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MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

DAPRODUSTAT FOR ANAEMIA IN CHRONIC KIDNEY DISEASE (CKD)

EXECUTIVE SUMMARY

Daprodustat is an investigational oral hypoxia-inducible factor prolyl hydroxylase (PHD) for stimulate production of erythropoietin.

It inhibits hypoxia-inducible factor prolyl hydroxylase (PHD) and prevents degradation of hypoxia-inducible factor (HIF) by stimulating production of erythropoietin. Two meta-analysis with trial sequential analysis and systematic review, seven clinical trials and one economic evaluation were included in this review. Daprodustat has been demonstrated to be effective in improving anaemia, enhancing iron utilisation and safe for anaemia patients with CKD. There was no cost-effectiveness study for daprodustat retrieved. However, the current drug suggested HIF-PHI to be cost-effective at a USD 29,295 (RM 123,185.48) per QALY for non-dialysis patient and incremental cost effective ratio (ICER) of USD 25,563 (RM 107,492.42) per QALY for five years' horizon.

Keywords: daprodustat, anaemia, chronic kidney disease, dialysis, non-dialysis

INTRODUCTION

Chronic kidney disease (CKD), characterised by progressive loss of kidney function, is a global public health burden with prevalence of 13%, and majority of the patients were in stage 3.[1] The risk factors for CKD include hypertension, diabetes, obesity, cardiovascular diseases aging factor and primary renal disorders.[2]

Anaemia is an important and frequent complication of CKD. However, it is often poorly diagnosed and undertreated in patients with early-stage CKD, who are not on dialysis. If untreated or undertreated, anaemia of CKD is associated with poor clinical outcomes, resulting in a substantial burden on patients and healthcare system.[1,3] The prevalence of CKD in Malaysia has increased from 9.1% in the 2011 to 15.5% in 2018.[4] The Malaysian

Dialysis and Transplant Registry reported that more than 7000 patients received dialysis in 2015 and increased to 39,711 by the end of 2016. If the present trend continues unchecked, the number of end stage kidney disease (ESKD) patients is estimated to reach more than 100,000 cases in 2040.[5,6] The increasing prevalence of diabetes, hypertension and the aging population is expected to increase CKD in the future.[2]

Anaemia is present in 75.8% of pre-dialysis Malaysian patients and it is more prominent as the disease progresses.[7,8,9,] Correcting renal anaemia can reduce mortality, hospitalisation, risk of CKD progression, and improve the health-related quality of life.

THE TECHNOLOGY

Daprodustat is an investigational oral hypoxia-inducible factor prolyl hydroxylase (PHD) developed by GlaxoSmithKline (GSK) for the treatment of anaemia in patients with chronic kidney disease (CKD). The inhibition of PHD prevents degradation of hypoxia-inducible factor (HIF), leading to the production of erythropoietin and subsequent induction of erythropoiesis. It is a highly protein-bound molecule and undergoes oxidative metabolism primarily in the liver by the CYP2C8 enzyme into six metabolites with an approximate half-life of up to four hours (100mg dose).[10] The available dosage is ranged from 5mg to 100mg daily by oral administration. The maximum daily dose should not exceed 24mg.[11]

Since June 2020, daprodustat received the first approval for the treatment of renal anaemia in Japan. The company filed the submission for FDA approval in the first half of 2022.[12,13]

On 1st March 2022, European Medicines Agency (EMA) accepted the marketing authorisation application for daprodustat based on the ASCEND Phase III clinical trial program which consisted of five trials that all met co-primary efficacy and safety endpoints. The EMA acceptance is the first major regulatory milestone for daprodustat since the drug been approved in Japan.[12]

On 19th April 2022, the United States Food and Drug Administration (USFDA) accepted New Drug Application (NDA) for daprodustat and has assigned a Prescription Drug User Fee Act (PDUFA) with action date of 1st February 2023.[14]

The mechanism of action of HIF-PHI is depicted in Figure 1.

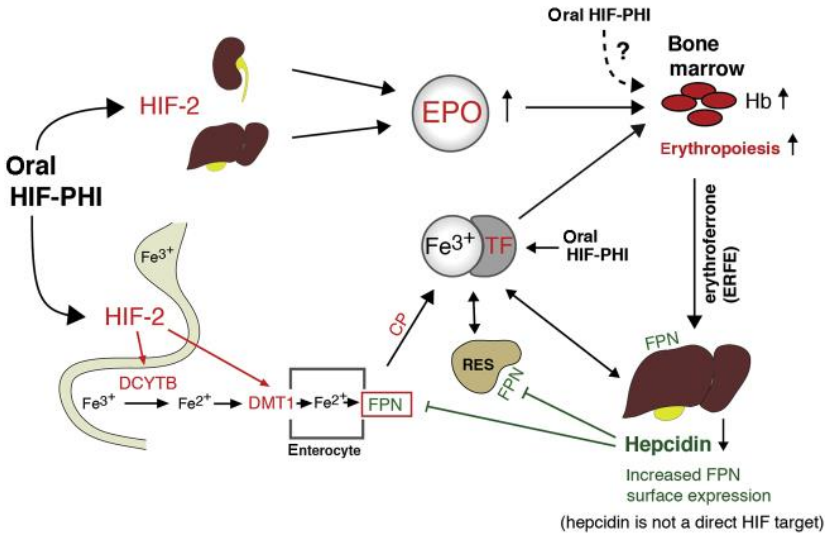


Figure 1: Mechanism of action of oral HIF-PHI.

