Received: 3 December 2020 | Revised: 30 April 2021 | Accepted: 6 May 2021

DOI: 10.1111/1744-9987.13686

ORIGINAL ARTICLE

Therapeutic Apheresis and Dialysis

WILEY

Efficacy and safety of daprodustat in Japanese peritoneal dialysis patients

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Abstract

Daprodustat is a hypoxia-inducible factor-prolyl hydroxylase inhibitor for the treatment of anemia of chronic kidney disease. This phase 3 study evaluated the efficacy and safety of daprodustat in an uncontrolled cohort of 56 Japanese peritoneal dialysis patients with anemia over 52 weeks. Subjects received daprodustat 4 mg orally once daily for 4 weeks and the dose was subsequently adjusted every 4 weeks. Mean baseline hemoglobin was 10.9 g/dL (95% CI 10.59, 11.12). Mean hemoglobin reached the target range (11.0–13.0 g/dL) at week 12 and was maintained until week 52. Mean hemoglobin during weeks 40–52 was 12.1 g/dL (95% CI 12.0, 12.2). The most frequent adverse events included nasopharyngitis (29%), catheter-site infection (18%), peritonitis (16%), diarrhea (14%), and nausea (11%). No deaths were reported. Once-daily oral daprodustat treatment was generally well tolerated and mean hemoglobin was achieved and maintained within the target range in Japanese peritoneal dialysis participants.

KEYWORDS

anemia, hypoxia, Japanese, peritoneal dialysis

1 | INTRODUCTION

Chronic kidney disease (CKD) is an important public health issue [1]. Anemia is a common complication in patients with CKD, characterized by relative erythropoietin deficiency and a decrease in hemoglobin and red blood cell count in circulating blood [2]. The incidence of anemia progressively increases with CKD stage severity, although anemia may develop even before reaching advanced stages of CKD [3,4].

Peritoneal dialysis (PD) is an effective treatment option for many patients with CKD. Receiving treatment at home potentially avoids the inconvenience of travel associated with frequent visits to clinics or hospitals for hemodialysis [5,6]. However, parenteral administration of erythropoiesis-stimulating agents (ESAs), considered the standard of care for treatment of anemia of CKD, as well as other treatments such as supplemental intravenous iron therapy and blood transfusions, require visits to treatment centers for patients who could

Previous presentation: Presented at the 9th Asia Pacific Chapter Meeting of the ISPD (APCM-ISPD 2019) in Nagoya, Japan, on 5–7 September 2019.

otherwise be treated at home, and may be associated with discomfort and local irritation [7,8]. The availability of an effective oral agent for the treatment of anemia of CKD in PD patients would offer benefits related to more convenient dosing and a reduced need to travel to treatment centers for parenteral treatment. Oral agents are easier to store (e.g., may not require refrigeration) and are not associated with biohazard waste such as used injectable devices.

Daprodustat (GlaxoSmithKline, Minato-ku, Tokyo, Japan) is an oral hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI), a new class of therapy for anemia of CKD for use in dialysis and nondialysis patients [9–11]. HIF-PHIs stimulate erythropoiesis by inhibiting prolyl hydroxylase domain (PHD) enzymes (PHD1, PHD2, PHD3), leading to activation of HIF-responsive genes that regulate the tissue response to hypoxia, including the gene that induces erythropoietin and genes involved in iron homeostasis [12]. In phase 2 studies, daprodustat increased and maintained hemoglobin levels in hemodialysis and nondialysis participants during a 6-month treatment period with a safety profile comparable to ESAs [9,10,13].

In Japanese phase 3 studies, daprodustat 1–24 mg daily was noninferior to ESA treatment in hemodialysis and nondialysis participants during a 1-year treatment period, as assessed by mean hemoglobin levels over weeks 40–52 [14,15]. In this study, we evaluated whether daprodustat could achieve and maintain hemoglobin target levels in Japanese PD patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a phase 3, open-label, multicenter study with an uncontrolled PD cohort to evaluate the efficacy and safety of daprodustat in Japanese PD patients with anemia of CKD (NCT02791763). The study was conducted between July 5, 2016 and December 25, 2017 at 21 centers in Japan and included a 4-week screening period, a 52-week treatment period, and a 4-week follow-up period. All participants (ESA users and ESA-naive patients) who met eligibility criteria received daprodustat 4 mg orally once daily for 4 weeks. Daprodustat dose was subsequently adjusted every 4 weeks within the dose range of 1–24 mg according to a prespecified algorithm to achieve and maintain hemoglobin levels within the target range of 11.0–13.0 g/dL based on Japanese guidelines [2] (Tables S1 and S2). Daprodustat could be administered without regard to food or dialysis.

