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ADISINSIGHT REPORT

Daprodustat: First Approval

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Abstract
Daprodustat (DUVROQ) is a small molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase (PHD) developed by GlaxoSmithKline for the treatment of anaemia in patients with chronic kidney disease (CKD). Inhibition of PHD prevents degradation of hypoxia-inducible factor (HIF), leading to the production of erythropoietin and subsequent induction of erythropoiesis. In June, daprodustat received its first approval in Japan for the treatment of renal anaemia. Clinical studies of daprodustat are underway in multiple countries worldwide. This article summarizes the milestones in the development of daprodustat leading to this first approval for the treatment of renal anaemia.

Daprodustat (DUVROQ): Key points

A small molecule PHD inhibitor is being developed by GlaxoSmithKline for the treatment of anaemia in patients with CKD

Received its first approval on 29 June 2020 in Japan

Approved for the treatment renal anaemia

1 Introduction

Progressive chronic kidney disease (CKD) is associated with several serious complications, including anaemia, increased incidence of cardiovascular disease, hyperlipidaemia and metabolic bone disease [1]. Anaemia of CKD is largely the result of the diseased kidney being unable to adequately respond to hypoxia and/or anaemia by inducing erythropoietin (EPO) production [2]. Other factors contributing to the development of anaemia include iron and vitamin deficiency, infection and inflammation [3]. Hypoxia-inducible factor (HIF) 1α and HIF2α are heterodimeric transcription factors mediating the cellular response to hypoxia by altering gene expression in certain cell types. This results in the increased production of EPO in the kidney and liver, which in turn promotes an erythropoietic response and upregulation of iron transport [2–4]. HIFα levels are regulated via the action of a family of HIF-prolyl hydroxylases (PHDs) that are important for maintaining the balance between oxygen availability and HIF activity [5]. PHDs tag HIFα for proteasomal degradation, and inhibition of these hydroxylases simulates conditions of mild hypoxia, leading to an erythropoietic response [5]. The central role of PHDs as the enzymatic gatekeepers of the adaptive response to hypoxia makes them attractive therapeutic targets for the treatment of anaemia.

Daprodustat (DUVROQ) is a small molecule inhibitor of PHD developed by GlaxoSmithKline for the treatment of anaemia in patients with CKD. On 29 June 2020 [6], daprodustat received its first approval in Japan for the treatment of renal anaemia [7]. In adults with CKD who are not undergoing dialysis, the recommended initial dosage of daprodustat in patients untreated with an erythropoiesis-stimulating agent (ESA) is 2 mg (for Hb levels ≥ 9.0 g/dL) or 4 mg (for Hb levels < 9.0 g/dL) given orally once daily, and in adults switching from an ESA is 4 mg given orally once daily. In dialysis-dependent patients, the recommended initial dosage of daprodustat is 4 mg administered orally once daily irrespective of whether patients are receiving ESAs or switching

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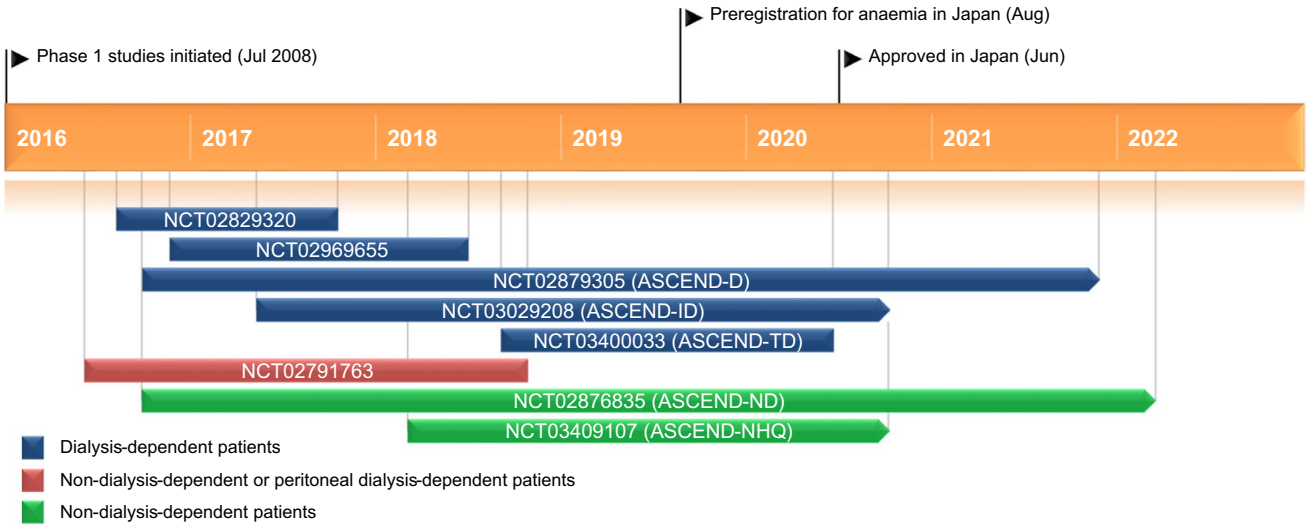


