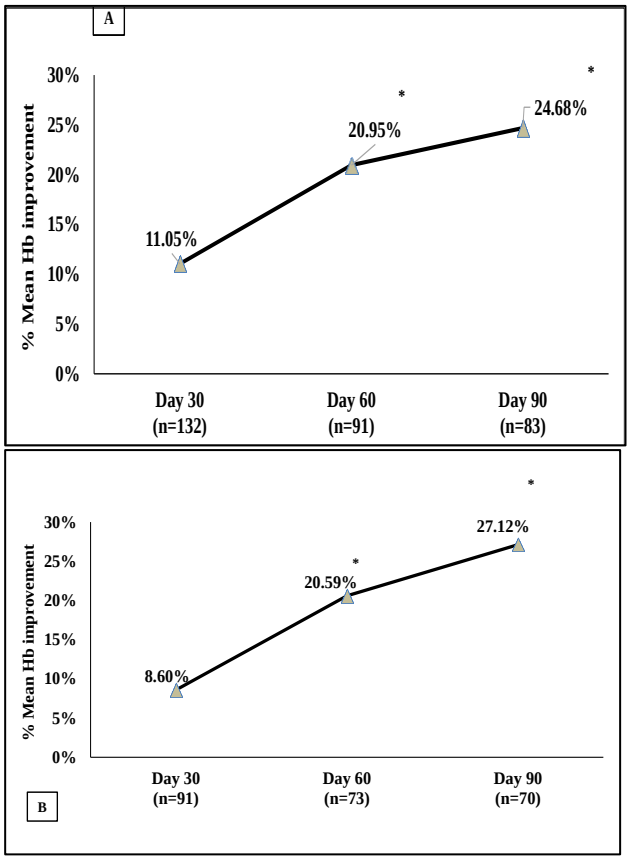


**Figure 2 (A and B): Mean percent improvement in Hb (g/dl) in weekly dose group and 10-day dose group over 30, 60 and 90 days with PegEPO.**

*p<0.0001. P value was calculated for increase in Hb from baseline at every time point.

***Improvement in Hb (g/dl) outcomes over 30, 60, and 90 days with PegEPO***

PegEPO showed improvement in Hb levels (g/dl) in both weekly and 10-day dose groups. The improvement in Hb level was significant from the baseline at Day 30, 60, and 90 (Table 3). At 60 days, the mean Hb level showed an improvement of 1.26 g/dl in the weekly whereas 1.61 g/dl in the 10-day group patients. The mean Hb levels at 90 days were 9.98 g/dl and 10.21 g/dl, respectively, for weekly and 10-day doses, achieving a target Hb level of 10 g/dl in this patient population (Table 2).

In the weekly dose group, from baseline, the mean percent improvement in Hb level was significant at Day 30 (11.05%), which continued improving at day 60 (20.95%) and 90 (24.68%) also (Figure 2A). Similarly, in the 10-day dose group, the mean percent improvements in Hb levels from baseline (8.0 g/dl) were also significant at all time points. From baseline to day 30, corresponding increase in mean percent Hb levels were (8.60%), which further improved at day 60 (20.59%) and day 90 (27.12%) (Figure 2B).

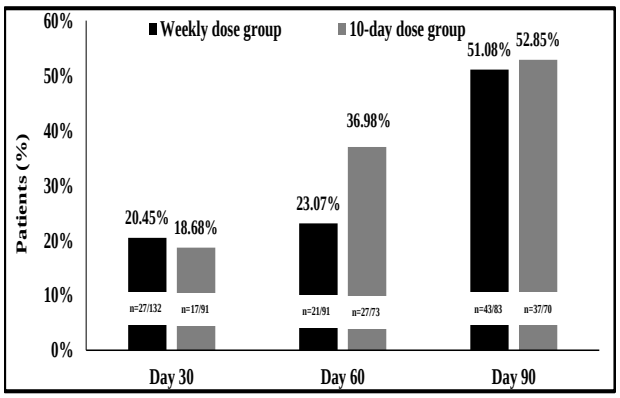


**Figure 3: Proportion of patients achieving target Hb levels of 10-12 g/dl at 30, 60 and 90 days with PegEPO.**

***Gender-wise comparison in increase in Hb (g/dl) with PegEPO***

The improvement in mean percent Hb level from baseline at day 90 in weekly dose group were significant in both males (24.68%, p<0.0001, 95% CI:-28.77, -20.58) as well as females (24.65%, p<0.0001, 95% CI:-30.06, -19.23), with no significant difference between gender (p=0.9945;