The study was approved by the institutional review board at every participating institution and was conducted according to the ethical standards and recommendations of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants prior to any study-specific procedures.

2.2 | Participants

Male and female patients 20 years or older on PD, with hemoglobin levels ≥8.0 and <11.0 g/dL for ESA-naive patients (no ESA use for ≥8 weeks prior to screening) or ≥9.0 g/dL and ≤13.0 g/dL for ESA users were eligible. Use of the same ESA for ≥8 weeks prior to screening was required for ESA users. Ferritin level >100 ng/mL or transferrin saturation (TSAT) >20% at screening was also required. Supplemental iron therapy could be administered if ferritin was ≤100 ng/mL and TSAT was ≤20%, although intravenous iron and dose changes for oral iron were not allowed from screening through week 4. Gemfibrozil and rifampin were excluded from screening to 7 days after treatment completion. Commercially available ESA use was prohibited during study treatment and for ESA-naive patients 8 weeks before screening. The complete inclusion, exclusion, and study medication stopping criteria are listed in Table S3.

2.3 | Study assessments and procedures

Hemoglobin was measured every 4 weeks. Hemoglobin levels were measured at a central laboratory (LSI Medience Corporation, Tokyo, Japan) for efficacy assessments and HemoCue (a point-of-care hemoglobin analyzer) measurement was used for eligibility, withdrawal, and dose adjustment criteria. Clinical laboratory testing, including iron metabolism parameters, was performed on day 1, week 4, and every 12 weeks.

Safety assessments included vital signs, clinical laboratory testing, the incidence of adverse events (AEs), serious AEs, and AEs of special interest, which was defined a priori based on findings of nonclinical studies of daprodustat, theoretical or potential risks based on the mechanism of action of daprodustat, and the known safety profile of ESAs. An internal Safety Review Team conducted periodic case reviews to evaluate which events constituted an AE of special interest. Protocol-specific ophthalmology examinations were performed by an ophthalmology specialist for each site at baseline, week 12, and week 48 to support the assessment of ocular AEs of special interest.

2.4 | Endpoints

Efficacy endpoints included mean hemoglobin, number (%) of participants with mean hemoglobin in the target range (11.0–13.0 g/dL), and the time spent in the hemoglobin target range during weeks 40–52. Additionally, hemoglobin change from baseline at week 4, distribution of daprodustat dose level at week 4, and hemoglobin at each assessment time point were assessed. Iron relative endpoints included number (%) of participants who used oral iron during weeks 40 to 52, and serum iron, total iron binding capacity (TIBC), TSAT, ferritin, and hepcidin were assessed.

Safety endpoints included incidence of AEs and AEs of special interest.

2.5 | Statistical analyses

The sample size of 50 participants was based on feasibility. Assuming a dropout rate of 25% and a standard deviation of 1.5 g/dL for hemoglobin, the half width of the 95% confidence interval (CI) for mean hemoglobin during weeks 40–52 was 0.493 g/dL based on the sample size of 38.

The efficacy PD population was the primary population for efficacy assessment and consisted of participants with a hemoglobin measurement at baseline and at ≥1 scheduled visit after baseline. The safety population included all participants who received ≥1 dose of study medication.

Mean hemoglobin during weeks 40–52 was summarized. Hemoglobin at each assessment visit was summarized descriptively overall, by prior ESA use (yes/no), and by baseline hemoglobin (<11.0 g/dL/ ≥11.0 g/dL for ESA user). Hemoglobin change from baseline at week 4 (number [%] of participants for categories of ≤−2, >−2 to ≤−1, >−1 to ≤0, >0 to ≤1, >1 to ≤2, and >2 g/dL) was summarized overall, by prior ESA use (yes/no), and by baseline hemoglobin (<11.0 g/dL/ ≥11.0 g/dL for ESA user). Daprodustat dose during weeks 40–52 was summarized descriptively. Number (%) of participants with mean hemoglobin in the target range during weeks 40–52 was summarized. As a post hoc analysis, a similar summary of the number of participants with mean hemoglobin in the target range was done for a modified analysis population that included participants who had ≥1 hemoglobin measurement during weeks 40–52.