Key milestones in the development of daprodustat in the treatment of renal anaemia, focusing on phase 3 trials

from ESAs. Thereafter, daprodustat dose may be adjusted (maximum 24 mg once daily) according to the severity of anaemia [7]. Clinical studies of daprodustat are underway in multiple countries worldwide. Development of daprodustat for diabetic foot ulcer, perioperative ischaemia, peripheral arterial disorders and tendon injuries has been discontinued.

1.1 Company Agreements

In November 2018 [8], GlaxoSmithKline (GSK) entered into an agreement with Kyowa Hakko Kirin for the commercialisation of daprodustat in Japan for use in patients with anaemia of CKD. Under the terms of the agreement, GSK is responsible for completion of the Japan clinical programme and regulatory submissions for marketing authorisation in Japan, while Kyowa Hakko Kirin is responsible for the distribution of daprodustat in Japan. Both the companies will jointly conduct launch activities, including engagement of healthcare professionals and commercial activities. Further financial details of the agreement were not disclosed [8]. The global programme for daprodustat outside of Japan is ongoing.

2 Scientific Summary

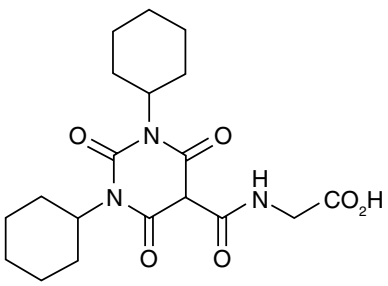
2.1 Pharmacodynamics

Daprodustat is a potent (≥ 1000-fold selectivity) inhibitor of PHDs 1–3, which results in the stabilization of cellular HIF1α and HIF2α, leading to the production of EPO and subsequent induction of erythropoiesis in in vivo preclinical studies [5]. In mice, a single oral dose of daprodustat increased EPO levels, with peak levels (11.2-fold higher than baseline) reached 12 hours after dosing. Increased production of EPO is believed to induce erythropoiesis, as demonstrated by significant ($p < 0.001$ vs. vehicle) increases in reticulocyte counts (211–673% increase) and haemoglobin levels (12–17% increase) in mice treated with oral daprodustat once daily for 8 days [5]. Daprodustat reduced mean ferritin levels, transferrin saturation and hepcidin levels and increased total iron binding capacity in non-dialysis-dependent patients, haemodialysis patients and peritoneal dialysis patients during ≤ 52 weeks treatment in phase 3 studies [7].

At 75 and 500 mg doses, daprodustat had no clinically significant effect on cardiac repolarization or QT interval (NCT02293148) [9].

2.2 Pharmacokinetics

The pharmacokinetic properties of oral daprodustat are based on data from healthy subjects and a population



Chemical structure of daprodustat

pharmacokinetic analysis based on data from non-dialysis-dependent patients, haemodialysis patients and peritoneal dialysis patients with anaemia of CKD [7].

Daprodustat exhibited linear pharmacokinetics after single-dose administration over the dose range 10–100 mg. Following administration of a single oral 4 mg dose of daprodustat, the median time to peak plasma concentration of daprodustat (t_{max}) was reached in 1.75 h (fasting state) or 2.75 h (after a meal) (NCT03493386) [7, 10]. Daprodustat exposure was slightly lower when the drug was administered after a standard CKD meal, as indicated by a 9% decrease in the area under the concentration-time curve (AUC) from 0 to infinity and an 11% decrease in the peak plasma concentration (C_{max}) (NCT03493386) [7, 10].