(Source: Haase VH. Hypoxia-inducible factor–prolyl hydroxylase inhibitors in the treatment of anaemia of chronic kidney disease. Kidney International Supplements. 2021;11(1):8-25).

PATIENT GROUP AND INDICATION

Daprodustat is indicated for anaemia in chronic kidney disease (CKD) for both dialysis and non-dialysis patients.

CURRENT PRACTICE

Anaemia in CKD is due to lack of endogenous erythropoietin production by kidney and decrease of iron absorption and bioavailability. Currently, renal anaemia patients are treated with erythropoietin stimulating agents (ESAs), iron supplementation (intravenous and/or oral), and/or blood transfusion.[16,17]

The other new class of HIF-PHI known as roxadustat is approved and marketed in the Chile, Japan, China, South Korea and European Union (EU) for anaemia patient with chronic kidney disease for both dialysis and non-dialysis dependent. However, USFDA (Cardiovascular and Renal Drugs Advisory Committee [CRDAC]) has not recommended the approval of roxadustat for the treatment of patients with chronic kidney disease-related anaemia due to cardiovascular safety concern.[18]

EFFICACY AND SAFETY

An electronic search of databases such as PubMed was conducted by using these keywords either singly or in any combination; chronic kidney disease, anaemia, hypoxia-inducible factor (HIF), daprodustat, dialysis, non-dialysis and cost-effectiveness of HIF. All searches were done up to 30th June 2022.

Two meta-analysis with trial sequential analysis and systematic review, seven clinical trials and one economic evaluation study were identified.

a) Clinical impact

A meta-analysis and trial sequential analysis (TSA) by Fu Z et al. reported the efficacy and safety of daprodustat and recombinant human erythpoetin (rhEPO).[19] A total of seven studies with 7933 patients comprised of dialysis and non-dialysis patients were included in this meta-analysis. Four studies were phase III clinical trials and the other three were phase II clinical trials.[16,20,21,22,23,24,25]

There was a significant increase in transferrin saturation (TSAT), total iron binding capacity (TIBC) and total iron observed in daprodustat groups compared with rhEPO groups in dialysis patients ($p<0.05$). The pooled results showed that no significant difference was found in IV therapy rate between the daprodustat and rhEPO groups in both non-dialysis and dialysis patients. (Table 1)

However, there was no significant difference in the changes in haemoglobin levels between the daprodustat and rhEPO groups (mean difference (MD) = −0.01, 95% CI: −0.38, 0.35, p= 0.95, I^2: 91%; MD = 0.15, 95% CI: −0.29, 0.60, p = 0.50, I^2: 93% respectively.[19]

Outcomes	Subgroup	Number of studies	Mean difference/risk ratio (95% CI)	p value	Heterogeneity I^2 (p value)
Discontinuation rate	non-dialysis	3	1.53 [0.27, 8.86]	0.63	52% (0.12)
	dialysis	3	2.93 [0.53, 16.06]	0.22	0% (0.60)
△Total iron-binding capacity (ug/dL)	**non-dialysis**	3	29.00 [19.65, 38.35]	**<0.01**	70% (0.04)
	dialysis	4	33.85 [25.06, 42.64]	**<0.01**	76% (< 0.01)
△Transferrin saturation (%)	non-dialysis	3	-9.71 [−19.94, 0.52]	0.06	48% (0.14)
	dialysis	4	2.64 [0.31, 4.97]	**0.03**	0% (0.92)
△Total iron (ug/dL)	**non-dialysis**	3	−2.10 [−3.71, −0.49]	**0.01**	0% (0.59)
	dialysis	4	11.46 [9.74, 13.19	**<0.01**	0% (0.48)
△ Hepcidin (ng/ml)	**non-dialysis**	3	−32.62 [−54.75, −10.49]	**<0.01**	90% (< 0.01)
	dialysis	4	−9.26 [−33.69, 15.16]	0.46	87% (< 0.01)
△ Ferritin (ng/ml)	**non-dialysis**	3	−20.18 [−31.73, −8.64]	**<0.01**	0% (0.76
	dialysis	4	−22.80 [−61.94, 16.34]	0.25	76% (< 0.01)
Intravenous iron therapy rate	non-dialysis	2	1.72 [0.79, 3.75]	0.17	0% (0.72
	dialysis	2	0.88 [0.65, 1.20]	0.42	59% (0.12)

Table 1: The outcomes of iron metabolism including changes in TIBC, TSAT, total iron, hepcidin and ferritin
(Note: △= changes)

(Source: Fu Z, Geng X, Chi K, et al. Efficacy and Safety of Daprodustat versus rhEPO for Anaemia in Patients with Chronic Kidney Disease: A Meta-Analysis and Trial Sequential Analysis. Front Pharmacol.701)

Another meta-analysis and systematic review by Zheng et al. reported changes in haemoglobin level, ferritin, transferrin saturation (TSAT), and total iron-binding capacity (TIBC) between daprodustat and control group.[26] Four studies were included and reported a total of 441 non-dialysis patients had changes for haemoglobin levels. Two studies by Holdstock et al. and Brigandi et al. in 2016 compared between daprodustat and control group, meanwhile two studies reported by Akizawa et al. and Holdstock et al. compared daprodustat and recombinant human erythropoietin (rhEPO).[23,24,27,29] Six RCTs that involved 618 patients reported haemoglobin level changes for dialysis patients. Among these, three studies were conducted to compare daprodustat and control group, and three studies were compared between daprodustat and rhEPO.