Additionally, oral iron use (number [%] of participants), monthly average oral iron dose at baseline and during weeks 40–52, and iron parameters (serum iron, TIBC, TSAT, ferritin, hepcidin) at each assessment visit were summarized descriptively.

For AEs, drug-related AEs, serious AEs, drug-related serious AEs, AEs leading to discontinuation of study treatment, and AEs of special interest, the number and percentage of subjects reporting at least one event were summarized by primary system organ class and preferred term of *Medical Dictionary for Regulatory Activities (MedDRA)* version 21.1.

Statistical analyses were performed with SAS version 9.4 (SAS, Cary, NC).

3 | RESULTS

Fifty-six participants (53 [95%] ESA users and 3 [5%] ESA-naive patients) were enrolled and received ≥1 dose of daprodustat (safety population). The efficacy PD population comprised 55 participants; 1 ESA user without a hemoglobin measurement after baseline was excluded. Forty-three participants (41 ESA users and 2 ESA naive) completed the study; 13 withdrew (12 ESA users and 1 ESA naive). The main reasons for withdrawal were AEs and meeting protocol-specified withdrawal criteria (e.g., change in dialysis modality; Figure 1). The median duration of daprodustat exposure was 365.0 days (range 27–370 days).

3.1 | Baseline participant characteristics

Baseline demographic and clinical characteristics of the safety population are shown in Table 1. In the overall population, most participants were male (79%), the mean age was 64.4 years, and the mean time on dialysis was 2.7 years. The mean baseline hemoglobin level was 10.9 g/dL (standard deviation [*SD*]: 0.96).

Among ESA users, the most commonly used ESA prior to the start of the study was epoetin beta pegol (68%), followed by darbepoetin alfa (32%). No participants had used epoetin.

3.2 | Hemoglobin levels

Overall, mean hemoglobin increased to 11.36 g/dL at week 12 and was subsequently maintained within the target range (11.0–13.0 g/dL) through week 52. Mean hemoglobin during weeks 40–52 was 12.1 g/dL (95% CI 12.0, 12.2). Hemoglobin levels remained within the target range for a mean duration of 10.3 weeks (*SD* 2.70) during weeks 40–52 (Table S4).

For ESA users, mean baseline hemoglobin level was 10.9 g/dL. Target range was reached at week 12 and mean hemoglobin was maintained within target range through week 52. For ESA users with baseline

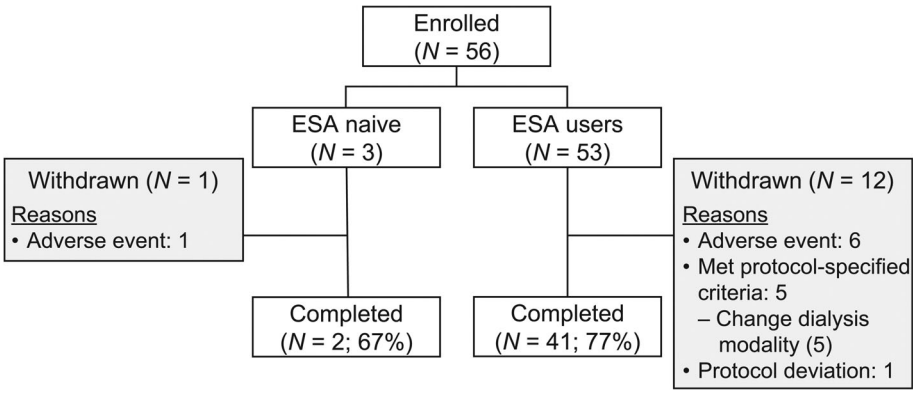

FIGURE 1 Patient disposition. ESA, erythropoiesis-stimulating agent

hemoglobin of <11.0 g/dL, mean baseline hemoglobin level was 10.1 g/dL and mean hemoglobin levels reached the target range at week 12 and were maintained within target range through week 52. For ESA users with baseline hemoglobin of ≥11.0 g/dL, mean baseline hemoglobin level was 11.6 g/dL and mean hemoglobin levels were maintained within the target range throughout the treatment period (Figure 2a–c).

