zydus
Dedicated To Life

PRODUCT MONOGRAPH DESIDUSTAT

For anemia in CKD patients

OXEMIA™

Desidustat 25/50mg tablet

Let freedom flow

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1. Introduction: Disease Burden of Chronic Kidney Disease Globally and in India

Chronic kidney disease (CKD) is a leading global public health challenge with an estimated prevalence of 13.4% (11.7-15.1%) worldwide.[1] In India, deaths from CKD increased from 0.59 million in 1990 to 1.18 million in 2016. Andhra Pradesh, Odisha, Maharashtra, Goa, and Tamil Nadu reported an exceptionally high burden.[2]

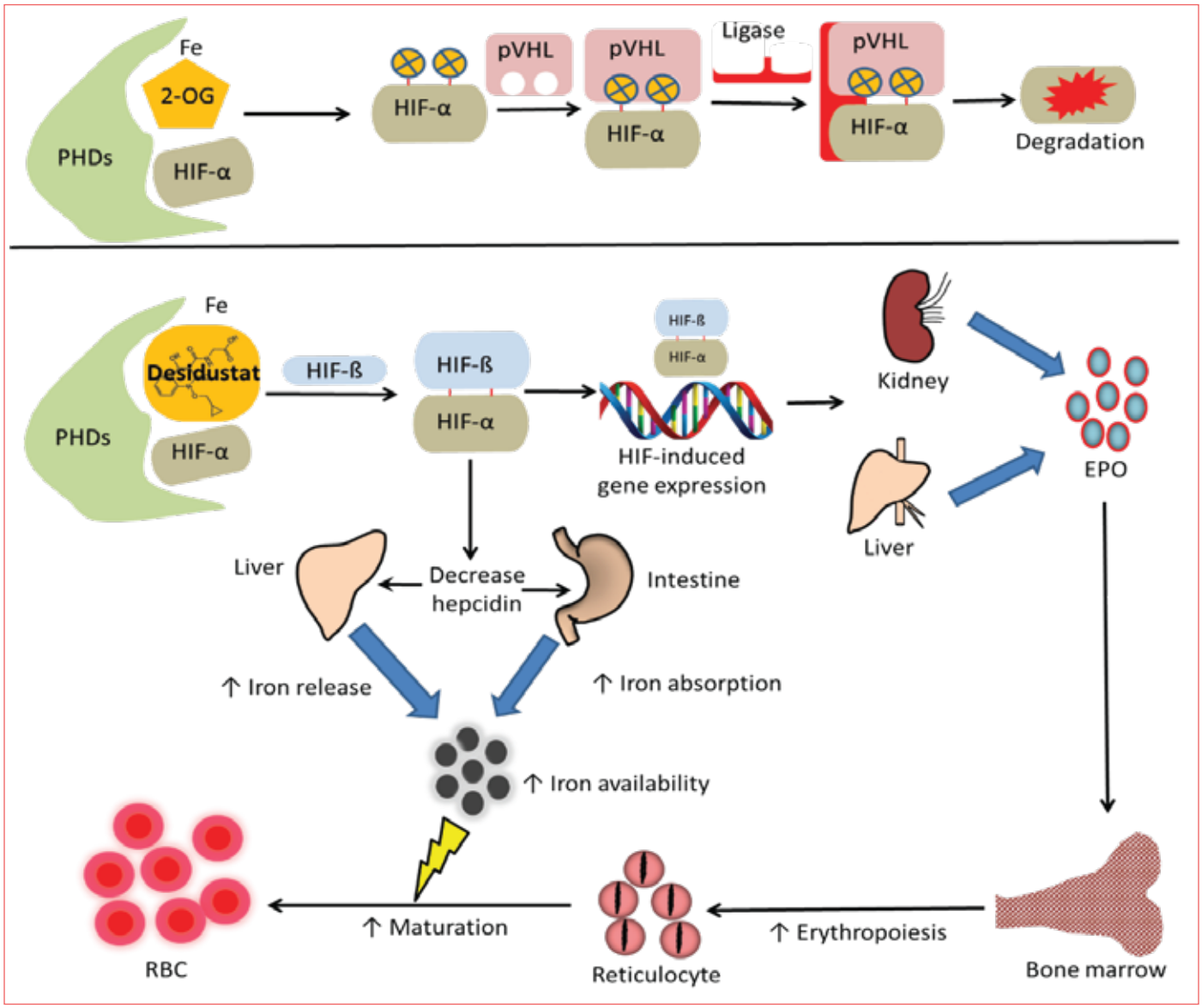
The global estimated prevalence of end-stage renal disease (ESRD) patients needing renal replacement therapy is between 4.902 and 7.083 million.[1] In India, owing to its growing population and ongoing demographic transitions, the rising incidence of CKD will likely constitute significant problems for both healthcare and the economy in the years to come.[3] The age-adjusted incidence rate of ESRD in India is estimated to be 229 per million population, with >100,000 new patients entering renal replacement programs annually in India. However, only 10% of the Indian ESRD patients receive renal replacement therapy, owing to inadequate resources. Therefore, community-based screening programs like Screening and Early Evaluation of Kidney Disease Project (SEEK) must help early detection of kidney disease and generate data to determine the prevalence and risk factors for CKD in India.[4] The increasing prevalence of diabetes mellitus, hypertension, obesity, and aging contribute significantly to the global surge in CKD, and in many countries, CKD is now among the top five causes of death.[1,3]

Kidney disease-related anaemia, a common complication of ESRD, correlates well with exalted morbidity, mortality, and healthcare costs. Anaemia begins to manifest when eGFR falls below 60 mL/min/1.73 m^2 (Stage 3).[5] The National Health and Nutrition Examination Survey (NHANES) analysis pronounced that 15.4% (~4.8 million people) had anaemia of CKD, and prevalence of anaemia was 17.4%, 50.3%, and 53.4% in CKD Stages 3, 4, and 5, respectively.[6] India has the highest prevalence of anaemia globally at 39.86% which increased from 66.6% at Stage 3 to 94.7% at Stage 5.[7,8]

For patients worldwide with CKD who are not undergoing dialysis, a delayed referral to nephrologists and concerns regarding the safety of erythropoiesis-stimulating agents (ESAs) could let anaemia remain undertreated for a prolonged period.[9] Increased healthcare costs and worsening quality of life are the other issues of concern in India. Anaemia is associated with an increased risk of cardiovascular comorbidities, prolonged hospital stays, reduced quality of life, and activity impairment.[10]

2. CKD-induced Anaemia: Pathophysiology

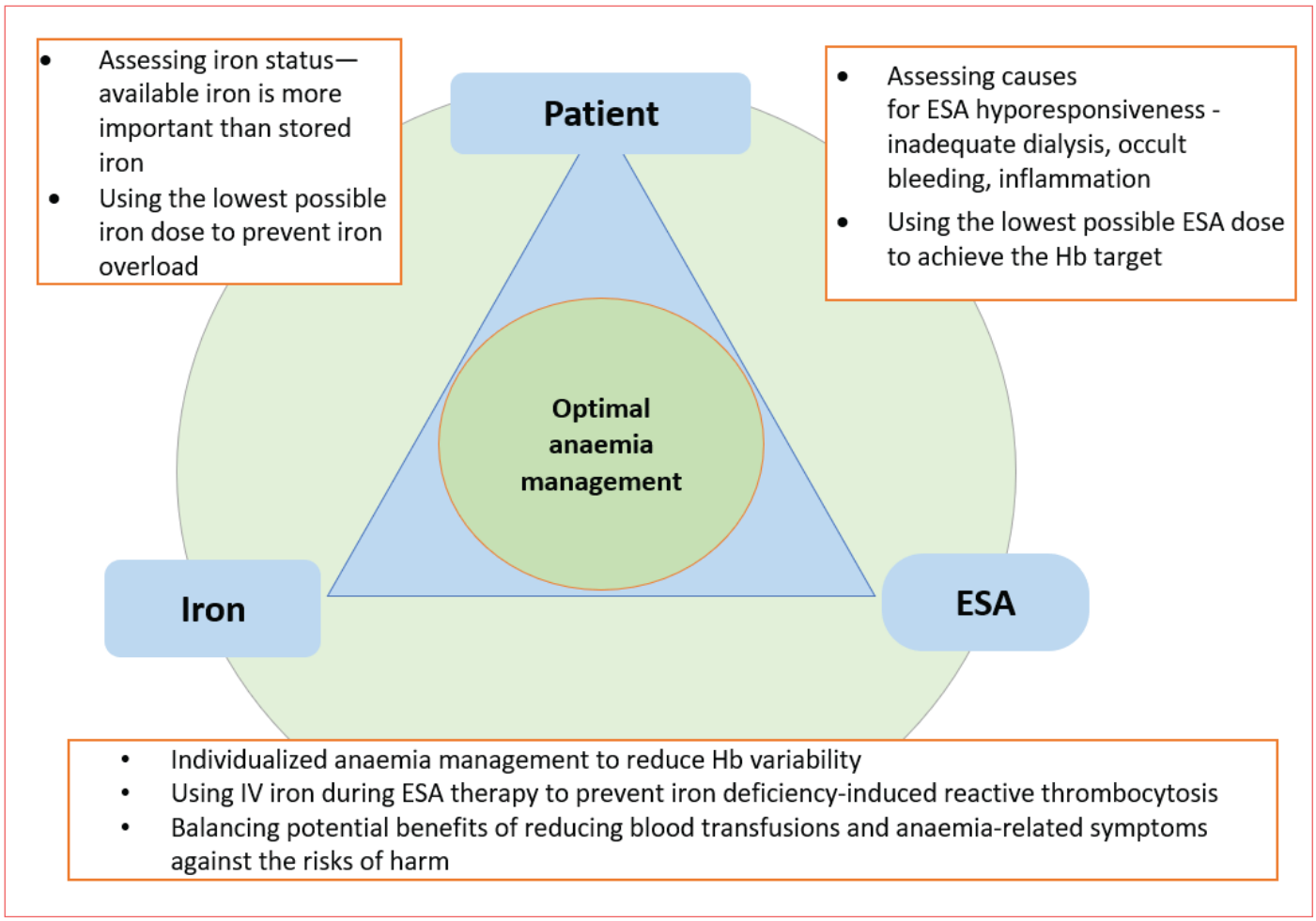
Figure 1: HIF-PHIs Improve Efficient Erythropoiesis by Inhibition of Prolyl Hydroxylase[11]



3. Management of CKD-induced Anaemia: Current Treatment Strategies

Oral or intravenous (IV) iron, erythropoiesis-stimulating agents (ESAs) (IV and subcutaneous), and red blood cell (RBC) transfusion comprise the current standard of care for anaemia of CKD, each of which has inherent problems and varying effectiveness.

Figure 2: Interaction of Patient, Erythropoiesis-Stimulating Agent (ESA), and Iron in the Management of Anaemia (in CKD)[12]



4. A Glimpse into the Current Clinical Practice Guidelines of Anaemia in CKD

Until recently, the safety of various iron formulations in CKD patients has been evaluated only in a few large-scale randomized trials; thereby, obscurity prevails in the most favorable measures to manage iron deficiency. The Kidney Disease Improving Global Outcomes (KDIGO) workgroup guidelines (2012) recommend balancing the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anaemia-related symptoms against the potential risks of iron supplementation. If the transferrin saturation (TSAT) is ≤30% and the serum ferritin is ≤500 ng/mL, KDIGO recommends a trial of iron repletion for adult patients with CKD and anaemia. The European Renal Best Practice (ERBP) guideline (2013), on the other hand, recommends a trial of iron repletion for TSAT levels of <20% and ferritin levels of <100 ng/mL with the goal of remaining below the ceiling of TSAT of 30% and ferritin of 500 ng/mL during supplementation.[13] The KDOQI (2015) guidelines recommends iron repletion to maintain TSAT levels >20% and ferritin >100 ng/mL during ESA treatment.[14] The most recent guidelines from the National Institute for Healthcare and Excellence (2015) and the Renal Association (2017) increased the ferritin ceiling to 800 ng/mL during iron supplementation considering the more recent evidence that many patients with CKD have ferritin levels >500 ng/mL.[13]

5. Unmet Needs with Current Therapy, Newer Treatment Options and Emerging Roles for Hypoxia-inducible Factor Prolyl Hydroxylase Inhibitors

There are many perils associated with IV iron, including oxidative stress that could lead to a higher risk of infection, atherosclerosis, and hospitalization. IV iron at high doses led to an increased risk of mortality and CV events. Rare cases of anaphylaxis have also been reported with IV iron formulations.[13,16] Labile iron in IV formulations generated an increased risk of hypotension, headaches, or hypersensitivity reactions.[15]

There have been well-documented evidences of the pitfalls of recombinant erythropoietin (EPO) with regard to serious cardiovascular and cerebrovascular outcomes, thromboembolic events, tumour progression, and increased mortality.[17] ESA hyporesponsiveness with ESA therapy may be predictive of less stable haemoglobin levels.

The risks associated with use of both IV iron and ESA therapy could complicate current treatment options for frail elderly patients with CKD, who have an increased mortality risk, and patients with multiple comorbidities, such as inflammation, type 2 diabetes, or cancer, hospitalized patients, and kidney transplant recipients, who often have reduced responsiveness to iron and/or ESA therapy and may have an increased risk of adverse outcomes with these agents.[16]

Iron deficiency and/or insufficient iron bioavailability emerges as a major limiting factor in the effectiveness of ESA therapy which has become the mainstay of anaemia therapy in CKD patients.[12]

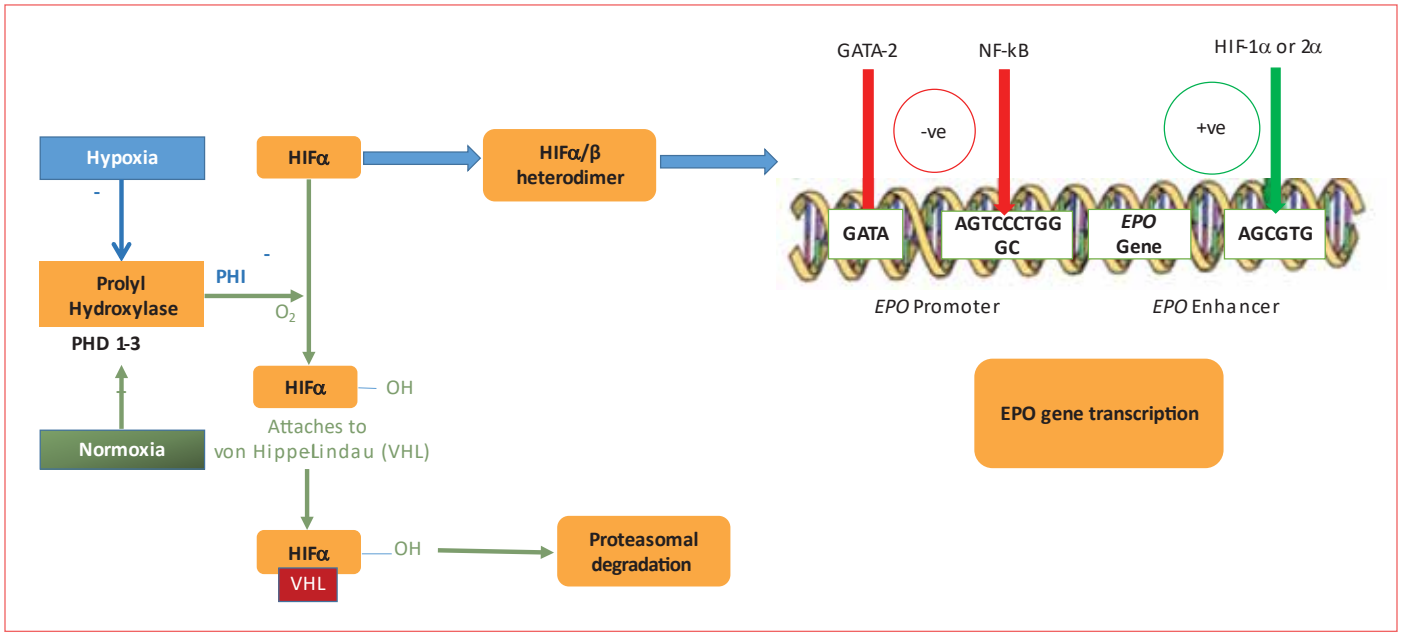
The newer therapies include soluble ferric pyrophosphate (SFP), EPO mimetic peptides, and hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). SFP slowly delivers iron via dialysate and replaces 5-7 mg of iron lost during each treatment to maintain iron balance and treat iron deficiency in hemodialysis patients. On entering the blood, SFP binds immediately to apo-transferrin, goes directly to the bone marrow, stabilizes haemoglobin concentration without increasing serum ferritin, and reduces ESA usage by 35%. The erythropoietin mimetic peptides are still in the development phase, and both *in vitro* and *in vivo* studies have shown encouraging results.