The pooled results showed that haemoglobin level changes were significantly higher in the daprodustat group than control group for both non-dialysis patients and dialysis patients (MD =1.73, [95% CI:0.34,3.12], p=0.01; MD=1.88, [95% CI: 0.68,3.09], p=0.002; respectively), but there was no significant difference between daprodustat and rhEPO in terms of changes in haemoglobin levels (MD=0.05, [95% CI: −0.49,0.59], p=0.86; MD=0.12, [95% CI: −0.28,0.52], p=0.55; respectively).[26]

For ferritin level changes, four studies reported by Akizawa et al., Holdstock et al., and Brigandi et al. involved 428 non-dialysis patients, and four studies reported by Holdstock et al., Brigandi et al., Akizawa et al., and Meadowcroft et al. included 236 dialysis patients.[20,23,24,25,27] Among these, for both non-dialysis patients and dialysis patients, two studies compared between daprodustat and control group, and two studies compared daprodustat and rhEPO. The pooled results showed that for non-dialysis patients and dialysis patients, ferritin levels changes were significantly lower in the daprodustat group than control group (MD = −85.40, [95% CI: −126.17, −44.64], p<0.0001; MD = −141.31, [95% CI: −196.02, −86.60], p<0.00001; respectively) or in the rhEPO group (MD = −28.66, [95% CI: −33.02, −24.30], p<0.00001; MD = −82.17, [95% CI: −146.51, −17.83], p=0.01; respectively).[26]

A pool results for two group involved 425 non-dialysis and 234 dialysis patients. The result showed the transferrin saturation levels for non-dialysis patients was significantly lower in the daprodustat group than control group or rhEPO groups (MD = −5.90, [95% CI: −11.31, −0.49], p=0.03; MD= −17.69, [95% CI: −19.92, −15.45], p<0.00001; respectively).[26]

For dialysis patients, there was no significant difference in transferrin saturation levels between daprodustat and control group or rhEPO (MD = −20.00, [95% CI: −82.70, 42.70], p=0.53; MD=3.03, [95% CI: −1.84, 7.90], p=0.22; respectively).[26]

There were four studies on changes of TIBC levels that involved 425 non-dialysis patients and five studies involved 318 dialysis patients. The pooled results showed that for both dialysis patients and non-dialysis patients, the TIBC levels changes was significantly higher in the daprodustat group than control group (MD =7.73, [95% CI: 3.97,11.48], p< 0.0001) or in the rhEPO group (MD=5.71, [95% CI, 1.60, 9.82], p=0.007; MD=6.28, [95% CI: 4.71, 7.84], p<0.00001; respectively), while there was no significant difference in TIBC levels between daprodustat and control group for dialysis patients (MD=8.10, [95% CI: -2.73,18.93], p=0.14).[26]

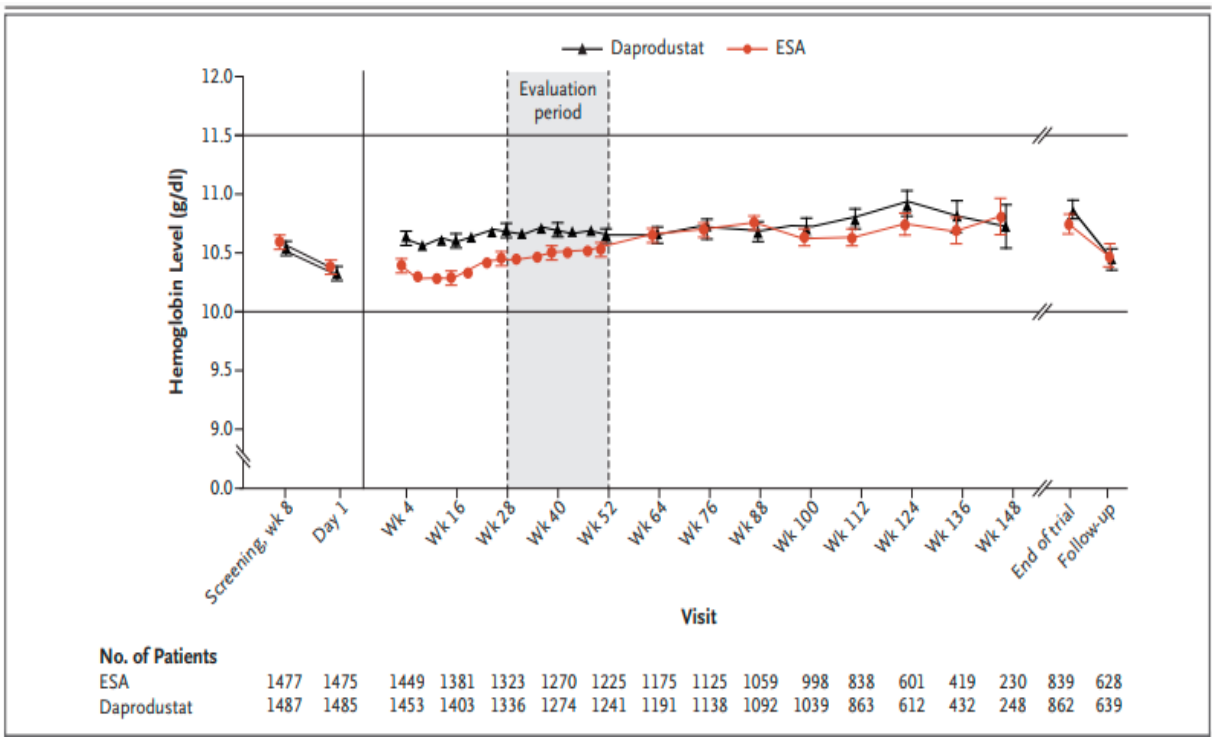
The global phase III program for daprodustat included five RCTs known as ASCEND (Anaemia Studies in Chronic Kidney Disease: Erythropoiesis via a novel prolyl hydroxylase inhibitor Daprodustat) programme to evaluate the efficacy and safety of daprodustat. The program involved over 8,000 patients who were treated for up to four years. The clinical trials comprised of ASCEND in Incident Dialysis (ASCEND-ID) (daprodustat administered daily, comparator darbepoetin), ASCEND-Three-times Weekly Dosing in Dialysis (ASCEND-TD) (daprodustat administered 3-times weekly, comparator epoetin or control group), ASCEND in Non-Dialysis Subjects Evaluating Haemoglobin and Quality of Life (ASCEND-NHQ) (daprodustat administered daily, comparator control group), ASCEND-dialysis (ASCEND-D) (daprodustat administered daily, comparator epoetin), and ASCEND-Non-Dialysis (ASCEND-ND)(daprodustat administered daily, comparator darbepoetin).[30,33,34,35]