For the three ESA-naive participants, baseline hemoglobin levels were 9.2, 9.6, and 9.7 g/dL. All three participants reached the target hemoglobin range by week 12.

In a post hoc analysis of participants who had ≥1 hemoglobin measurement during weeks 40–52, 95% (42/44) of participants had a mean hemoglobin level within the target range.

Mean change from baseline in hemoglobin at week 4 was −0.09 g/dL (95% CI −0.33, 0.16). For ESA users, mean change from baseline in hemoglobin at week 4 was −0.15 g/dL (95% CI −0.39, 0.09). For ESA users with baseline hemoglobin of <11.0 g/dL, mean change from baseline in hemoglobin at week 4 was 0.00 g/dL (95% CI −0.37, 0.36). For ESA users with baseline hemoglobin of ≥11.0 g/dL, mean change from baseline in hemoglobin at week 4 was −0.27 g/dL (95% CI −0.61, 0.06). One participant (baseline hemoglobin <11 g/dL) experienced a rapid increase in hemoglobin of >2.0 g/dL at 4 weeks. For the 3 ESA-naive participants, hemoglobin changes from baseline at week 4 were 0.2, 0.9, and 2.0 g/dL.

3.3 | Daprodustat dose

The median dose of daprodustat during weeks 40–52 was 5.7 mg (interquartile range [P25, P75]: 2.7 mg, 8.7 mg, [min, max]: 0 mg, 24 mg).

3.4 | Iron

Thirty-five percent (19/55) of participants used oral iron at baseline and 50% (22/44) used it during weeks 40–52. None of the subjects used intravenous iron during the treatment period.

For the efficacy PD population, serum iron levels remained near baseline (Figure 3a). TIBC increased from baseline, consistent with the increase in transferrin observed (transferrin at baseline [safety population]: 1.96 g/L, change from baseline at week 52: 0.495 g/L) (Figure 3b). TSAT, ferritin, and hepcidin decreased from baseline in the efficacy PD population (Figure 3c,d,e).

3.5 | Safety

A summary of AEs is shown in Table 2. The percentage of participants experiencing ≥1 AE during the 52-week treatment period was 96%. The most frequently observed AEs were nasopharyngitis (29%), catheter-site infection (18%), peritonitis (16%), diarrhea (14%), and nausea (11%). Hyperkalemia was reported in one participant (2%). The percentage of participants with ≥1 AE of special interest was 21% (Table S5). The percentage of participants with at least one drug-related AE was 14%, and nausea was the only drug-related event reported in more than one participant (reported in two participants). The percentage of subjects with AEs leading to withdrawal from study/discontinuation of study treatment was 13% (7 participants). Of these, only nausea ($n = 2$, 4%) occurred in 2 or more participants. Pulmonary embolism, pulmonary hypertension, and deep vein thrombosis all occurred in a single participant (2%) and both cough and dermatitis acneiform were reported in another participant (2%). Other adverse events leading to withdrawal that occurred in one participant each (2%) included acute respiratory distress syndrome, hemoglobin decreased, and transient ischemic attack. At least one serious AE was experienced by 46% of participants. The serious AEs reported in >1 participant were peritonitis (9 participants, 16%) and congestive heart failure (3 participants, 5%). There were no deaths.

Mean systolic and diastolic blood pressures at baseline were 137.2 mm Hg (*SD* 20.63) and 79.7 mm Hg

TABLE 1 Patient baseline characteristics (safety population)