HIF-PHD inhibitors (HIF-PHIs) are a novel class of drugs that have been developed for the treatment of anaemia. They selectively inhibit hypoxia inducible factor prolyl hydroxylases (HIFPH) thereby stabilizing HIF. HIF-PHIs promote erythropoiesis primarily through increased endogenous EPO production, increased transferrin production, and decreased hepcidin. There are five HIF-PHIs that have completed phase III trials and are now being marketed and prescribed in clinical practice in Japan: daprodustat, roxadustat, vadadustat, molidustat, and enarodustat.[18] Desidustat has completed phase III trials (DREAM-ND - ClinicalTrials.gov Identifier: NCT04012957) and (DREAM-D ClinicalTrials.gov Identifier: NCT04215120).

6. Development of Hypoxia-inducible Factor Prolyl Hydroxylase Inhibitors Hypoxia Inducible Factor (HIF) - What is it?

HIF, a critical intracellular modulator of hypoxia-induced reactions and first discovered in the 1950s, comprises two different subunits, alfa and beta chains. The alfa chains are all oxygen sensitive and have 3 main forms (HIF-1α, HIF-2α and HIF-3α), whereas the beta chains are constitutively expressed (also known as the aryl hydrocarbon nuclear translocator (ARNT). Both HIF-1α and HIF-2α together with ARNT form HIF-1 and HIF-2 transcription factors respectively. HIF-α subunits are immediately degraded under normoxic conditions. HIF2 α plays an important role in regulating erythropoiesis through 3 different mechanisms as shown by previous studies: EPO production, iron absorption, and hepcidin suppression.

Figure 3: Role of HIF in Anaemia and its Regulation[16]



Once HIF-2 α activation is triggered by hypoxia, the expression of EPO is facilitated which in turn stimulates erythropoiesis in bone marrow. HIF-2 α also enhances the enteral iron absorption by boosting production of divalent metal transporter 1 and duodenal cytochrome B, improving iron transportation from the intestinal lumen to the enterocytes. Additionally, it inhibits hepcidin production which suppresses iron uptake and mobilization. This enables mature erythrocytes to be produced for oxygen delivery to mitigate the hypoxia in tissues. HIF-2 α is quickly hydroxylated by prolyl hydroxylase enzymes (PHD) and then degraded through uquibitination by proteasomes, stopping the downstream reactions. In CKD patients, there is a discrepancy between oxygen supply and demand in the kidneys, disturbing the hypoxia-induced signaling in renal EPO-producing cells. Inhibition of PH will restore the HIF-2 α pathway and stimulate erythropoiesis in CKD patients, improving renal anaemia. HIF-PHI has been developed and put into clinical trials to test its efficacy and safety in CKD patients.[19,20]

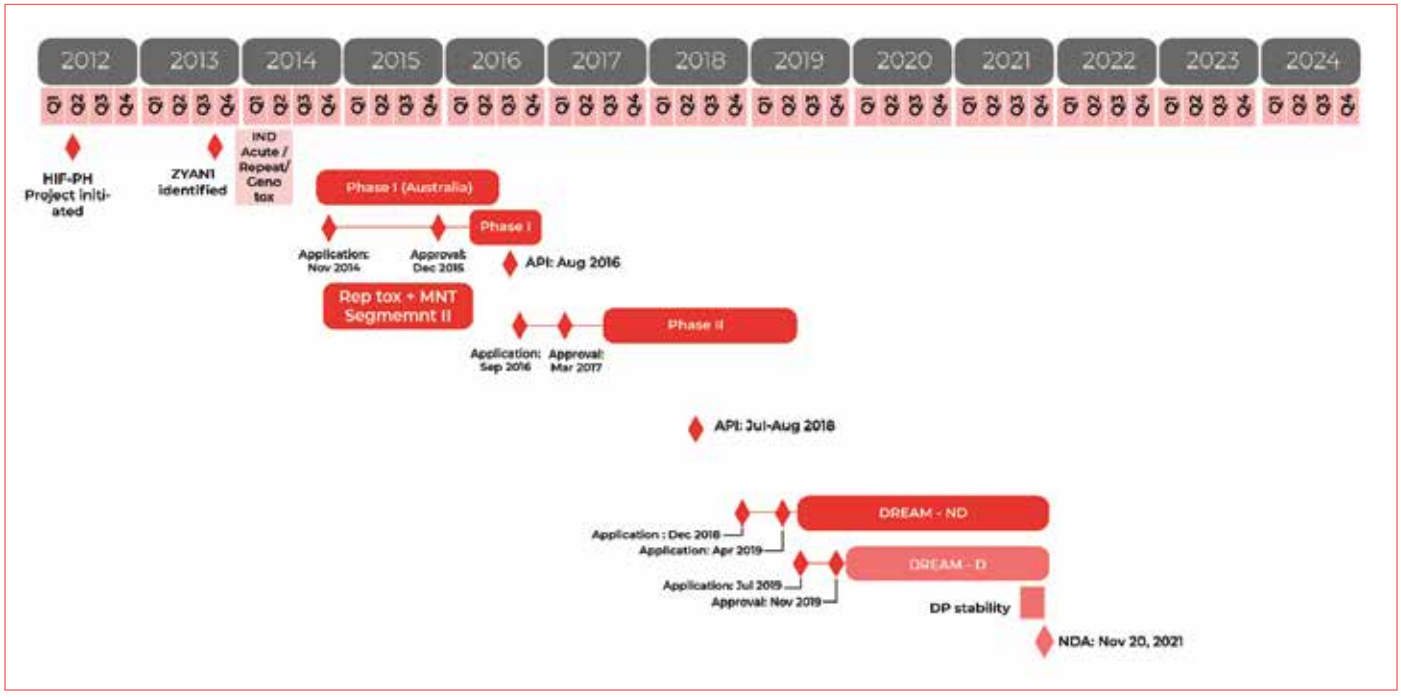
Rationale for Developing HIF-PHI

HIF-PHIs stimulate erythropoiesis in a dose-dependent manner and have consistently shown clinical efficacy in phase 2 and 3 studies in both non-dialysis-dependent (NDD) and dialysis-dependent (DD) CKD anaemia patients.[21] HIF degradation is prevented by the inhibition of prolylhydroxylases leading to increase in endogenous EPO concentration within the physiological range, rather than the pharmacological levels achieved by current ESAs. The rate of adverse events related to the high EPO levels should therefore be expected to be lower than with ESAs. Potential beneficial effects of HIF were seen in pre-clinical and early clinical studies such as an improved iron utilization, HDL and LDL lowering effect, ischemia protection and a protective effect on CKD progression, improved neo-vascularization or better blood pressure control.[15] These These aforesaid benefits are seen because HIF also modulates many other non-erythropoietic genes. However, tumor progression, enhanced vascular calcification, enhanced growth of renal cysts, worsening of retinopathy, or an increase in pulmonary artery pressure are the adverse effects observed due to the modulation of other genes with this new class of drugs. Moreover, it is not known if prolyl-hydroxylase inhibitors inhibit other di-oxygenases beyond HIF-PHIs. Data from large phase III trials are yet to be published and should hopefully provide some insights in this regard.[15]

7. An Introduction to Desidustat: A Peek into the Development Journey

Desidustat is a new therapeutic approach to treat anaemia secondary to chronic kidney disease (CKD). Structurally, desidustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that stimutlates erythropoiesis by stabilizing hypoxia-inducible factor (HIF) via prolyl hydroxylase inhibition.

Figure 4: Development Journey of Desidustat

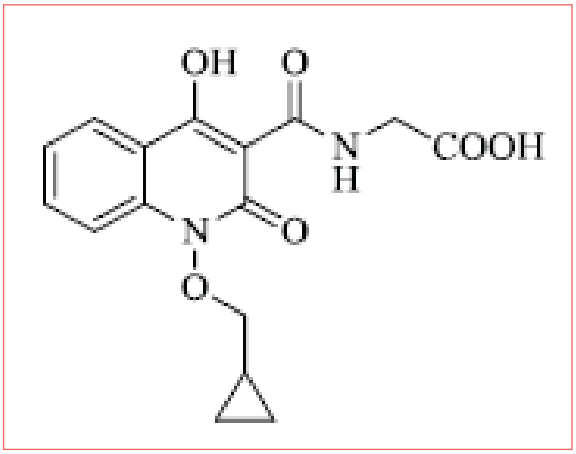


7.1 Desidustat: Physical and Chemical properties

Chemical Name	Glycine, N-[[1-(cyclopropylmethoxy)-1,2-dihydro-4-hydroxy-2-oxo-3-quinolinyl]carbonyl]
Zydus Cadila Compound Code	ZYAN1
International Nonproprietary Name	Desidustat
Molecular formula	$C_{16}H_{16}N_2O_6$
Molecular Weight	332.31 g/mol
Physical Form	White to off white colored round shape uncoated biconvex tablet **having plain surface on both sides**

Figure 5: Structural Formula of Desidustat

Structural Formula



Desidustat: Formulation

Each uncoated tablet contains:

Desidustat	**25 mg, 50 mg**
Excipients	**q.s.**

Inactive ingredients in the tablet are microcrystalline cellulose, lactose, croscarmellose sodium, hypromellose, talc and magnesium stearate.

An *in vitro* sensitive liquid chromatography tandem-mass spectrometry (LC–MS/MS) assay was used to thoroughly validate ZYAN1 stability in whole blood and urine. ZYAN1 was found stable in diluted blood matrix under benchtop for 24h, freeze–thaw cycle for four cycles, 97h for processed sample waiting for injection, freezer stability for up to 60 days at -20° C and for 336-343 days at -80° C. (Table 1) In urine matrix, ZYAN1 stability included benchtop stability: 25h, freeze-thaw cycles: four cycles, processed sample's stability: 66h, freezer stability up to 190-191 days at -20° C and 696 days at -80° C. (Table 1)[22]

Table 1: Stability Data of ZYAN1 in Human Blood and Urine[22]						
Stability parameter	Blood mean nominal conc. (ng/mL)			Urine mean nominal conc. (ng/mL)		
	6	3750	100,000 (DQC)	6	3750	100,000 (DQC)
Processed stability (97h at RT for blood and 66h at RT for urine)	6.26 ± 0.08	3990 ± 82.3	—	5.47 ± 0.18	4000 ± 103	—
Reinjection stability (119h at RT for blood and 66h at RT for urine)	6.78 ± 0.11	3780 ± 88	104,000 ± 2040	5.71 ± 0.22	4090 ± 52.0	—
Long-time stability (-20° C) (60 days for blood and 190 days for urine)	5.78 ± 0.82	3870 ± 291	104,000 ± 1900	5.95 ± 0.35	3770 ± 109	96,200 ± 2950
Long-time stability (-80° C) (336 days for blood and 696 days for urine)	5.23 ± 0.13	3470 ± 226	88,100 ± 4350	6.16 ± 0.27	4010 ± 139	106,000 ± 3790
Benchtop stability (4h for blood and 5h for urine)	6.46 ± 0.13	4020 ± 123	110,000 ± 2000	6.38 ± 0.28	4030 ± 61.3	107,000 ± 2500
Benchtop stability (24h for blood and 25h for urine)	6.50 ± 0.18	3980 ± 105	110,000 ± 1370	6.54 ± 0.26	3960 ± 63.1	105,000 ± 2640
Freeze/thaw stability (-20° C, 4 cycle)	6.21 ± 0.29	4030 ± 133	110,000 ± 2480	6.50 ± 0.23	3970 ± 60.2	107,000 ± 2070
Freeze/thaw stability (-80° C, 4 cycle)	6.54 ± 0.11	4000 ± 145	113,000 ± 4280	6.47 ± 0.22	4040 ± 84.6	107,000 ± 2900

Value reported as mean ± SD, *n* = 6 replicates at each level. RT: Room temperature; DQC: Dilution quality control.

8. Desidustat: Pre-clinical Evidences

8.1 Effects on Erythropoiesis

The pharmacodynamic effects of acute (single dose) and chronic (administered on alternate days for 28 days) dosing of ZYAN1 were assessed in normal and 5/6 nephrectomized Wistar rats. Acute treatment with ZYAN1 increased circulating EPO levels (10.3 ± 3.7 and 40.0 ± 8.5-fold rise at 15 and 30 mg/kg, respectively), reticulocyte count (4.2 ± 0.5 and 6.0 ± 0.2-fold rise at 15 and 30 mg/kg, respectively) and stabilized HIF (28% increase at 45 mg/kg) in normal rats (Figure 6). Dose-related pharmacodynamic effects were also seen in nephrectomized rats.[22] Chronic treatment of ZYAN1 in rats with anaemia induced by five-sixth nephrectomy demonstrated increase in hemoglobin (1.9 ± 0.3 and 2.5 ± 0.4 g/dL) and RBC count (10.7 ± 4.0 and 14.0 ± 4.1%) at 15 and 30 mg/kg, respectively (Figure 7). ZYAN1 demonstrated hematinic potential by combined effects on EPO release and efficient iron utilization.[23]

Figure 6: Effect of Acute Treatment of ZYAN1 on a) Plasma EPO, b) % Reticulocyte Count, c) Hepatic HIF-1 and d) Renal HIF-1 in Normal Wistar Rats, e) Plasma EPO, f) % Reticulocyte Count and g) Hepatic HIF-1 in Nephrectomized Wistar Rats.[23]