95% CI: -8.60, 8.66). Similar results with significant improvements in Hb levels were also seen in the 10-day dose group for males (27.24%, p<0.0001, 95% CI: -32.52, -21.95) and females (25.20%, p<0.0001, 95% CI: -31.05, -19.34) at day 90, with no significant difference in gender effectiveness (p=0.6632, 95% CI: −7.27, -11.35).

***The proportion of patients achieving target Hb levels of 10-12 g/dl with PegEPO***

The proportion of patients achieving target Hb levels of 10-12 g/dl within 3 months was 51.08% in the weekly dose group and 52.85% in 10-day dose group (Figure 3).

***The proportion of patients with an increase in Hb of ≥1 and ≥2 g/dl***

In the weekly dose group, an increase in the Hb levels by ≥1 and ≥2 g/dl was observed in 68.67% and 45.78% patients, respectively. Similarly, 77.14% and 50.00% patients showed an increase in Hb levels by ≥1 g/dl and ≥2 g/dl, respectively, in the 10-day dose group at 3 months (Figure 4). Overall, no study-related adverse effects were reported.

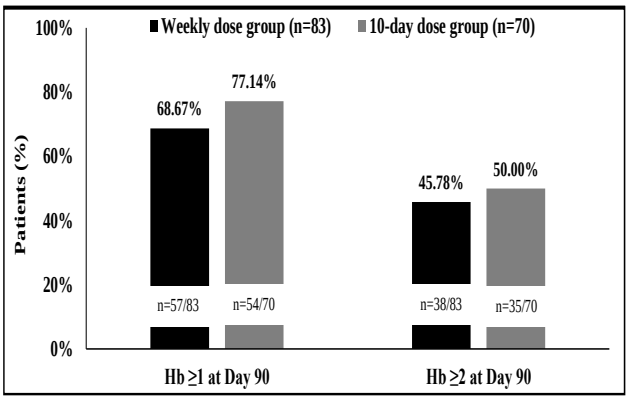


**Figure 4: Proportion of patients with increase in Hb by ≥1 and ≥2 g/dl at day 90 with PegE.**

## DISCUSSION

Prospective clinical studies have provided strong evidence on the efficacy and safety of CERA for the treatment of anaemia associated with CKD.[3,12-14] However, they may not completely reflect the conditions found in a routine clinical setting due to their restrictive design and inclusion and exclusion criteria. The purpose of this study was to collect real-world data and analyse the effectiveness and safety of biosimilar PegEPO for improvement in Hb levels in renal anaemia patients on dialysis in routine clinical setting. Our study demonstrated that PegEPO administered at both weekly and 10-day dosing schedules significantly improved the Hb levels starting at 1 month to 3 months study duration. In our study, the PegEPO treatment resulted in a significant improvement in the mean Hb levels from baseline throughout the study duration of 90 days. The mean percent improvement in Hb level was 24.68% and 27.12% for weekly and 10-day dose groups, respectively. The corresponding mean Hb levels at 3 months were 9.98 g/dl and 10.21 g/dl, respectively, for weekly and 10-day doses. These results are in line with the previously published studies, which have suggested a target Hb level of >10 g/dl in this patient population.[16,17,22] In this study, approximately half (51.46%) of the patients achieved Hb levels >10 g/dl at 3 months in both weekly and 10-day dose groups.

