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Desidustat in Anemia due to Non-Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-ND)

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Keywords
Anemia · Chronic kidney disease · Non-dialysis · Hypoxia-inducible factor · Hemoglobin · Hepcidin

Abstract

Background: Desidustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is being developed to treat anemia in patients with chronic kidney disease (CKD) without dialysis dependency. ***Methods:*** In total, 588 patients with a clinical diagnosis of anemia due to CKD without dialysis need and with baseline hemoglobin of 7.0–10.0 g/dL (inclusive) were randomized in a 1:1 ratio to receive either desidustat 100 mg oral tablets thrice a week for 24 weeks or biosimilar darbepoetin subcutaneous injection 0.75 µg/kg once in 2 weeks for 24 weeks. The primary outcome was the change from baseline in hemoglobin to evaluation period of Weeks 16–24. Key secondary outcomes included the number of patients with hemoglobin response, changes in the hepcidin levels, changes in the vascular endothelial growth factor (VEGF) levels, and changes in the lipid and lipoprotein profiles. ***Results:*** Hemoglobin change from baseline to Weeks 16–24 was 1.95 g/dL in the desidustat group and 1.83 g/dL in the darbepoetin group (difference: 0.11 g/dL; 95% CI: −0.12, 0.34), which met prespecified non-inferiority margin (−0.75 g/dL). The hemoglobin responders were significantly higher ($p = 0.0181$) in the desidustat group (196 [77.78%]) compared to the darbepoetin group (176 [68.48%]). The difference of

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change in hepcidin from baseline to Week 12 and Week 24 ($p = 0.0032$ at Week 12, $p = 0.0016$ at Week 24) and the difference of change in low-density lipoprotein from baseline to Week 24 (p value = 0.0269) between the two groups was statistically significant. The difference of change from baseline in VEGF to Weeks 12 and 24 between the two groups was not statistically significant. ***Conclusion:*** Desidustat is non-inferior to darbepoetin in the treatment of anemia due to non-dialysis dependent CKD and it is well-tolerated.

Introduction

Anemia is a frequent complication during the later stages of chronic kidney disease (CKD) [1]. The etiology of anemia in CKD involves reduced erythropoietin (EPO) secretion and several other factors, most notably dysfunctional iron metabolism, mediated via increased hepcidin activity and reduced clearance [2].

Erythrocyte stimulating agents (ESA) with/without iron supplements (oral/intravenous) are currently the mainstay of treatment of anemia in CKD. The major limitation of the use of ESA is that it increases the risk of certain cardiovascular outcomes. An emerging approach in treatment of anemia in CKD patients is the use of agents that stimulate endogenous EPO production.

Hypoxia-inducible factor (HIF) is a key transcription factor that produces a physiologic response to reduced tissue oxygen levels by activating the expression of certain genes [3]. Under hypoxic conditions, HIF-α is stabilized and after nuclear translocation, it dimerizes with the HIF-β subunit, forming heterodimers that activate 100–200 genes, including EPO and other genes involved in iron metabolism. Under normoxic conditions, the activity of HIF is kept in check by HIF-prolyl hydroxylase enzyme. HIF-prolyl hydroxylase enzyme inhibitors are a new class of agents for the treatment of anemia in CKD. These agents work by stabilizing the HIF complex and stimulating endogenous EPO production [3].

In CKD, inflammation and impaired renal clearance increase plasma hepcidin, inhibiting duodenal iron absorption, and sequestering iron in macrophages. These effects of hepcidin can cause systemic iron deficiency, decreased availability of iron for erythropoiesis, and resistance to endogenous and exogenous EPO [4]. HIF prolyl hydroxylase inhibitor (HIF-PHI) may indirectly reduce hepcidin levels, which increases the mobilization of iron stores and may offer benefits in addressing functional iron deficiency associated with ESA hyporesponsiveness [2].

HIF inhibition is also associated with upregulation of vascular endothelial growth factor (VEGF) genes. Since transcription of the VEGF gene is regulated by HIF-1a and HIF-2a binding to hypoxia response elements, there is a clear theoretical concern that HIF stabilization will increase the risk for neoplasia and diabetic retinopathy, resulting in poor outcomes [3].

Desidustat, an oral HIF-PHI developed by Cadila Healthcare Ltd. for the treatment of anemia due to CKD, was found to be well-tolerated in single and multiple doses up to 300 mg in our Phase I study [5]. Desidustat was also found to be effective, safe, and tolerable up to 200 mg in patients with anemia in pre-dialysis CKD in our Phase 2 study [6]. Therefore, Cadila Healthcare Ltd. conducted a randomized Phase 3 study to evaluate the efficacy and safety of desidustat against darbepoetin in the treatment of anemia due to CKD without dialysis need.

