



Desidustat: First Approval

Sohita Dhillon¹

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Abstract

Desidustat (Oxemia™) is an orally bioavailable, small molecule, hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitor developed by Zydus Cadila for the treatment of anaemia associated with chronic kidney disease (CKD), COVID-2019 infections and chemotherapy induced anaemia. Desidustat inhibits prolyl hydroxylase domain enzymes, resulting in the stabilisation of hypoxia-inducible factor which stimulates erythropoietin production and erythropoiesis. In March 2022, desidustat received its first approval in India for the treatment of anaemia in adults with CKD who are either on dialysis or not on dialysis. Desidustat is in clinical development in China for the treatment of anaemia in patients with CKD, in Mexico for the management of COVID-2019 infections and in the USA for the treatment of chemotherapy induced anaemia. This article summarizes the milestones in the development of desidustat leading to this first approval for anaemia associated with CKD.

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Desidustat (Oxemia™): Key Points

An orally bioavailable, small molecule, HIF-PH inhibitor is being developed by Zydus Cadila for the treatment of anaemia associated with CKD, COVID-2019 infections and chemotherapy induced anaemia

Received its first approval on 7 March 2022 in India

Approved for the treatment of anaemia in adults with CKD who are either on dialysis or not on dialysis

1 Introduction

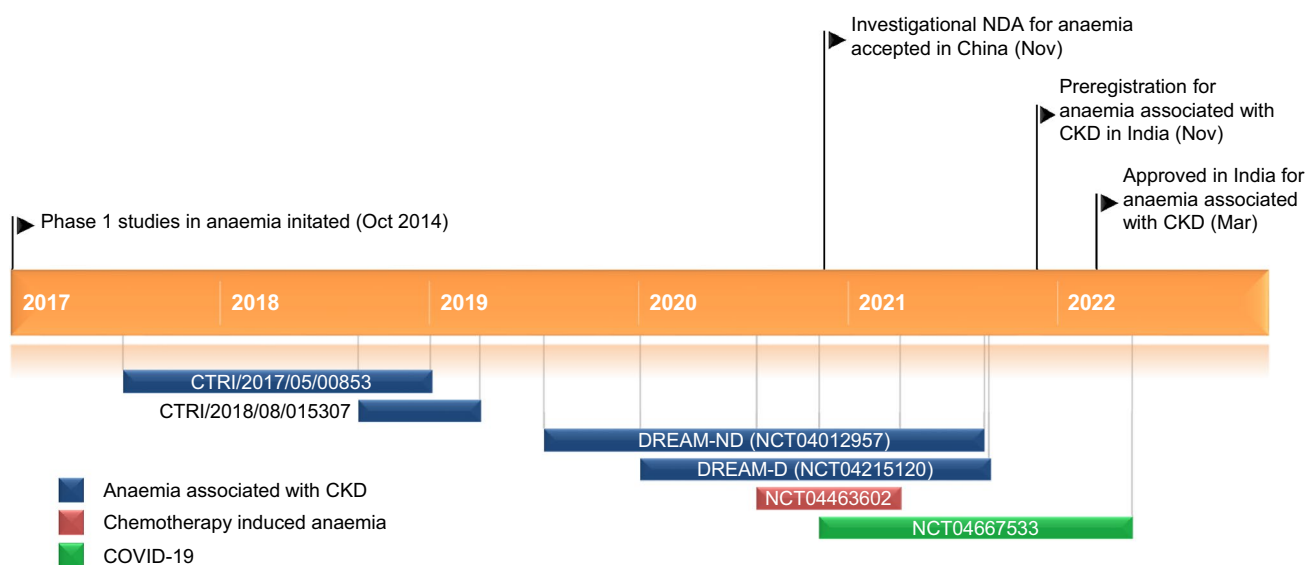
Renal anaemia is a common complication of chronic kidney disease (CKD), resulting from low erythropoietin (EPO) production by the failing kidney and immune activation [1, 2]. Hypoxia-inducible factors (HIF-1 α , HIF-2 α and HIF-3 α) are heterodimeric transcription factors that regulate cellular response to hypoxia by altering gene expression in certain cell types [3, 4]. HIF-2 α plays a key role in regulating erythropoiesis and iron metabolism [1, 3]. Under normal oxygen conditions, HIF- α subunits are targeted for hydroxylation by prolyl-hydroxylase domain enzymes (PHD1, PHD2, and PHD3) and then degraded, thereby inhibiting downstream signalling [1–3]. However, under hypoxic conditions, PHD-mediated hydroxylation of HIF- α is inhibited, resulting in the accumulation of HIF- α . HIF- α is then translocated to the nucleus where it heterodimerizes with HIF- β , resulting in the induction of hypoxia-responsive genes and ultimately stimulating production of endogenous EPO, improving iron metabolism and promoting erythropoiesis [1–3]. Given its central role in the hypoxic regulation of erythropoiesis, the HIF-PHD pathway is an attractive therapeutic target for the treatment of anaemia.

