Safety and tolerability of prescribed usage of Derise® (Darbepoetin Alfa, Hetero) in symptomatic anemia: A Phase IV Post-Authorization Study

Shubhadeep Sinha
Hetero Drugs
Vamsi Krishna Bandi
Hetero Drugs
Bala Reddy Bheemareddy
Hetero Drugs
Pankaj Thakur (Pankaj.Thakur@heterodrugs.com)
Hetero Group, Clinical Development and Medical Affairs, Hetero Corporate, Hyderabad, India
https://orcid.org/0000-0003-2772-7464
Sreenivasa Chary
Hetero Drugs
Leela Talluri
Hetero Drugs
Sheejith Kakkunnath
Hetero Drugs
Priyanka Das
Hetero Drugs
Srinivasa Sanka
Hetero Drugs

Research article

Keywords: Anemia, Chronic renal failure, Darbepoetin alfa, Post-marketing surveillance,

Posted Date: April 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-23193/v1

Abstract

Background This phase IV, post–authorisation safety & efficacy study evaluated the safety, immunogenicity and tolerability of prescribed usage of Darbepoetin alfa, (DA-α, manufactured by Hetero Biopharma) for the treatment of symptomatic anemia in Indian patients with chronic renal failure.

Methods Adults patients of either gender suffering from anemia associated with chronic renal failure patients were prescribed and treated with DA-α and followed up for 1 year. 503 patients were enrolled into the study, of which 121 patients were evaluated for immunogenicity at the end of treatment phase (up to 24 weeks) and after 1-year (52 weeks after start of treatment) follow up. Safety end points were the incidence of treatment emergent adverse events (TEAEs) and immunogenicity as assessed by anti-drug antibody titers using validated enzyme linked immunosorbent assay (ELISA) methods. Efficacy end point included improvement in the hemoglobin, mean change in Hemoglobin (Hb) levels from baseline to end of treatment (up to 24 weeks). Statistical analyses were performed to explore and analyze details of individual case safety reports of adverse events such as incidence, severity, seriousness, outcome, duration, action taken, and causality relationship of individual adverse event (AE) to the prescribed study drug.

Results 87 AEs were reported in this study and most of them were mild to moderate in intensity. No deaths or serious adverse events (SAEs) were reported in this study. Anti-drug antibodies were not detected in any subject at the end of treatment phase and after 12 months long term follow up period. Baseline mean Hemoglobin value was 8.34 (SD 1.24) g/dL and last visit mean Hemoglobin value was 10.42 (SD 1.28) g/dL. The mean difference between baseline and last visit was 2.10 [2.00, 2.20], statistically significant (p-value <.0001).

Clinical Trial Registry Number: CTRI/2017/04/008338 [Registered on CTRI http://ctri.nic.in/Clinicaltrials/login.php : 12/04/2017]; Trial Registered Retrospectively

Background

Key-points

- Biosimilars improve patient's accessibility to Darbepoetin alfa with potentially low drug prices resulting in reduced treatment cost for patients and healthcare
- Hetero Biopharma Ltd. has developed Darbepoetin Alfa which in this phase IV study showed that it is effective and safe for the treatment of symptomatic anemia in patients with chronic renal failure.

Anemia is almost an inevitable complication of malignant disease, chemotherapy, chronic kidney disease (CKD) and untreated anemia significantly contributes to increased morbidity and reduced quality of life.1 CKD is a global clinical concern across the world, diabetic nephropathy, hypertension, chronic

