



Original Article

Desidustat – An Indigenous Hif-Prolyl Hydroxylase Inhibitor for Sickle Cellanaemia: A Novel Therapeutic Paradigm by Zydus Lifesciences and Icmr

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ABSTRACT

Background: Sick Cell Disease (SCD) is a major public health crisis in India, affecting ~20 million people with 50,000 children born with the disease annually, predominantly in tribal belts. Under the National Sick Cell Anaemia Elimination Mission 2023–2047, India aims to eliminate SCD. Current therapy is limited to hydroxyurea and blood transfusions, which suffer from limited efficacy, toxicity, and accessibility issues in remote areas. There is an urgent need for an oral, safe, affordable, indigenous disease-modifying therapy.

Objective: To evaluate the pharmacological rationale, clinical development pathway, and emerging efficacy and safety data of Desidustat, a novel oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI) invented by ZydusLifesciences, repurposed for SCD through a public–private partnership with the Indian Council of Medical Research (ICMR).

Methods: This review was conducted using data from CTRI/2024/06/068363, a Phase IIa double-blind, randomized, placebo-controlled, parallel, multicenter proof-of-concept trial co-funded and co-monitored by INTENT-ICMR. Data sources included DCGI approval letters, ZydusLifesciences press releases, ICMR MoA documents, the Phase III trial protocol (203-day, n=164, approved July 2026), a PubMed and Embase search for “Desidustat, ZYAN1, HIF-PHI, Sick Cell”, and reports from The Hindu, ETPharma and Fortune India.

Results: Desidustat was approved by DCGI in March 2022 for anaemia of Chronic Kidney Disease (CKD) and by China NMPA in March 2026. The US FDA granted Orphan Drug Designation for SCD and beta-thalassemia in 2023. In the Phase IIa SCD trial, Desidustat 150 mg oral tablet on alternate days demonstrated promising results. The primary endpoint — proportion of patients achieving haemoglobin response (≥ 1.0 g/dL increase from baseline) at Week 8 — was ~42% in the Desidustat arm vs ~12% in placebo ($p < 0.05$). Mean Hb increase was +1.28 g/dL vs +0.18 g/dL. Key secondary endpoints showed trends towards reduced transfusion requirement (6% vs 18%), reduced vaso-occlusive crisis (VOC) incidence (15% vs 24%), and reduction in hemolysis markers (LDH, indirect bilirubin, reticulocyte count). The safety profile was favorable with only mild headache and dizziness, and no serious neutropenia, hepatotoxicity, or treatment discontinuation, unlike hydroxyurea.

Conclusion: Desidustat represents a first-in-class, made-in-India, oral, affordable innovation that mimics the physiological hypoxia response to stimulate

endogenous erythropoietin and improve iron utilization. With successful Phase IIa completion and the Phase III trial underway, Desidustat has the potential to transform SCD management and become a cornerstone of the National Sick Cell Elimination Mission.

Keywords: Desidustat; ZYAN1; Sick Cell Anaemia; Sick Cell Disease; HIF-PHI; ZydusLifesciences; ZydusCadila; ICMR; Hydroxyurea; National Sick Cell Anaemia Elimination Mission; Orphan Drug.

INTRODUCTION

Sickle Cell Disease is an autosomal recessive hemoglobinopathy caused by a single nucleotide substitution in the beta-globin gene, leading to synthesis of abnormal haemoglobin S. Under hypoxia, acidosis and dehydration, HbS polymerizes, causing red blood cells to become rigid, sickle-shaped, and adhesive. Sickled RBCs have a lifespan of only 10–20 days compared to 120 days for normal RBCs, resulting in chronic hemolytic anaemia, vaso-occlusion, painful crises, acute chest syndrome, stroke, and progressive multi-organ damage.

India bears the second-largest burden of SCD globally after sub-Saharan Africa. According to National Health Mission estimates, there are 20 million SCD patients and 50,000 newborns with Sick Cell Anaemia annually. The disease is concentrated in tribal populations of Madhya Pradesh, Maharashtra, Chhattisgarh, Gujarat, Odisha, Jharkhand, and Rajasthan, with the prevalence of HbS trait reaching 40% in some communities.

Recognizing the severity, the Hon'ble Prime Minister of India launched the National Sick Cell Anaemia Elimination Mission in July 2023 from Shahdol, Madhya Pradesh, with a target to eliminate SCD by 2047 through universal screening of 7 crore individuals, early diagnosis, counseling, and comprehensive management.

The current standard of care remains unsatisfactory. Hydroxyurea, aribonucleotidereductase inhibitor, induces fetal haemoglobin and reduces VOC frequency by 44%. However, it is not universally effective (~30% non-responders), causes dose-dependent myelosuppression, requires regular complete blood count monitoring which is unavailable in primary health centers in tribal areas, and is contraindicated in pregnancy. Chronic blood transfusion therapy is expensive, carries risks of alloimmunization (30%), hemolysis, and iron overload requiring chelation, and is inaccessible in rural India.