There are two on-going phase II clinical trials evaluating daprodustat effect on blood pressure (BP) for dialysis patient and iron absorption for non-dialysis patient.

In the ASCEND-ID trial, the result showed mean (SD) haemoglobin was 10.5 (1.0) g/dL and 10.6 (0.9) g/dL (daprodustat versus darbepoetin). There was no significant difference in mean (SE) monthly intravenous (IV) iron use 145 (10.9) mg versus 125 (11.0) mg (daprodustat versus darbepoetin and both group maintained target range of haemoglobin in a high-risk dialysis patient.[30,31]

According to ASCEND-DD phase III clinical trial, a total of 2964 patients were involved and received daprodustat (n=1487) or injectable ESA (n=1477). The haemoglobin level during the treatment ranged between 8.0 to 11.5 g/dl. (Figure 2)[35]

Overall, the means baseline haemoglobin level was 10.4±1.0 g/dl between the two groups. The primary efficacy outcome showed the mean change in the haemoglobin level from baseline to weeks 28 through 52 was 0.28±0.02 g/dl with daprodustat and 0.10 ± 0.02 g/dl with ESA therapy, for a difference of 0.18 g/dl (95% CI: 0.12, 0.24), which met the pre-specified non-inferiority margin for daprodustat.[35]



Shown are the mean haemoglobin levels among patients with chronic kidney disease who were undergoing dialysis and who were assigned to receive daprodustat or an erythropoietin-stimulating agent (ESA) during the trial. Visits on or before day 1 include only pretreatment values. Visits after day 1 include all available values after randomization regardless of whether the patient received the trial treatment. The haemoglobin target range for dose changes was 10.0 to 11.0g per deciliter. The horizontal lines represent the haemoglobin analysis range (10.0 to 11.5g per deciliter), which is an extension of the target range to allow for variability. The I bars indicate 95% confidence intervals.

Figure 2: Haemoglobin level according to visit (intention-to-treat population).

(Source: Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the Treatment of Anaemia in Patients Undergoing Dialysis. N Engl J Med. 2021;385(25):2325-2335)

During the first four weeks, a rapid increase in the haemoglobin level was reported 4.1% in the daprodustat group (n=50/1218) and 1.6% in the ESA group (n=20/1247). Thereafter, for any four weeks' period during the first year, the percentage of patients with a rapid increase in the haemoglobin level was 2% or less in the two treatment groups.

In the daprodustat group, the level of hepcidin decreased and the TIBC increased from baseline and relative to the ESA group, whereas the ferritin level decreased in both groups. Transferrin saturation levels were similar in both groups and were slightly lower than baseline levels. Total iron levels slightly increased with daprodustat but not with ESA.[35]

A total of 3872 non dialysis patients (daprodustat, n=1937, darbepoetin alfa, n=1935) were involved in ASCEND study.[21] The median glomerular filtration rate (GFR) for daprodustat was 17.0 (95% CI: 12.0, 26.0), and darbepoetin alfa was 18.0 (95% CI: 12.0, 27.0). The mean changes in the haemoglobin level from baseline to week 28 through 52 was 0.74 ± 0.02 g/dL in the daprodustat group and 0.66 ± 0.02 g/dL in the darbepoetin alfa group (difference, 0.08 g/dL; 95% CI: 0.03,0.13), which met the pre-specified non-inferiority margin of −0.75 g/dL. In the ITT population during treatment, the iron parameters showed the decreases of hepcidin level and transferrin saturation. The TIBC increased from baseline and greater in the daprodustat group than in the darbepoetin alfa group. However, there was a similarity of reduction level of ferritin and stable total iron in both groups.[21]