Desidustat (Oxemia™) is an orally bioavailable, small molecule, HIF-prolyl hydroxylase (HIF-PH) inhibitor developed by Zydus Cadila, for the treatment of anaemia associated with CKD, COVID-2019 infections and chemotherapy induced anaemia. Desidustat inhibits PHD,

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✉ Sohita Dhillon
dru@adis.com

¹ Springer Nature, Mairangi Bay, Private Bag 65901, Auckland 0754, New Zealand



Key milestones in the development of desidustat in the treatment of anaemia in adults with chronic kidney disease. *CKD* chronic kidney disease, *NDA* new drug application

resulting in the stabilisation of HIF which stimulates erythropoietin production and erythropoiesis. On 7 March 2022 [5], desidustat received its first approval in India for anaemia associated with CKD in patients either on dialysis or not on dialysis [6]. The recommended starting dosage in dialysis-dependent patients is desidustat 100 mg administered orally three times weekly [6]. In patients not on dialysis and untreated with an erythrocyte stimulating agent (ESA) agent, the recommended starting dosage is desidustat 100 mg three times weekly, and in patients switching from an ESA the recommended dosage is desidustat 100, 125 or 150 mg three times weekly, depending on the previous dose of epoetin, darbepoetin or methoxy polyethylene glycol-epoetin beta. Thereafter, desidustat dosage should be adjusted based on haemoglobin levels assessed every 4 weeks, with a maximum dosage of 150 mg three times weekly [6]. Desidustat is in clinical development in China for the treatment of anaemia in patients with CKD, in Mexico for the management of COVID-2019 infections and in the USA for the treatment of chemotherapy induced anaemia. Clinical development of desidustat has been discontinued in Australia.

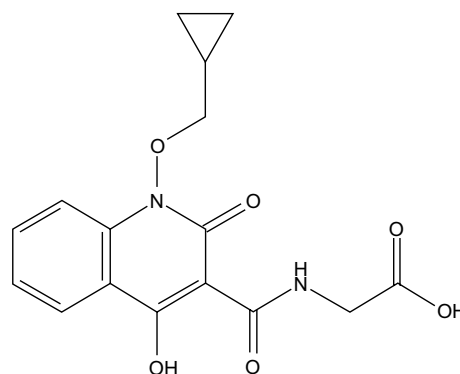
1.1 Company Agreements

In January 2020, Zydus entered into a licensing agreement with China Medical System Holdings Limited (CMS) for the development and commercialization of desidustat in Greater China (Mainland China, Hong Kong Special Administrative Region, Macao Special Administrative Region and Taiwan) [7].

2 Scientific Summary

2.1 Pharmacodynamics

In preclinical studies, desidustat significantly and dose-dependently increased plasma EPO and reticulocyte counts, increased liver HIF-1 α levels, decreased liver hepcidin levels and increased serum iron levels in normal and/or nephrectomized rats [8]. Desidustat also increased haemoglobin, haematocrit and red blood cell (RBC) counts in a chemotherapy (cisplatin)-induced anaemia mouse model [8]. Rodent models of acute and chronic renal failure suggested that the pharmacokinetics of desidustat are unlikely to be altered in CKD patients [9]. Desidustat reversed inflammation-induced anaemia in rodent models, as indicated by increased EPO, haemoglobin, haematocrit and iron levels, increased



Chemical structure of desidustat

reticulocyte and RBC counts and decreased hepcidin levels [10].