Participant characteristic	Overall (*N* = 56)	ESA users (*N* = 53)
Sex		
Female, *n* (%)	12 (21)	11 (21)
Male, *n* (%)	44 (79)	42 (79)
Age (years)		
Mean (*SD*)	64.4 (9.64)	64.1 (9.59)
Weight (kg)		
Mean (*SD*)	64.8 (13.72)	64.9 (13.86)
Body mass index (kg/m^2)		
Mean (*SD*)	24.0 (3.55)	24.0 (3.63)
Time on dialysis (years)		
Mean (*SD*)	2.7 (2.69)	2.6 (2.71)
Medical conditions, *n* (%)		
Hypertension	54 (96)	51 (96)
Hyperlipidemia	34 (61)	32 (60)
Diabetes	13 (23)	13 (25)
Angina pectoris	8 (14)	8 (15)
Eye disorders	11 (20)	11 (21)
Diabetic retinopathy	9 (16)	9 (17)
Hemoglobin (g/dL)		
Mean (*SD*)	10.9 (0.96)	10.9 (0.93)
Ferritin (μg/L)[a]		
Geometric mean (CV%)	155.6 (94.1)	154.5 (95.7)
TSAT (%)[a]		
Mean (*SD*)	37.1 (13.43)	33.9 (18.89)
Hepcidin (ng/mL)[a]		
Geometric mean (CV%)	98.5 (104.6)	98.6 (106.9)
Prior ESA, *n* (%)		
Epoetin beta pegol	—	36 (68)[b]
Darbepoetin alfa	—	17 (32)[c]
Oral iron use, *n* (%)	19/55 (35)	18/52 (35)
Monthly average iron dose (mg)[a]		
Mean (*SD*)	1962.0 (5325.55)	

Abbreviations: ESA, erythropoiesis-stimulating agent; PD, peritoneal dialysis; *SD*, standard deviation; TSAT, transferrin saturation.
[a]Efficacy PD population.
[b]Mean dose is 26.5 (*SD*, 17.88) μg/week.
[c]Mean dose is 20.1 (*SD*, 13.07) μg/week.

(14.27), respectively. No change from baseline at week 52 was seen for systolic or diastolic blood pressure (Table S6).