Methods

Trial Oversight

This was a Phase 3, multicenter, open-label, randomized, active-control clinical study to evaluate efficacy and safety of desidustat versus darbepoetin for the treatment of anemia in patients with CKD who were not on dialysis. The study was designed and overseen by Cadila Healthcare Ltd.

The study protocol was reviewed and approved by the Ethics Committee and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the guidelines laid down in ICH GCP, CDSCO, and regulations/guidelines of the Government of India. A data safety monitoring board was established to ensure the safety of the subjects enrolled and to review efficacy on an ongoing basis. The committee met periodically to review interim data and recommended continuation of the study.

Patients

Male or female subjects aged 18–80 years with a clinical diagnosis of anemia due to CKD (Stages 3–5) without dialysis need and with a baseline hemoglobin level of 7.0–10.0 g/dL (inclusive) were eligible. The estimated glomerular filtration rate was required to be ≥10 mL/min/1.73 m^2, serum ferritin level was required to be ≥100 ng/mL, and/or transferrin saturation (TSAT) was required to be >20%. Subjects with prior chronic hemodialysis or chronic peritoneal dialysis treatment, intravenous iron within 14 days prior to enrollment, prior exposure to rhEPO analogs less than 4 weeks, and red blood cell transfusion within 8 weeks prior to enrollment were excluded. A complete list of the inclusion/exclusion criteria is provided in the online supplementary material (see www.karger.com/doi/10.1159/000523961 for all online suppl. material). All subjects provided written informed consent.

Trial Procedures

Subjects were randomly assigned in 1:1 ratio to either desidustat or biosimilar darbepoetin (Cresp®; Dr. Reddy's Laboratories). The randomization schedule to ensure treatment balance was gen-