In healthy volunteers receiving single-dose desidustat 10–300 mg, desidustat doses of 100–300 mg more consistently increased haemoglobin by > 0.5 g% and increased mean EPO levels in a dose-dependent manner [11]. The mean time to peak serum levels of EPO ranged from 10 to 72 h, with mean serum EPO returning to baseline levels within 24 h. Desidustat multiple doses of 100–300 mg also increased serum EPO, with peak levels reached 6–8 h after peak desidustat concentration is reached (t_{\max}). In individuals receiving multiple dose desidustat 100–300 mg or placebo on days 1, 3 and 5, a dose-dependent increase in serum EPO was observed with desidustat 200 and 300 mg, and more desidustat than placebo recipients had haemoglobin increases of > 0.1% g and > 0.5% g at any time-point. There was no apparent change in mean haematocrit, haemoglobin, and reticulocyte counts over time or between treatments in individuals receiving single or multiple doses of desidustat versus placebo [11].

Desidustat 100–200 mg increased EPO levels and decreased hepcidin and low-density lipoprotein cholesterol (LDL-C) levels versus placebo in a phase 2 study in pre-dialysis patients with CKD (CTRI/2017/05/008534) [12]. In the phase 3 DREAM-ND study (NCT04012957; Sect. 2.3.1.2) in non-dialysis-dependent patients with CKD, hepcidin levels reduced from baseline to greater extent with desidustat than with darbepoetin alfa at weeks 12 ($p = 0.0032$) and 24 ($p = 0.0016$) [13]. LDL-C levels were also significantly lower with desidustat than with darbepoetin alfa at week 24 ($p = 0.0269$), but no significant between-group differences were seen for the changes from baseline in high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, total cholesterol, triglycerides and alipoprotein levels [13]. In the phase 3 DREAM-D study (NCT04215120; Sect. 2.3.1.1) in dialysis-dependent patients with CKD, there was no significant difference between desidustat and epoetin alfa recipients for the decrease from baseline in hepcidin levels at weeks 12 and 24 [14]. The decrease from baseline in total cholesterol and LDL-C at week 12 and alipoprotein at week 24 was greater with desidustat than with epoetin alfa (all $p < 0.01$) [14].

2.2 Pharmacokinetics

The pharmacokinetics of oral desidustat have been assessed in healthy volunteers [6], pre-dialysis CKD patients [6, 12] and dialysis-dependent CKD patients [6]. In healthy volunteers, peak plasma concentration (C_{\max}) of desidustat is reached in ≈ 1.3 h after a single oral dose of desidustat 50 mg under fasting condition [6]. Food delayed desidustat t_{\max}

and reduced desidustat exposure [C_{\max} and area under the concentration-time curve from time 0 to t (AUC_t)] [6].

In patients with dialysis-dependent CKD who received single-dose desidustat 50, 100 or 150 mg within 2 h of dialysis ($n = 8/\text{dose}$), t_{\max} is reached ≈ 2.5 h after dosing [6]. In pre-dialysis CKD patients, desidustat exposure (C_{\max} and AUC_t) increased in a dose-dependent manner after single and multiple doses following treatment with desidustat 100, 150 or 200 mg ($n = 11/\text{dose}$) on alternate days for 6 weeks in a phase 2 study (CTRI/2017/05/008534) [6, 12]. No accumulation of desidustat was observed after multiple-dose administration (accumulation index ≈ 1) [6, 12]. Desidustat is highly ($\approx 99\%$) plasma protein bound and is not preferentially distributed in erythrocytes [6].

In vitro desidustat was metabolically stable when incubated with human liver microsomes, human hepatocytes or recombinant human CYP isoforms. In pre-dialysis patients, desidustat was metabolized into two minor metabolites, hydroxylated and hydroxyl-glucuronide metabolites [6, 12]. Desidustat does not form reactive glutathione-protein adducts [6]. After a single oral dose of desidustat 10–300 mg in healthy volunteers in fasting condition, 27–41% of desidustat was excreted as unchanged drug in the urine; the hydroxylated and hydroxyl-glucuronide metabolites were also detected in the urine. The mean elimination half-life of desidustat was 6–15 h after a single 50–150 mg dose in dialysis-dependent CKD patients and 6–14 h after multiple-dose desidustat 100–200 mg on alternate days for 6 weeks in pre-dialysis CKD patients [6].