Following multiple-dose administration, the median t_{max} of daprodustat was 1–3.25 h in healthy subjects receiving daprodustat 15–100 mg once daily, and 1–4 h in patients with anaemia of CKD receiving daprodustat 1–24 mg once daily [7]. The absolute bioavailability of daprodustat after oral administration of 6 mg of this drug was 65% and its volume of distribution after intravenous administration was 14.3 L. Daprodustat (0.2–10 µg/mL) was highly (≈99%) protein bound to human plasma proteins (mainly albumin), according to in vitro data [7].

Daprodustat is largely metabolized by CYP2C8 and to a small extent by CYP3A4 in in vitro studies [7]. After oral administration of a radiolabelled dose of daprodustat, 40% of total radioactivity in the plasma was accounted for by the parent drug and 60% by metabolites. Oral daprodustat is primarily excreted in the faeces (73.6% of a radiolabelled dose), with renal excretion a secondary route of elimination (21.4%). The mean urinary excretion of oral daprodustat was < 0.05% of the dose [7]. The elimination half-life of oral daprodustat after a single 4 mg dose in healthy subjects was 3.24 h (fasting state) or 3.22 h (after a meal) (NCT03493386) [7, 10].

Moderate [estimated glomerular filtration rate (eGFR) 30–59 mL/min/1.73 m^2) or severe (eGFR 15–29 mL/min/1.73 m^2) renal impairment did not affect the pharmacokinetics of daprodustat to a clinically meaningful extent (NCT02293148 and NCT02243306) [7, 11]. The AUC values of all daprodustat metabolites assessed were higher in anaemic non-dialysis-dependent CKD stage 3/4 subjects (up to 2.84-fold) and in anaemic subjects on haemodialysis (up to 6.2-fold) than in subjects with normal renal function ($CL_{CR} \geq 90$ mL/min/1.73 m^2) [7, 11]. Mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment also did not affect the pharmacokinetics of daprodustat [7, 12]. As daprodustat is metabolized by CYP2C8, coadministration with CYP2C8 inhibitors may increase the plasma concentration of daprodustat (NCT01376232 and NCT02371603) [7, 13, 14], and coadministration with CYP2C8 inducers may reduce the plasma concentration of daprodustat [7].

Features and properties of daprodustat

Alternative names	1278863; DUVROQ[a]; GSK-1278863; GSK-1278863A
Class	Anti-ischaemics; antianaemics; pyrimidines; skin disorder therapies; small molecules
Mechanism of action	Inhibits of prolyl hydroxylases, thereby preventing the degradation of hypoxia-inducible factor, leading to the production of erythropoietin and subsequent induction of erythropoiesis
Route of administration	Oral
Pharmacodynamics	Increased erythropoietin levels, reticulocyte counts and haemoglobin levels in mice
	Reduced mean ferritin levels, transferrin saturation and hepcidin levels and increased the total iron binding capacity in patients with anaemia of chronic kidney disease
Pharmacokinetics	T_{max} 1–4 h, plasma protein binding ≈99%, excreted largely in the faeces, $t_{½}$ ≈3 h
Adverse effects	
< 1%	Retinal haemorrhage, hypersensitivity (rash, dermatitis, urticaria) and high blood pressure
Serious	Thromboembolism
ATC codes	
WHO ATC code	B03 (antianemic preparations); C (cardiovascular system); C01 (cardiac therapy); D03 (preparations for treatment of wounds and ulcers); M09A-X (other drugs for disorders of the musculoskeletal system)
EphMRA ATC code	B3 (antianaemic preparations); C1 (cardiac therapy); C6A (other cardiovascular products); D3A (wound healing agents); M5X (all other musculoskeletal products)
Chemical name	*N*-[(1,3-Dicyclohexylhexahydro-2,4,6-trioxopyrimidin-5-yl)carbonyl]glycine