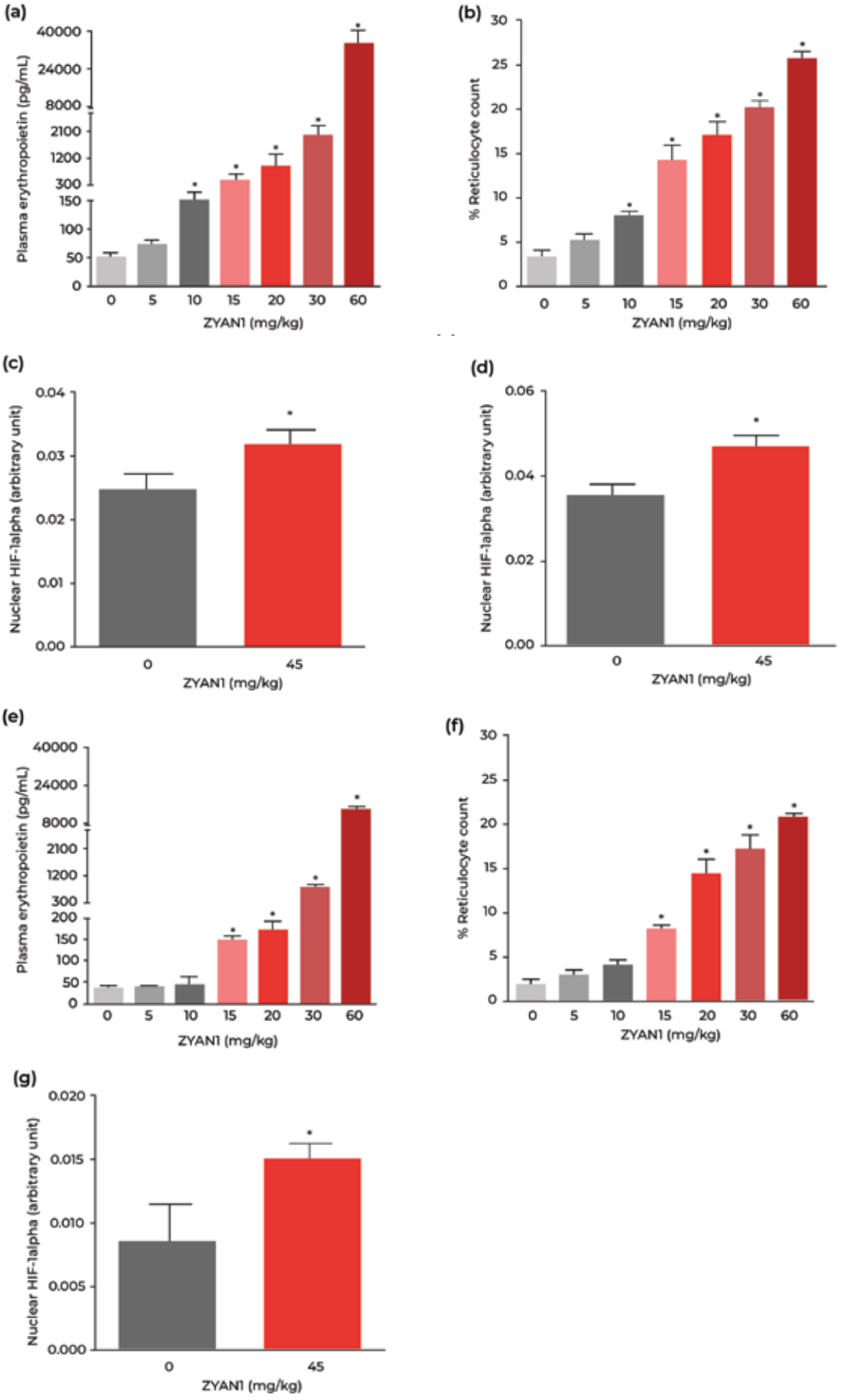
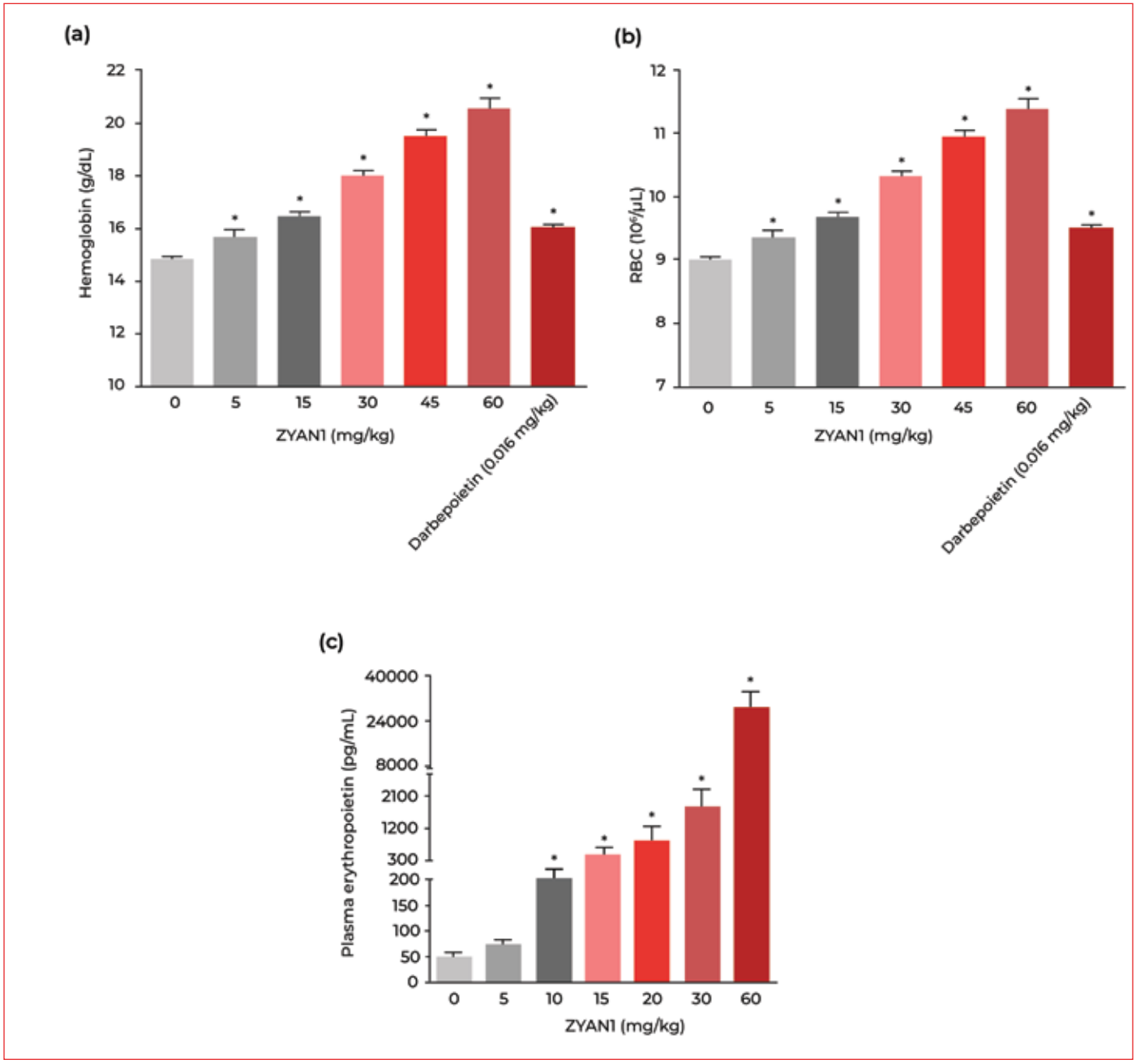


Figure 7: Effect of Chronic Treatment of ZYAN1 on a) Hemoglobin, b) RBC Count and c) Plasma EPO in Normal Wistar Rats.[23]



8.2 Effect on Renal Fibrosis and Inflammation

The effect of desidustat on the inflammatory and fibrotic changes in preclinical models of acute and chronic kidney injury in male Sprague Dawley rats (given desidustat-15 mg/kg, PO) and male C57 mice (CKD induced) treated with desidustat (15 mg/kg, PO, alternate day) treatment for 14 days, was estimated. Results indicated that desidustat prevented increase in serum creatinine, urea, IL-1β, IL-6, and kidney injury molecule-1 (KIM-1), and elevated the EPO levels in rats that were subjected to acute kidney injury (Figure 8). In the CKD induced mice, desidustat treatment caused improvement in serum creatinine, urea, hemoglobin and reduced hepatic and serum hepcidin (Figure 9). Also, desidustat caused a significant reduction in IL-1β, IL-6, myeloperoxidase (MPO), oxidative stress and renal fibrosis which may translate to protective effects in CKD patients.[24]

Figure 8: Effect of Desidustat on (a) Serum Creatinine and (b) Serum Urea, (c) Serum KIM-1, and (d) Serum EPO, after Acute Renal Injury in Male SD Rats[24]

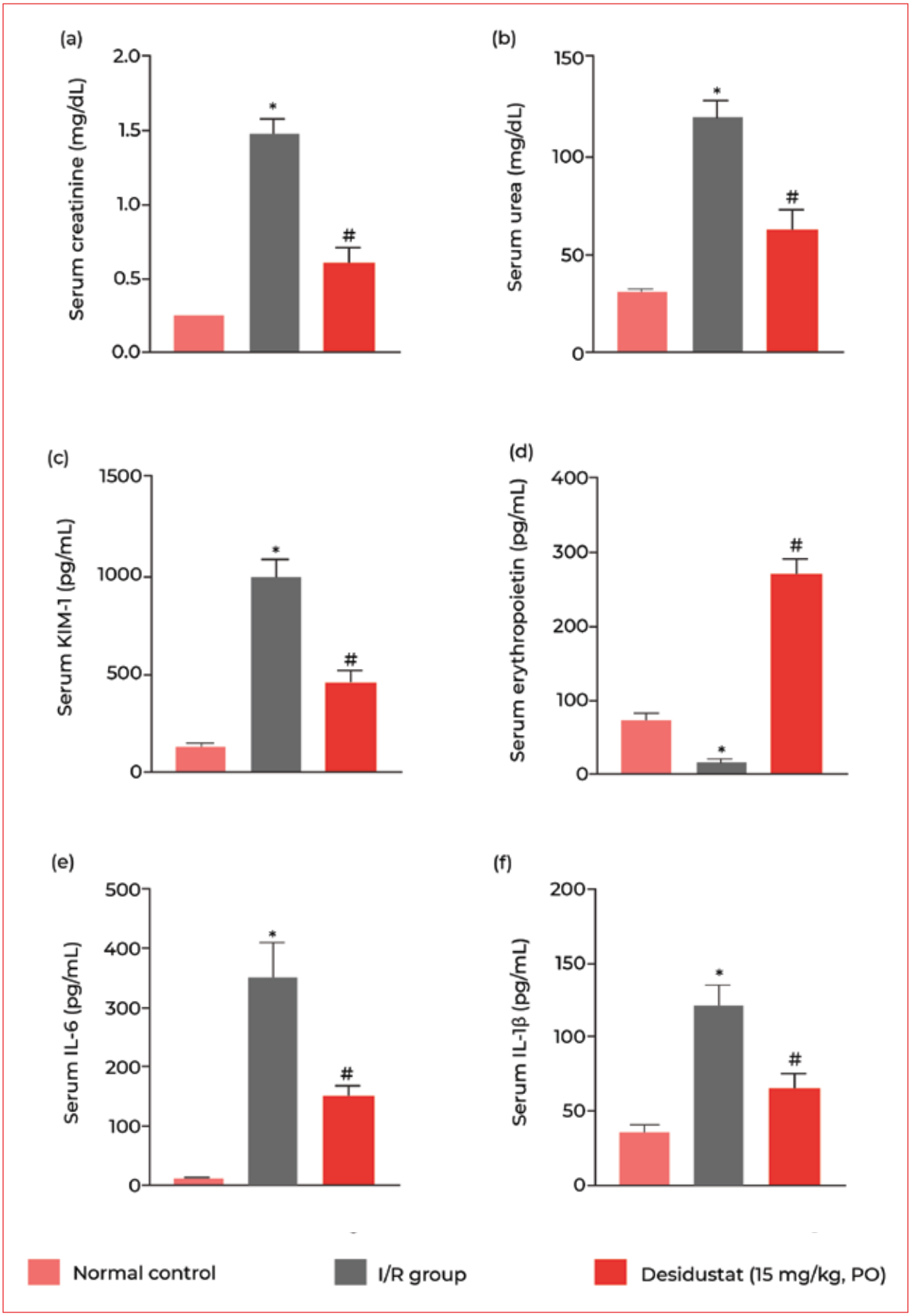
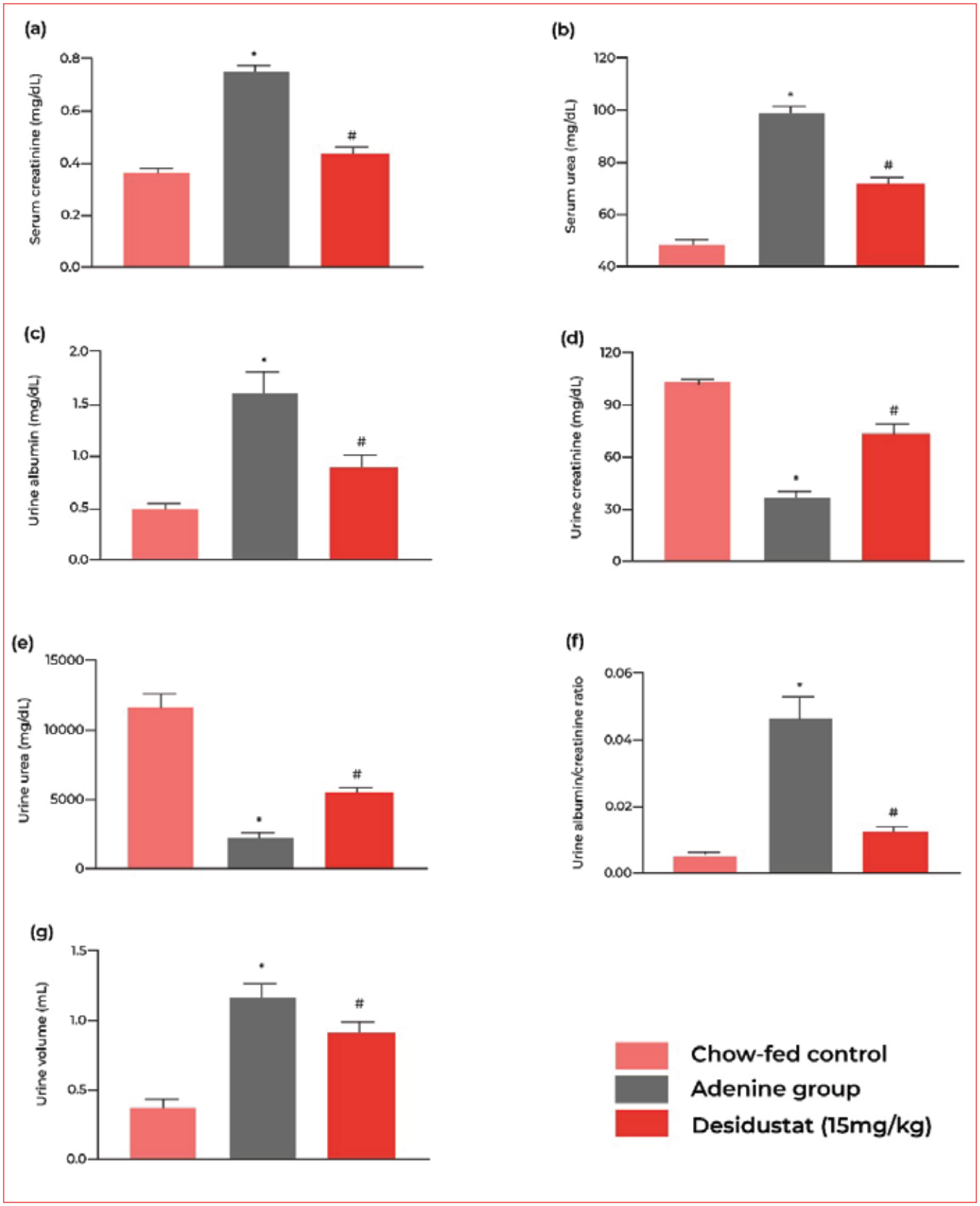


Figure 9: Effect of Desidustat on (a) Serum Creatinine, (b) Serum Urea, (c) Urine Albumin, (d) Urine Creatinine, (e) Urine Urea, (f) Urine Albumin/Creatinine Ratio, (g) Urine Volume, in Adenine-induced Renal Fibrosis in C57 Mice[24]



8.3 Preclinical Safety and Toxicity Evaluation of Animal Toxicology or Pharmacology Carcinogenesis

The carcinogenicity study of desidustat was conducted using alternate day dosing regimen by oral gavage for a period of 24-months in Wistar rats. No evidence of carcinogenicity was noticed in rats following oral administration of desidustat for a duration of 2 years at doses up to 20 mg/kg in males and 30 mg/kg in females (approximately 1-2 times the maximum recommended human dose (MRHD) for treating anaemia in patients with chronic kidney disease on mg/kg basis). Desidustat at highest tested dose levels did not enhance mortality.

Mutagenesis

Desidustat did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Desidustat was not mutagenic in the Ames test and did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo.*

Impairment of fertility

No adverse effects on male or female fertility were identified in rats administered desidustat orally at doses up to 30 mg/kg (2 times the MRHD for treating anaemia in patients with chronic kidney disease on mg/kg basis) prior to and during mating and early pregnancy.