At therapeutically relevant concentrations, desidustat has minimal potential to cause CYP-mediated drug-drug interactions [6]. In in vitro studies, desidustat did not significantly inhibit CYP enzymes 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4/5 half maximal inhibitory concentrations > 300 μM) and was not a time dependent inhibitor of CYP3A4/5. Desidustat 100 μM was not an inducer of CYP1A2 or CYP3A4 [6].

2.3 Therapeutic Trials

2.3.1 Anaemia in CKD

Phase 3 DREAM-D Study Oral desidustat was noninferior to subcutaneous biosimilar epoetin alpha in the treatment of anaemia (haemoglobin 8.0–11.0 g/dL) in patients with CKD (stage 5) on dialysis (≥ 2 times a week for ≥ 12 weeks) who were participating in the 24-week, randomized, open-label, multicentre, phase 3 DREAM-D study (NCT04215120) [14]. Patients (both ESA users and nonusers; mean age ≈ 51 years) were randomized to receive desidustat ($n = 196$) or epoetin alfa ($n = 196$) three times weekly for 24 weeks. The initial dose of desidustat was 100 mg in ESA-naïve patients

Features and properties of desidustat

Alternative names	Oxemia™; ZYAN-1; ZYAN-1-1001
Class	Acetic acids; amides; anti-anaemics; cyclopropanes; quinolines; small molecules
Mechanism of action	Inhibits HIF-PH resulting in the stabilisation of HIF which stimulates EPO production and erythropoiesis
Route of administration	Oral
Pharmacodynamics	Decreased hepcidin, increased EPO, serum iron, haematocrit and haemoglobin levels, and increased reticulocytes and RBCs in normal/nephrectomized rats and/or rodent models of chemotherapy-or inflammation-induced anaemia Increased haemoglobin and EPO levels in healthy volunteers Decreased hepcidin levels to a greater extent than darbepoetin alfa in patients with non-dialysis-dependent CKD Decreased hepcidin levels to a similar extent as epoetin alfa in patients with dialysis-dependent CKD
Pharmacokinetics	Time to peak plasma concentration 2.5 h after single 50–150 mg dose in dialysis-dependent patients No accumulation after multiple dose administration Mean elimination half-life 6–15 h after single 50–150 mg dose in dialysis-dependent CKD patients and 6–14 h after multiple doses of 100–200 mg on alternate days for 6 weeks in pre-dialysis CKD patients
Adverse events	
Most frequent	Pyrexia, vomiting, asthenia, peripheral oedema
ATC codes	
WHO ATC code	B03X-A (other antianemic preparations); J05A-X (other antivirals)
EphMRA ATC code	B3X (other anti-anaemic products, including folic acid, folinic acid); J5B9 (antivirals, others)
Chemical name	2-[[1-(cyclopropylmethoxy)-4-hydroxy-2-oxoquinoline-3-carbonyl]amino]acetic acid

CKD chronic kidney disease; EPO erythropoietin, HIF hypoxia-inducible factor, HIF-PH hypoxia-inducible factor-prolyl hydroxylase, RBC red blood cells

and 100, 125 or 150 mg in ESA-experienced patients (based on prior ESA dose); epoetin alfa was administered at a dose of 50 IU/kg. Dosage adjustments were permitted during weeks 4–20 based on haemoglobin levels; iron supplementation was permitted to maintain adequate iron status. Mean haemoglobin level at baseline was 9.61 g/dL in the desidustat group and 9.55 g/dL in the epoetin alfa group. In the modified intent-to-treat population (mITT), the least-squares mean change in haemoglobin from baseline to weeks 16–24 (primary endpoint) in patients receiving desidustat ($n = 184$) was noninferior to that in patients receiving epoetin alfa ($n = 189$) [0.95 vs 0.80 g/dL], as the lower limit of the two-sided 95% confidence interval for the between-group difference was greater than the pre-specified noninferiority margin of -1.0 g/dL (0.14 g/dL; 95% CI -0.13 to 0.42). The proportion of haemoglobin responders was significantly higher in the desidustat group than in the epoetin alfa group (59.2% vs 48.4%; $p = 0.038$), where response was defined as achievement of target haemoglobin of 10–12 g/dL (average of weeks 16, 20 and 24) and posttreatment increase of ≥ 1 g/dL in haemoglobin by week 24. The median time to achieve target haemoglobin was significantly less in patients receiving desidustat than in patients receiving epoetin alfa (4 vs 8 weeks; $p = 0.042$) [14].