glomerulonephritis and hypertensive nephrosclerosis are the common causes of CKD in India2. Majority of the patients with stage 5 CKD suffer from anemia3 and reported to have about two fold higher risk of cardiovascular (CV) disease than those without anemia. The reported rates of CKD in India due to undetermined etiology, chronic glomerulonephritis and hypertensive nephrosclerosis in this registry were 16%, 14% and 13% respectively. Indian CKD registry reported close to 48% patients presenting in stage V. Anemia leads to a decrease in oxygen delivery to vital organs, which is initially compensated by increased cardiac output, but may eventually result in maladaptive left ventricular hypertrophy, a well-recognized risk factor for CV disease and all-cause mortality.4 The primary cause of renal anemia is the deficiency of endogenous erythropoietin mainly produced by kidneys,3 progression of renal anemia not only increases the risk of CV disease, but also is an independent risk factor for the deterioration of renal function, causing the vicious cycle known as cardio-renal anemia syndrome. 5 Darbepoetin alfa is an erythropoiesis-stimulating protein with a unique amino acid sequence, greater sialic acid content, longer half-life (74 hours in cancer patients).6 Darbepoetin alfa was originally licensed for treatment of chemotherapy-induced anemia in many regions of the world, including the United States and Europe, based on a weekly 2.25- μ g/kg dose.7,8 Darbepoetin alfa has similar mechanism for erythropoiesis as native & recombinant human erythropoietin (rHuEPO). Because of differences in the pharmacokinetic properties of

darbepoetin alfa and rHuEPO, darbepoetin alfa can be administered less frequently than rHuEPO without changes in efficacy and safety. Darbepoetin alfa proven to achieve significant reductions in RBC transfusion requirements and clinically relevant improvements in fatigue and other patient-reported outcomes. Erythropoietin alfa is the standard of care for treatment of anemia related to CKD undergoing dialysis and not on dialysis. Darbepoetin alfa has 3-fold longer elimination half-life and decreased clearance compared to erythropoietin alfa. This ensures a comparatively reduced number of (Darbepoetin alfa) injections in treatment of anemia in CKD patients. Largescale clinical studies in Europe and the US, which include CREATE9 , CHOIR 10 and TREAT 11, raised questions about correcting almost normal hemoglobin (Hb) levels with ESAs. These clinical studies claimed that targeting higher Hb levels in CKD increases CV risk and probably increases the risk of end-stage renal disease and death12, 13but majority of patients recruited in these studies had diabetes or a high risk of CV disease.

In our Phase-III interventional clinical studies conducted with Darbepoetin alfa (DA-α, manufactured by Hetero Biopharma) previously showed efficacy and safety in improving anemia associated with CKD undergoing dialysis and those not on dialysis(CTRI/2012/07/002835) who were administered DA-α for a period of 12-24 weeks.14,15 Subsequently, after marketing authorization, an observational, phase-IV, active post-marketing surveillance study was conducted as per regulatory requirements and approvals to evaluate safety, tolerability and immunogenicity with long-term usage of DA-α in symptomatic anemia associated with chronic renal failure in Indian patients.

Methods

The study results are presented in accordance with the CONSORT statement.

Study Design

This was an observational, multicenter, prospective, non- interventional post-marketing surveillance study performed at nine centers across India between Jun 2016 to Sep 2018 to evaluate the safety and tolerability of DA-α (manufactured by Hetero Biopharma) in daily medical practice conditions. A total of 503 patients are included in this study to evaluate the safety and tolerability of DA-α in prescribed settings. Clinical information included: patient demography, patient's medical history, concomitant medications, action taken with respect to DA-α, AE details, periodic hemoglobin levels and abnormal laboratory tests results. Dosing frequency was categorized as once weekly (QW) or once every 2 weeks (Q2W). Safety and tolerability data during and after study drug treatment was recorded in the respective post- marketing surveillance (PMS) forms.

This study was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki, 1964 as revised in 2013, Post Authorization Safety Studies (Post Marketing Surveillance study, (PMS)), as per the guidelines of Schedule Y (amended Drug &Cosmetic Act 2013), and Guidelines for Similar Biologics 2012, India along with subsequent amendments and Indian regulatory laws governing biomedical research in human patients. The study was approved by the Drugs Controller General, India (DCGI), CDSCO and subsequently registered with clinical trial registry (CTRI/2017/04/008338) retrospectively. Institutional ethics committee approval was obtained from each participating study center before initiating the study. Although the study was an observational, non- interventional study, for the purpose of good documentation practices written informed consent was obtained from each subject before enrolling them in the study.