Another study by Coyne et al. known as ASCEND-TD reported positive efficacy results for three-times weekly dosing of daprodustat compared with recombinant human erythropoietin (rhEPO) among haemodialysis (HD) patients for 52 weeks. A total of 407 patients (daprodustat; n=270, rhEPO; n=137) were involved in this study with baseline haemoglobin n (Hb) of 8 to 11.5 g/dL for both groups. The three times weekly of daprodustat was non-inferior to rhEPO for mean change in haemoglobin (model-adjusted mean treatment difference [daprodustat-rhEPO] -0.05; 95% CI: -0.21, 0.10). In the evaluation period, mean (SD) haemoglobin was 10.45 (0.549) g/dL and 10.51 (0.849) g/dL for daprodustat and rhEPO groups, respectively. Approximately 80% of patients in daprodustat group compared to 63.6% in the rhEPO group, with a difference of 16.5% for mean haemoglobin (Hb: 10 to 11.5 g/dL; p=0.0007).[30,31]

A study by Johansen et al. known as ASCEND-NHQ reported a total of 614 non-dialysis of CKD patients were evaluated for haemoglobin level and SF-36 quality of life vitality score for fatigue assessment over 28 weeks. The baseline demographic characteristics were balanced for both groups ((9.73 g/dL daprodustat, 9.71g/dL control group). The adjusted mean difference (AMD) for haemoglobin changes was 1.40 g/dL (95% CI: 1.23, 1.56; p<0.001). There was an increase of haemoglobin level from baseline for daprodustat (≥1 g/dL, 77% versus 18%; p<0.001).[34]

The SF-36 vitality responders' difference was 58% on daprodustat and 40% on control group (13%, 95% CI: 4%, 22%). The adjusted mean (SE) scoring increased by 7.3 (1.1) points for daprodustat compared to 1.9 (1.2) points in control group. At week 28, the adjusted mean difference (AMD) was 5.4 (95% CI: 2.2, 8.6; p<0.001). The overall effect on blood pressure was not significant between daprodustat and control group (32% daprodustat versus 26% control group, p=0.07).[34]

A phase III clinical trial by Akizawa et al. among Japanese patients who were on haemodialysis with anaemia of CKD compared the efficacy (non-inferiority) and safety of daprodustat with darbepoetin alfa for 52 weeks. A total 267 patients (n=133, daprodustat and n=134, darbepoetin) were included in this study. The mean haemoglobin level during weeks 40 to 52 were maintained within the target range in both groups (10.9 g/dl [95% CI: 10.8, 11.0] for daprodustat, and 10.8 g/dl [95% CI: 10.7,11.0] for darbepoetin alfa.[20]

The haemoglobin efficacy (ITT population) is shown in Table 2.

Haemoglobin (Hb)	**Daprodustat**	**Darbepoetin alfa**
Baseline haemoglobin, g/dl		
n	133	n=134
	10.9 (0.8)	10.8 (0.7)
Mean (SD) haemoglobin during week 40 to 52, g/dl		
n	120	125
Mean (SD)	10.9 (0.7)	10.8 (0.6)
Change from baseline (SD)	0.0 (1.0)	0.0 (0.8)
Adjusted mean haemoglobin during week 40 to 52, g/dl		
Adjusted mean (95% CI)	10.9 (10.8 to 11.0)	10.8 (10.7 to 11.0)
Adjusted treatment difference (95% CI) for mean haemoglobin during week 40 to 52	0.1 (20.1 to 0.2)	
No. (%) of participants with mean haemoglobin within target during week 40 to 52[a]		
n	120	125
No. of participants (%)	105 (88)	113 (90)

Change from baseline in mean haemoglobin during weeks 40 to 52 was performed in a post hoc analysis. Adjusted values were estimated by a mixed model for repeated measures as specified in statistical analyses. 95% CI, 95% confidence interval. [a]modified ITT population.

Table 2: Haemoglobin efficacy data among dialysis Japanese patients

(Source: Akizawa T, Nangaku M, Yonekawa T, et al. Efficacy and Safety of Daprodustat Compared with Darbepoetin Alfa in Japanese Hemodialysis Patients with Anaemia: A Randomized, Double-Blind, Phase 3 Trial. Clinical Clin J Am Soc Nephrol. 2020;15(8):1155-1165)

The mean haemoglobin levels were remain constant within the target range for both groups during the treatment period. After switching to daprodustat, mean haemoglobin levels were lower relative to baseline from week four to week 16; however, the mean changes from baseline were 0.5 g/dL and the mean haemoglobin levels remained within target range. The mean haemoglobin returned to baseline by week 20 after subsequent dose adjustment (median dose increased from 4 mg/daily to 6 mg/daily by week 12).