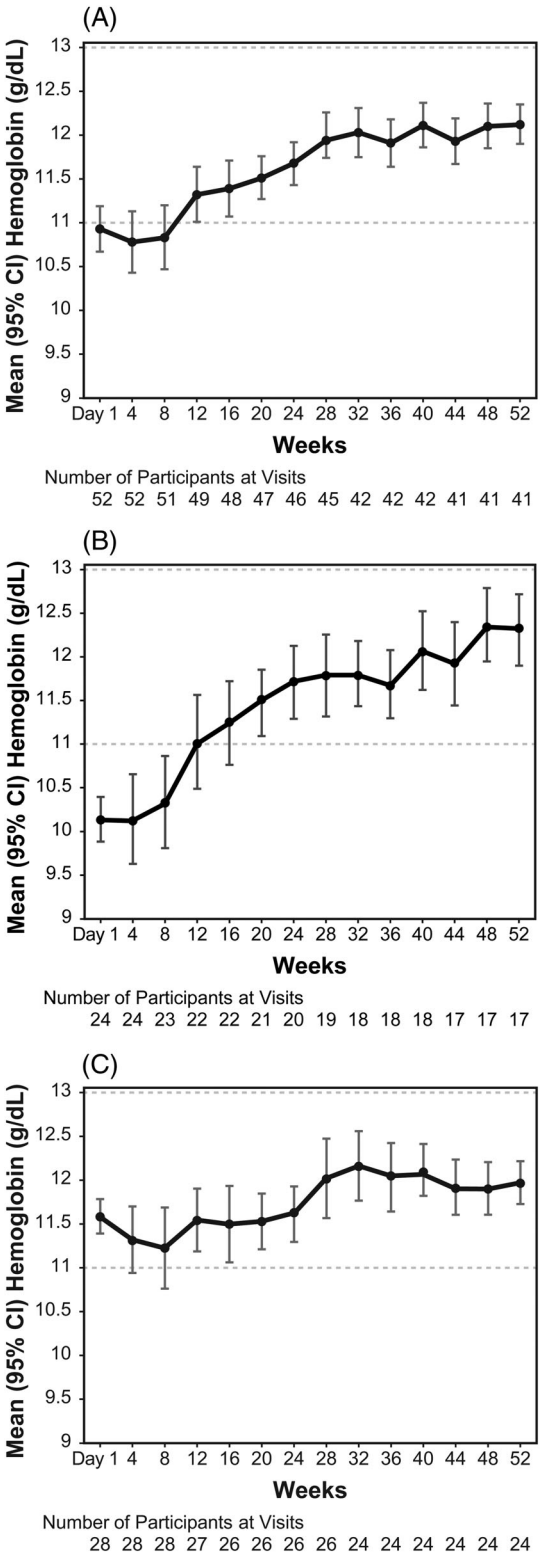

FIGURE 2 Mean hemoglobin over time (efficacy PD population). (a). ESA users. (b). ESA users with baseline hemoglobin <11.0 g/dL. (c). ESA users with baseline hemoglobin ≥11.0 g/dL. CI, confidence interval; ESA, erythropoiesis-stimulating agent; PD, peritoneal dialysis