Participants

In this study, adult patients of either gender with CKD suffering from renal anemia and clinically indicated to be administered DA-α (manufactured by Hetero Biopharma) or any other patient to be prescribed DA-α (manufactured by Hetero Biopharma) as per prescribing physician’s discretion were enrolled. Major exclusion criteria were pregnant women or lactating patients, reported hypersensitive to study drug substances, patients receiving hormonal agents and therapeutic biologic products.

Efficacy and Safety assessments

The primary end point was safety and secondary endpoint was efficacy. Treatment-emergent adverse events (TEAEs) and immunogenicity were assessed as safety end points. Immunogenicity was assessed by anti-drug antibody titers using validated enzyme linked immunosorbent assay (ELISA) methods. Immunogenicity was evaluated by assessing serum for the presence of anti-darbepoetin alfa antibodies at baseline, end of initial treatment (up to 24 weeks) and one year (52 weeks after start of treatment) after the baseline. Immunogenicity assessment of antidrug antibodies (ADAs) was performed at accredited central laboratory (BAL- II/MOA/039, Electrochemiluminescence immunoassay). Efficacy endpoint included improvement in the hemoglobin, mean change in Hemoglobin (Hb) levels from baseline to end of treatment (up to 24 weeks). Administration of DA-α was made according to the dosage recommended

in the package insert, as per the inclusion and exclusion criteria. All adverse and serious AE's, whether previously known or unknown, were recorded in the PMS and AE form with description of seriousness, severity, action taken, duration, outcome and opinion about causal relationship to DA-α.

Statistical analysis

The targeted sample size was 503 patients prescribed DA-α in daily medical practice conditions in India. Proportions of patients in the safety analysis set with AEs and ADRs were analyzed by patient characteristics using Fisher's exact test. Laboratory HB summarized by treatment group, and summary statistics for change from baseline to end of study & comparison between visits done by paired t-test. Adverse events (AEs) and adverse drug reactions (ADRs) were summarized by system organ class (SOC) and by preferred terms using the Medical Dictionary for Regulatory Activities Terminology (MedDRA v21) endorsed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The grading of the severity of the AE's were done as per common terminology criteria for AE (Common Terminology Criteria for Adverse Events, CTCAE (v4). The causality assessment of the AE with DA-α was done as per the WHO-UMC causality assessment system. The incidence of AEs was compared across the treatment groups using Fisher's exact test. This study gathered the data of 503 DA-α prescribed patients, as per the regulatory requirement. All statistical analysis was performed using SAS® Version 9.4 (SAS Institute Inc., NC, USA).

Results

Patient characteristics

Between June 2016 and September 2018, a total of 503 patient data of post treatment of DA-α in prescribed settings were included in this study to evaluate the safety and tolerability. Of these, a total of 121 patients were evaluated for immunogenicity at the end of treatment and after one year. The PMS form was the primary data collection instrument for the study. All data requested on the PMS were recorded. PMS forms were updated at regular intervals, in every patient visit for treatment and for a week thereafter, to ideally capture the entire duration of DA-α therapy.

Safety evaluation

The causality assessment for adverse events by investigators were most found to be unrelated to DA-α treatment and were attributable to underlying diseases including CKD or it's other complications. A total of 87 patients (17.3%) reported adverse events in this study that were determined to be possibly (8.0%), probably (1.0%), Unclassifiable (0.2%), Unlikely (7.8%) or certainly (0.4%) related to the study drug by the treating investigator. Most of the AEs were reported in SOC (System Organ Class) of Gastrointestinal Disorders 19 (3.8%), Nervous system disorders 27 (5.4%), General disorders and administration site conditions 24 (4.8%) (Fig:2;

Table:2). Out of 87 AEs reported, 3 (0.59%) AEs were severe, 22 (4.37%) AEs were moderate and 62 (12.3%) AEs were mild in intensity. The most frequently reported AEs were headache, pyrexia and pain. A total of 47 AEs were related and 40 AEs were not related to the study drug. Most of the AEs were mild to moderate in intensity. There were no deaths, life threatening and serious adverse events reported in this study.