The iron parameters included the changes of TSAT, TIBC, serum iron, ferritin and hepcidin up to week 52. In the daprodustat group, the serum iron and TIBC level increased, ferritin and hepcidin decreased, and TSAT remained near baseline. The mean ferritin decreased from baseline in both treatment groups. The mean hepcidin decreased in both groups but decreased more in the daprodustat group (percent change from baseline at week 52 was -37% for daprodustat and -20% for darbepoetin alfa; adjusted ratio, 0.74; 95% CI: 0.57, 0.95). (Table 3).[20]

Baseline mean transferrin levels (measured as a safety parameter) were 2.0 g/L in both treatment groups). The transferrin levels increased in the daprodustat group (mean change from baseline at week 52: 0.3 g/L [SD 0.5 g/L] for daprodustat and 0.0 g/L [SD 0.3 g/L] for darbepoietin alfa), which was aligned with TIBC changes.[20]

Iron parameter	Daprodustat, n=133	Darbepoetin alfa, n=134
n	115	120
TSAT at week 52, %[a]		
Mean (SD)	27.0 (12.3)	24.6 (9.1)
Change from baseline (SD)	0.3 (13.2)	-22.1 (11.4)
Adjusted treatment difference (95% CI)	2.8 (0.1 to 5.4)	
TIBC at week 52, mg/dl		
Mean (SD)	303 (64)	257 (44)
Change from baseline (SD)	49 (56)	6 (34)
Adjusted treatment difference (95% CI)	41 (30 to 53)	
Serum iron at week 52, mg/dl		
Mean (SD)	78 (29)	63 (24)
Change from baseline (SD)	11 (34)	-24 (28)
Adjusted treatment difference (95% CI)	16 (10 to 22)	
Ferritin, mg/L[b]		
Geometric mean (CV %)	66.7 (143.5)	74.9 (127.8)
Percent change from baseline (CV %)	-22 (132.2)	-20 (124.1)
Adjusted ratio for percent change from baseline (95% CI)	0.95 (0.75 to 1.19)	
Hepcidin, ng/ml[b]		
Geometric mean (CV %)	37.9 (103.8)	51.5 (111.5)
Percent change from baseline (CV %)	-37 (116.1)	-20 (133.6)
Adjusted ratio for percent change from baseline (95% CI)	0.74 (0.57 to 0.95)	

TSAT, transferrin saturation; 95% CI, 95% confidence interval; TIBC, total iron-binding capacity; CV %, coefficient of variation. [a] The distribution in TSAT had been assumed to be skewed but was found not to be skewed after the data review; therefore, the analysis of TSAT on the basis of a non-log transformation was done as a post hoc analysis. [b] The distributions were assumed to be skewed and required a log transformation for the analysis. The distribution in ferritin had been assumed not to be skewed but was found to be skewed after the data review; therefore, the analysis of ferritin on the basis of a log transformation was done as a post hoc analysis.

Table 3: Iron parameters at end of treatment (intent-to-treat population)

(Source: Akizawa T, Nangaku M, Yonekawa T, et al. Efficacy and Safety of Daprodustat Compared with Darbepoetin Alfa in Japanese Hemodialysis Patients with Anaemia: A Randomized, Double-Blind, Phase 3 Trial. Clinical Clin J Am Soc Nephrol. 2020;15(8):1155-1165)

Another phase III clinical trial by Nangaku et al. evaluated the efficacy and safety of daprodustat and epoetin beta pegol (continuous erythropoietin receptor activator- CERA). A total of 355 patients (n=299 were non-dialysis with anaemia of CKD stages G3, G4 and G5 and n= 56 were on peritoneal dialysis) were involved in this study. The stages were based on Japanese Society of Nephrology Chronic Kidney Disease Initiatives formula which categorised the eGFR of G3a (eGFR; 45–59 mL/min/1.73m^2), G3b (eGFR; 30–44 mL/min/1.73m^2), G4 (eGFR; 15–29 mL/min/1.73m^2) and G5 (eGFR; <15 mL/min/1.73m^2).[22]

The mean haemoglobin levels during weeks 40 to 52 were 12.0 g/dL in the daprodustat group (n =108; 95% CI: 11.8, 2.1) and 11.9 g/dL for CERA (n=109; 95% CI 11.7,12.0). The difference between the groups was 0.1 g/dL (95% CI: −0.1,0.3 g/dL). In the modified ITT population, 92% of the patients (n=81/88; daprodustat, n=80/87; CERA) had a mean haemoglobin level within the target range (11.0 to 13.0 g/dL) during the primary efficacy evaluation period (odds ratio daprodustat versus CERA, 1.01; 95% CI: 0.33,3.04). The following Table 4 and Table 5 showed the efficacy analysis of mean haemoglobin and the mean duration within the target range for haemoglobin level during the primary efficacy evaluation period.

Overall, mean haemoglobin levels reached the target range at eighth week in both treatment groups and were maintained within the target range until week 52. For ESA-naïve patients, mean haemoglobin levels reached the target range at week eight in both treatment groups and were maintained until week 52. For ESA users, mean haemoglobin levels were maintained within the target range throughout the treatment period in both treatment groups.[22]

Analysis of mean haemoglobin during the primary efficacy evaluation period			
	Mean haemoglobin (g/dL)[a], (95% CI)		Treatment difference
	Daprodustat, n =108	CERA, n=109	(g/dL), (95% CI)
Overall	12.0 (11.8, 12.1), n = 50	11.9 (11.7,12.0), n = 50	0.1 (-0.1, 0.3)
ESA-naïve	11.9 (11.8, 12.0), n = 58	11.7 (11.5,11.8), n =59	0.2 (0.0, 0.5)
ESA User	12.0 (11.8,12.2)	12.0 (11.8,12.2)	-0.0 (-0.3,0.2)
Analysis of number (%) of participants with mean haemoglobin in the target range (11.0–13.0 g/dL) during the primary efficacy evaluation period			
Overall	Responder[b], n (%)		Odds ratio (95% CI)
	n = 88	n = 87	
	81 (92), n = 45	80 (92), n = 36	1.0 (0.3, 3.0)
ESA-naïve	43 (96), n = 43	32 (89), n = 51	2.4 (0.4,14.2)
ESA User	38 (88)	48 (94)	0.5 (0.1,2.3)