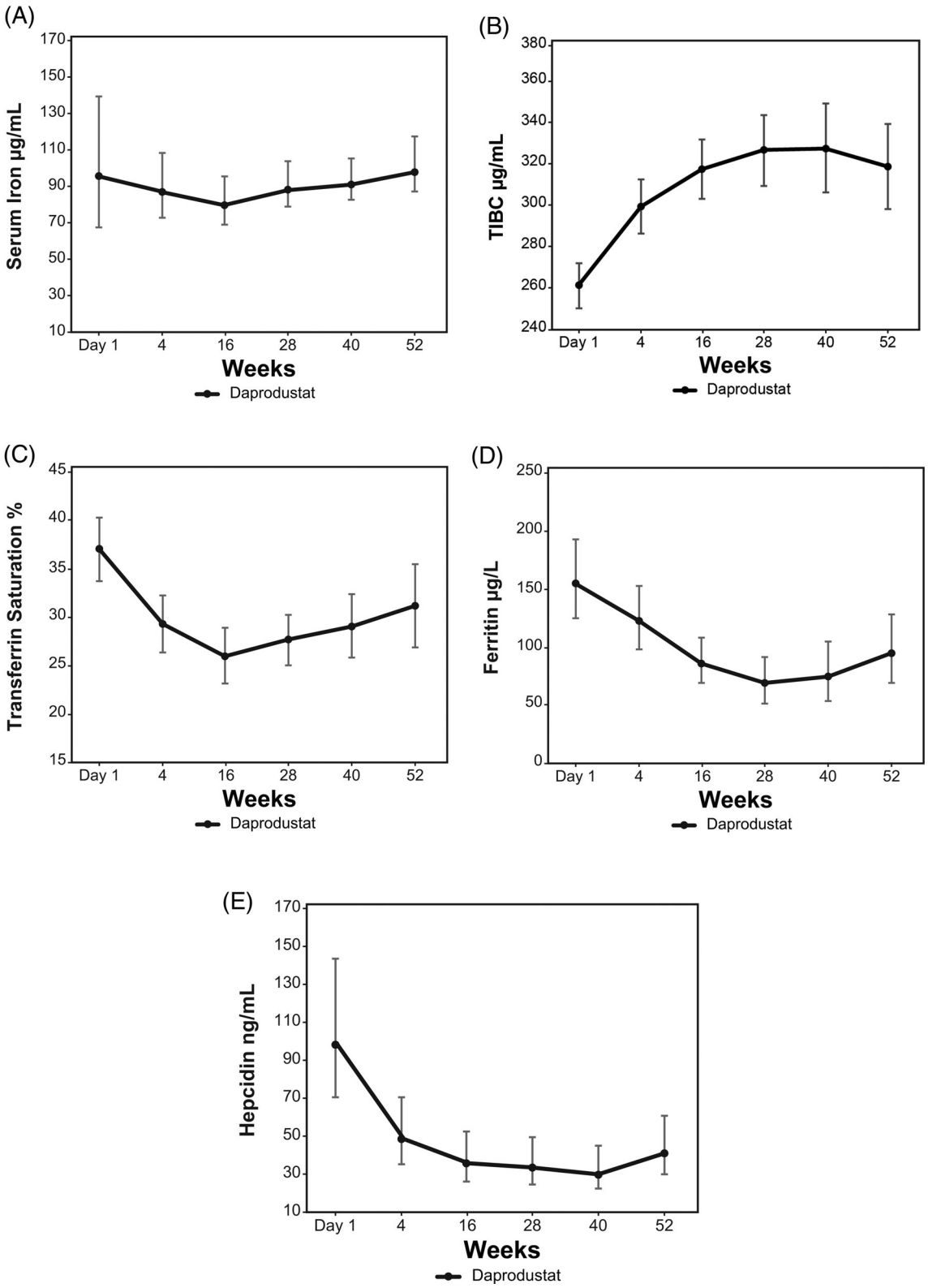

FIGURE 3 Iron parameters over time (efficacy PD population). (a). Mean (95% CI) serum iron. (b). Mean (95% CI) TIBC. (c). Mean (95% CI) TSAT. (d). Geometric mean (95% CI) ferritin. (e). Geometric mean (95% CI) hepcidin. The distribution in ferritin had been assumed not to be skewed but was found to be skewed after the data review; therefore, the analysis of ferritin based on a log-transformation was done as a post hoc analysis. 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 based on not transformed values was done as a post hoc analysis. CI, confidence interval; ESA, erythropoiesis-stimulating agent; PD, peritoneal dialysis; TIBC, total iron-binding capacity; TSAT, transferrin saturation

TABLE 2 Summary of on-therapy AEs (safety population)

Overview of AEs	Daprodustat ($N = 56$)
AEs, *n* (%)	54 (96)
Drug-related AEs, *n* (%)	8 (14)
Serious AEs, *n* (%)	26 (46)
Drug-related SAEs, *n* (%)	1 (2)
AEs leading to withdrawal from study/ permanent discontinuation of study treatment, *n* (%)	7 (13)
AEs occurring in ≥5%, *n* (%)	
Nasopharyngitis	16 (29)
Catheter-site infection	10 (18)
Peritonitis	9 (16)
Diarrhea	8 (14)
Nausea	6 (11)
Back pain	5 (9)
Gastroesophageal reflux disease	5 (9)
Hypertension	5 (9)
Decreased appetite	5 (9)
Device-related infection	5 (9)
Bronchitis	4 (7)
Pyrexia	4 (7)
Arthralgia	3 (5)
Cardiac failure congestive	3 (5)
Cough	3 (5)
Vomiting	3 (5)

Abbreviations: AE, adverse event; SAE, serious adverse event.

Decreases from baseline in the total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were observed and no change was apparent from baseline in the LDL/HDL cholesterol ratio (Table S7). No participants experienced elevated potassium >6.0 mmol/L.

4 | DISCUSSION

This is the first phase 3 study to evaluate the efficacy and safety of daprodustat in the PD population. During weeks 40 to 52, a high proportion (95%, 42/44) of Japanese PD participants achieved and maintained hemoglobin levels within the target range. Daprodustat was effective regardless of prior ESA use or baseline hemoglobin levels (<11.0 g/dL or ≥11.0 g/dL) in ESA users. Efficacy results are consistent with other randomized controlled phase 3 studies in hemodialysis and nondialysis patients, suggesting that daprodustat is also an effective treatment option for PD patients [14,15]. A recent study demonstrated the effectiveness of another oral HIF-PHI, roxadustat, to maintain hemoglobin within a target range in Japanese PD patients with a treatment duration of 24 weeks [5]. In our study, ESA users with baseline hemoglobin below the target range (<11.0 g/dL) as well as ESA users with hemoglobin within the target range (11.0–13.0 g/dL) were enrolled, and effectiveness to achieve/maintain hemoglobin within the target range during weeks 40–52 was confirmed in both populations. These findings suggest that daprodustat may be an effective oral agent to achieve and maintain target hemoglobin levels in PD patients, including ESA users with hemoglobin below the target level (<11.0 g/dL) [2].