[a]Trademarks are owned by or licensed to the GSK group of companies

2.3 Therapeutic Trials

2.3.1 Phase 3 Studies

Daprodustat achieved and maintained target Hb levels (10–12 g/dL) during 24 weeks' treatment in Japanese haemodialysis patients who were not receiving an ESA, according to results of an open-label, multicentre phase 3 study (NCT02829320) [15]. Patients ($n = 28$) aged ≥ 20 years with Hb levels ≥ 8 to < 10 g/dL and ferritin levels > 100 ng/mL received dosages of daprtodustat (determined as per pre-defined treatment algorithm) for 24 weeks. The mean change in Hb from baseline to week 4 (coprimary endpoint) was 0.79 g/dL (mean Hb level increased from 9.10 g/dL at baseline to 9.90 g/dL at week 4). The majority (86%) of patients experienced an Hb increase of > 0 to 2.0 g/dL, with 46% experiencing an increase of > 0 to 1.0 g/dL and 39% an increase of > 1.0 to 2.0 g/dL (coprimary endpoint). The target Hb level was achieved by week 8 and maintained within the target range over the 24-week period [15].

Daprodustat was noninferior to darbepoetin alfa in maintaining target Hb levels (10–12 g/dL) in Japanese haemodialysis patients with anaemia of CKD who were treated with ESAs, according to results of a randomized, double-blind, multicentre, phase 3 study (NCT02969655) [16]. Eligible patients were randomized to receive titration algorithm-determined dosages of daprodustat ($n = 136$) or darbepoetin alfa ($n = 135$) for 52 weeks. Mean Hb level at baseline was 10.94 g/dL in the daprodustat group and 10.82 g/dL in the darbepoetin group. During weeks 40–52 of treatment, the mean Hb level in patients receiving daprodustat was noninferior to that in patients receiving darbepoetin alfa (10.89 vs. 10.83 g/dL; primary endpoint), as the lower limit of 95% confidence interval was greater than the pre-specified noninferiority margin of − 1.0 g/dL (between-group difference 0.06 g/dL; 95% CI − 0.11 to 0.23). The majority of patients receiving daprodustat (88%) or darbepoetin alfa (90%) had Hb levels within the target range over weeks 40–52 of therapy [16].

Daprodustat was noninferior to epoetin beta pegol (an ESA) for the treatment of anaemia in non-dialysis-dependent Japanese patients with CKD (stages 3, 4 or 5; CKD-3/4/5), according to results of a 52-week, open-label, multicentre study (NCT02791763) [7]. Patients (both ESA users and non-users) received the titration algorithm-determined dosages of daprodustat ($n = 108$) or epoetin beta pegol ($n = 109$) for 52 weeks. Following treatment with daprodustat or epoetin beta pegol (doses adjusted to achieve/maintain haemoglobin levels of 10–13 g/dL), the mean haemoglobin level at the time of primary efficacy analysis (weeks 40–52) was noninferior between patients receiving daprodustat and those receiving epoetin beta pegol (11.97 vs. 11.86 g/dL; primary endpoint). The lower margin of the 95% CIs of the between-group difference (0.10; 95% CI − 0.07 to 0.28) was above the non-inferiority margin of − 1.0 g/dL, indicating the noninferiority of the two treatment groups. The study also assessed the efficacy of daprodustat (titration algorithm-determined dosage) in treating anaemia in 56 patients on peritoneal dialysis. At the time of primary analysis (weeks 40–52), patients receiving daprodustat had a mean Hb level of 12.09 g/dL, which was within the target Hb level of 11–13 g/dL [7].

2.3.2 Phase 2 Studies

Daprodustat dose-dependently increased Hb levels over the first 4 weeks and maintained Hb target levels (10–11.5 g/dL) over 24 weeks of treatment in haemodialysis patients with stable Hb levels (9–11.5 g/dL) who were previously receiving a stable dose of recombinant human erythropoietin (rhEPO), according to a 24-week, randomized, open-label multicentre, global phase 2b study (NCT01977482) [17]. Patients were stratified by region (Japan vs. non-Japan) and prior rhEPO dose and randomized to receive daprodustat at starting doses of 4–12 mg once daily ($n = 177$) or placebo ($n = 39$) for 4 weeks, with doses adjusted thereafter to achieve and maintain target Hb levels. The mean Hb level changed from baseline to week 4 (primary endpoint) in a dose-dependent manner in patients receiving daprodustat (mean change from baseline − 0.29 to 0.69 g/dL with daprodustat vs. − 0.72 g/dL), with changes evident from week 2 [17].