[a]Participants with haemoglobin at only baseline and Week 2 are not included in the analysis.
[b]Responder is defined as a participant with the mean Hgb within the target range during the primary efficacy evaluation period. (CERA, continuous erythropoietin receptor activator (epoetin beta pegol). CI: confidence interval; ESA: erythropoietin-stimulating agent;

Table 4: Mean haemoglobin during primary efficacy evaluation period (ITT population) between daprodustat and CERA in Japanese population

(Source: Nangaku M, Hamano T, Akizawa T, et al. Daprodustat compared with epoetin beta pegol for anaemia in Japanese patients not on dialysis: a 52-week randomized open-label phase 3 trial. Am J Nephrol. 2021;52(1):26-35)

	Mean time within target range (weeks)[a], (SD)		Treatment difference (Weeks) [b] daprodustat CERA , (95% CI)
	Daprodustat	CERA	
Overall	n = 88 10.2 (2.8)	n = 87 9.4 (3.3)	0.8 (–0.1,1.7)
ESA-naïve	n = 45 10.5 (2.6)	n = 36 8.7 (3.6)	1.8 (0.4,3.2)
ESA user	n = 43 9.9 (2.9)	n = 51 9.9 (3.0)	0.0 (–1.2,1.2)

[a]Time within range is calculated for participants with haemoglobin measurements observed in both scheduled and unscheduled visits on and after week 40.
[b]Treatment difference (daprodustat – CERA) for the weeks within the target range is provided.
CERA: continuous erythropoietin receptor activator (epoetin beta pegol); CI: confidence interval; ESA: erythropoietin-stimulating agent; SD: standard deviation.

Table 5: Mean duration within the target range for haemoglobin level

(Source: Nangaku M, Hamano T, Akizawa T, et al. Daprodustat compared with epoetin beta pegol for anaemia in Japanese patients not on dialysis: a 52-week randomized open-label phase 3 trial. Am J Nephrol. 2021;52(1):26-35)

The effect of daprodustat on iron metabolism in ITT population reported the serum iron levels were unchanged in the daprodustat group after a year of trial. However, the serum iron level slightly increased from weeks 28 to 52 for CERA group (daprodustat; from 87 µg/dL baseline to 90 µg/dL, CERA; from 83 µg/dL baseline to 92 µg/dL CERA).[22]

Throughout the treatment period until week 52, the mean TIBC levels increased from baseline for daprodustat group (from 272 µg/dL to 316 µg/dL). However, the level remained near baseline for CERA (from 267 µg/dL to 268 µg/dL) in this study. In the safety population, the mean serum transferrin level was 2.0 g/L at baseline in both treatment groups and increased to 2.4 g/L for daprodustat group compared to CERA group that remained near baseline. For mean TSAT, the levels decreased from 32% to 29% in daprodustat group compared to CERA group (from 32% to 34%). The mean ferritin levels decreased for daprodustat group (from 159 µg/L to 106 µg/L) and CERA group (from 144 µg/L to 122 µg/L). There was a 45% reduction in hepcidin level from baseline for daprodustat group (from 63 ng/mL to 35 ng/mL) and 10% increase for CERA group (from 53 ng/mL to 64 ng/mL).[22]

b) Safety

The meta-analysis results involved six studies of 825 dialysis patients and four studies of 691 non-dialysis patients reported the incidence of serious adverse events (SAEs). Among dialysis patients, three studies were compared between daprodustat and placebo, meanwhile another three studies compared daprodustat and rhEPO. For non-dialysis patients, two studies compared daprodustat and placebo and another two studies compared daprodustat and rhEPO. The pooled results showed that for both dialysis and non-dialysis patients, there was no significant difference in the incidence of SAEs between daprodustat and placebo (RR=1.09, [95% CI: 0.26, 4.68], p=0.91; RR=0.79, [95% CI: 0.26, 2.43], p=0.68; respectively). Additionally, the incidence of SAEs in the daprodustat group was significantly lower than that in the rhEPO group (RR=0.71, [95% CI: 0.52, 0.97], p=0.03; RR=0.60, [95% CI: 0.42, 0.87], p=0.007) respectively.[19,26]

During a median follow up of 2.5 years (IQR: 2.2, 2.9) of ASCEND-DD trial, a major adverse cardiovascular event (MACE) was evaluated among patients with coexisting condition of cardiovascular diseases. There were cardiac events occurred in 374 of 1487 patients (25.2%) in the daprodustat group and in 394 of 1477 (26.7%) in the ESA group (HR: 0.93; 95% CI: 0.81, 1.07), which also met the prespecified non-inferiority margin for daprodustat. The incidence of prespecified adverse events of special interest were similar in the two treatment groups (daprodustat versus ESA). The incidence of death from any cause was similar in the two groups (HR: 0.96; 95% CI: 0.82,1.13). There were no significant changes

on the use of antihypertensive medications. The additional time-to-event analyses including the components of the MACE composite are shown in Table 6.[35]