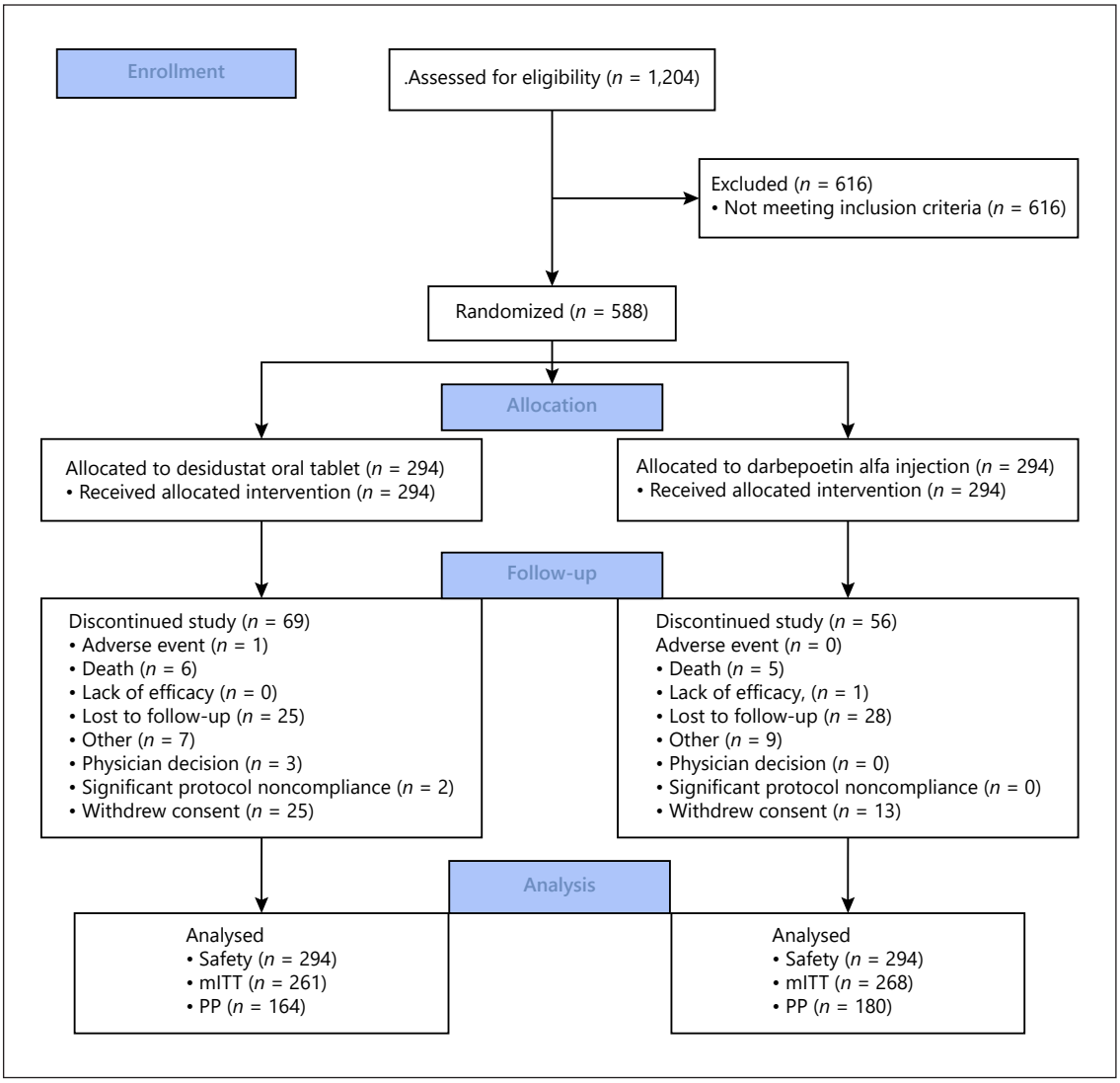

Fig. 1. Patient disposition. A total of six patients in the darbepoetin group experienced fatal events during study. Out of 6 patients, 5 were discontinued due to death, while 1 subject was included in the analysis as he experienced a fatal event after completion of the study.

erated using SAS® software. No stratification was used in the randomization. Subjects received desidustat 100 mg oral tablets thrice a week for 24 weeks or biosimilar darbepoetin 0.75 μg/kg subcutaneous injection once in 2 weeks for 24 weeks as per the package insert. Dose adjustment was permitted from Weeks 4 to 20. An Interactive Web Response System was used for the selection of doses during the study on the basis of hemoglobin level. The dose modification strategy is provided for both the treatment groups in the online supplementary material. For the dose titration and dose selection, the average hemoglobin value assessed using Hemocue was considered, while for primary and secondary endpoint analysis, the central laboratory hemoglobin value was considered.

The serum ferritin, serum iron, and TSAT were assessed at baseline and at regular intervals post-baseline. Accordingly, an oral iron/intravenous supplement was given as per the serum ferritin and TSAT level. A necessary rescue medication (e.g., ESA and red blood cell transfusion) was reserved to be given along with continued treatment with desidustat or darbepoetin in case the hemoglobin level dropped <6.5 g/dL. A safety follow-up was conducted 2 weeks after the end of treatment.

Outcomes

The primary outcome was change from baseline in hemoglobin during evaluation period of Week 16 through Week 24 (Week 16–24). The secondary outcomes included the number of subjects with hemoglobin response (defined as target level of 10–12 g/dL and posttreatment increase of 1 g/dL or more by Week 24), time to achieve target range hemoglobin level of 10–12 g/dL, percentage of time spent in the target hemoglobin range, change in hepcidin levels, change in potassium levels, change in quality of life per SF-36, number (%) of subjects on rescue therapy, change in VEGF, change in the lipid, and lipoprotein profile.

Table 1. Demographics and baseline characteristics (safety analysis population)