The efficacy and safety of biosimilar PegEPO in the treatment of anaemia due to CKD in patients who were not on dialysis were established in a prospective, randomized, multicentre study in comparison with the innovator reference product. Biosimilar PegEPO showed no significant differences (70.24% vs 68%; p=0.83) when compared with reference product for achieving a pre-specified Hb target (Hb level ≥11 g/dl or an increase in Hb by ≥2 g/dl); mean dose and duration to achieve the target Hb was also not significantly different between the drugs.[19] Overall, this phase III clinical study demonstrated that the efficacy and safety of biosimilar PegEPO were comparable with reference product[19] and this led to its regulatory approval in India.[20] At this point of time it is not justifiable to compare the present study results with the phase III results of PegEPO as the data presented in this study includes dialysis patients only; the majority being pre-treated and presenting with multiple confounding and contributing factors in real-world population. The phase III study in comparison was a randomized clinical trial conducted on non-dialysis patients with a transferrin saturation level of ≥20% and a ferritin level of ≥100 ng/mL.

PegEPO has been used in Indian patients in previous studies for Hb correction in CKD patients. A study by Nand and colleagues in Indian patients with renal anaemia demonstrated better treatment outcomes with PegEPO when compared with darbepoetin alfa in terms of maintenance of stable Hb levels.[23] A population-based observational clinical practice study demonstrated that the efficacy and safety of biosimilar ESAs were similar to the originator products in CKD patients.[24] These findings strengthen the evidence on the usage of biosimilar PegEPO in anaemic patients with CKD. PegEPO is usually administered once every two weeks or at a monthly interval.[15] Several reports have established the efficacy of a biweekly dosing schedule in maintaining Hb levels with a low average dose.[16,17,22,25,26] In a randomized trial, Kakimoto-Shino et al indicated that weekly CERA administration can also improve iron utilization for erythropoiesis and subsequently increase Hb levels.[27] Recently, Kawai and colleagues established the efficacy and safety of weekly CERA administration on erythropoiesis in comparison with biweekly dosing schedule in renal anaemia patients on maintenance haemodialysis in a randomized clinical study. The total dose required to maintain the target Hb levels was similar for weekly and biweekly dosing groups, and management

of anaemia was similar in weekly or biweekly CERA administration groups.[17] In line with these reports, the dosing used in our patients included a weekly dose or once every 10 days.

In the present study, the mean percent improvement in the Hb levels was significant from baseline throughout the study duration. The mean Hb levels at 3 months were 9.98 and 10.21 with weekly and 10-day dosing in our study. In the study by Kawai et al a weekly CERA administration showed mean Hb levels of 10.9 g/dl at the 3-month evaluation period in patients undergoing hemodialysis.[17] The target Hb levels of 10-11.5 g/dl was achieved in 41.7% of patients with weekly CERA in the study by Kawai et al.[17] Similarly, in our study, PegEPO led to the achievement of target Hb levels of 10-12 g/dl in 51.08% and 52.85% patients in the weekly and 10-day dose groups at 3 months, respectively. The mean improvements in Hb with PegEPO at 3 months were 1.82 and 2.21 g/dl in the weekly and 10-day dose group. Previous studies with a biweekly CERA administration have shown a mean improvement of Hb of 2.08 g/dl at 4 months[28] to 2.6 g/dl at 6 months.[29] The increase in Hb by ≥1 g/dl at 3 months was reported in 68.67% and 77.14% patients with weekly and 10-day dosing in our study. In a study by Vankar et al all 35 (100%) renal anaemic patients, who were not on dialysis, achieved an Hb increase by ≥1 g/dl at 6 months with CERA.[29]

A previous randomized phase III STRIATA study has demonstrated maintenance of Hb levels with CERA administration in patients on dialysis who had received previous treatment with darbepoetin alfa.[30] Consistent with this study, a majority (77.27%) of the patients had previously received ESA therapies including darbepoetin and rHuEPO. In Indian patients, Nainan et al reported that CERA treatment was effective in renal anaemia patients who had not received previous ESA therapies within the past 8 weeks.[28] PegEPO in our study also showed an improvement in Hb in patients who had previously received treatment with other ESAs. However, a subgroup analysis in ESA naive versus pretreated patients was not carried out as the volume of ESA naive patients was not comparable. In our study, the PegEPO treatment resulted in significant improvements in the Hb levels in both men and women. The gender-wise analysis showed no significant difference in the Hb improvements. Previous published studies such as MICENAS II did not report any significant difference in Hb improvements between men and women.[3]