9. Clinical Evidences of Desidustat

9.1 Phase I studies

The phase I study of ZYAN1 was a randomized, double-blind, placebo-controlled study (Australian New Zealand Clinical Trials-Registry trial ID ACTRN12614001240639) conducted to evaluate the safety, tolerability and pharmacokinetics following oral administration in healthy volunteers (100 subjects). The study involved three parts: part I—single-dose study with ZYAN1 10, 25, 50, 100, 150, 200, and 300 mg (n = 56); part II—multiple-dose study with every other day dosing of ZYAN1 100, 150, 200, and 300 mg (n = 32); and part III—sex and food effect study with ZYAN1 150 mg (n = 12; open-label) (Figure 10). ZYAN1 was safe and well-tolerated in healthy volunteers following single escalating oral doses (10–300 mg) and multiple (given once every 2 days) escalating oral doses (100–300 mg) (Figure 11,13). Over the studied 30-fold dose range of ZYAN1, both the maximum concentration (Cmax) and area under the curve (AUC) parameters showed an almost dose-proportional increase (Figure 12). The mean elimination half-life (t1/2) of ZYAN1 ranged from 6.9 to 13h with negligible accumulation. The time to maximum plasma concentration (T_{max}), C_{max}, AUC values were decreased in fed conditions as compared with the fasting conditions after administration of ZYAN1. The mean serum EPO Cmax values showed dose response (i.e., 6.6 and 79.9 mIU/L for 10 and 300 mg ZYAN1 doses, respectively), thereby demonstrating the pharmacodynamic effect of ZYAN 1.[25]

Figure 10: Figure 10: Phase I Study Flow[25]

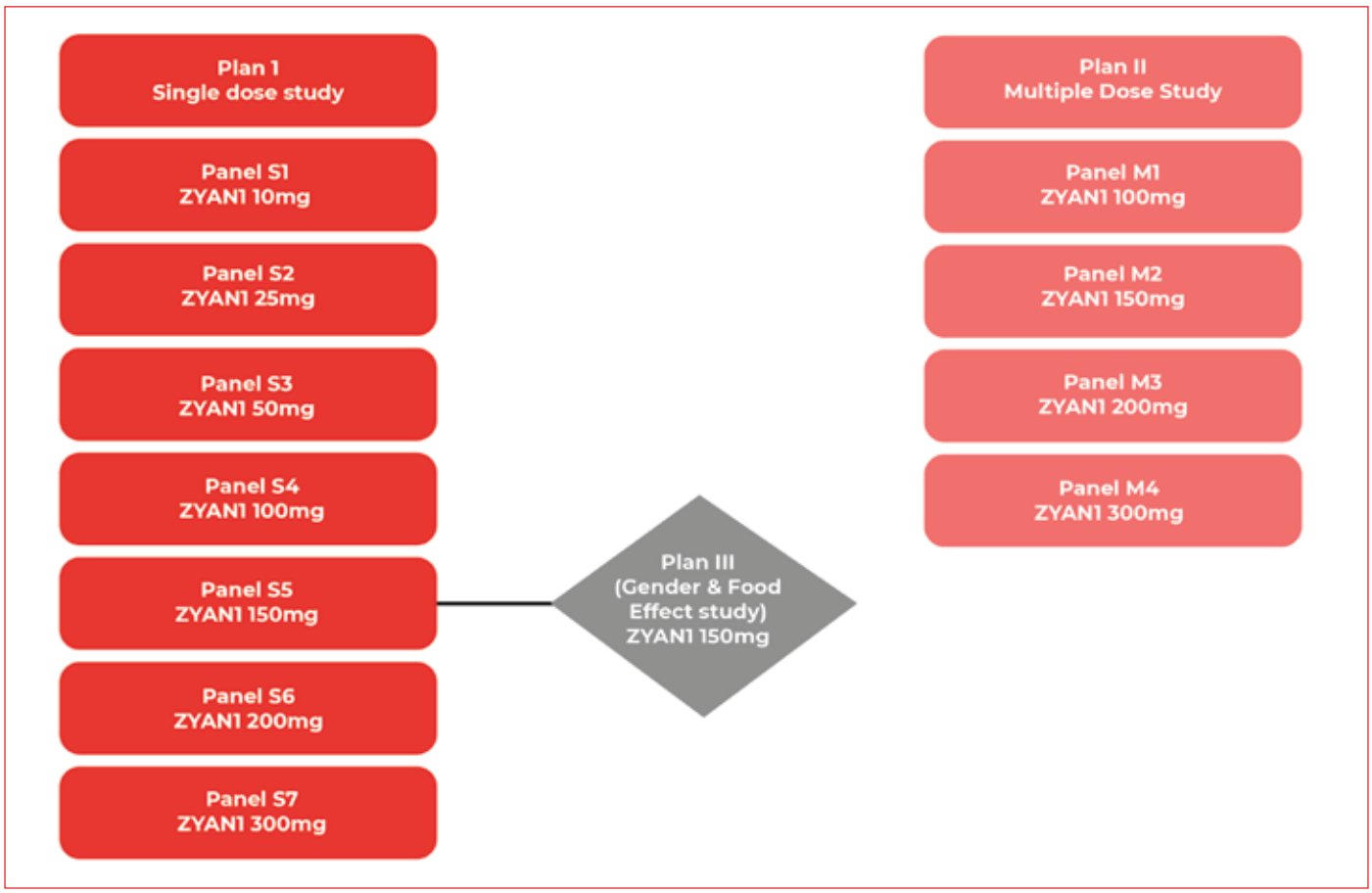


Figure 11: Mean Concentration *vs.* Time Graph with Error Bars for Part I[25]

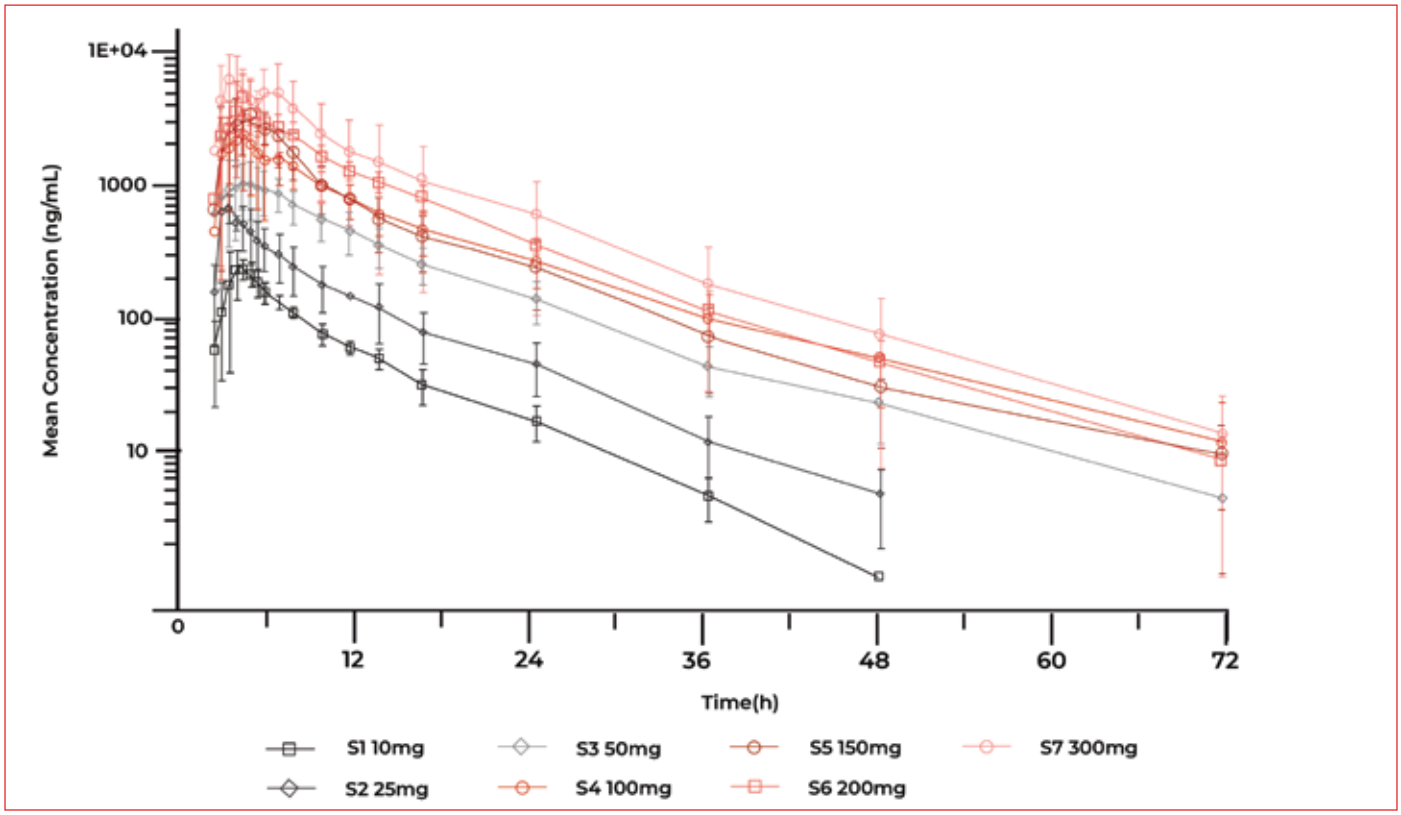


Figure 12: Dose Linearity Plot of Maximum Concentration (Cipt) and Area Under the Concentration–Time Curve for Part I[25]

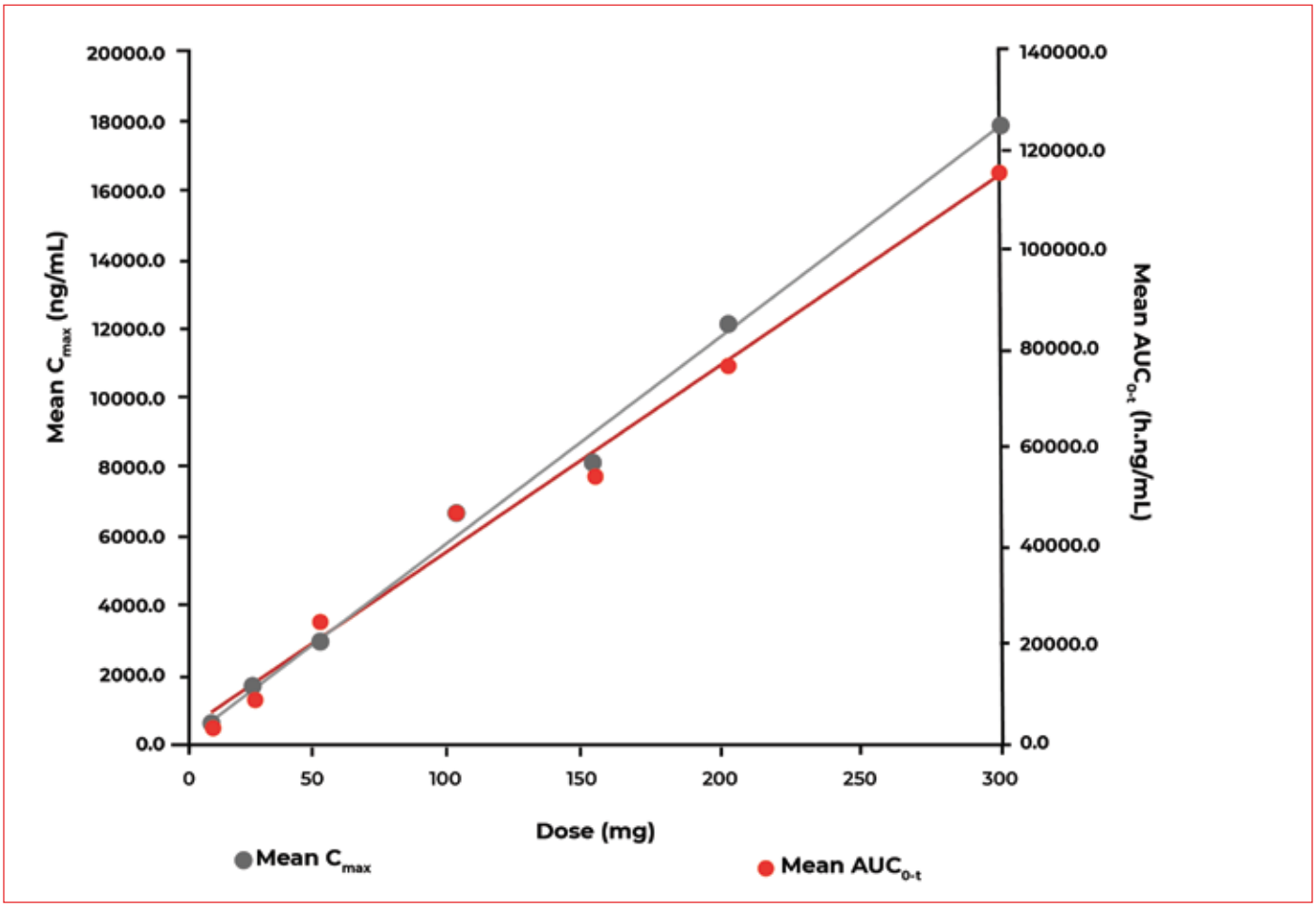
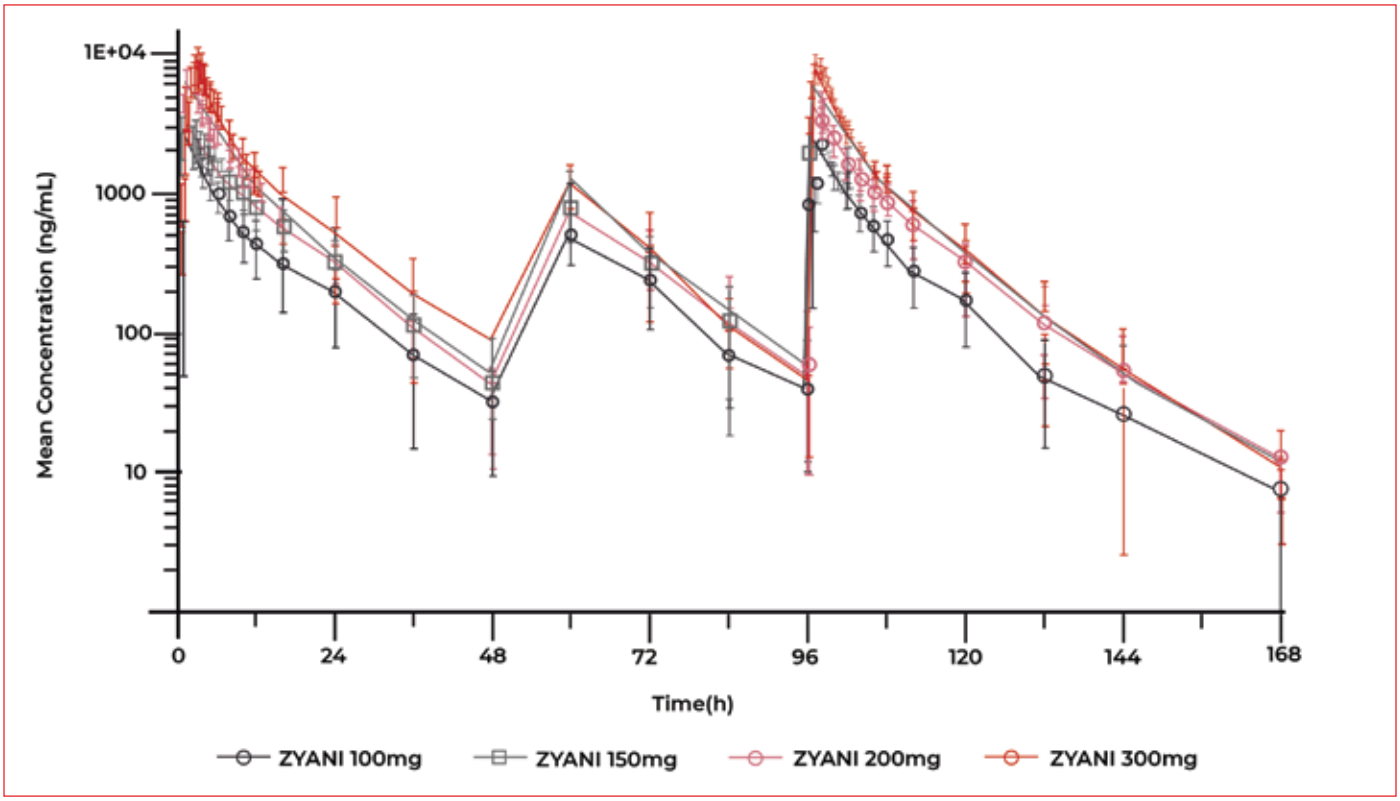


Figure 13: Mean Concentration vs. Time Graph with Error Bars for Part II[25]



9.2 Phase II studies

The phase II trial, a randomized, double-blind, 6-week, placebo-controlled study evaluated the safety, tolerability, and efficacy of desidustat in adult CKD patients (117 eligible patients) with anaemia, who were not on dialysis.[26]