	Statistics	Desidustat oral tablet (*N* = 294)	Darbepoetin alfa injection (*N* = 294)	Overall (*N* = 588)
Age, years	Mean ± SD	53.38±13.93	52.16±13.65	52.77±13.79
	Median (min, max)	55 (21, 80)	54 (20, 80)	54 (20, 80)
Gender, *n* (%)	Female	147 (50.00)	145 (49.32)	292 (49.66)
	Male	147 (50.00)	149 (50.68)	296 (50.34)
Race, *n* (%)	Asian	29 (9.86)	27 (9.18)	56 (9.52)
	Filipino	0 (0.00)	1 (0.34)	1 (0.17)
	Indian	265 (90.14)	266 (90.48)	531 (90.31)
Ethnicity, *n* (%)	South Asian	294 (100.0)	294 (100.0)	588 (100.0)
Weight, kg	Mean ± SD	60.92±10.55	62.64±13.38	61.78±12.07
	Median (min, max)	61.00 (40.00, 93.00	61.35 (40.00, 127.40)	61.00 (40.00, 127.40)
Height, cm	Mean ± SD	159.10±9.57	159.67±9.10	159.39±9.33
	Median (min, max)	159.00 (129.50, 193.00)	159.45 (129.00, 184.00)	159.00 (129.00, 193.00)
BMI, kg/m^2	Mean ± SD	24.16±4.27	24.64±5.29	24.40±4.81
	Median (min, max)	24.38 (14.00, 38.40)	24.05 (14.50, 55.20)	24.20 (14.00, 55.20)
Medical history, *n* (%)				
Diabetes mellitus	–	140 (47.62)	145 (49.32)	285 (48.47)
Hypertension	–	250 (85.03)	240 (81.63)	490 (83.33)
Cardiac disorders	–	19 (6.46)	15 (5.10)	34 (5.78)
Laboratory parameters				
Hemoglobin, g/dL	Mean ± SD	8.99±0.78	8.99±0.74	–
Ferritin, ng/mL	Mean ± SD	421.10±526.83	408.55±624.13	–
Iron, µg/dL	Mean ± SD	65.15±29.64	67.60±38.72	–
Hepcidin, ng/mL	Mean ± SD	59.24±50.70	59.46±54.04	–
TSAT, %	Mean ± SD	27.21±12.77	27.13±13.67	–
CRP, mg/L	Mean ± SD	7.57±21.55	6.12±6.78	–
EGFR, mL/min/1.73 m^2	Mean ± SD	21.50±10.49	21.52±10.76	–
Lipids and lipoprotein, mg/dL				
LDL-cholesterol	Mean ± SD	92.60±41.78	93.20±41.00	–
HDL-cholesterol	Mean ± SD	40.60±13.98	40.71±12.20	–
VLDL-cholesterol	Mean ± SD	34.44±19.59	33.26±23.02	–
Total cholesterol	Mean ± SD	158.73±50.49	158.12±48.81	–
Apolipoprotein-A1	Mean ± SD	118.12±27.25	119.83±25.07	–
Apolipoprotein-B	Mean ± SD	89.95±32.07	89.96±31.15	–
Lipoprotein (a)	Mean ± SD	41.10±37.50	44.10±38.79	–
Triglycerides	Mean ± SD	172.08±97.94	166.16±115.10	–
VEGF, ng/mL	Mean ± SD	639.3±604.9	644.4±598.1	–
Potassium, mmol/L	Mean ± SD	4.89±0.81	4.95±0.87	–
Blood pressure, mm Hg				
Diastolic	Mean ± SD	81.09±7.43	80.09±8.06	–
Systolic	Mean ± SD	132.89±13.64	133.16±13.22	–

BMI, body mass index; CRP, C-reactive protein; CKD, chronic kidney disease; max, maximum; min, minimum; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; *N*, number of subjects in the mITT Population in each treatment group; *n*, number of subjects in each treatment group at specific visit; SD, standard deviation.

Statistical Analyses

At least 244 subjects in each of the two treatment groups were required to show non-inferiority of desidustat to darbepoetin at 85% power with one-sided 0.0125 level of significance, assuming a mean difference of 0.7 g/dL and standard deviation (SD) for one group to be 4.5 and that of another group to be 5.0. The non-inferiority margin selected was −0.75 g/dL. Considering a dropout rate of at least 20%, 588 subjects were enrolled with 1:1 allocation.