Another 24-week, randomized, open-label, multicentre, phase 2b study (NCT01977573) showed that daprodustat effectively achieved/maintained target Hb levels over 24 weeks in non-dialysis-dependent CKD-3/4/5 patients with anaemia who were rhEPO naïve or who had switched from existing rhEPO therapy [18]. Patients who were rhEPO naïve ($n = 180$) were randomized 3:1 to receive daprodustat (1, 2 or 4 mg based on baseline Hb) once daily or control (rhEPO per standard of care), and rhEPO-users ($n = 72$) were randomized 1:1 to daprodustat 2 mg once daily or control (rhEPO per standard of care) for 4 weeks, thereafter daprodustat doses could be adjusted to achieve and maintain target Hb levels (9–10.5 g/dL in Cohort 1 and 10–11.5 g/dL in Cohort 2). At week 24, the mean Hb levels (primary endpoint) in the daprodustat group were 10.2 g/dL (Cohort 1) and 10.9 g/dL (Cohort 2) and in the control group were 10.7 g/dL (Cohort 1) and 11.0 g/dL (Cohort 2). Between weeks 12 and 24, target Hb levels were maintained within the target range in a median of 82% and 66% of patients in the daprodustat and control groups, respectively [18].

A 4-week, randomized, single-blind, multicentre, phase 2a study (NCT01047397) in anaemic non-dialysis-dependent patients with CKD-3/4/5 ($n = 70$) and anaemic haemodialysis patients with CKD stage 5D (CKD-5D; $n = 37$)

determined that daprodustat induced a robust response (i.e. rate of increase and the absolute level of Hb) and daprodustat doses of < 10 mg once daily were suitable for further study in long-term clinical trials [19]. Patients were ESA-naive with Hb levels ≤ 11.0 g/dL or if ESA treatment was discontinued for ≥ 7 days or equivalent to the interval between scheduled ESA doses [19]. A 4-week, randomized, placebo-controlled phase 2a study ($n = 72$; NCT01587898) in non-dialysis-dependent patients with anaemia of CKD (baseline Hb 8.5–11.0 g/dL) and who were not receiving rhEPO showed that daprodustat 0.5–5 mg once daily produced dose-dependent increases in Hb levels, with the highest dose resulting in a mean increase of 1 g/dL [20].

A 4-week, randomized, double-blind, placebo-controlled phase 2 study ($n = 97$; NCT02019719) in Japanese haemodialysis patients who were not receiving ESA (baseline Hb level 8.5–10.5 g/dL) also showed that daprodustat 4–10 mg once daily induced a dose-dependent increase in Hb levels relative to placebo [21]. In a 4-week, randomized, rhEPO-controlled phase 2a study ($n = 82$; NCT01587924), daprodustat 5 mg was found to maintain mean Hb levels in haemodialysis patients with anaemia of CKD (baseline Hb 9.5–12.0 g/dL) who had switched from rhEPO; mean Hb levels decreased in patients receiving lower daprodustat doses (0.5 or 2 mg once daily) [20]. A 29-day, randomized, double-blinded, placebo-controlled phase 2 study ($n = 103$; NCT02689206) determined that daprodustat 10–30 mg administered three times weekly in haemodialysis patients who were switched from stable doses of rhEPO (baseline Hb 9–11.5 g/dL) also produced dose-dependent increases in Hb levels [22].