Immunogenicity Analysis

Overall 121 patients were included for immunogenicity analysis. Out of 121 patients, 111 patients completed initial treatment phase (24 weeks) and 102 patients completed long-term immunogenicity period (52 weeks). Potential immunogenicity is an important safety concern with all recombinant protein therapies. No anti – darbepoetin alfa antibodies were detected in this population of patients receiving DA-α immediately after treatment and after 12 months of follow up period.

Efficacy evaluation

In this DA-α PMS study, of the 503 patients in the effectiveness analysis set, 445 patients with available Hb levels at the same evaluation point were included in the analysis. The baseline mean Hemoglobin value was 8.34 (SD 1.24) g/dL and last visit (24 weeks) mean Hemoglobin value was 10.42 (SD 1.28) g/dL (Fig:1). The mean difference between baseline and last visit is 2.10 [95% CI 2.00, 2.20] with p-value of <.0001. The result of this study shows the significant improvement in the hemoglobin values in patients treated with DA-α (manufactured by Hetero Biopharma) in prescribed settings.

Discussion

Darbepoetin alfa (DA-α manufactured by Hetero Biopharma) is the first long-acting ESA with extended dosing intervals and thus has an advantage over epoetins alfa and beta. This study was conducted to explore the factors that affect the safety and efficacy of long-term usage of DA-α (manufactured by Hetero Biopharma) in treatment of symptomatic anemia associated with chronic renal failure. Patients who were treated with DA-α (manufactured by Hetero Biopharma) could effectively maintain their Hb levels in the target therapeutic ranges and no patients developed antibodies up to 24 weeks (treatment Phase) and after 52 weeks of follow up period. No new safety concerns were identified in the present study. A total of 87 AEs were reported in this study with mild to moderate in intensity. Regarding ADRs classified by SOC, nervous system disorders occurred in 5.4% of patients, general disorders and administration site conditions occurred in 4.8% patients, gastrointestinal disorders occurred in 3.8% patients, respiratory, thoracic and mediastinal disorders occurred in 1.8% patients, Skin and subcutaneous tissue disorders occurred in 0.6% patients, musculoskeletal and connective tissue disorders occurred in 0.4% patients. Earlier, in our phase III safety and efficacy clinical study of DA-α (manufactured by Hetero Biopharma) in patients with anemia associated with chronic kidney disease

(CKD) undergoing dialysis, Hb levels were increased gradually from baseline to the end of 24 weeks, with the mean change in Hb levels of 1.84. In the DA-α group, 25 (39.7%) patients and 32 (50.8%) patients in EPO group experienced at least one mild to moderately severe TEAE during the study period. The most commonly reported TEAEs by SOC were; respiratory, thoracic and mediastinal disorders (14.3%), general disorders and administration site conditions (12.7%), investigations (9.5%), and infections and infestations (7.9%).14 And in renal anemia patients with CKD at the pre-dialysis stage, the mean change in Hb from baseline to 24 weeks of treatment was similar in the DA-α (11.28 g/dL) and EPO (11.02 g/dL) groups. Eight (25.80%) patients in DA-α group and 8 (25%) patients in EPO group experienced at least one mild or moderate in severity TEAE during the study period The most commonly reported events were cough (9.67%), iron binding capacity total decreased (3.22%), oedema peripheral (6.45%), thrombocytopenia (3.22%), and serum ferritin decreased (6.45%). None of the patients in phase III study reported TEAE that was related to the study drug Darbepoeitin alpha 15. Taken together, these results suggest that there is no apparent risk for life threatening or serious adverse events under clinical conditions where DA-α (manufactured by Hetero Biopharma) is prescribed for the management of anemia. DA-α has played an important role in the effective management of anemia and is preferred over epoetins/biosimilar epoetins for patients requiring less-frequent administration of ESAs.16 Generally, darbepoetin is well tolerated, but like other ESAs some patients may develop adverse events following administration of darbepoetin. AE profile of darbepoetin is more or less similar to that of rHuEPO. There is a theoretical concern regarding development of antibodies against darbepoetin leading to loss of its effectiveness; however, long term experience shows no antibodies have been reported against it, possibly because of its protective structural nature.17 Darbepoetin alfa and epoetin-alfa, both proven to achieve significant reductions in RBC transfusion requirements and clinically relevant improvements in fatigue and other patient-reported outcomes18,19,20,21,22 The DREAM-J surveillance study reported safety and effectiveness of long-term use of darbepoetin alfa in nondialysis patients with chronic kidney disease, in the safety analysis set (5547 patients), AEs and ADRs occurred in 44.4 and 7.1% of patients, respectively. In the effectiveness analysis set (5024 patients), mean Hb levels remained between 10.0 and 10.6 g/dL (Weeks 4–156). Three months after darbepoetin administration, patients with Hb ≥ 11 g/dL presented fewer composite renal endpoints than those with Hb < 11 g/ dL ($p = 0.0013$), and the cumulative proportion of renal survival was higher in those with Hb ≥ 11 g/dL vs. Hb < 11 g/dL($p < 0.0001$)23. In another clinical trials of darbepoetin showed greater benefits in terms of quality of life and preserving cardiac and renal functions in Japanese non-dialysis CKD patients.24,25,26