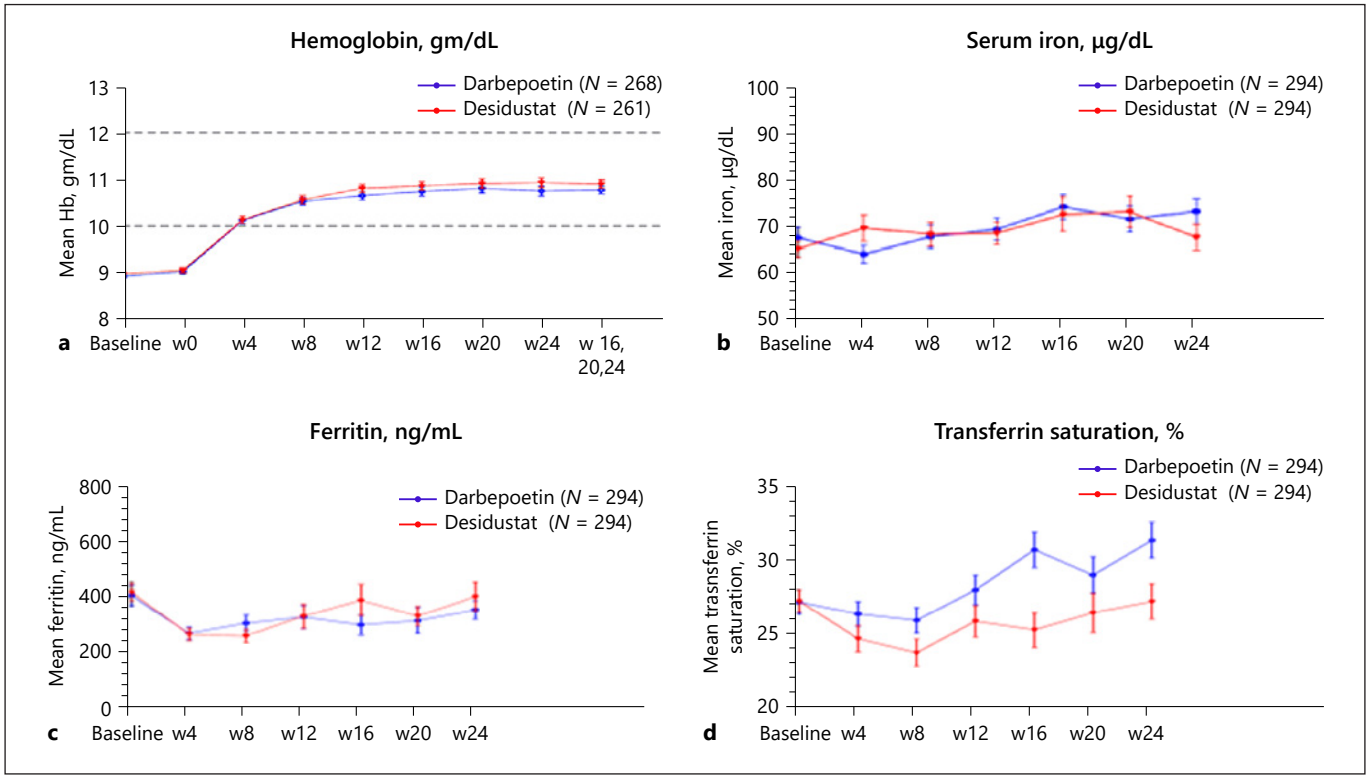

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Fig. 2. a Summary of hemoglobin levels over time (mITT population). **b–d** Serum iron, serum ferritin, and TSAT levels over time (safety population).

The change in hemoglobin from baseline to Week 16–24 between treatments was evaluated using the analysis of covariance (ANCOVA) model with treatment as fixed effect and baseline value as covariate. The two treatment groups were compared using the difference in least-square mean (LSM) and *p* value from the ANCOVA model. Non-inferiority was established if the lower limit of the two-sided 95% confidence interval for the treatment difference (desidustat – darbepoetin) was above −0.75.

The secondary efficacy end point of hemoglobin responders and number of subjects requiring rescue medication were analyzed using the χ^2/Fisher exact test. The quantitative secondary end points of change in hepcidin, potassium, and VEGF were analyzed similar to the primary end point using ANCOVA. For the end point of time to achieve target range, the first occurrence of incidence was taken into consideration. The end points of time to achieve target range and the percentage of time spent in target hemoglobin range were summarized by median and interquartile range and were analyzed using the Wilcoxon test.

Those patients who withdrew from the study due to any reason but had at least one post-baseline efficacy data were included in the modified intent-to-treat (mITT) population for efficacy analysis using the last observation carried forward imputation method for post-baseline missing values. Baseline values were not carried forward for the imputation of missing values.

All primary and secondary efficacy end points were analyzed using mITT population defined as all randomized patients who had taken at least one dose of study treatment and had at least one post-baseline efficacy data. Per Protocol population, defined as all randomized patients who completed the treatment and had not violated protocol that could affect efficacy outcome, was considered for supportive analyses.

Results

Characteristics of Patients

From July 5, 2019, to January 23, 2021, a total of 588 patients were randomly assigned in 1:1 ratio to receive desidustat or darbepoetin at 59 centers in two countries (India and Sri Lanka). Patient disposition is provided in Figure 1. In total, 463 patients completed the study: 225 patients in the desidustat group and 238 patients in the darbepoetin group. Overall, the two groups were well-balanced with respect to baseline characteristics (Table 1).

Outcomes

The LSM change in hemoglobin from baseline to Weeks 16–24 was 1.9452 g/dL in the desidustat group and 1.8332 g/dL in the darbepoetin group (difference: 0.1120

Table 2. Summary of common TEAEs (≥2% either treatment group) by PT (safety population)