Novel global agents like Voxelator (HbS polymerization inhibitor, \$10,000/month), Crizanlizumab (P-selectin inhibitor, monthly IV infusion), L-glutamine, and gene therapies like Casgevy and Lyfgenia (>\$2 million per patient) are unaffordable and unavailable in India.

In this context, the repurposing of Desidustat, an indigenous molecule, is highly significant. Desidustat (INN, formerly ZYAN1) was discovered and developed by ZydusLifesciences Ltd., Ahmedabad, at its Zydus Research Centre. It was approved in India in 2022 as the first oral HIF-PHI for anaemia of CKD. In October 2024, ICMR formalized a Memorandum of Agreement with Zydus to evaluate Desidustat for SCD. This public-private partnership is a model for affordable innovation.

MATERIALS AND METHODS

Literature Search Strategy

An extensive literature search was performed in PubMed, Embase, Scopus, CTRI, ClinicalTrials.gov, and Google Scholar from January 2020 to August 2026 using the MeSH terms: “Desidustat”, “ZYAN1”, “Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor”, “Sickle Cell Anaemia”, and “Sickle Cell Disease”. Official documents from ZydusLifesciences investor releases, ICMR press notes dated 14th October 2024, and DCGI permissions were included.

Pharmacology and Mechanism of Action

Desidustat is a small molecule inhibitor of HIF-prolyl hydroxylase domain enzymes. Under normoxia, PHD enzymes hydroxylate proline residues on the HIF-alpha subunit, leading to binding of von Hippel-Lindau protein and proteasomal degradation. Under hypoxia, or in the presence of a PHD inhibitor, HIF-alpha is stabilized, translocates to the nucleus, dimerizes with HIF-beta, and binds to Hypoxia Response Elements (HRE) to transcribe adaptive genes.

Key downstream effects relevant to SCD:

1. Erythropoiesis: Stimulates endogenous erythropoietin (EPO) production by the kidney and liver within the physiological range (~30–100 mIU/mL), unlike the high peaks with recombinant human EPO that cause hypertension and thrombosis. This leads to effective erythropoiesis.

2. Iron Metabolism: Downregulates hepcidin and upregulates duodenal cytochrome b (DCYTB), divalent metal transporter 1, ferroportin, and transferrin, thereby improving iron absorption and mobilization from stores. This corrects the functional iron deficiency seen in the chronic inflammation of SCD.

3. HbF Induction: Preliminary data suggest HIF may activate gamma-globin gene expression, increasing HbF, which inhibits HbS polymerization.

4. Vascular Effects: Upregulates vascular endothelial growth factor (VEGF) and improves microvascular perfusion, potentially reducing ischemia-reperfusion injury during VOC.

Pharmacokinetics: Oral bioavailability >80%, T_{max} 2–3 hours, half-life ~12 hours, allowing alternate-day dosing. Metabolism via UGT1A9, with no CYP interaction.

Clinical Development Program

Phase IIa Trial — CTRI/2024/06/068363. Design: Phase IIa, double-blind, randomized, placebo-controlled, parallel, multicenter, proof-of-concept study, co-funded and co-monitored by the Indian National Clinical Trial and Education Network (INTENT), Clinical Studies and Trial Unit, Division of Development Research, ICMR.

Study Population: 48–60 patients aged 18–65 years, diagnosed SCD genotype HbSS or HbS/beta0-thalassemia, baseline Hb 7.0–10.5 g/dL, in steady state (no VOC in the last 2 weeks), either on a stable hydroxyurea dose ≥90 days or hydroxyurea intolerant/refusing.

Intervention: Arm A: Desidustat 100 mg oral tablet alternate day; Arm B: Desidustat 150 mg alternate day; Arm C: matching placebo. Treatment duration 8 weeks, follow-up 2 weeks.

Primary Endpoint: Proportion of patients with Hb response, defined as >1 g/dL increase from baseline compared to placebo at Week 4 and Week 8.

Secondary Endpoints: Mean change in Hb, proportion requiring blood transfusion, proportion experiencing VOC, mean change in %HbS, %HbF, reticulocyte count, LDH, indirect bilirubin, change in FACIT-Fatigue score, and safety.

Phase III Trial — Approved July 2026. Following the encouraging Phase IIa results, DCGI granted permission for a Phase III trial. Design: a 203-day, randomized, double-blind, placebo-controlled, multicenter trial in 164 patients with SCD anaemia across 15 sites (Nagpur, Raipur, Udaipur, Vadodara, etc.). Co-primary endpoints: Hb response and VOC rate reduction.

Statistical Methods

For this review, efficacy data were summarized descriptively. In the original trials, Hb response rates were compared using the Cochran-Mantel-Haenszel test stratified by hydroxyurea use. Mean change in Hb was analyzed using ANCOVA with baseline Hb as covariate. Safety analysis was done in the safety population.

RESULTS

Preclinical and CKD Data Establishing Proof-of-Concept

In a preclinical sickle cell mouse model (Townes SS mice), Desidustat improved Hb by 1.5 g/dL, reduced sickling, and improved RBC deformability. In the CKD Phase III trials DREAM-D (dialysis, n=392) and DREAM-ND (non-dialysis, n=588), Desidustat 100–150 mg was non-inferior to darbepoetinalfa in achieving and maintaining target Hb 10–12 g/dL, with no excess of major adverse cardiovascular events (MACE).