Phase 3 DREAM-ND Study Oral desidustat was non-inferior to subcutaneous biosimilar darbepoetin alfa in the treatment of anaemia (haemoglobin 7.0–10 g/dL) in

non-dialysis-dependent patients with CKD (stages 3–5) who were participating in the 24-week, randomized, open-label, multicentre, phase 3 DREAM-ND study (NCT04012957) [13]. Patients (mean age ≈ 53 years) were randomized to receive initial doses of desidustat 100 mg three times weekly ($n = 294$) or darbepoetin alfa 0.75 $\mu\text{g}/\text{kg}$ ($n = 294$) for 24 weeks; dosage adjustments were permitted during weeks 4–20 based on haemoglobin levels. Iron supplement was given based on serum ferritin and transferrin saturation levels. Mean haemoglobin level at baseline was 8.99 g/dL in the desidustat and darbepoetin alfa groups. In the mITT population, the least-squares mean change in haemoglobin from baseline to weeks 16–24 (primary endpoint) in patients receiving desidustat ($n = 268$) was noninferior to that in patients receiving darbepoetin alfa ($n = 261$) [1.95 vs 1.83 g/dL], as the lower limit of the two-sided 95% confidence interval for the between-group difference was greater than the pre-specified noninferiority margin of -0.75 g/dL (0.11 g/dL; 95% CI -0.12 to 0.35). The proportion of haemoglobin responders was significantly higher in the desidustat group than in the darbepoetin alfa group (77.8% vs 68.5%; $p = 0.018$), where response was defined as achievement of target haemoglobin of 10–12 g/dL (average of weeks 16, 20 and 24) and posttreatment increase of ≥ 1 g/dL in haemoglobin by week 24. The median time to achieve target haemoglobin was similar in patients receiving desidustat and those receiving darbepoetin alfa (4 weeks in both groups) [13].

2.3.2 Phase 2 Study

Desidustat dose-dependently increased haemoglobin levels in patients with anaemia due to non-dialysis-dependent CKD who were participating in a 6-week, randomized, double-blind, placebo-controlled, phase 2, dose-ranging study ($n = 117$; CTRI/2017/05/008534) [12]. Patients (mean age ≈ 48 years) were randomized to receive desidustat 100, 150 or 200 mg or placebo on alternate days for 6 weeks in fasting conditions ($n = 29$ – 30 per group). At week 6, a mean increase of 1.57, 2.22, and 2.92 g/dL was observed with desidustat 100, 150 and 200 mg, respectively, versus 0.46 g/dL with placebo in the mITT population (primary endpoint). Haemoglobin response rates (haemoglobin increase of ≥ 1 g/dL from baseline to week 6) in the mITT population were 66%, 75% and 83% with desidustat 100, 250 and 200 mg, respectively, versus 23% with placebo [12].

2.3.3 COVID-19

Desidustat treatment increased red blood cell production and improved oxygen delivery to tissues in patients with COVID-19 infection who were participating in a randomized, open-label, comparator-controlled, phase 2b study (NCT04463602) [15]. None of the hospitalized patients receiving desidustat compared with 25% of patients receiving standard of care treatment required mechanical ventilation. These results suggest that treatment with desidustat could potentially help to prevent acute respiratory distress syndrome in patients with COVID-19 [15].

2.4 Adverse Events

Desidustat was generally well tolerated in the pivotal phase 3 DREAM-D [14] and DREAM-ND [13] studies in patients with anaemia of CKD who were (NCT04215120) [14] or were not (NCT04012957) [13] on dialysis.