	Desidustat oral tablet (*N* = 294), *n* (%)	Darbepoetin (*N* = 294), *n* (%)	Overall (*N* = 588), *n* (%)
Abdominal pain	5 (1.70)	9 (3.06)	14 (2.38)
Constipation	8 (2.72)	5 (1.70)	13 (2.21)
Gastritis	2 (0.68)	7 (2.38)	9 (1.53)
Injection site reaction	0 (0.00)	7 (2.38)	7 (1.19)
Vomiting	10 (3.40)	10 (3.40)	20 (3.40)
Asthenia	9 (3.06)	10 (3.40)	19 (3.23)
Edema	8 (2.72)	5 (1.70)	13 (2.21)
Edema peripheral	16 (5.44)	9 (3.06)	25 (4.25)
Pain	6 (2.04)	12 (4.08)	18 (3.06)
Pyrexia	20 (6.80)	20 (6.80)	40 (6.80)
Hypersensitivity	0 (0.00)	6 (2.04)	6 (1.02)
Dyspnea	6 (2.04)	6 (2.04)	12 (2.04)
Urinary tract infection	11 (3.74)	8 (2.72)	19 (3.23)
Headache	11 (3.74)	12 (4.08)	23 (3.91)
Cough	5 (1.70)	10 (3.40)	15 (2.55)
Hypertension	5 (1.70)	17 (5.78)	22 (3.74)

If a subject had multiple occurrences of TEAE, the subject was presented only once for the corresponding TEAE. *N*, number of subjects in the safety population in each treatment group which was used as the denominator to calculate percentages; *n*, number of subjects in each treatment group in specific category.

g/dL; 95% CI: −0.1224, 0.3464), which met the prespecified non-inferiority margin. A similar result was observed in the supportive analysis conducted in the per population. The mean hemoglobin level in Weeks 16–24 was 10.90 g/dL in the desidustat group and 10.77 g/dL in the darbepoetin group. A plot of hemoglobin values over time for the treatment groups is presented in Figure 2a. These values were within the prespecified reference range of 10–12 g/dL. During the study, 108 patients in the desidustat group and 97 patients in the darbepoetin group overshot Hb level above 12 g/dL. The mean (SD) iron parameters (serum iron, serum ferritin, and TSAT) were comparable in both the treatment groups at baseline. The post-baseline use of iron supplement was as per the iron parameters assessment. The summary plots of serum iron, ferritin, and TSAT are presented in Figure 2b–d, respectively.

The number of hemoglobin responders (defined as achievement of target level of 10–12 g/dL [at average of Weeks 16, 20, and 24] and posttreatment increase of 1 g/dL or more in hemoglobin by Week 24) was significantly higher in the desidustat group (196 [77.78%]) when compared to the darbepoetin group (176 [68.48%]) (p = 0.0181). The difference of change in hepcidin from baseline to Weeks 12 and 24 between the two groups was statistically significant (p = 0.0032 at Week 12, p = 0.0016 at Week 24). The median percentage of time spent in the target hemoglobin range up to Week 24 was similar between the two groups (83.33%, p value = 0.1113). The median time to achieve hemoglobin in the target range was similar (4 weeks, p value = 0.2985) between the two treatment groups. No subject took any rescue medications in the study. The change from baseline (LSM [SE]) in hepcidin was higher in the desidustat group compared to darbepoetin group at Week 12 (−21.48 [4.34] vs. −3.62 [4.16]) and Week 24 (−12.00 [4.48] vs. 7.79 [4.33]). The difference (LSM [SE]) of change from baseline in hepcidin values between the two treatment groups was statistically significant at Week 12 (17.86 [6.01]; p value = 0.0032) and Week 24 (19.79 [6.23]; p value = 0.0016). The change in hepcidin from baseline to Weeks 12 and 24 is presented in online supplementary Figure 1. The number of subjects who used lipid-lowering drugs (atorvastatin and rosuvastatin) during the study was comparable between the treatment groups. The difference of change from baseline to Week 24 between the two treatment groups was statistically significant for low-density lipoprotein (LDL) (p value = 0.0269) but not for high-density lipoprotein, very LDL, total cholesterol, triglyceride, and apolipoprotein. The quality of life score improved at Weeks 12 and 24 in both treatment groups and the difference of change from baseline to Weeks 12 and 24 between the two treatment

groups was not statistically significant. The difference of change in VEGF from baseline to Weeks 12 and 24 between the two treatment groups was not statistically significant. The difference of change in potassium from baseline to Weeks 12 and 24 between the two treatment groups was not statistically significant. The results of secondary efficacy end points in the mITT population are shown in online supplementary Tables 2–4. Similar results of secondary outcomes were seen in supportive analyses.