Daprodustat was started at 4 mg once daily regardless of previous ESA use. At week 4, the mean hemoglobin remained near baseline for both ESA users with baseline hemoglobin of <11.0 g/dL (mean change: 0.00 g/dL) and ESA users with baseline hemoglobin of ≥11.0 g/dL (mean change: −0.27 g/dL), with only one participant experiencing a rapid increase in hemoglobin (>2 g/dL) at week 4. Hemoglobin levels increased for all 3 ESA-naive participants at week 4. Our findings suggest that the 4-mg starting dose was appropriate for the Japanese PD population in which ESA dose is generally low and the dose range is narrow. Based on the median dose (P25–P75) during weeks 40–52, it could be suggested that hemoglobin levels can be maintained within the target range with daprodustat doses of <10 mg once daily for most Japanese PD patients. While doses of <10 mg daprodustat are generally sufficient to achieve and maintain hemoglobin levels within the target range, some participants in the current study required doses of 12–24 mg. Although patients treated with high ESA doses tended to require a higher daprodustat dose (<4500 IU/week subgroup: 2/28 patients used ≥12 mg, ≥4500 IU/week subgroup: 9/24 patients used ≥12 mg at the final visit), the reasons for this response difference are unclear. Therefore, monitoring hemoglobin response upon initiating treatment with daprodustat is recommended.

The changes in iron metabolism parameters were aligned with findings in hemodialysis and nondialysis participants in our previous phase 2 and phase 3 studies [9,13–15]. The decrease in hepcidin, accompanied by decreases in ferritin, results from a shift from iron storage to erythrocyte development. However, interpretation of the data regarding change in iron parameters is complicated by the use of iron supplementation during the study and merits further evaluation.

The incidence rates of peritonitis and device-related/ catheter-site infection in this study, which are unique events for PD patients, were similar to the rates reported

for the general PD population, and the incidence rates for other infections/infestations were low [16,17]. Ocular AEs of special interest (proliferative retinopathy, macular edema, and choroidal neovascularization) were evaluated because of concern that increases in vascular endothelial growth factor, which might be due to increased HIF, could exacerbate proliferative retinopathy and macular edema. Prior phase 2 studies with daprodustat have shown moderate increases in endogenous erythropoietin with no change in circulating vascular endothelial growth factor levels [9,10,13]. In our study, considering that 16% (9/56) of participants had diabetic retinopathy at baseline and macular edema was reported as an AE in one participant, daprodustat treatment did not appear to exacerbate these conditions. These findings, together with results from other phase 3 clinical trials in hemodialysis and nondialysis patients, suggest that daprodustat treatment for 52 weeks does not induce and/or worsen ocular AEs [14,15]. The AE profile of daprodustat in the Japanese PD population in our study is similar to what has been reported in epidemiological data for the PD population and consistent with the results of a phase 3 study of roxadustat for PD patients [16,17].

4.1 | Limitations of the study

Limitations of this study include the small sample size and the lack of a comparator arm with the open-label design. The small sample size limits the ability to detect rare safety events. Because of the lack of a comparator arm, evaluating results relative to standard of care is difficult.

5 | CONCLUSION

Once-daily treatment with oral daprodustat was generally well tolerated and achieved and maintained hemoglobin within the target range in Japanese peritoneal dialysis participants. No new safety concerns were identified in the peritoneal dialysis participants.

ACKNOWLEDGMENTS

Funding for this study (NCT02791763 available from www.clinicaltrials.gov) was provided by GlaxoSmithKline (GSK). All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. Editorial support (assembling tables and figures, collating author comments, copyediting, fact checking, and referencing) (Allyson Lehrman, DPM) and graphic services were provided by AOIC, LLC, and were funded by GSK.

CONFLICT OF INTEREST

We have read and understood Peritoneal Dialysis International's policy on conflicts of interest disclosure and declare the following interests: HK has received personal fees from Baxter International, Chugai Pharmaceutical Co., Ltd. (Chugai), Kyowa Kirin Co., Ltd. (KKC), Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Terumo Corporation, Torii Pharmaceutical Co., Ltd. (Torii), and Bayer Yakuhin, Ltd. (Bayer). MN has received grants and personal fees from Astellas Pharma Inc., Chugai, Daiichi Sankyo Co., Ltd., GlaxoSmithKline (GSK), KKC, Tanabe-Mitsubishi Pharma Corporation, and Torii; grants from Bayer, Ono Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd.; and personal fees from AstraZeneca and JT Pharmaceuticals. RN is an employee of GSK. NO, KK, TN, YE, and AC are employees and hold equity stock in GSK.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Kanai H, Nangaku M, Nagai R, et al. Efficacy and safety of daprodustat in Japanese peritoneal dialysis patients. Ther Apher Dial. 2021;25:979–987. https://doi.org/10.1111/1744-9987.13686