Desidustat was administered every alternate day for 6 weeks in fasting conditions. The primary endpoint was change in hemoglobin (Hb) from baseline to Week 6. The desidustat arms (100, 150, and 200 mg treatment arms) displayed a mean Hb increase of 1.57, 2.22, and 2.92 g/dL, respectively, compared to the 0.46 g/dL in the placebo arm in the modified intent-to-treat (mITT) population (Figure 14). Mean Hb increase of 1.70, 2.55, and 3.28 g/dL was observed in 100, 150, and 200 mg treatment arms, respectively, compared with 0.02 g/dL in placebo arm in per protocol (PP) population (Table 2). Eighteen patients had at least one treatment emergent adverse event (TEAE). (Table 3) No death or serious adverse event was reported during the trial.[26]

Table 2: Change from Baseline (BL) in Hb (g/dL) at Week 6[26]

Treatment	mITT				PP			
	BL, mean ± SD	change, mean ± SD	95% CI	*p* value	BL, mean ± SD	change, mean ± SD	95% CI	*p* value
Desidustat 100 mg (*n* = 29)	9.53±1.41	1.57±1.07	0.00–1.73	0.05	9.51±1.46	1.70±1.09	0.68–2.25	<0.001
Desidustat 150 mg (*n* = 28)	9.73±1.16	2.22±1.74	0.73–2.45	<0.001	9.58±1.01	2.55±1.51	1.59–3.15	<0.001
Desidustat 200 mg (*n* = 29)	9.55±1.25	2.92±2.13	1.37–3.09	<0.001	9.50±1.20	3.28±1.98	2.28–3.88	<0.001
Placebo (*n* = 26)	10.22±1.14	0.46±1.64			10.00±1.05	0.02±0.85		

Figure 14: Proportion of Responders in the Treatment Arms (mITT Population)[26]

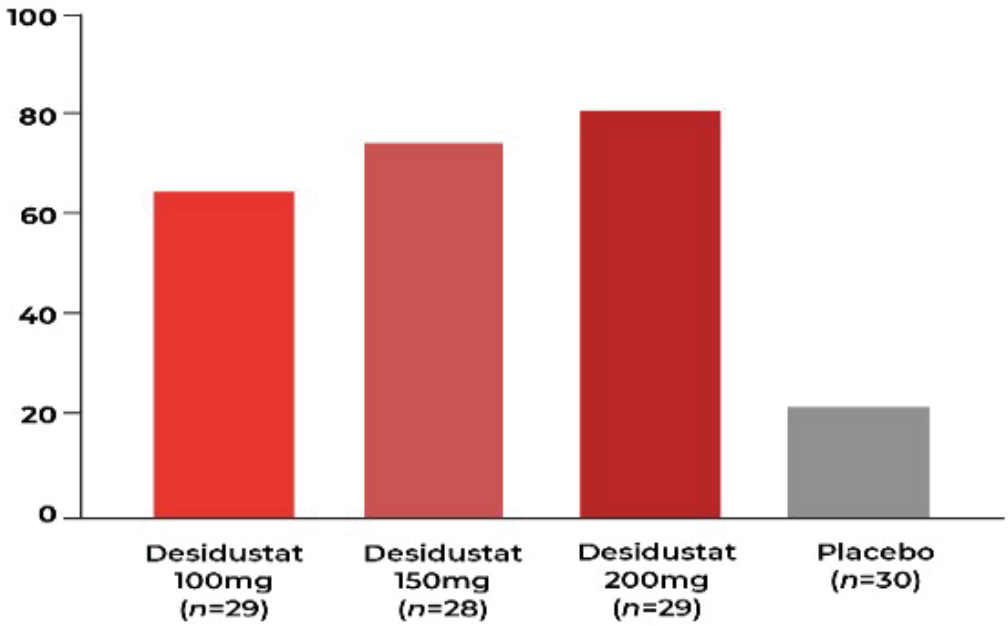
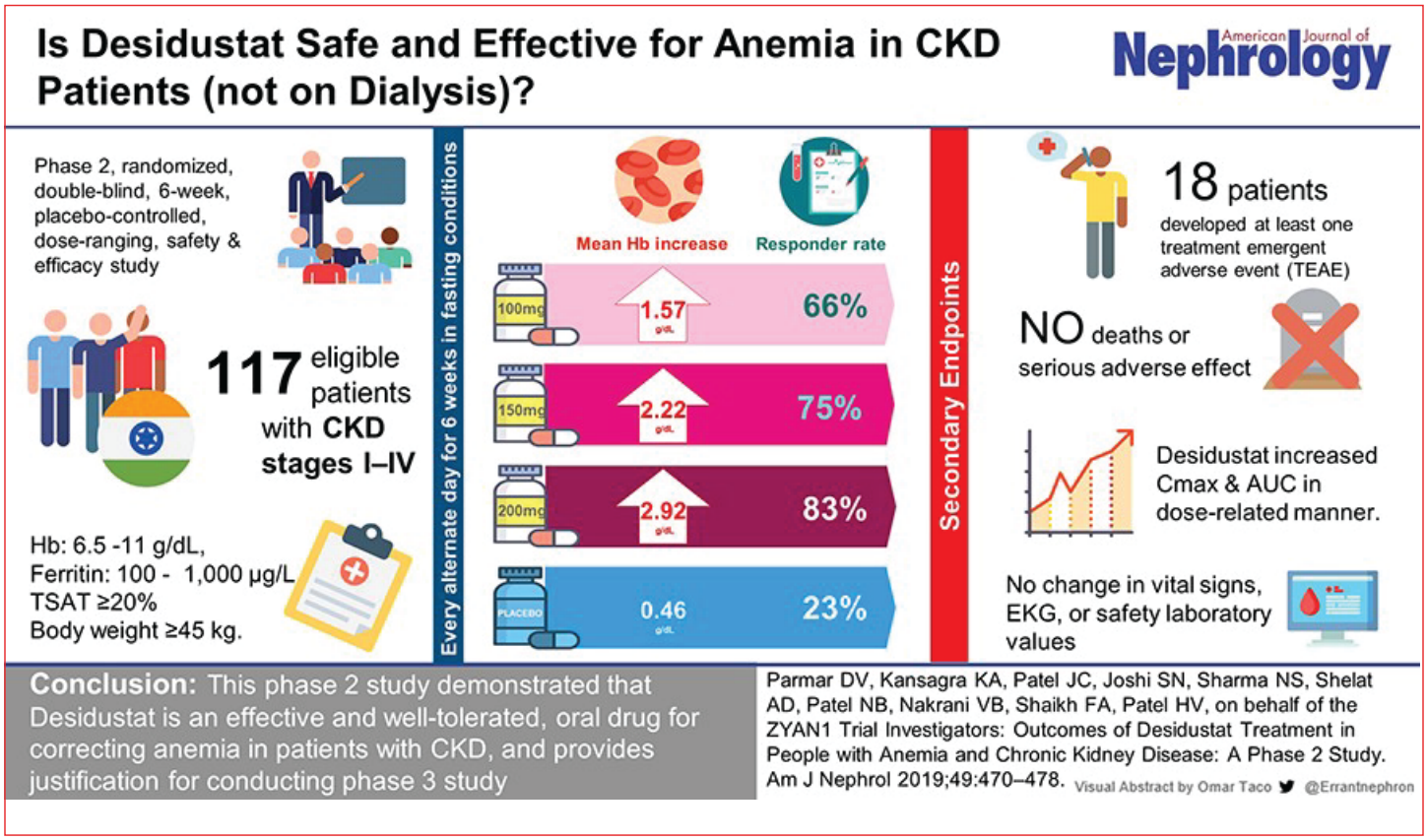


Table 3: Adverse Events in the Safety Population[26]				
Category	Number of patients, n (%)			
	Desidustat 100 mg (*n* = 29)	Desidustat 150 mg (*n* = 29)	Desidustat 200 mg (*n* = 29)	Placebo (*n* = 30)
Number of patients with at least one TEAE	2 (6.90)	5 (17.24)	5 (17.24)	6 (20.00)
Number of patients with at least one possibly related TEAE	0 (0.00)	3 (10.34)	1 (3.45)	1 (3.33)
Gastrointestinal disorders				
Abdominal pain	0 (0.00)	1 (3.45)	1 (3.45)	3 (10.00)
Vomiting	1 (3.45)	1 (3.45)	2 (6.90)	1 (3.33)
Nervous system disorders	1 (3.45)	1 (3.45)	0 (0.00)	2 (6.67)
Headache	1 (3.45)	1 (3.45)	0 (0.00)	2 (6.67)

Figure 15: Summary of Phase II Study



9.3 Phase III studies

Phase III: Pre-dialysis Patients with Anaemia

Desidustat oRal Evaluation in Anaemia Management-Non-Dialysis (DREAM-ND)

Trial No.:	DESI.18.001
Title:	A Phase 3, Multicentre, Multi-country, Open-label, Randomized, Active-controlled Clinical Trial to Evaluate the Efficacy and Safety of Desidustat versus Darbepoetin for the Treatment of Anaemia in Patients with Chronic Kidney Disease (CKD) who are not on Dialysis (DREAM-ND).
Investigational Product:	Desidustat Oral Tablet [three times a week (TIW)]
Name of the Reference Drug:	Darbepoetin alpha Injection
Sample Size:	588
Potential Indication:	Anaemia in CKD not on dialysis
Study treatment duration:	24 weeks

- The **DREAM-ND** Phase III trial of 588 patients with stage 3-5 CKD, aged 18-80 years old and having Hb level between 7-10 g/dL was randomized to receive either desidustat oral tablet or darbepoetin alfa injection for 24 weeks [ClinicalTrials.gov Identifier: NCT04012957].

- As an initial dose, desidustat 100 mg was orally administered three times a week in anemic patients with CKD who are not on dialysis for a period of 24 weeks. Dosing has been done 2 days apart (e.g.- Monday, Wednesday, Friday or Tuesday, Thursday, Saturday). Dose adjustment was permitted during Week 4 to Week 20 based on Hb level assessment. (Table 4).

- Primary efficacy end point is mean change in Hb levels from baseline to evaluation (Week 16 to Week 24) period in mITT population.

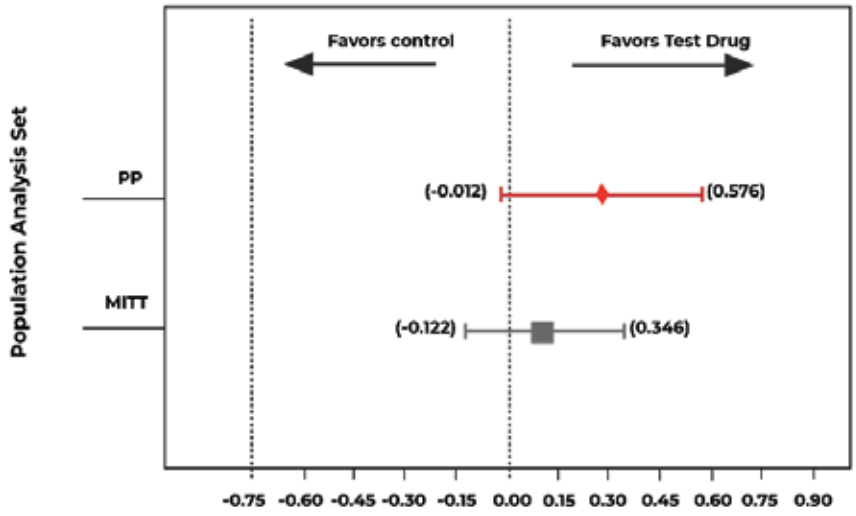
- The least squares mean (LSM) change from BL to Hb (16–24) was 1.94 g/dL and 1.83 g/dL for desidustat and darbepoetin, respectively, with the estimated difference of 0.11 g/dL (95% CI, –0.12 to 0.35 g/dL) between the two groups; the lower limit of the 95% CI was above the predefined non inferiority margin of –0.75 g/dL, confirming the non-inferiority of desidustat to darbepoetin (Table 5, Figure 16).

Table 4: Desidustat: Dose Adjustment Plan, every 4 weeks				
Change in Hb g% level over 04 weeks	**Hb <10 g%**	**Hb 10 to <11 g%**	**Hb 11 to <12 g%**	**Hb ≥12 g%**
<1.0 increase	Increase the dose	Increase the dose	Maintain the dose	Stop the treatment for 14 days, Initiate one lower dose if Hb <11.5 g%
>1.0 increase	Maintain the dose	Maintain the dose	Decrease the dose	
>2.0 increase	Maintain the dose	Decrease the dose	Decrease the dose	
Change in Hb g% level was monitored every 2 weeks (first 8 weeks)				

Primary endpoint analysis

Table 5: Analysis of Change from Baseline in Hemoglobin (g/dL) in mITT Population		
	Desidustat oral tablet (*n* = 261)	**Desidustat oral tablet (*n* = 261)**
Baseline Hb (Mean± SD)	8.97 ± 0.73	8.92 ± 0.70
Average Hb of Week 16, 20 and 24 (Mean ±SD)	10.90 ± 1.36	10.77 ± 1.46
Change from Baseline (Mean ± SD)	1.93 ± 1.37	1.84 ± 1.46
LSM (SE)	1.94 (0.08)	1.83 (0.08)
Difference of LSM (SE)	0.11 (0.12)	
95% Confidence Interval	-0.12 ,0.34 (*p*-value: 0.3483)	
Lower margin of 95% CI of difference of LSM (SE) is less than -0.75 g/dL- non-inferiority achieved.		

Figure 16: Non- Inferiority graph (DREAM-ND)



Plot of 95% CI of Difference (%) in Hb between Desidustat and Darbepoetin

Secondary endpoint analysis

- Desidustat was superior compared to darbepoetin in non-dialysis patients as represented by secondary end points, i.e., for time to achieve target Hb, and for percentage of responders.
- Desidustat showed a significant reduction in low density lipoprotein (LDL)-cholesterol at Week 24 compared to baseline.
- A statistically non-significant reduction was observed in hepcidin and levels of vascular endothelial growth factor (VEGF) by Week 24 from BL parameters.

Table 6: Time to Achieve Target Range Hb Level up to Week 24

Population	Treatment arm	Time to achieve target HB level in weeks (mean + SD)	Median (Weeks)	*p*-value
mITT population	Desidustat (*n* = 261)	6.58 ± 4.11	4.00	0.2985
	Darbepoetin alfa (*n* = 268)	7.29 ± 5.08	4.00	
PP population	Desidustat (*n* = 164)	7.11 ± 4.50	4.00	0.3126
	Darbepoetin alfa (*n* = 180)	7.92 ± 5.35	4.00	

Table 7: Percentage of Time Spent in Target Hb Range up to Week 24			
Population	**Treatment arm**	**% of time spent in target range - mean (±SD)**	***p*-value**
mITT population	Desidustat (*n* = 261)	82.75 ± 22.35	0.1113
	Darbepoetin alfa (*n* = 268)	77.10 ± 27.72	
PP population	Desidustat (*n* = 164)	67.56 ± 24.26	0.0568
	Darbepoetin alfa (*n* = 180)	61.65 ± 27.25	

Table 8: Change in Lipid and Lipoprotein Profile from Baseline to Week 24 in mITT Population					
Lipid parameter	**Normal range**	**Treatment Arm**	**Baseline**	**Week 24**	**Change from baseline**
Cholesterol-Total (mg/dL)	0-200 mg/dL	Desidustat	159.7 ± 51.72	149.7 ± 48.54	-9.51 ± 48.98
		Darbepoetin-alfa	158.6 ± 48.23	159.9 ± 50.12	-1.33 ± 51.25
HDL-Cholesterol (mg/dL)	40-60 mg/dL	Desidustat	40.65 ± 14.36	35.91 ± 12.56	-3.15 ± 14.32
		Darbepoetin-alfa	40.89 ± 12.28	37.93 ± 12.84	-2.01 ± 13.00
LDL-Cholesterol (mg/dL)	0-100 mg/dL	Desidustat	92.97 ± 42.62	82.45 ± 39.02	**-9.41 ± 42.34***
		Darbepoetin-alfa	93.55 ± 40.72	93.61 ± 42.87	-2.81 ± 43.14
VLDL-Cholesterol (mg/dL)	5-40 mg/dL	Desidustat	35.30 ± 20.23	38.08 ± 23.12	0.34 ± 21.88
		Darbepoetin-alfa	33.33 ± 23.23	35.56 ± 22.16	0.26 ± 25.62
Difference of LSM of LDL cholesterol between desidustat and darbepoetin alfa is statistically significant (*p* = 0.0268)					