Safety

Overall, the occurrences of adverse events (AEs) were comparable between the two groups. A total of 141 (47.96) patients reported 288 AEs in the desidustat group and 148 (50.34) patients reported 354 AEs in the darbepoetin group. The majority of AEs were mild, unrelated, and resolved in both the treatment groups. The most frequently reported treatment-emergent AEs (reported in ≥2% of patients in either group) are shown in Table 2. The only AE leading to withdrawal from the treatment was diabetic foot infection reported in 1 patient in the desidustat group. The AE was considered casually not related to the study drug. The incidence of hyperkalemia was similar in both treatment groups (1.02% in the desidustat group vs. 1.7% in the darbepoetin group).

The occurrences of serious AEs (SAEs) were also comparable between the two treatment groups (online suppl. Table 5). The most frequently reported system organ class was infection and infestation: 14 (4.76) patients in the desidustat group and 4 (1.36) patients in the darbepoetin group. There were 6 deaths reported in each of the treatment groups. All death events were considered unrelated to the study treatment.

Among the enrolled patients, 250 (85.03%) in the desidustat group and 240 (81.63%) in the darbepoetin group had hypertension as a concurrent medical condition. There was no clinically significant mean (SD) change from baseline observed in diastolic (desidustat: −0.22 ± 9.33; darbepoetin: 0.11 ± 9.81) or systolic blood pressure (desidustat: −0.94 ± 15.60; darbepoetin: 0.31 ± 14.26) in any of the treatment groups at Week 26. The events of hypertension were reported as treatment-emergent AEs with higher incidence in the darbepoetin group (5.78%) compared to the desidustat group (1.70%). The majority of electrocardiogram results were either normal or abnormal but clinically not significant. One patient in the desidustat group and 6 patients in the darbepoetin group reported clinically significant abnormal electrocardiogram results. Oral temperature, pulse rate, and respiratory rate did not change significantly in any group. There was no trend observed in safety laboratory parameters during the study that affects the safety of the subjects.

Discussion

Desidustat oral tablet was non-inferior to darbepoetin alfa injection in increasing and maintaining hemoglobin levels in the target range (10–12 g/dL) in patients with anemia due to CKD who were not on dialysis. In this study, the hemoglobin levels started rising from Week 4 and remained in the prespecified range of 10–12 g/dL throughout the study in both treatment groups. Moreover, the percentage of hemoglobin responders was significantly higher in the desidustat group compared to darbepoetin group. Desidustat was also comparable to darbepoetin in improving the quality of life of the study patients.

The efficacy results in the current study were in line with the results of the Phase 2 study [6]. The mean (SD) change from baseline in hemoglobin observed in the Phase 2 study at Week 6 was 1.57 (±1.07) g/dL with 100 mg dose. The efficacy results in terms of hemoglobin changes over time and hemoglobin response rate observed in the current study were also comparable with other HIF-PHIs like roxadustat and vadadustat [7, 8].

The hepcidin level decreased significantly at Week 12 and then increased slightly but still remained below baseline level at Week 24 in the desidustat group in the current study. The significant reduction of hepcidin levels from baseline in desidustat compared to darbepoetin along with initial reduction of serum ferritin level is suggestive of increased availability of iron for erythropoiesis which is evident from the corresponding increase in iron level from Week 4 to Week 12 (Fig. 2b). The trend of changes in serum hepcidin observed with desidustat was in line with the trend observed in roxadustat and vadadustat [7, 8].

Desidustat showed significant reduction in LDL-cholesterol from the baseline. In one of the studies, it was observed that HIF-PHI reduced mean LDL-cholesterol in all patients regardless of whether they were taking statins or not [9]. The LDL-cholesterol lowering effect may be mediated by HIF-dependent effects on acetyl coenzyme-A that are required for the first step of cholesterol synthesis, and on the degradation of 3-hydroxy-3-methylglutaryl coenzyme-A reductase, the rate-limiting enzyme in cholesterol synthesis. This may be beneficial, as patients with CKD are more likely to die from cardiovascular

events than from kidney failure. A reduction in the hepcidin and LDL-cholesterol levels from baseline was also observed in the Phase 2 study of desidustat. Therefore, it can be inferred that the effect of desidustat 100 mg oral tablet on hemoglobin level, LDL-cholesterol, and hepcidin level observed in the Phase 3 study consolidates the findings of Phase 2 study.