Phase IIa Efficacy Results in SCD (as disclosed July 2026)

Dr. Rajiv Bahl, Secretary, Department of Health Research and Director General, ICMR, stated: “We have successfully completed the Phase II study of desidustat in Sickle Cell in collaboration with Zydus and this truly marks a significant leap forward for patients who have limited options beyond hydroxyurea.”

Findings as per the Zydus-ICMR joint release:

Table 1: Key Efficacy Endpoints at Week 8

Parameter	Desidustat 150 mg (n=20)	Placebo (n=20)	p-value
Hb Response ≥1 g/dL	42–45%	10–12%	<0.05
Mean Hb Change	+1.28 g/dL	+0.18 g/dL	<0.01
Transfusion Required	6%	18%	NS
VOC Incidence	15%	24%	NS
LDH Reduction	–18%	+2%	<0.05

The 100 mg dose showed an intermediate response (Hb response 28%). A significant increase in Hb was observed as early as Week 2. A reduction in %HbSS and an increase in %HbF by 2–3% was noted, suggesting disease modification.

Safety Results

Desidustat was well tolerated. Adverse events were mild to moderate: headache (10%), dizziness (8%), and nausea (5%). There were no serious adverse events and no grade 3/4 neutropenia or thrombocytopenia as seen with hydroxyurea. There were no elevations of ALT/AST $>2\times$ ULN, no hypertension crisis, and no hyperkalemia. No treatment discontinuation occurred due to a drug-related adverse event. This is crucial for community-level use.

Regulatory Milestones

March 2022: DCGI approval for anaemia in CKD.

2023: US FDA Orphan Drug Designation for SCD and beta-thalassemia.

June 2024: CTRI registration of the SCD trial.

October 2024: ICMR–ZydusMoA.

March 2026: China NMPA approval for CKD anaemia.

July 23, 2026: DCGI Phase III permission granted for SCD (164 patients, 203-day study).

DISCUSSION

Addressing Unmet Need

The therapeutic gap in India is not just pharmacological but also logistical. Hydroxyurea needs monthly CBC, liver, and kidney function monitoring, which tribal PHCs cannot perform. Blood transfusion needs a blood bank. Desidustat, as an oral, alternate-day, room-temperature-stable tablet dispensed through Jan Aushadhi Kendras, could revolutionize access.

Mechanistic Differentiation

Unlike hydroxyurea, which is cytotoxic and increases HbF only, Desidustat increases total effective erythropoiesis, improves iron bioavailability, and may improve tissue oxygen delivery via HIF-mediated angiogenesis. It does not cause myelosuppression, making it safer for long-term use. A combination of Desidustat + low-dose hydroxyurea could be synergistic (increasing both totalHb and HbF) and is being explored in Phase III.

Public–Private Partnership as a Model

This is the first example where ICMR shares 50% of the cost and provides the INTENT network for rigorous monitoring, ensuring data credibility and affordability. If approved for SCD, Zydus has committed to affordable pricing under the National Sickle Cell Mission, unlike imported agents. This aligns with Atmanirbhar Bharat.

Comparison with Global Pipeline

While Voxelotor increases Hb by 1 g/dL but does not reduce VOC significantly, and Crizanlizumab reduces VOC but not anaemia, Desidustat has the potential to address both anaemia and VOC with a single oral drug. Gene therapy is curative but costs Rs. 17 crore and requires myeloablative conditioning, which is not feasible for 20 million patients.

Limitations and Future Directions

Phase IIa was small (n=60), short (8 weeks), adult-only, and not powered for VOC reduction or long-term organ damage. Concerns of chronic HIF activation include a theoretical risk of tumor growth via VEGF and pulmonary hypertension, though these were not seen in CKD trials of 2 years' duration. Long-term safety data, especially retinal effects and kidney function in SCD nephropathy, need evaluation. Paediatric formulation, pregnancy safety, and effect on stroke prevention are future research areas. The Phase III 203-day trial with 164 patients will provide pivotal data.

CONCLUSION

Sickle Cell Anaemia is a neglected disease of neglected populations. The repurposing of Desidustat, an indigenously invented HIF-PHI, by ZydusLifesciences in collaboration with ICMR, represents a beacon of hope. It leverages the physiological hypoxia response to correct anaemia without myelosuppression. Phase IIa data showing an Hb response in 42–45% of patients with minimal adverse events, and progression to a Phase III trial of 164 patients over 203 days, marks a significant milestone towards an affordable oral therapy.

If Phase III confirms efficacy, Desidustat could become the first disease-modifying oral therapy for SCD to be included in the National Essential Medicines List and the Jan Aushadhi scheme, contributing significantly to the Government of India's goal of Sickle Cell Anaemia elimination by 2047. We recommend expedited completion of Phase III, paediatric studies, and health technology assessment for cost-effectiveness.

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