Conclusion

Our study results demonstrate that DA-α (manufactured by Hetero Biopharma) is safe and tolerable in treating patients with anemia associated with chronic renal failure with significant improvement in hemoglobin levels. This data provides a trend of its safety profile and efficacy in real world scenario of prescribed settings and is consistent with the phase-III study and published literature.27,28

Abbreviations

ADAs: antidrug antibodies; ADRs: Adverse drug reactions; AE: adverse event; CDSCO: Central Drugs Standard Control Organization; CKD: chronic kidney disease; CTCAE : Common Terminology Criteria for Adverse Events ; DCGI: Drugs Controller General India; ELISA: Enzyme linked immunosorbent assay; EMA: European Medicines Agency; Hb: Hemoglobin; ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; MedDRA: Medical Dictionary for Regulatory Activities Terminology; PAES: Post-authorization efficacy studies; PASS: Post Authorization Safety Studies; PMS: post- marketing surveillance; QW: once weekly; Q2W: once every 2 weeks; rHuEPO: recombinant human erythropoietin; SOC: system organ class; SAEs: serious adverse events; TEAEs: Treatment emergent adverse events; WHO: World Health Organization; UMC: Uppsala Monitoring Centre

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki, 1964 as revised in 2013, Schedule Y along with subsequent amendments and Indian regulatory laws governing biomedical research in human patients. Institutional ethics committee approval was obtained from each participating study center before initiating the study. The study was an observational, non-interventional postmarketing surveillance (PMS) study based on prescribed usage of the darbepoetin alpha in patients having diseases as per approved indications. As per the applicable regulatory guidelines, written informed consent is not mandatory to be obtained from the subjects in who are being prescribed the marketed study drug in these studies. However, for the purpose of good documentation practices & upholding the ethics considerations, written informed consent was obtained from each subject before enrolling them into the study. The study was registered with the clinical trial registry (CTRI/2017/04/008338) retrospectively.

Ethics committee name and address

1. Institutional Ethics Committee Situated at M/s. King George Hospital, Vishakhapatnam-530002, Andhra Pradesh. ECR/197/Inst/KGH/2013
2. Ethics Committee St. Thereas’s Hospital Erragadda Santhnagar Hyderabad – 500018, Andhra Pradesh. ECR/230/Inst/AP/2013
3. Bodyline Hospital, Institution Ethics Committee opp Annapurna Hall, Nr. Dev Status, Vikas Gruh road, Paldi, Ahmedabad, Gujurat. ECR/476/Inst/GJ/2013
4. Medilink Ethics Committee, Basement Medilink Hospital, Nr. Shyamal Cross Road, 132 ft. ring Road, Satellite, Ahmedabad-380015. ECR/344/Inst/GJ/2013
5. Ethics Committee GSVM Medical College, Opp. CRS Complex GSVM Medical college, Kanpur-208005. ECR/680/Inst/UP/2014
6. Fortis Hospital Ethics Committee 154/9 Bannerghatta Road, Opp IIM-B, Bangalore-560076, Karnataka. ECR/378/Inst/KA/2013