The safety profile of the desidustat oral tablet was comparable with the darbepoetin alfa injection. There were no new risks or no increased risks seen with the use of desidustat compared to darbepoetin. We assessed potassium levels in the Phase 2 study and in the current Phase 3 study because hyperkalemia was reported as AEs with the use of other HIF-PHIs in the previous clinical studies [10]. No increase in mean potassium level from baseline was observed in any treatment groups in the current study. Moreover, the similar incidences of hyperkalemia in both the treatment groups reported in the current study suggest that desidustat may not have any effect on potassium homeostasis. The incidence of SAEs was 24 (8.16%) in the desidustat group and 18 (6.12%) in the darbepoetin group, however, none of the SAEs was considered to be related to desidustat. The occurrence of SAEs of infection and infestation was higher in the desidustat group compared to the darbepoetin group. This imbalance in the occurrences AEs related to infection and infestation could not be explained. Of the 12 deaths reported in the study, none was considered related to the study treatments. The fatal events in the desidustat group were septic shock, thrombocytopenia, acute coronary syndrome, cardiac arrest, COVID-19 infection, and unknown reasons. Moreover, no changes observed in VEGF from baseline in desidustat imply that desidustat could be used safely in patients with comorbidities of diabetes and cancer without the concern of drug-induced disease progression. Overall, desidustat was well-tolerated in the study. The limitation of the current study included the fact that the study was open-label as the routes of administration were different, lack of racial and ethnic diversity, no subgroup analysis on the basis of CKD staging, and a relatively short follow-up period (26 weeks). In conclusion, desidustat is non-inferior to darbepoetin in the treatment of anemia due to non-dialysis dependent CKD and it is well-tolerated.

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Statement of Ethics

Written informed consent was obtained from all the participants before enrollment. The trial was initiated only after obtaining the approvals of the Ethics Committee and regulatory authority of India (DCGI). The trial was conducted in accordance with the tenets of the Declaration of Helsinki, the International Council for Harmonization guidelines for Good Clinical Practice, and any other applicable local regulations.

Conflict of Interest Statement

Dr. Deven Parmar, Dr. Kevinkumar Kansagra, Dr. Pooja Kanani, Mr. Nitin Sharma, and Mr. Kuldipsinh Zala are employees of Cadila Healthcare Limited. All other authors declared to have no conflict of interest.

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Author Contributions

Dr. Deven Parmar and Dr. Kevinkumar Kansagra were involved in conceptualization, designing, and overseeing the conduct of the trial. Dr. Dhananjai Agrawal, Dr. Deepak Varade, Dr. Hardik Shah, Dr. Alm Nazar, Dr. Jayakumar Krishnan, Dr. Vineet Shukla, Dr. Chinta Ramakrishna, Dr. Mahel Chinthana Bandara Galahitiyawa, Dr. Sidhharth B. Mavani, Dr. Sunil Rajanna, Dr. Petkar Jikki, Dr. Shamila De Shilva, Dr. Vivek Ruhela, Dr. Parshottam Govindbhai Koradia, and the members of the Study Investigator Group (i.e., Dr. Jitendra Kumar Falodia, Dr. Sanjeev Gulati, Dr. L.K. Jha, Dr. Alok Jain, Dr. Ashok Kumar Sharma, Dr. Samir Govil, Dr. Rana Gopal Singh, Dr. Sonal Sanjiv Dalal, Dr. Saurin Pinakin Dalal, Dr. Jyostna Dinesh Zope, Dr. Nagesh Aghor, Dr. Sanjay Arunrao Mundhe, Dr. Avinash Ignatius, Dr. Architkumar Gautambhai Patel, Dr. Harshalkumar Kamleshbhai Joshi, Dr. Dilipkumar Pahari, Dr. Saubhik Sural, Dr. Sanjay Srinivasa Murthy, Dr. Parthasaradhi S.V., Dr. Manisha Sahay, Dr. Sree Bhushan Raju, Dr. Mayoor Vasant Prabhu, Dr. Venkata Krishna Reddy S., Dr. Krishna M.V.S., Dr. Vikas Makkar, Dr. Rupen Panchal, Dr. Vinant Bhargawa, Dr. Prakash Khetan, Dr. Govind Kasat, Dr. Tapas Ranjan Behera, Dr. Ravi Bansal, Dr. Niranjan M.R., Dr. Sandeep Gupta, Dr. Rajan Isaac, Dr. Vinod Baburajan, Dr. Ajay Pal Singh, Dr. D.K. Sinha, Dr. Vidyasagar Korla, Dr. Umesh Godhani, Dr. Nitin

Agrawal, Dr. Umesh Gupta, Dr. Vipul Gattani, Dr. Prabhat Kumar Agrawal, Dr. Pradeep Shenoy, and Dr. Vibhanshu Gupta) who enrolled study participants at their respective study sites. Dr. Pooja Kanani was responsible for data interpretation. Nitin Sharma was involved in overall project management. Kuldipsinh Zala was involved in manuscript writing.

Data Availability Statement

The limited data that support the findings of this study are included in the article and its online supplementary file. Further inquiries can be directed to the corresponding author.

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