Key clinical trials of daprodustat sponsored by GlaxoSmithKline

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Daprodustat	CKD anaemia in HD pts	3	Completed	Japan	NCT02829320; 204716
Daprodustat, darbepoetin alfa	CKD anaemia in HD pts	3	Completed	Japan	NCT02969655; 201754
Daprodustat, epoetin beta pegol	CKD anaemia in ND or PD pts	3	Completed	Japan	NCT02791763; 201753
Daprodustat, epoetin alfa	CKD anaemia in HD pts	3	Completed	Multinational	NCT03400033; 204837; 2017-004372-56; ASCEND-TD
Daprodustat placebo	CKD anaemia in ND pts	3	Ongoing	Multinational	NCT03409107; 205270; 2017-002270-39; ASCEND-NHQ
Daprodustat, darbepoetin alfa	CKD anaemia in ID	3	Ongoing	Multinational	NCT03029208; 201410; 2016-000507-86; ASCEND-ID
Daprodustat, rhEPO	CKD anaemia in HD pts	3	Ongoing	Multinational	NCT02879305; 200807; 2016-000541-31; ASCEND-D
Daprodustat, darbepoetin alfa	CKD anaemia in ND pts	3	Recruiting	Multinational	NCT02876835; 200808; 2016-000542-65; ASCEND-ND
Daprodustat, placebo	CKD anaemia in ND and HD pts	2	Completed	Multinational	NCT01047397; 112844; PHI112844
Daprodustat, placebo	CKD anaemia in ND pts	2	Completed	USA, Canada, Germany	NCT01587898; 116581
Daprodustat, rhEPO	CKD anaemia in HD pts	2	Completed	Multinational	NCT01587924; 116582
Daprodustat, rhEPO	CKD anaemia in ND pts	2	Completed	Multinational	NCT01977573; 113747
Daprodustat, rhEPO	CKD anaemia in HD pts	2	Completed	Multinational	NCT01977482; 113633
Daprodustat, placebo	CKD anaemia in HD pts	2	Completed	Japan	NCT02019719; 116099
Daprodustat, placebo	CKD anaemia in HD pts	2	Completed	Multinational	NCT02689206; 204836; 2015-004790-32
Daprodustat, epoetin alfa	CKD anaemia in HD pts	2	Recruiting	USA	NCT03029247; 205665; ASCEND-BP
Daprodustat, rhEPO	CKD anaemia in ND pts	2	Recruiting (suspended)	USA	NCT03457701; 201771; ASCEND-Fe

HD haemodialysis-dependent, *ID* incident dialysis, *L-NMMA* L-*N*-monomethyl arginine acetate, *ND* non-dialysis-dependent, *PD* peritoneal dialysis-dependent, *pts* patients, *rhEPO* recombinant human erythropoietin

2.4 Adverse Events

Daprodustat was generally well tolerated in the phase 3 studies in haemodialysis patients with anaemia of CKD who were (NCT02969655) [16] or were not (NCT02829320) [15] treated with an ESA, as well as in non-dialysis-dependent and peritoneal dialysis patients with anaemia of CKD (NCT02791763) [7]. Adverse reactions reported with daprodustat include retinal haemorrhage, hypersensitivity (rash, dermatitis, urticaria) and high blood pressure (BP) [all < 1% in frequency]. Daprodustat has also been associated with serious thromboembolic AEs in 0.8% of patients, including AEs such as cerebral infarction (0.3%), pulmonary embolism (0.3%), retinal vein occlusion (0.3%), deep vein thrombosis (0.3%), vascular access thrombosis (e.g. shunt occlusion; frequency unknown) [7].

In haemodialysis patients with anaemia of CKD who were not receiving an ESA (NCT02829320), treatment-emergent AEs were reported in 89% (25/28) of patients over 24 weeks' daprodustat therapy; AEs occurred in 82% (9/11) of patients initiating dialysis and 94% (16/17) of patients on maintenance dialysis [15]. The most common (≥ 2 patients) treatment-emergent AEs with daprodustat were nasopharyngitis (32% [9 of 28]), infected dermal cyst (7% [2 of 28]), shunt occlusion (7% [2 of 28]) and shunt stenosis (7% [2 of 28]). The majority of AEs were of mild or moderate severity. No treatment-emergent AE resulted in discontinuation of therapy or withdrawal from the study. Two patients had treatment-related AEs, with a decrease in blood cholesterol reported in a patient on maintenance dialysis and erythema reported in a patient initiating dialysis. A total of four serious AEs occurred in three patients and included shunt occlusion (considered severe) in two patients and device dislocation (intraocular lens dislocation) in one patient; all AEs resolved, and none were considered treatment related. Of the ophthalmologic assessments undertaken for ocular AEs, only one ocular AE (retinal haemorrhage) was reported in the study [15].