7. Care Hospital Care Convergence Centre, H. No. 8-2-595/2/B, Road No. 10, Banjara Hills, Hyderabad-500034. ECR/94//Inst/AP/2013
8. Ethics Committee Rajiv Gandhi Institute of Medical Sciences & RIMS Government General Hospital Situated at Srikakulam-532001, Andhra Pradesh, India. ECR/492/Inst/AP/2013
9. Institutional Ethics Committee, Jeevan Jyoti Hospital & Research Centre, 1625, Bai Ka Bagh, Lowther road, Allahabad 211003. ECR/285/Inst/UP/2013

Consent for publication

Not applicable

Availability of data and materials

Data supporting the findings are presented within the manuscript and additional datasets used are available from the corresponding author on request.

Competing interests

SD, VB, BB, PT, SC, LT, SK, PD and SS are the employees of Hetero Biopharma Limited, India

and involved from conception of study to the approval of the manuscript. All the authors declare no other competing interests.

Funding

This study was sponsored by Hetero Biopharma Limited, India including the study related materials and study drugs. The study was designed and executed by Hetero Biopharma Limited, India in line with local and international regulatory requirements. The publication of this manuscript is funded by the Hetero Biopharma Limited, all the authors are the employees of the Hetero and were involved in the design of the study and the collection, analysis, and interpretation of data and writing the manuscript.

Authors' contributions:

Concept and design of trial, SD, VB, BB, SC, PT: Overall project management, data collection, statistical analysis, data interpretation and conclusion analysis, drafting of manuscript, revising manuscript: SD, SC, PT, LT, SK, PD, SS, corresponding author: PT. All authors read and approved the final manuscript.

Acknowledgements

Authors would like to thank Darbepoetin investigator group (Dr. Ramesh Chandra, Dr. B. Sudhakar, Dr. Javed M. Vakil, Dr. Bhavin Mehtalia, Dr. Vishal Kumar Gupta, Dr. R. Sreedhara, Dr. P. Vikranth Reddy, Dr. P. Sarat Jyostna, Dr. Anurag Singh) for conducting this study. Authors would also like to thank all the study subjects for their valuable participation in this study.

Author details

[1]Clinical Development and Medical Affairs, Hetero Group, Hetero Corporate, 7-2-A2, Industrial Estates, Sanath Nagar, Hyderabad, Andhra Pradesh, India.

References

1. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst 1999; 91: 1616 – 34
2. Varma PP. Prevalence of chronic kidney disease in India - Where are we heading. Indian J of Nephrology. 2005; 25:133-5
3. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012; 23:1631–4.
4. Salem DN, et al. Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease. J Am Soc Nephrol. 2005; 16:3403-10
5. Silverberg D. Outcomes of anaemia management in renal insufficiency and cardiac disease. Nephrol Dial Transplant. 2003;18(Suppl 2): ii7–12
6. Glaspy J, Henry D, Patel R, Tchekmedyian S, Applebaum S, Berdeaux D, et al. Effects of chemotherapy on endogenous erythropoietin levels and the pharmacokinetics and erythropoietic response of darbepoetin alfa: a randomised clinical trial of synchronous versus asynchronous dosing of darbepoetin alfa. Eur J Cancer 2005; 41: 1140 – 9.
7. US Prescribing information of Aranesp (darbepoetin alfa). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103951s5378lbl.pdf Accessed on 20th January 2020
8. Aranesp (darbepoetin alfa) [summary of product characteristics].Available at: https://www.ema.europa.eu/en/documents/product-information/aranesp-epar-product-pdf Accessed on 20th January 2020
9. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. CREATE investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006; 355:2071–84
10. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. CHOIR investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355:2085–98.
11. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D,Eckardt KU, et al. TREAT investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med.2009; 361:2019–32.
12. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. 2007;369:381–8.

13. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Tonelli M, Garg AX, et al. Meta- analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. Ann Intern Med.2010; 153:23–33.
14. Sinha SD, Bandi VK, Bheemareddy BR, Pankaj Thakur, Sreenivasa Chary, Kalpana Mehta, et al. Efficacy, tolerability and safety of darbepoetin alfa injection for the treatment of anemia associated with chronic kidney disease (CKD) undergoing dialysis: a randomized, phase-III trial [published correction appears in BMC Nephrol. 2019; 20:415
15. Mehta KS, Sinha SD, Vamsi B, Bala Reddy, N R Naidu, P A Thakur, et al. Darbepoetin Alfa Versus Erythropoietin Alfa for Treatment of Renal Anemia in Patients with Chronic Kidney Disease at the Pre-Dialysis Stage: A Randomized Non-Inferiority Trial. J Assoc Physicians India. 2019; 67:62–66
16. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. CHOIR investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355:2085–98.
17. Macdougall IC. Darbepoetin alfa: A new therapeutic agent for renal anemia. Kidney Internationa. Suppl. 2002; 55-61
18. Deicher R, Horl WH. Anemia as a risk factor for the progression of Chronic Kidney Disease. Curr Opin Nephrol Hypertens 2003; 12: 139-43
19. Chandra M, Clemons GK, McVicar MI. Relation of serum Erythropoietin levels to renalexcretory function: evidence for lowered set point Erythropoietin production in chronicrenal failure. J Pediatr 1988; 113: 1015-21
20. Egrie JC and Browne JK. Development and characterization of novel erythropoiesis stimulating protein. Nephrol Dial Transplant 2001; 16 (Suppl 3): 3-13
21. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: Incidence and treatment. J Natl Cancer Inst 1999; 91: 1616 – 34
22. Vansteenkiste J, Pirker R, Massuti B, Fernando Barata, Albert Font, Michael Fiegl, et al. Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy. J Natl Cancer Inst. 2002; 94:1211–1220
23. Tetsuhiro Tanaka, Masaomi Nangaku, Enyu Imai, Yoshiharu Tsubakihara, Masatoshi Kamai, Michihito Wada, et al. Safety and effectiveness of long-term use of darbepoetin alfa in nondialysis patients with chronic kidney disease: a post-marketing surveillance study in Japan Clinical and Experimental Nephrology (2019) 23:231–243
24. Akizawa T, Gejyo F, Nishi S, Iino Y, Watanabe Y, Suzuki M, et al. Positive outcomes of high hemoglobin target in patients with chronic kidney disease not on dialysis: a randomized controlled study. Ther Apher Dial. 2011; 15:431–40
25. Akaishi M, Hiroe M, Hada Y, Suzuki M, Tsubakihara Y, Akizawa T, et al. Effect of anemia correction on left ventricular hypertrophy in patients with modestly high hemoglobin level and chronic kidney disease. J Cardiol. 2013; 62:249–56
26. Tsubakihara Y, Gejyo F, Nishi S, Iino Y, Watanabe Y, Suzuki M, et al. High target hemoglobin with erythropoiesis-stimulating agents has advantages in the renal function of non- dialysis chronic

kidney disease patients. Ther Apher Dial. 2012; 16:529–40

27. Locatelli F, Canaud B, Giacardy F, Martin-Malo A, Baker N, Wilson J. Treatment of anaemia in dialysis patients with unit dosing of darbepoetin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). Nephrol Dial Transplant. 2003;18(2):362-9.
28. Clinical Review of BLA 99-1492/ STN103951 Amgen, : Darbepoetin alfa(ARANESPTM) for the treatment of anemia associated with chronic renal failure. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/103951Orig1s5173PharmR.pdf Accessed on 20th January 2020

Tables

Table 1: Patient demographics

Variable	Gender	N	Mean	Mode	SD	Min/Max	P-value
Age	Male	310.00	50.85	53.00	11.51	23/76	0.4224
	Female	188.00	49.27	48.00	12.12	27/77	
Weight	Male	311.00	60.33	58.00	8.46	36/84.6	0.1413
	Female	192.00	58.19	58.00	9.30	38/93.4	
HB	Male/Female	503	8.34	7.80	1.24	0.9/14.1	-