Table 9: Change in VEGF Level from Baseline to Week 12 and Week 24			
Population	VEGF (123 – 1205 pg/mL)	Desidustat oral tablet	Darbepoetin Alfa Injection
mITT population	Baseline (Mean ± both SD)	646.4 ± 627.1	638.7 ± 612.5
	Week 12 (Mean ± SD)	674.6 ± 768.6	706.2 ± 769.4
	Change from baseline to week12 (Mean ± SD)	39.6 7± 599.8	85.41 ± 635.1
	Week 24 (Mean ± SD)	630.6 ± 619.2	653.2 ± 661.2
	Change from baseline to week 24 (Mean ± SD)	9.05 ± 553.1	22.17 ± 679.1
PP population	Baseline (Mean ± SD)	606.1 ± 480.8	657.0 ± 623.6
	Week 12 (Mean ± SD)	657.9 ± 727.7	732.1 ± 794.9
	Change from baseline to week 12 (Mean ± SD)	1.27 ± 558.5	99.92 ± 703.3
	Week 24 (Mean ± SD)	672.2 ± 698.7	662.3 ± 648.4

Figure 17: Change in Hepcidin at Week 12 and Week 24

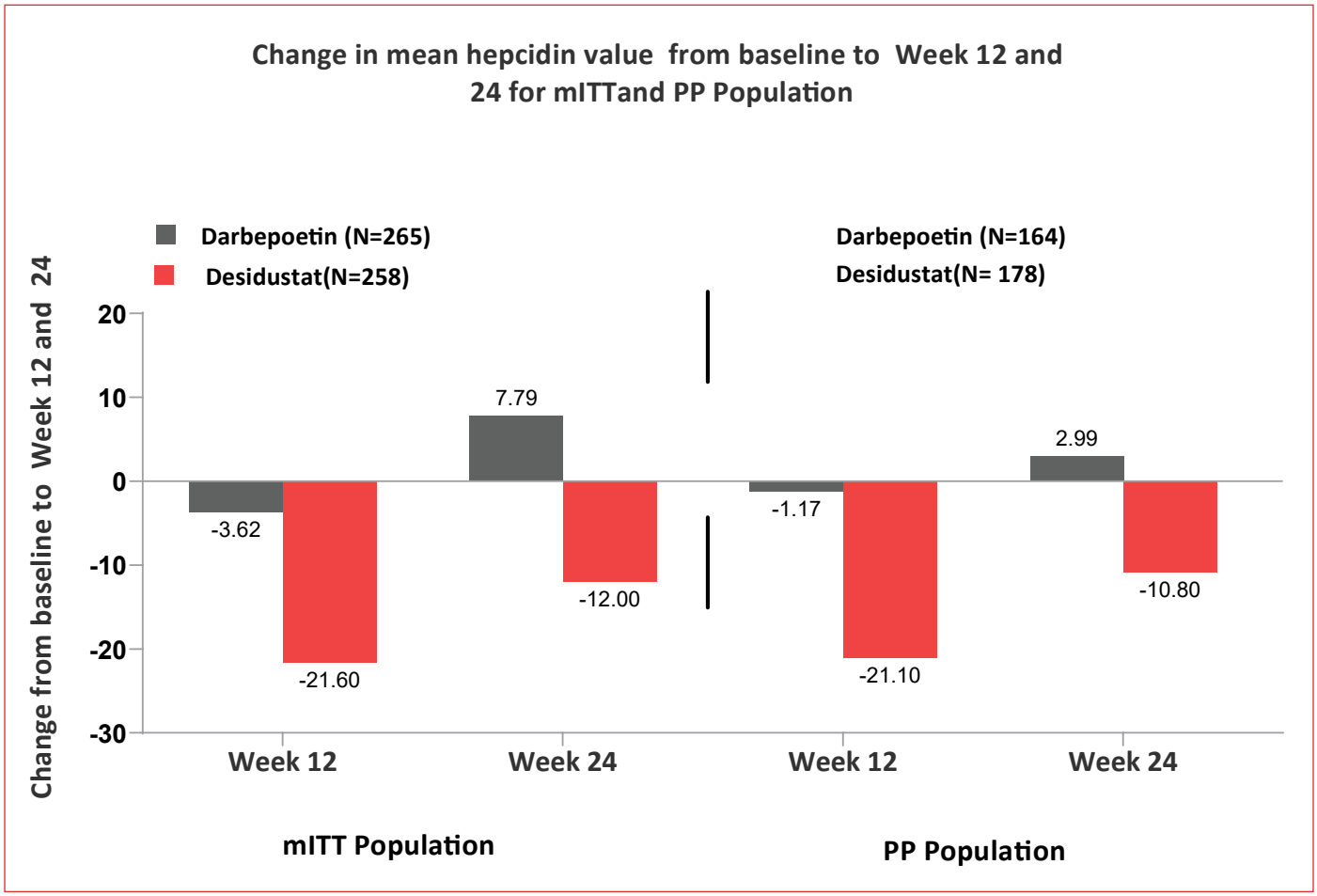
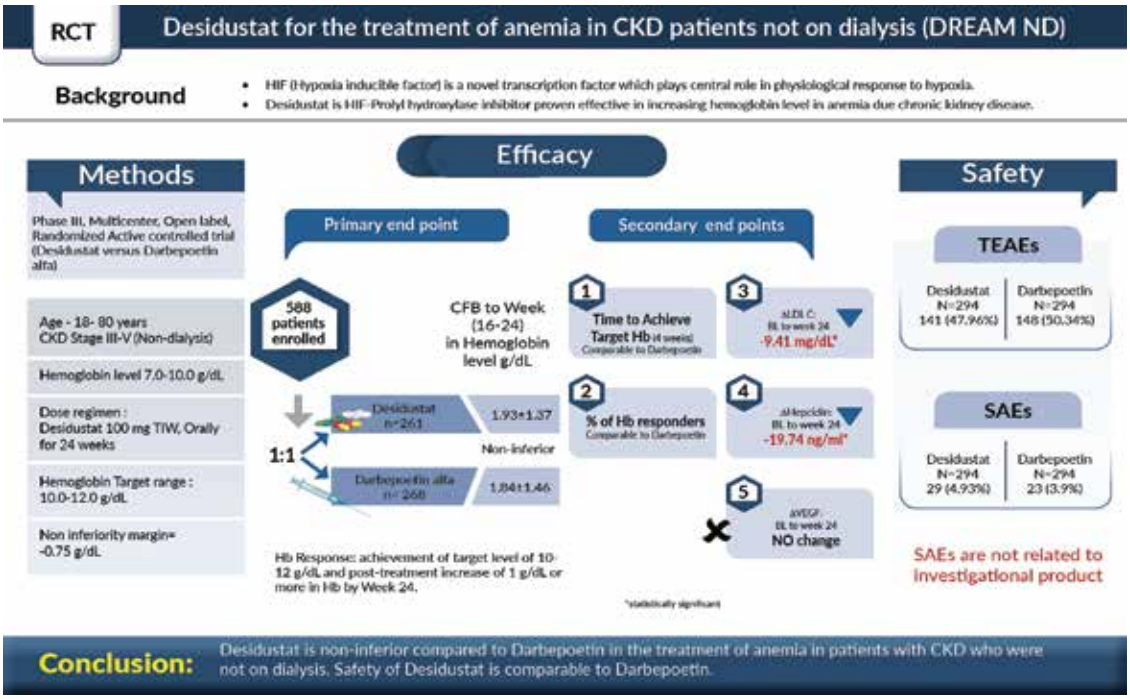


Figure 18: Summary of DREAM-ND Study



Phase III: Dialysis Patients with Anaemia
Desidustat oRal Evaluation in Anaemia Management – Dialysis (DREAM-D)

Trial No.:	**DESI.19.001**
Study Title:	A Phase 3, Multicentre, Open-label, Randomized, Active-controlled Study to Evaluate the Efficacy and Safety of Desidustat Tablet versus Epoetin Alfa Injection for the Treatment of Anaemia in Patients with Chronic Kidney Disease (CKD) on Dialysis. (DREAM-D)
Investigational Product(s):	Desidustat Oral Tablet
Name of Reference Product:	Epoetin alfa Injection
Indication:	Anaemia in CKD on dialysis
Study Population:	Patients with anaemia in CKD on dialysis
Number of subjects:	392
Study treatment duration	24 weeks

• The DREAM-D Phase III trial, an open label trial of 392 patients of dialysis dependent CKD (stage V) with Hb levels between 8-11 g/dL, subjects were randomized to receive either desidustat oral tablets or epoetin alfa injections for 24 weeks. [ClinicalTrials.gov Identifier: NCT04215120].
• Initial dose of desidustat was 100-150 mg (depending on subject's weight and prior use of erythropoietin analogue) orally three times a week. Dose adjustment were done based on Hb levels assessed every 4 weeks, if required. (Table 10)
• Patients randomized to receive desidustat discontinued prior EPO analogue therapy.
• The starting dose of desidustat was based on the average weekly EPO analogue dose during screening visit 4 weeks prior (for patients treated with epoetin alfa or darbepoetin alfa) or the average monthly dose 8 weeks prior (for patients treated with Mircera®). (Table 11)
• Patients previously treated with darbepoetin or Mircera® and randomized to the epoetin group received epoetin at doses based on a conversion factor. (Table 12)
• Primary efficacy endpoint was evaluation of difference of mean change of Hb from baseline to evaluation period (Week 16-24) between desidustat group and epoetin alfa group.
• The LSM change from baseline to Hb (16–24) was 0.95 g/dL and 0.80 g/dL for desidustat and epoetin, respectively, with the estimated difference of 0.14 g/dL (95% CI, –0.1304 to 0.4202 g/dL) between the two groups; the lower limit of the 95% CI was above the predefined non inferiority margin of –1.0 g/dL, confirming the non-inferiority of desidustat to epoetin alfa. (Table 13, Figure19)

Table 10: Dose Adjustment during Week 4 to Week 20

Change in Hb g% level over 4 weeks	Hb <10 g%	Hb 10 to <11 g%	Hb 11 to <12 g%	Hb ≥12 g%
<1.0 increase	Increase the dose	Increase the dose	Maintain the dose	Stop the treatment for 14 days, initiate one lower dose if Hb <11.5 g%
≥1.0 increase to ≤2.0 increase	Maintain the dose	Maintain the dose	Decrease the dose	
>2.0 increase	Maintain the dose	Decrease the dose	Decrease the dose	
Change in Hb g% level was monitored every 2 weeks (first 8 weeks)				

Table 11: Desidustat Dose Initiation for Patients already on EPO Analogue

Darbepoetin (µg/week)	Mircera® (µg/month)	Epoetin (IU/week)	Desidustat (mg)
<40	<120	<8000	100
40-80	120-200	8000 to 16000	125
>80	>200	>16000	150

Table 12: Epoetin Alfa Dose as per Previous Darbepoetin/Mircera®

	Conversion Ratio	Examples of converted initial Epoetin alfa dose (IU/week)
Darbepoetin (µg/week)	x 200	20 µg/week x 200 = 4000 IU/week
Mircera® (µg/month)	x 70 to 80 Lower conversion ratio can be used as per discretion of investigator	80 µg/month x 70 = 5600 IU/week 150 µg/month x 70 = 10500 IU/week

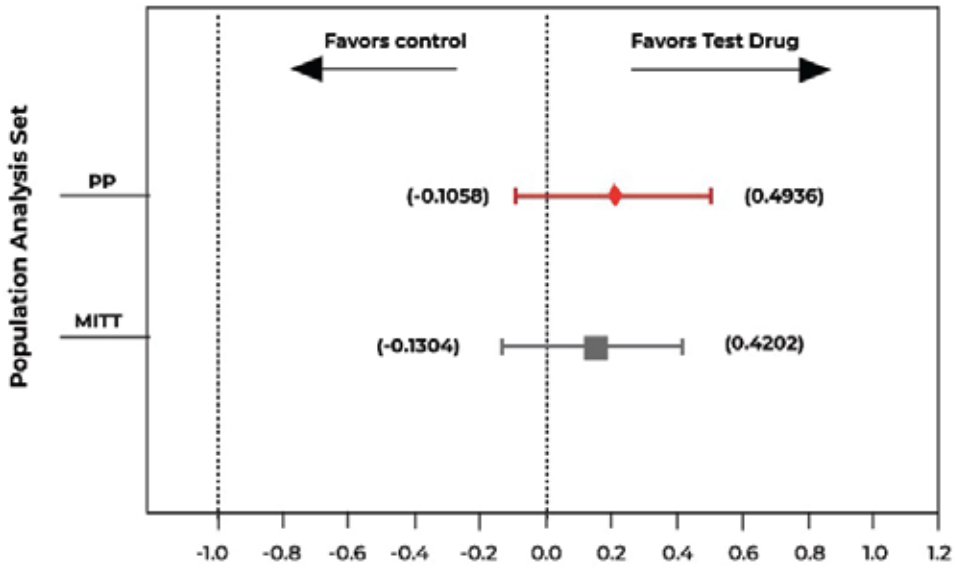
Primary Endpoint Analysis

Table 13: Analysis of Change from Baseline in Hemoglobin (g/dL) in mITT Population

Population	Desidustat oral tablet (n = 184)	Epoetin alfa Injection (n = 189)
Baseline Hb (Mean ± SD)	9.57 ± 0.98	9.46 ± 1.14
Average Hb of Week 16,20 and 24 (Mean± SD)	10.47 ± 1.37	10.32 ± 1.41
Change from baseline (Mean ± SD)	0.92 ± 1.44	0.85 ± 1.56
LSM (SE)	0.95 (0.10)	0.80 (0.10)
Difference of LSM (SE)	0.14 (0.14)	
95% Confidence Interval	-0.13, 0.42 (*p* value- 0.301)	

The lower limit of the 95% CI was above the predefined non inferiority margin of –1 g/dL, confirming the noninferiority of desidustat to epoetin alfa

Figure 19: Non- Inferiority Graph (DREAM-D)



Secondary Endpoint Analysis

• Desidustat was superior compared to epoetin in dialysis patients as represented by secondary end points, i.e., for time to achieve target Hb, and for percentage of responders.

• Desidustat showed a significant reduction in low density lipoprotein (LDL)-cholesterol at Week 12 when compared to baseline

• A statistically non-significant reduction in the levels of vascular endothelial growth factor (VEGF) and hepcidin by Week 24 from baseline parameters was also observed.

Table 14: Time to Achieve Target Range Hb Level up to Week 24

Population	Treatment arm	Time to achieve target HB level in weeks (mean + SD)	Median (Weeks)	*p*-value
mITT population	Desidustat (n= 184)	7.20 ± 4.69	4.00	**0.041***
	Epoetin alfa (n= 189)	9.57 ± 6.85	8.00	
PP Population	Desidustat (n= 156)	8.08 ± 5.38	8.00	0.0845
	Epoetin alfa (n= 163)	10.20 ± 6.97	8.00	

* *p*-value <0.005 was considered as statistically significant

Table 15: Change in Lipid and Lipoprotein Profile from Baseline to Week 12

Lipid parameter	Normal range	Treatment Arm	Baseline	Week 12	Change from baseline
Apolipoprotein-A1 (mg/dL)	108-225 mg/dL	Desidustat	110.4 ± 21.85	101.5 ± 24.60	-9.23 ± 24.53
		Epoetin-alfa	109.2 ± 18.48	103.9 ± 20.39	-4.93 ± 21.07
Apolipoprotein-B (mg/dL)	60-117 mg/dL	Desidustat	75.05 ± 25.05	69.67 ± 24.66	**-6.97 ± 22.55***
		Epoetin-alfa	75.93 ± 24.20	79.43 ± 25.55	2.80 ± 22.81
Lipoprotein (a) (mg/dL)	<30 mg/dL	Desidustat	39.52 ± 38.91	32.21 ± 32.12	-6.74 ± 26.16
		Epoetin-alfa	40.96 ± 33.74	36.20 ± 33.15	-4.01 ± 24.40
Triglycerides (mg/dL)	<150mg/dL	Desidustat	133.1 ± 82.39	137.4 ± 85.87	4.05 ± 77.49
		Epoetin-alfa	139.2 ± 90.40	146.4 ± 91.84	6.45 ± 65.89

*Difference of LSM of apolipoprotein-B between desidustat and epoetin alfa is statistically significant (p<0.0001).