In haemodialysis patients with anaemia of CKD who were treated with ESAs (NCT02969655), the most frequent (incidence ≥ 10%) treatment-emergent AEs with daprodustat or darbepoetin alfa during 52 weeks' therapy were nasopharyngitis, diarrhoea, shunt stenosis, contusion and vomiting [16]. Most treatment-emergent AEs were of mild or moderate severity and no deaths were reported in the study. The incidence of ocular AEs (e.g. proliferative retinopathy, macular edema choroidal neovascularisation) was similar between the two treatment groups.

In non-dialysis-dependent patients with anaemia of CKD (NCT02791763), treatment-related AEs occurred in 6% (9/149) of patients receiving daprodustat, including increased Hb levels, increased BP, increase in eosinophil counts, hypertension, abdominal distention, epigastric pain, gastroesophageal reflux disease, retinal haemorrhage and cerebral infarction (each < 1%; 1/149) [7]. In peritoneal dialysis patients with anaemia of CKD, treatment-related AEs were reported in 14% (8/56) of patients, including nausea (4%; 2/56) and diarrhoea, cough, pulmonary embolism, pulmonary hypertension, retinal haemorrhage, liver function abnormality, decreased haemoglobin, acne-like dermatitis and deep vein thrombosis (each 2%; 1/56) [7].

2.5 Ongoing Clinical Trials

Several phase 3 efficacy and safety trials of daprodustat are ongoing, including the randomized, double-blind ASCEND-NHQ trial (NCT03409107) in ≈ 600 non-dialysis-dependent patients with anaemia of CKD. The study is comparing the efficacy, safety and health-related quality of life in patients receiving daprodustat versus those receiving placebo. The primary endpoint of the study is the mean change from baseline to the evaluation period (weeks 24–28) in Hb levels and secondary endpoints include the proportion of patients with a ≥ 1.0 g/dL increase in Hb level, proportion of Hb responders and the mean change from baseline in the Short Form-36 (SF-36) questionnaire vitality domain score. Recruitment is underway in the randomized, open-label, multicentre, phase 3 ASCEND-ND trial (NCT02876835) that is comparing the efficacy and safety of daprodustat with that of darbepoetin alfa in an estimated 4500 non-dialysis-dependent patients with anaemia of CKD. The coprimary endpoints of the study are the time to first occurrence of adjudicated major adverse cardiovascular event (MACE) and the mean change from baseline in Hb levels over the evaluation period (weeks 28–52).

Also ongoing is the randomized, open-label, multicentre, phase 3 ASCEND-D trial (NCT02879305) in ≈ 2964 dialysis patients with anaemia of CKD that is comparing the efficacy and safety of daprodustat with that of rhEPO following a switch from ESAs. The coprimary endpoints of the study are the time to first occurrence of MACE and the mean change from baseline in Hb levels over the evaluation period (weeks 28–52). In addition, the randomized, open-label, multicentre, phase 3 ASCEND-ID trial (NCT03029208) is evaluating the efficacy and safety of daprodustat versus that of rhEPO in ≈ 300 patients with anaemia of CKD who are initiating dialysis. The primary endpoint of the study is the mean change from baseline over the evaluation period (weeks 28–52) in the Hb level and secondary endpoints include the monthly intravenous iron dose, change from baseline to week 52 in systolic BP (SBP), diastolic BP (DBP) and mean arterial BP (MAP). The phase 3 ASCEND-TD trial (NCT03400033) in haemodialysis patients with anaemia of CKD is also ongoing and is comparing the efficacy and safety of daprodustat with that of epoetin alfa. The primary endpoint is the mean change from baseline in Hb levels over the evaluation period (weeks 28–52).

Recruitment is underway in the randomized, open-label, phase 2 ASCEND-BP trial (NCT03029247), which will assess the effect of daprodustat on BP in haemodialysis in an estimated 62 patients with anaemia of CKD who will switch from a stable dose of ESA. The primary endpoint of the study is the average of 6-h post dose SBP at day 57 and secondary endpoints include the average of 6-h post dose SBP, DBP and MAP at day 1. Recruitment was underway in the randomized, open-label, phase 2 ASCEND-Fe trial (NCT03457701), which was designed to compare the effect of daprodustat compared with rhEPO on oral iron absorption in non-dialysis-dependent patients with anaemia of CKD; however, the study has been suspended due to the COVID-19 pandemic.

3 Current Status

On 29 June 2020 [6], daprodustat received its first approval in Japan for the treatment of renal anaemia [7].

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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