Renal anaemia is more prevalent in diabetic than non-diabetic CKD patients as reported in the Prevalence of anaemia in early renal insufficiency (PAERI) study (52.7 vs 39.4%; p<0.01).[31] The use of CERA has been effective in this patient population as reported by Vankar and colleagues who evaluated the effects of CERA in Indian diabetic CKD patients' not on dialysis and concluded its efficacy in correcting Hb levels.[29] In line with the aforementioned data, majority (42.39%) of our study patients had diabetes as a comorbidity, wherein PegEPO was effective.

***Limitations***

The study provides valuable insights on efficacy of PegEPO 30 µg/0.3 mL in patients on dialysis having renal anaemia. However, the study has certain limitations which include absence of a comparative/control/reference arm, small sample size and limited duration of three months. In addition, this observational study includes non-randomized 90 days outcome study design and retrospective evaluation of the data. The details regarding blood transfusion, hepcidin (key mediator of iron metabolism), ferritin, transferrin, iron status and adverse events were not available, hence, could not be analysed.

## CONCLUSION

PegEPO 30 µg/0.3 mL was effective in renal anaemia patients on dialysis when administered weekly or every 10 days over 3-month treatment period. Besides standard monthly or biweekly administration, PegEPO showed improvement in Hb levels at weekly and 10-day dosing schedule. PegEPO demonstrated effectiveness for Hb improvements in diabetic and ESA pre-treated renal anaemic patients on dialysis. Large scale randomized studies would further help establish the effectiveness and safety of PegEPO.

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## REFERENCES

1. Babitt JL and Lin HY. Mechanisms of Anemia in CKD. J Am Soc Nephrol. 2012;23:1631-4.
2. Portolés J, Martín L, Broseta JJ. Anemia in Chronic Kidney Disease: From Pathophysiology and Current Treatments, to Future Agents. Front Med. 2021;8.
3. Martínez-Castelao A, Cases A, Coll E. C.E.R.A. administered once monthly corrects and maintains stable hemoglobin levels in chronic kidney disease patients not on dialysis: the observational study MICENAS II. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia. 2015;35:80-86.