In DREAM-D in patients with anaemia due to dialysis-dependent CKD, the incidence of treatment-emergent adverse events (AEs) was similar between patients receiving desidustat and those receiving epoetin alfa (48% vs 46%) [14]. The majority of AEs were mild in severity, unrelated to treatment and resolved without dosage modification in either treatment group. The most common (incidence $> 4\%$) AEs in desidustat and epoetin alfa groups were pyrexia (8.2% vs 5.1%), vomiting (4.1% vs 3.6%), asthenia (4.1% vs 3.6%), headache (3.6% vs 4.6%) and dyspnoea (2.6% vs 4.6%). Serious AEs occurred in 8.2% of desidustat and 10.7% of epoetin alfa recipients, with the most common event being infection and infestation (4.1% vs 3.6%); no serious AE was considered treatment related. No treatment related deaths were reported in either treatment group. At baseline, the majority of patients in the desidustat (92.4%) and epoetin alfa (90.8%) groups had comorbid hypertension [mean systolic blood pressure (BP) ≈ 143 mmHg and diastolic BP ≈ 82 mmHg]. At week 26, no clinically significant change from baseline in sitting systolic BP (mean change $- 4.8$ vs $- 4.6$ mmHg) or sitting diastolic BP ($- 1.8$ vs $- 1.0$ mmHg) was observed with desidustat or epoetin alfa [14].

In DREAM-ND in patients with anaemia due to non-dialysis-dependent CKD, the incidence of treatment-emergent AEs was similar between patients receiving desidustat and those receiving darbepoetin alfa (48% vs 50%) [13]. The majority of AEs were mild in severity, unrelated to treatment and resolved in both treatment groups. The most common (incidence $> 4\%$) AEs in desidustat and darbepoetin alfa groups were pyrexia (6.8% vs 6.8%), peripheral oedema (5.4% vs 3.1%), headache (3.7% vs 4.1%) and hypertension (1.7% vs 5.8%). Hyperkalaemia occurred in $< 2\%$ of patients in the desidustat and darbepoetin alfa groups (1.0% vs 1.7%). Serious AEs occurred in 8.2% of desidustat and 6.1% of darbepoetin alfa recipients, with the most common event being infection and infestation (4.8% vs 1.4%); no serious AE was considered treatment related. No treatment related deaths were reported in either treatment group. One patient

Key clinical trials of desidustat sponsored by Zydus Cadila

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Desidustat, epoetin alfa	CKD on dialysis	3	Completed	India	DREAM-D; NCT04215120; DESI.19.001.01
Desidustat, darbepoetin alfa	CKD not on dialysis	3	Completed	India	DREAM-ND; NCT04012957; DESI.18.001
Desidustat, Placebo	CKD not on dialysis	3		China	ChiCTR2100052908
Desidustat, placebo	CKD not on dialysis	2	Completed	India	CTRI/2017/05/008534
Desidustat, standard of care	COVID-19	2	Completed	Mexico	NCT04463602; DESI.20.004
Desidustat	CKD on dialysis	1b/2a	Completed	India	CTRI2018-08-015307
Desidustat	Chemotherapy induced anaemia	1	Completed	India	NCT04667533; DESI.20.001

withdrew from treatment in the desidustat due to an AE (diabetic foot infection), which was considered unrelated to treatment. At baseline, the majority of patients in the desidustat (85.0%) and darbepoetin alfa (82%) groups had comorbid hypertension [mean systolic BP \approx 133 mmHg and diastolic BP \approx 81 mmHg]. At week 26, no clinically significant change from baseline in sitting systolic (mean change -0.94 vs $+0.31$ mmHg) or sitting diastolic BP (-0.22 vs $+0.11$ mmHg) was observed with desidustat or darbepoetin alfa. Clinically significant abnormal electrocardiogram results were reported in one patient in the desidustat group and six patients in the darbepoetin alfa group [13].

3 Ongoing Trials

A randomized, double-blind, placebo-controlled, phase 3 trial (ChiCTR2100052908) is planned that will evaluate the efficacy and safety of desidustat in \approx 150 patients with anaemia due to non-dialysis-dependent CKD in China.

4 Current Status

Desidustat received its first approval in India on 7 March 2022 [5] for the treatment of anaemia in adults with CKD who are either on dialysis or not on dialysis [6].

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Declarations

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