Table :2 List of Adverse events occurred in CKD Patients Treated with DA-α

Adverse Event	Patients Treated with DA-α N=503, n (%)
Any Treatment-Emergent Adverse Event	87 (17.3)
Gastrointestinal Disorders	**19 (3.8)**
Abdominal Distension	1 (0.2)
Abdominal Pain	1 (0.2)
Abdominal Pain Upper	1 (0.2)
Constipation	4 (0.8)
Diarrhoea	4 (0.8)
Nausea	5 (1.0)
Vomiting	3 (0.6)
General Disorders and Administration Site Conditions	**24 (4.8)**
Asthenia	1 (0.2)
Chills	1 (0.2)
Malaise	1 (0.2)
Oedema Peripheral	2 (0.4)
Pain	7 (1.4)
Pyrexia	13 (2.6)
Investigations	**1 (0.2)**
Blood Pressure Abnormal	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	**2 (0.4)**
Back Pain	2 (0.4)
Nervous System Disorders	27 (5.4)
Dizziness	1 (0.2)
Headache	25 (5.0)
Pain	1 (0.2)
Psychiatric Disorders	**3 (0.6)**
Autism Spectrum Disorder	1 (0.2)
Somnolence	2 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**9 (1.8)**
Cough	2 (0.4)
Nasopharyngitis	2 (0.4)
Pain	1 (0.2)

Adverse Event	Patients Treated with DA-α N=503, n (%)
Rhinorrhoea	1 (0.2)
Sneezing	3 (0.6)
Skin And Subcutaneous Tissue Disorders	**3 (0.6)**
Pruritus	1 (0.2)
Rash	2 (0.4)

Adverse events are classified by System Organ Class [a] Preferred Term as defined by the Med DRA v21, N = number of patients in specified treatment; n = number of patients at specified category

Figures

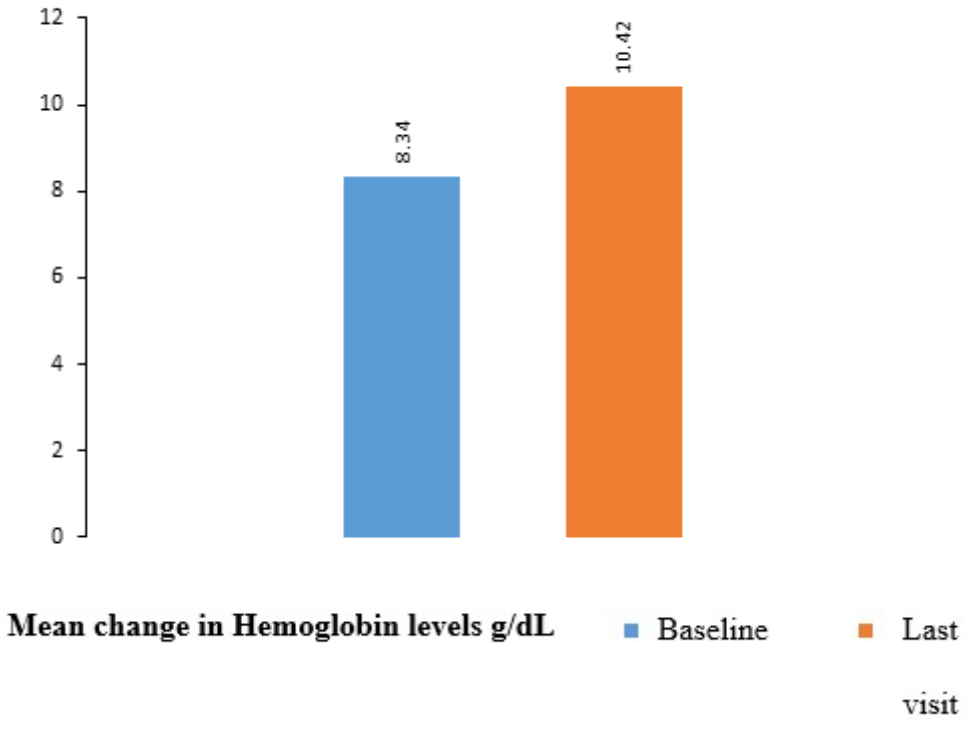

Figure 1

Improvement in the hemoglobin values from Baseline to last visit by DA-α

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010ChecklistP1PMS.pdf