4. Hayat A, Haria D and Salifu MO. Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Prefer Adherence. 2008;2:195-200.
5. Gafter-Gvili A, Schechter A and Rozen-Zvi B. Iron Deficiency Anemia in Chronic Kidney Disease. Acta Haematologica. 2019;142:44-50.
6. Cheng HW, Chan KY, Lau HT. Use of Erythropoietin-Stimulating Agents (ESA) in Patients With End-Stage Renal Failure Decided to Forego Dialysis: Palliative Perspective. Am J Hospice Palliative Care. 2017;34:380-84.
7. Mimura I, Tanaka T and Nangaku M. How the Target Hemoglobin of Renal Anemia Should Be? Nephron 2015;131:202-9.
8. Drüeke TB and Parfrey PS. Summary of the KDIGO guideline on anemia and comment: reading between the (guide)line(s). Kidney Int. 2012;82:952-60.
9. Locatelli F, Covic A, Eckardt K-U. Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP). Nephrol Dialysis Transplantation. 2008;24:348-54.
10. Macdougall I. CERA (Continuous Erythropoietin Receptor Activator): A new erythropoiesis-stimulating agent for the treatment of anemia. Curr Hematol Rep. 2005;4:436-40.
11. El-Komy MH, Widness JA and Veng-Pedersen P. Pharmacokinetic analysis of continuous erythropoietin receptor activator disposition in adult sheep using a target-mediated, physiologic recirculation model and a tracer interaction methodology. Drug Metab Dispos. 2011;39:603-9.
12. Frimat L, Mariat C, Landais P. Anaemia management with C.E.R.A. in routine clinical practice: OCEANE (Cohorte Mircera patients non-dialyses), a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis. BMJ Open. 2013;3.
13. Heidenreich S, Leistikow F, Zinn S. Monthly administration of a continuous erythropoietin receptor activator provides efficient haemoglobin control in non-dialysis patients during routine clinical practice: results from the non-interventional, single-cohort, multicentre, SUPRA study. Clin Drug Investigation. 2012;32:99-110.
14. Minutolo R, Zamboli P, Chiodini P. Conversion of darbepoetin to low doses of CERA maintains hemoglobin levels in non-dialysis chronic kidney disease patients. Blood Purification. 2010;30:186-94.
15. MIRCERA (methoxy polyethylene glycol-epoetin beta). Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125164s078lbl.pdf. Accessed on 12 March, 2023.
16. Levin NW, Fishbane S, Cañedo FV. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). Lancet (London, England). 2007;370:1415-21.
17. Kawai Y, Toya Y, Wakui H. Comparison of the effects of weekly and biweekly intravenous CERA administration on erythropoiesis: A randomized controlled trial. Journal of clinical hypertension (Greenwich, Conn). 2021;23:870-78.
18. Erypeg® Prescribing Information. Intas Pharmaceuticals Limited. 2021.
19. Mehta KD. On Behalf of ERYPEG Study Group. Comparative clinical efficacy and safety of erypeg®; a biosimilar of pegylated erythropoietin (pegepo) in the treatment of adult patients with anaemia of ckd who were not on dialysis. Poster Presentation. Indian J Nephrol. 2016;26(S2):52-136.
20. Central Drugs Standard Control Organisation (CDSCO). r-DNA based drugs approved in country. Intas Pharmaceuticals Limited. Peg-EPO. MF-84/2015 BULK-83/2015. Available at https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadBiologicalrDNA/rdnaform46.pdf. Accessed on on 12 March, 2023.
21. Bhatt A. Conducting real-world evidence studies in India. Perspect Clin Res. 2019;10:51-6.
22. Sulowicz W, Locatelli F, Ryckelynck JP. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. Clin J Am Society Nephrol. 2007;2:637-46.
23. Nand N, Nandan R and Jain D. Comparative Effects of Pegylated Erythropoietin and Darbepoetin Alfa on Erythropoietin Hyporesponsive Anemia of Patients with Chronic Kidney Disease on Maintenance Hemodialysis. J Asso Physicians of India. 2021;69:62-5.
24. Trotta F, Belleudi V, Fusco D. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: a population-based cohort study in Italy. BMJ Open. 2017;7:e011637.
25. Toida T, Sato Y, Shibata N. A randomized control study on the procedure for switching epoetin beta (EPO) to epoetin beta pegol (CERA) in the treatment of renal anemia in maintenance hemodialysis patients. Blood Purification. 2014;38:174-9.
26. Morikami Y, Fujimori A, Okada S. Twice-monthly administration of a lower dose of epoetin beta pegol can maintain adequate hemoglobin levels in hemodialysis patients. Therapeutic Apheresis Dialysis. 2015;19:138-43.
27. Kakimoto-Shino M, Toya Y, Kuji T. Changes in hepcidin and reticulocyte hemoglobin equivalent levels in response to continuous erythropoietin receptor activator administration in hemodialysis patients: a randomized study. Therapeutic Apheresis Dialysis. 2014;18:421-6.
28. Nainan GK, Pathak VR, Dalal SS. A single arm, prospective, open label, multicentre study for evaluation of efficacy and safety of IV CERA for

treatment of chronic renal anaemia in dialysis patients not currently treated with ESA. J Asso Physicians India. 2014;62:232-6.
29. Vankar SG, Dutta P, Kohli HS. Efficacy & safety of continuous erythropoietin receptor activator (CERA) in treating renal anaemia in diabetic patients with chronic kidney disease not on dialysis. Indian J Med Res. 2014;139:112-6.
30. Canaud B, Mingardi G, Braun J. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. Nephrol Dialysis Transplantation. 2008;23:3654-61.
31. Astor BC, Muntner P, Levin A. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Internal Med. 2002;162:1401-8.

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