Table 16: Change in VEGF Level from Baseline to Week 12 and Week 24

Population	VEGF (123 – 1205 pg/mL)	Desidustat oral tablet	Epoetin Alfa Injection
mITT population	Baseline (Mean ± SD)	783.7 ± 592.8	689.2 ± 458.9
	Week 12 (Mean ± SD)	764.8 ± 630.2	756.3 ± 463.3
	Change from baseline to week12 (Mean ± SD)	-18.4 ± 802.4	65.36 ± 548.4
	Week 24 (Mean ± SD)	931.1 ± 1165	732.9 ± 538.4
	Change from baseline to week 24 (Mean ± SD)	143.9 ± 1299	51.58 ± 590.4
PP Population	Baseline (Mean ± SD)	776.9 ± 617.7	695.4 ± 461.9
	Week 12 (Mean ± SD)	735.8 ± 635.1	744.9 ± 459.7
	Change from baseline to week 12 (Mean ± SD)	-36.5 ± 823.7	40.38 ± 556.1
	Week 24 (Mean ± SD)	926.4 ± 1206	736.1 ± 546.4
	Change from baseline to week 24 (Mean ± SD)	149.5 ± 1343	43.03 ± 603.3

Table 17: Percentage of Time Spent in Target Hb Range up to Week 24

Parameter	Statistics	Desidustat Tablet (*n* = 184) *n* (%)	Epoetin Alfa Injection (*n* = 189) *n* (%)
Percentage of time spent in target Hb range	n	160	156
	mean ± SD	70.73 ± 26.42	63.68 ± 29.78
	Q1	50.00	33.33
	median	83.33	66.67
	Q3	100.0	91.67
	minimum	16.67	16.67
	maximum	100.0	100.0
	p-Value		0.045

Figure 20: Change in Hepcidin at Week 12 and Week 24

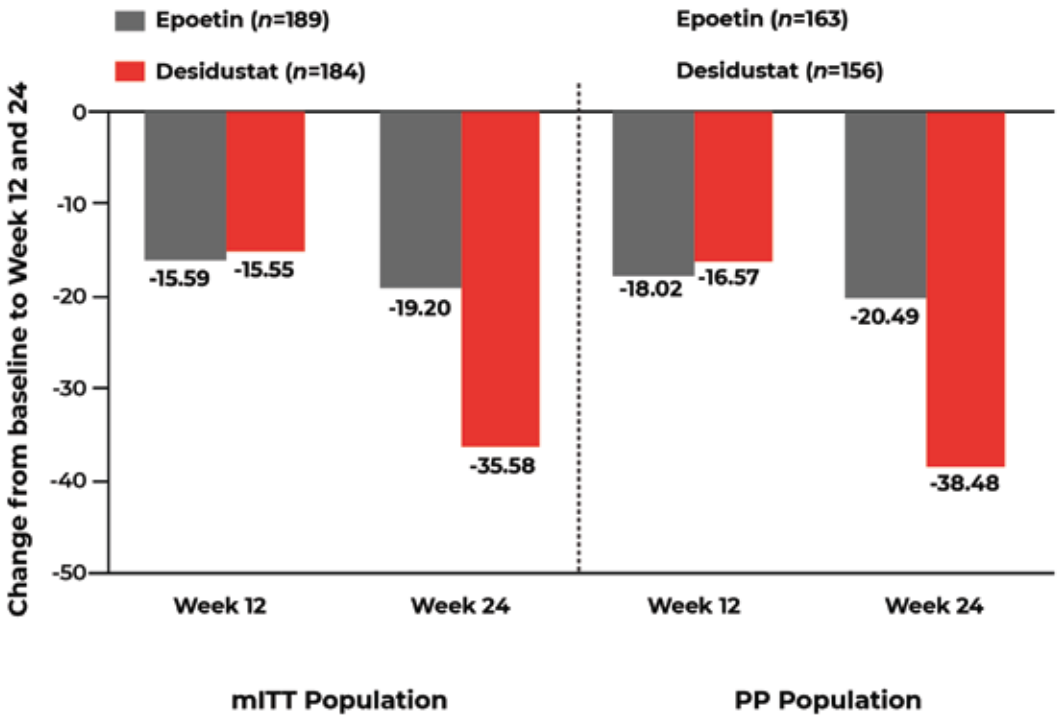
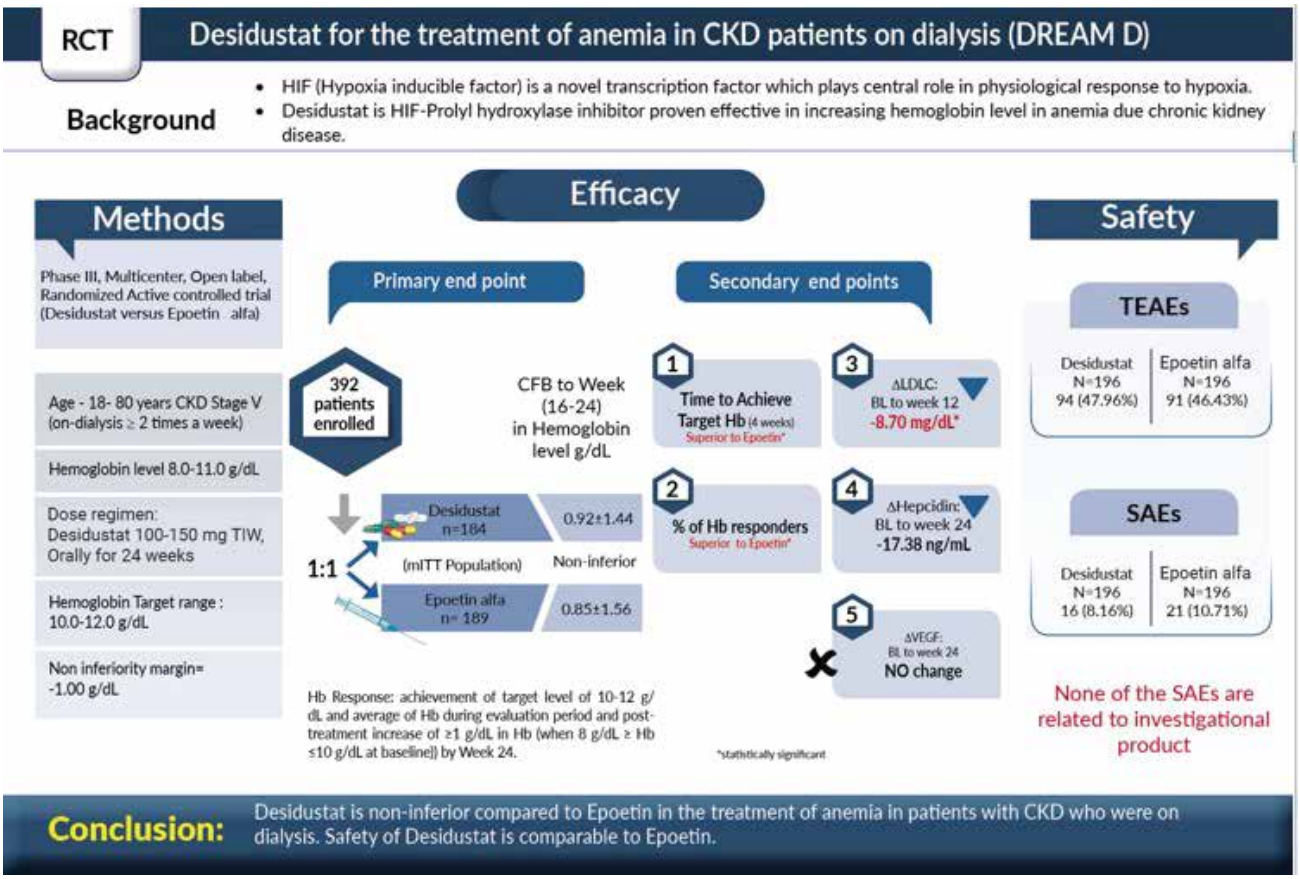


Figure 21: Summary of DREAM-D Study



9.4 Safety, Toxicity, Tolerability Related to Desidustat

Adverse Reactions

Table 18: Overall Summary of Adverse Events (AEs) Reported Through DREAM-ND Trial

	Desidustat Oral Tablet (N = 294) n (%)	Epoetin Alfa Injection (N = 294) n (%)	Total (n= 588) n (%)
Number of AE	288	354	642
Number of subjects with at least one treatment emergent adverse event (TEAE)	137 (46.6)	146 (49.66)	283 (48.13)
Number of serious adverse event (SAE)	29 (4.93)	23 (3.9)	52 (8.84)
Number of subjects with at least one TEAE leading to death	6 (2.04)	6 (2.04)	12 (2.04)

Table 19: Overall Summary of AEs Reported Through DREAM-D Trial

	Desidustat Oral Tablet (N = 196) n (%)	Epoetin Alfa Injection (N = 196) n (%)	Total (n= 392) n (%)
Number of AE	196	196	373
Number of subjects with at least one TEAE	94 (47.96)	94 (47.96)	185 (47.19)
Number of SAE	16 (8.16)	16 (8.16)	38 (9.69)
Number of subjects with at least one TEAE leading to death	4 (2.04)	7 (3.5)	11 (2.81)

• The number of patients experiencing AEs during the trial do not significantly differ (p>0.05) in the treatment and placebo arms.

• The majority of TEAEs were mild in severity.

• Overall, only one patient discontinued from DREAM-ND trial due to AE

• No deaths due to SAEs occurred during the trial.

Cardiovascular Safety Results[25]

• Safety outcomes from Phase 2 studies showed no trends of electrocardiography (ECG) abnormalities in patients receiving desidustat treatment.

• No significant change in systolic pressure, diastolic pressure and pulse rate from baseline were seen following 6 weeks of desidustat administration.

10. Prescribing Information for Desidustat

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

10.1 THERAPEUTIC INDICATION

Desidustat is indicated for the treatment of

• Anaemia in adult patients with CKD irrespective of dialysis status

10.2 CONTRAINDICATIONS

• Hypersensitivity to desidustat or any of the excipients used in the formulation.

10.3 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Dosage form and strength

Desidustat tablets are available as white to off white colored round shape uncoated biconvex tablet having plain surface on both sides, for oral administration.

Each tablet of Desidustat contains 25 mg or 50 mg of Desidustat.

Qualitative and quantitative composition

Each uncoated tablet contains:

Desidustat 25 mg

Excipients q.s.

Each uncoated tablet contains:

Desidustat 50 mg

Excipients q.s.

Inactive ingredients in the tablet are microcrystalline cellulose, lactose, croscarmellose sodium,

hypromellose, talc and magnesium stearate

Packaging information

Desidustat is available as uncoated tablets for oral administration. Desidustat tablets are supplied in blister pack.

10.4 DOSAGE AND ADMINISTRATION

Posology and method of administration

• Do not consume any food 1 hour before and 2 hours after taking desidustat.

For Non-Dialysis Patients:

• The starting dose of desidustat is 100mg orally three times a week [Dosing will be done 2 days apart (e.g.-Monday, Wednesday, Friday or Tuesday, Thursday, Saturday) but not 4 days apart]. The dose should be then adjusted according to the patient's Hb level every 4 weeks. However, the maximum dose should not exceed 150 mg three times a week.

For Dialysis Patients:

• The starting dose of desidustat is 100 mg or 125 mg or 150 mg three times a week [Dosing will be done 2 days apart (e.g.-Monday, Wednesday, Friday or Tuesday, Thursday, Saturday) but not 4 days apart] depending upon the previous epoetin/darbepoetin/methoxy polyethylene glycol-epoetin beta dose. The starting dose for treatment naïve patients is 100 mg orally three times a week. The dose should be then adjusted according to the patient's Hb level every 4 weeks. However, the maximum dose should not exceed 150 mg thrice in a week.

• It is recommended that desidustat is to be taken after completion of the dialysis session

10.5 OVERDOSAGE

No incidence of overdose with desidustat has been reported. In case of overdose with desidustat, general supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status.

10.6 MISSED DOSE

When a patient misses a dose of desidustat, next scheduled dose will be administered to the subjects. However, missed dose will not be administered to the subject.

10.7 WARNINGS AND PRECAUTIONS

No drug related severe or serious adverse event or any life-threatening condition which requires special attention was observed during the study

10.8 USE IN SPECIAL POPULATIONS

Pregnancy

The safety of desidustat in pregnant women has not been established as there is no adequate and well controlled study carried out in pregnant women. Women who become pregnant during desidustat treatment should contact their physicians. Desidustat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal developmental and reproduction studies, no fetal toxicity or maternal toxicity or evidence of malformations in fetus was noticed in pregnant rabbits up to 135 mg/kg after desidustat administration by oral route. In pregnant rats, no embryofetal toxicity was noticed up to 60 mg/kg but delayed (incomplete) ossification of caudal vertebrae and unossified sternebrae in fetus was noticed at 120 mg/kg. No maternal

toxicity and malformations in fetus in rats were noticed up to 120 mg/kg. When desidustat was given orally to pregnant or lactating female rats, no adverse effects were noticed in the development of conceptus and post-natal parameters up to 30 mg/kg, however fertility index of F1 generation was low at 30 mg/kg. The no-observed-adverse-effect-level (NOAEL) of pre- and post-natal development study was considered to be 15 mg/kg in rats.

Nursing mothers

Nursing mothers should not use desidustat because it is not known whether desidustat is excreted into the breast milk.

Pediatric use

Safety and efficacy of desidustat in pediatric patients have not been established.

Geriatric use

Considering the comorbidity and concomitant medications in elderly patients, Desidustat should be used with caution in geriatric patients.

Effects on ability to drive and use machines

Desidustat does not have any influence on the ability to drive and use machines.

10.9 ADVERSE REACTIONS

Adverse Events (AEs) Reported from Phase-III Studies

Study: DESI.18.001 (DREAM-ND)

A phase III, open label and comparative study on 588 anemic CKD patients not dependent on dialysis comparing efficacy and safety of desidustat tablet with darbepoetin injection revealed that a total of 642 adverse event in 289 subjects (288 AEs in desidustat arm and 354 in darbepoetin alfa arm) were reported during 24 weeks treatment period. The most frequently reported TEAEs (reported in ≥2% of subjects in the either of the treatment groups) is presented (Table 20). The number of subjects with at least one TEAE were 137 (46.60%) in the desidustat arm and 146 (49.66%) in the darbepoetin alfa arm.