Cardiovascular outcome (assessed for superiority)	Daprodustat	ESA	Hazard ratio (95% CI)
	No. of first events (%)	No. of first events (%)	
Death from any cause (coronary artery disease, heart failure, valvular heart disease, angina pectoris, atrial fibrillation, myocardial infarction, stroke, transient ischemic attack, cardiac arrest	294 (19.8)	300 (20.3)	0.96 (0.82, 1.13)
Cardiovascular mortality*	117 (7.9)	121 (8.2)	0.95 (0.74, 1.23)
Fatal and non-fatal thromboembolic events	185 (12.4)	215 (14.6)	0.84 (0.69, 1.02)
Vascular access thrombosis	162 (10.9)	195 (13.2)	-
Deep venous thrombosis	17 (1.1)	14 (<1)	-
Pulmonary embolism	6 (<1)	6 (<1)	-
Fatal and non-fatal hospitalisation for heart failure	112 (7.5)	101 (6.8)	1.10 (0.84, 1.45)

*Includes all deaths indicated as having a cardiovascular primary cause of death as well as deaths with an undetermined primary cause of death that are indicated to be either presumed sudden death or presumed cardiovascular death. Unknown deaths are excluded.

Table 6: Additional Secondary Time-to-Event Analysis Results (ITT Population)

(Source: Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the Treatment of Anaemia in Patients Undergoing Dialysis. N Engl J Med. 2021;385(25):2325-2335)

For ASCEND-NDD trial, the safety parameter was included the MACE of primary and secondary cardiovascular outcome and secondary renal outcome. The safety profile of daprodustat was generally similar to darbepoetin alfa. (Table 7) [21]

Cardiovascular outcome (assessed for superiority)	Daprodustat	Darbepoetin alfa	Hazard ratio (95% CI)
	No. of first events (%)	No. of first events (%)	
Death from any cause	301 (15.5)	298 (15.4)	1.03 (0.87, 1.20)
Cardiovascular mortality*	109 (5.6)	92 (4.8)	1.20 (0.91, 1.58)
Fatal and non-fatal myocardial infarction	103 (5.3)	97 (5.0)	1.06 (0.80, 1.40)
Fatal and non-fatal stroke	45 (2.3)	34 (1.8)	1.33 (0.85, 2.07)
Fatal and non-fatal thromboembolic events	64 (3.3)	51 (2.6)	1.27 (0.88, 1.84)
Vascular access thrombosis	44 (2.3)	31 (1.6)	-
Deep venous thrombosis	14 (<1)	19 (<1)	-
Pulmonary embolism	6 (<1)	1 (<1)	-
Fatal and non-fatal hospitalisation for heart failure	140 (7.2)	115 (5.9)	1.22 (0.95,1.56)
*Includes all deaths indicated as having a cardiovascular primary cause of death as well as deaths with an undetermined primary cause of death that are indicated to be either presumed sudden death or presumed cardiovascular death. Unknown deaths are excluded.			

Table 7: MACE of primary and secondary cardiovascular outcome and secondary renal outcome.

(Source: Singh AK, Carroll K, McMurray JJ, et al. Daprodustat for the treatment of anaemia in patients not undergoing dialysis. N Engl J Med. 2021;385 (25):2313-2324)

There was similar incidence of treatment-emergent adverse events between daprodustat and rhEPO (75% versus 79%).[33] Overall effect on blood pressure was similar between daprodustat and control group. A mild blood pressure elevation occurred in daprodustat as compared to control group (32% versus 26%, p=0.07). The rates of adverse events were

similar for both groups (daprodustat 69% versus control group 71%).[34] However, there was no significant of SAEs daprodustat and rhEPO in non-dialysis patients (RR =1.03, 95% CI= 0.76, 1.38, p= 0.86, I^2 = 58%) and dialysis patients (RR = 0.74, 95% CI=0.48, 1.15, p= 0.18, I^2 = 67%) during follow up period from 22 to 28 weeks.[19,26]

ESTIMATED COST

According to the Japanese market, the price for daprodustat is USD 1190 (RM 5300) for 100 tablet with dosage 6mg.[11]

There was no cost-effectiveness analysis (CEA) study for daprodustat. However, the current drug known as roxadustat which marketed in China and Japan with similar indication may be beneficial for reference purposes. Roxadustat treatment (70 mg, three times per week) provided an additional 0.49 quality-adjusted life year (QALY) at a cost of USD 12,526 (RM 52,671.83) in the time horizon of five years, resulting in an ICER of USD 25,563 (RM 107,492.42) per QALY, with approximately 60% probability to be cost-effective at a USD 29,295 (RM 123,185.48) per QALY willingness-to-pay (WTP) for non-dialysis patient.[32]

POTENTIAL IMPACT

Daprodustat as a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHIs) may offer a promising alternative oral treatment option for anaemia associated with CKD. By stabilising HIF, it increases the secretion of endogenous erythropoietin and the production of red cells. Several studies have suggested that daprodustat is effective in increasing haemoglobin levels for short-term use for the treatment of anaemia in CKD patients in both dialysis and non-dialysis patient.[19,26]

However, a further cost-effectiveness analysis (CEA) study and economic evaluation for HIF-PHIs are warranted.

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