Table 20: TEAEs Reported in >2% of Subjects in Desidustat and Darbepoetin Alfa up to Week 24

AE term	Desidustat Oral Tablet (N = 294) n (%)	Epoetin Alfa Injection (N = 294) n (%)
Abdominal pain	5 (1.70)	9 (3.06)
Gastritis	2 (0.68)	7 (2.38)
Constipation	8 (2.72)	5 (1.70)
Vomiting	10 (3.4)	10 (3.4)
Asthenia	9 (3.06)	10 (3.4)
Injection site reaction	0 (0.0)	7 (2.38)
Oedema	8 (2.72)	5 (1.70)
Peripheral oedema	16 (5.44)	9 (3.06)
Pain	6 (2.04)	12 (4.08)
Pyrexia	20 (6.80)	20 (6.80)
Hypersensitivity	0 (0.0)	6 (2.04)
Urinary tract infection	11 (3.74)	8 (2.72)
Headache	11 (3.74)	12 (4.08)
Cough	5 (1.70)	10 (3.4)
Dyspnea	6 (2.04)	6 (2.04)
Hypertension	5 (1.70)	17 (5.78)

A total of 42 SAEs were observed during the trial of which, 24 events were observed in desidustat group and 18 observed in darbepoetin group. In total, 12 (2.04%) subjects reported at least one TEAE leading to death: 6 (2.04%) in each of the treatment group. All the deaths are not related to study medication as per sponsor however 3 cases (2 in reference arm and 1 in test arm) have been evaluated to be related to the IP by regulatory authority. Subjects with at least one SAE is presented below. (Table 21)

Table 21: SAEs Reported in Desidustat and Darbepoetin Alfa Group up to Week 24

System Organ Class term/ Preferred term	Desidustat Oral Tablet (N = 294) n (%)	Darbepoetin Alfa Injection (N = 294) n (%)	Total (N = 588) n (%)
Number of Subjects with at least one Serious Adverse Event	24 (8.16)	18 (6.12)	42 (7.14)
Blood and lymphatic system disorders	1 (0.34)	0 (0.00)	1 (0.17)
Immune thrombocytopenic purpura	1 (0.34)	0 (0.00)	1 (0.17)
Cardiac disorders	1 (0.34)	4 (1.36)	5 (0.85)
Acute coronary syndrome	0 (0.00)	1 (0.34)	1 (0.17)
Acute myocardial infarction	0 (0.00)	1 (0.34)	1 (0.17)
Angina unstable	1 (0.34)	1 (0.34)	2 (0.34)
Wellens' syndrome	0 (0.00)	1 (0.34)	1 (0.17)
Gastrointestinal disorders	0 (0.00)	2 (0.68)	2 (0.34)
Hematemesis	0 (0.00)	1 (0.34)	1 (0.17)
Vomiting	0 (0.00)	1 (0.34)	1 (0.17)
General disorders and administration site conditions	4 (1.36)	3 (1.02)	7 (1.19)
Asthenia	1 (0.34)	0 (0.00)	1 (0.17)
Cardiac death	1 (0.34)	0 (0.00)	1 (0.17)
Death	2 (0.68)	2 (0.68)	4 (0.68)
Generalized oedema	0 (0.00)	1 (0.34)	1 (0.17)
Infections and infestations	14 (4.76)	4 (1.36)	18 (3.06)
COVID-19	1 (0.34)	0 (0.00)	1 (0.17)
Cellulitis	3 (1.02)	0 (0.00)	3 (0.51)
Dengue fever	1 (0.34)	0 (0.00)	1 (0.17)
Diabetic foot infection	1 (0.34)	1 (0.34)	2 (0.34)
Epididymitis	1 (0.34)	0 (0.00)	1 (0.17)
Intervertebral discitis	1 (0.34)	0 (0.00)	1 (0.17)
Lower respiratory tract infection	2 (0.68)	0 (0.00)	2 (0.34)
Pyelonephritis	0 (0.00)	1 (0.34)	1 (0.17)
Sepsis	0 (0.00)	1 (0.34)	1 (0.17)
Septic shock	1 (0.34)	0 (0.00)	1 (0.17)

Table 21: SAEs Reported in Desidustat and Darbepoetin Alfa Group up to Week 24

System Organ Class term/ Preferred term	Desidustat Oral Tablet (N = 294) n (%)	Darbepoetin Alfa Injection (N = 294) n (%)	Total (N = 588) n (%)
Urinary tract infection	4 (1.36)	1 (0.34)	5 (0.85)
Urosepsis	1 (0.34)	0 (0.00)	1 (0.17)
Injury, poisoning and procedural complications	1 (0.34)	0 (0.00)	1 (0.17)
Radius fracture	1 (0.34)	0 (0.00)	1 (0.17)
Investigations	0 (0.00)	1 (0.34)	1 (0.17)
Electrocardiogram abnormal	0 (0.00)	1 (0.34)	1 (0.17)
Metabolism and nutrition disorders	1 (0.34)	2 (0.68)	3 (0.51)
Electrolyte imbalance	0 (0.00)	1 (0.34)	1 (0.17)
Hypoglycaemia	1 (0.34)	1 (0.34)	2 (0.34)
Nervous system disorders	1 (0.34)	3 (1.02)	4 (0.68)
Cerebrovascular accident	0 (0.00)	1 (0.34)	1 (0.17)
Cervical radiculopathy	0 (0.00)	1 (0.34)	1 (0.17)
Diabetic hyperosmolar coma	1 (0.34)	0 (0.00)	1 (0.17)
Generalised tonic-clonic seizure	0 (0.00)	1 (0.34)	1 (0.17)
Renal and urinary disorders	1 (0.34)	1 (0.34)	2 (0.34)
Acute kidney injury	1 (0.34)	0 (0.00)	1 (0.17)
Chronic kidney disease	0 (0.00)	1 (0.34)	1 (0.17)
Respiratory, thoracic and mediastinal disorders	1 (0.34)	2 (0.68)	3 (0.51)
Dyspnoea	0 (0.00)	1 (0.34)	1 (0.17)
Pulmonary oedema	1 (0.34)	1 (0.34)	2 (0.34)
Skin and subcutaneous tissue disorders	1 (0.34)	0 (0.00)	1 (0.17)
Diabetic foot	1 (0.34)	0 (0.00)	1 (0.17)
Vascular disorders	1 (0.34)	0 (0.00)	1 (0.17)
Secondary hypertension	1 (0.34)	0 (0.00)	1 (0.17)

Study: DESI.19.001 (DREAM-D)

A phase III, open label clinical trial comparing efficacy and safety of desidustat oral tablet with epoetin alfa injection on 392 patients with anaemia in CKD dependent on dialysis reported a total of 373 AEs during the trial. Total 185 subjects, 94 (47.96%) subjects in desidustat group and 91 (46.43%) subjects in epoetin alfa group, were reported with at least one TEAE during the trial. The most frequently reported TEAEs (reported in ≥2% of subjects in the either of the treatment groups) is presented (Table 22). The number of subjects with at least one TEAE were 94 (47.96%) in the desidustat arm and 91 (46.43%) in the epoetin alfa arm.

Table 22: TEAEs Reported in >2% of Subjects in Desidustat and Darbepoetin Alfa up to Week 24

Preferred term	Desidustat Oral Tablet (N = 196) n (%)	Epoetin Alfa Injection (N = 196) n (%)
Nausea	7 (3.57)	3 (1.53)
Vomiting	8 (4.08)	7 (3.57)
Diarrhea	4 (2.04)	5 (2.55)
Chills	5 (2.55)	1 (0.51)
Oedema	4 (2.04)	1 (0.51)
Asthenia	8 (4.08)	7 (3.57)
Pyrexia	16 (8.16)	10 (5.10)
COVID-19	9 (4.59)	6 (3.06)
Blood alkaline phosphatase increased	4 (2.04)	1 (0.51)
Blood potassium increased	12 (6.1)	5 (2.5)
Headache	7 (3.57)	9 (4.59)
Dyspnea	5 (2.55)	9 (4.59)
Cough	3 (1.53)	4 (2.04)
Hypertension	5 (2.55)	5 (2.55)

A total of 38 serious adverse events were observed during the trial, out of which, 16 events were observed in desidustat group and 22 observed in epoetin group. In total, 11 (2.81%) subjects reported at least one TEAE leading to death: 4 (2.04%) in Desidustat group and 7 (3.57%) subjects were in epoetin group. None of the serious adverse events are related to study medication. Subjects with at least one SAE is presented (Table 23).

Table 23: SAEs Reported in Desidustat and Epoetin Alfa Group up to Week 24

Preferred term	Desidustat Oral Tablet (N = 196) n (%)	Epoetin Alfa Injection (N = 196) n (%)
Number of Subjects with at least one SAE	16 (8.16)	21 (10.71)
Atrial fibrillation	1 (0.51)	0 (0.00)
Left ventricular failure	1 (0.51)	0 (0.00)
Death	1 (0.51)	4 (2.04)
Pyrexia	0 (0.00)	1 (0.51)
Bacterial infection	1 (0.51)	0 (0.00)
Bronchitis	0 (0.00)	1 (0.51)
COVID-19	4 (2.04)	3 (1.53)
COVID-19 pneumonia	0 (0.00)	1 (0.51)
Catheter related infection	1 (0.51)	0 (0.00)
Gastroenteritis	0 (0.00)	1 (0.51)
Lower respiratory tract infection viral	1 (0.51)	0 (0.00)
Mucor mycosis	0 (0.00)	1 (0.51)
Pneumonia	0 (0.00)	1 (0.51)
Pulmonary sepsis	1 (0.51)	0 (0.00)
Femur fracture	1 (0.51)	0 (0.00)
Hypercalcemia	0 (0.00)	1 (0.51)
Brain injury	1 (0.51)	0 (0.00)
Hypertensive encephalopathy	0 (0.00)	1 (0.51)
Metabolic encephalopathy	0 (0.00)	1 (0.51)
Dyspnea	0 (0.00)	1 (0.51)
Pulmonary oedema	1 (0.51)	1 (0.51)
Respiratory distress	1 (0.51)	0 (0.00)
Renal transplant	0 (0.00)	2 (1.02)
Accelerated hypertension	0 (0.00)	2 (1.02)
Jugular vein thrombosis	1 (0.51)	0 (0.00)
Venous thrombosis	0 (0.00)	1 (0.51)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

10.10 DRUG INTERACTIONS

The in vitro assays did not reveal any significant inhibition of major drug metabolizing enzymes CYPs 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4/5 (IC50 >300 μM). Desidustat is also not a time dependent inhibitor of CYP3A4/5. Desidustat was not an inducer of CYP1A2 and CYP3A4 at 100 μM. Based on available data, desidustat has a minimal potential to cause CYP-mediated clinical drug-drug interaction at therapeutically relevant concentrations in human.

Desidustat was not found to be a substrate for human drug transporters P-gp or BCRP at gastrointestinal pH 5.5. Desidustat did not interact significantly with other human drug transporters such as OATP1B1, OATP1B3, OAT1, OCT2 at 30 μM, but it showed interaction with OAT3 (IC50 of 1.7 μM).

10.11 ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Desidustat is an oral hypoxia-inducible factor prolyl hydroxylase domain (PHD) inhibitor (HIF-PHI) that stimulates erythropoiesis.

Pharmacokinetic properties

Study in Pre-dialysis Patients:

Desidustat was administered orally once every other day (alternate-day dosing) for 6 weeks at three dose levels (100, 150, 200 mg) in pre dialysis chronic kidney disease patients (n = 11/dose): the exposure (C_{max} and AUC) of desidustat was increased in dose-related manner from 100 to 200 mg dose, no drug accumulation following a multiple doses and mean elimination half-life was ranged from 6 to 14h.

Study in Dialysis Patients:

A single oral dose of desidustat was administered in dialysis chronic kidney disease patients at three dose levels (50, 100, 150 mg, n=8/dose) within 2h of dialysis. The time to achieve peak blood concentration was observed at about 2.5h post dosing, the exposure (C_{max} and AUC) was increased at 50 and 100 mg dose, the geometric mean elimination half-life ranged from 6-15h.

Absorption

Following single dose oral administration at 50 mg in healthy human under the fasting condition, the time to achieve peak blood concentration (median T_{max}) was about 1.3h and mean elimination half-life was about 8.7h. Food delayed the time to reach peak blood levels (Tmax), reduced Cmax and exposure (AUC_{0-t}).

Distribution

In vitro study revealed that desidustat was highly bound to plasma protein (about 99%) and is not preferentially distributed in erythrocytes.

Metabolism

Desidustat was metabolically stable when incubated with human liver microsomes, human hepatocytes or recombinant human CYP isoforms. In vivo, two minor metabolites (<10%) were identified one represented

hydroxylation and another hydroxyl-glucuronide in clinical pharmacology (non-radiolabeled) study. Desidustat did not show potential to form reactive glutathione (GSH) adduct.

Excretion

Following a single oral dose administration in healthy adult male subjects with an empty stomach, the urinary excretion of unchanged desidustat was about 27 to 41% across the tested dose range (10 to 300 mg). The minor metabolites, hydroxylated and hydroxyl-glucuronide metabolites were also excreted in human urine (non-radiolabel study).

10.12 PHARMACEUTICAL PARTICULARS

Incompatibilities

There are no known incompatibilities of desidustat tablets.

Storage and Shelf-life

Storage and Handing Instructions

Store below 30° C. Keep out of reach of children.

Shelf-life

12 Months.

Patient Counselling Information

- Do not use desidustat tablet for a condition for which it was not prescribed.
- Do not consume any food 1 hour before and 2 hours after taking desidustat.
- Do not give desidustat tablet to other people, even if they have the same symptoms you have.
- Contact your healthcare provider if you develop any symptoms after consumption of desidustat

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12. Abbreviations

AEs, Adverse Events; API, Active Pharmaceutical Ingredient; AUC, Area Under the Curve; BCRP, Breast Cancer Resistance Protein; BL, Baseline; C, Celsius; CERA, Continuous Erythropoietin Receptor Activator; CI, Confidence Interval; CKD, Chronic Kidney Disease; Cmax, the maximum concentration; conc., Concentration; CV, Cardiovascular; CYP, Cytochrome P450; DA, Darbepoetin Alfa; dL, Deciliter; DMT, Divalent Metal Transporter; DNA, Deoxyribonucleic Acid; DP, Drug Product; DQL, Dilution Quality Control; eGFR, estimated Glomerular Filtration Rate; EPO, Erythropoietin; ERBP, European Renal Best Practice; ESAs, Erythropoiesis-stimulating Agents; ESRD, End-Stage Renal Disease; g, Gram; GBD, Global Burden of Disease; GSH, Glutathione; h, Hour; Hb, Hemoglobin; HIF, Hypoxia-Inducible Factor; HIFPH, Hypoxia Inducible Factor Prolyl Hydroxylases; IL, Interleukin; IND, Investigational New Drug; IV, Intravenous; KDIGO, Kidney Disease Improving Global Outcomes; kg, Kilogram; KIM, Kidney Injury Molecule; LC/MS, Liquid Chromatography tandem–Mass Spectrometry; LSM, Least Squares Mean; m, Meter; mg, Milligram; mL, Milliliter; min, Minute; mITT, modified intent-to-treat; mIU/L, Milli International Unit/ Liter; mol, Mole; MPO, Myeloperoxidase; MRHD, Maximum Recommended Human Dose; µm, Micrometer; NDA, New Drug Application; NDD, Non-dialysis-dependent; ng, Nanogram; NHANES, National Health and Nutrition Examination Survey; NOAEL, No-Observed-Adverse-Effect-Level; OAT, Organic Anion Transporter; OCT, organic cation transporter; OATP, organic-anion-transporting polypeptides; P-gP, P Glycoprotein; PHI, Prolyl Hydroxylase Inhibitor; PO, Per Os; PP, Per Protocol; q.s, Quantum Satis; RBC, Red Blood Cell; RT, Room Temperature; SAE, Serious Adverse Event; SD, Sprague Dawley; SE, Standard Error; SEEK, Screening and Early Evaluation of Kidney Disease Project; SFP, Soluble Ferric Pyrophosphate; $t_{1/2}$, mean elimination half-life; TEAE, Treat¬ment Emergent Adverse Event; Tmax, time taken to reach the maximum concentration; TSAT, Transferrin Saturation

For anemia in CKD patients

OXEMIA™

Desidustat 25/50mg tablet

Let freedom flow

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Composition: Each uncoated tablet contains Desidustat 25 mg or 50 mg. Indication: Treatment of Anemia in Adult Patients with Chronic Kidney Disease (CKD) not on Dialysis and on Dialysis. Dosage and administration: For non dialysis patients, The starting dose of Desidustat is 100 mg (4 tablets of 25mg OR 2 Tablets of 50 mg) orally thrice in a week. For dialysis patients, The Starting dose of Desidustat is 100 mg (4 tablets of 25mg OR 2 Tablets of 50 mg) or 125 mg (5 tablets of 25mg OR 2 Tablets of 50 mg and 1 tablet of 25 mg) or 150 mg (6 tablets of 25mg OR 3 Tablets of 50 mg) thrice in a week. It is recommended that Desidustat is to be taken after completion of the dialysis session. Contraindications: Hypersensitivity to Desidustat or any of the excipients used in the formulation. Special warnings and precautions for use: No drug related severe or serious adverse event or any life-threatening condition which requires special attention observed during the study. Drug interactions: The in vitro assays did not reveal any significant inhibition of major drug metabolizing enzymes. Pregnancy Category: C. Nursing mothers should not use Desidustat because it is not known whether Desidustat is excreted into the breast milk. Safety and efficacy of Desidustat in pediatric patients have not been established.Desidustat should be used with caution in geriatric patients. Adverse events: Most common AEs (>2%) reported from phase III includes Gastrointestinal symptoms including nausea , vomiting and abdominal pain, Headache, UTIs, Pyrexia and Peripheral edema. Overdose: No incidence of overdose with Desidustat has been reported. In case of overdose with Desidustat, general supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status. Storage and handing instructions: Store below 30°C. Keep out of reach of children. Shelf life: 12 months. FOR FULL INFORMATION, PLEASE REFER TO THE FULL PRESCRIBING INFORMATION

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