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A Single-Dose, Open-Label, Randomized, Two-Way Crossover Study in Healthy Japanese Participants to Evaluate the Bioequivalence and the Food Effect on the Pharmacokinetics of Daprodustat

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Abstract

Daprodustat is a prolyl hydroxylase inhibitor that stimulates erythropoiesis in a manner similar to the natural response to hypoxia, whereby inhibition of hypoxia inducible factor (HIF) prolyl-4-hydroxylases by daprodustat ultimately results in increased levels of HIF-responsive genes. Daprodustat is under development as an emerging new class of agents for the treatment of anemia associated with chronic kidney disease (CKD). This was a single-center, single-dose, open-label, randomized, 2-way crossover study in healthy Japanese male participants consisting of 2 parts. The primary objective was to evaluate the bioequivalence (BE) between daprodustat tablet strengths (part 1) and to evaluate the food effect on the pharmacokinetics (PK) of daprodustat (part 2). A total of 64 healthy Japanese male participants were enrolled; 52 participants were included in part 1 and 12 in part 2. BE was demonstrated between the daprodustat 2-mg tablet and the daprodustat 4-mg tablet. A standard CKD meal did not have a large effect on the PK parameters of daprodustat after a single oral dose of daprodustat 4 mg. Administration of single oral doses of daprodustat 4 mg was generally well tolerated in the healthy Japanese participants, and no new safety signals were identified without regard to food.

Keywords

bioequivalence, daprodustat, food effect, healthy subject, Japanese, pharmacokinetics, safety, single dose

Anemia, which is frequently observed in patients with chronic kidney disease (CKD), has been associated with decreased circulating levels of a glycoprotein hormone, erythropoietin.[1–3] This hormone is primarily produced by the kidneys and, to a lesser extent, by the liver, and it stimulates normal red blood cell production, maturation, and survival.[2,3] Daprodustat[4,5] is a prolyl hydroxylase inhibitor that stimulates erythropoiesis in a manner similar to the natural response to hypoxia, whereby inhibition of hypoxia inducible factor (HIF) prolyl-4-hydroxylases (PHD1, PHD2, PHD3) by daprodustat ultimately results in increased levels of HIF-responsive genes. Daprodustat is under development as an oral dose as an emerging new class of agent for treatment of anemia associated with CKD.

From clinical studies with the oral daprodustat programs, daprodustat was found to be rapidly absorbed following oral administration (time to maximum concentration [T_{max}] of 1.0 to 2.5 hours) and exhibited dose-proportional increases in exposure over the 10- to 100-mg dose range in healthy Japanese and

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Caucasian participants.[6] The pharmacokinetic (PK) properties of steady-state daprodustat maximum observed drug concentration (C_{max}), daprodustat area under concentration-time curve (AUC), and time to maximum observed drug concentration (T_{max}) were comparable in healthy and CKD subjects.[7] In addition, there was no clinically relevant difference in these properties in the hemodialysis subjects between a dialysis and nondialysis day, and the renal clearance of daprodustat was minimal.

The cytochrome (CYP) P450 enzymes that are involved in the oxidative metabolism of daprodustat have been evaluated both in vitro (human liver microsomes) and in clinical studies. Using in vitro assays of human liver microsomes and CYP supersomes, daprodustat was found to be primarily metabolized through CYP P450 enzymes, suggesting that it undergoes first-pass metabolism.[4] Drug-drug interactions were evaluated with a 100-mg oral dose of daprodustat, a dose 4 times higher than the highest daily dose investigated in clinical trials. The strong CYP2C8 inhibitor gemfibrozil markedly increased the $AUC_{0\text{-}t}$ of daprodustat by 18.6-fold and C_{max} by 3.9-fold. In a subsequent study,[8] when daprodustat 25 mg was coadministered with a weak CYP2C8 inhibitor, trimethoprim (200 mg), the AUC of daprodustat was increased by 48% and C_{max} by 28%. However, when daprodustat was coadministered with pioglitazone (CYP2C8 probe) and rosuvastatin (organic anion transporting peptide 1B1 probe), daprodustat did not affect the PK of these 2 probes, suggesting very low interaction potential with these drugs.

Daprodustat is formulated as immediate-release tablets with dose strengths of 1, 2, 4, and 6 mg in Japan. The dissolution profiles of these tablets have been evaluated according to the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms and Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (Japanese bioequivalence guidelines), and the dissolution test results across tablet strengths demonstrated equivalence, with the exception of the 2-mg tablet versus the 4-mg tablet test in water. Administration of daprodustat in development with a high-fat/-calorie breakfast led to a 1.0-hour delay in T_{max} and 29% decrease in C_{max} and an 8% decrease in AUC in healthy non-Japanese participants.[4]

The primary objective of our study was to evaluate the bioequivalence (BE) of daprodustat tablet strengths (2 versus 4 mg) in healthy Japanese male participants according to the Japanese BE guideline (part 1) and to evaluate the food effect on the PK of daprodustat in healthy Japanese male participants with reference to Japanese Notification for Clinical Pharmacokinetic Studies of Pharmaceuticals (part 2). This part assessed the PK of a single oral dose of daprodustat under a fasted state and following a standard CKD meal.

Methods

Ethics

The study was conducted between April 24, 2018, and June 9, 2018, at the SOUSEIKAI Global Clinical Research Center, Fukuoka Mirai Hospital in Japan in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, all applicable participant privacy requirements, and the ethical principles outlined in the current version of the Declaration of Helsinki. The study protocol and informed consent documents were approved by the Institutional Review Board of the Hakata Clinic. Written informed consent was obtained from each participant before any screening evaluations.

Study Design and Study Population

This was a single-center, single-dose, open-label, randomized, 2-way crossover study to evaluate the BE between daprodustat tablet strengths and to evaluate the food effect on the PK of daprodustat following single oral doses in healthy Japanese male participants (ClinicalTrials.gov identifier: NCT03493386). Part 1 of this study was the BE part, in which participants received single dose of 2 tablets of 2-mg daprodustat and a single dose of 1 tablet of 4-mg daprodustat according to the Japanese BE guideline. Part 2 was the food effect part, in which participants received a single dose of a 4-mg daprodustat tablet in fasting and fed states in a crossover manner. To investigate the food effect in the closer clinical practice, a standard meal as recommended by the Japanese Society of Nephrology for CKD[9] was used in part 2.

In both parts (part 1 and part 2), healthy participants had a screening visit within 30 days prior to the first dose of study intervention, 2 intervention periods, and revisit 7 ± 1 days after the second dose for follow-up. All participants were administered daprodustat as a single oral dose, with assessments conducted for up to 24 hours postdose. At least a 5-day washout period occurred between each intervention period. In part 1, participants refrained from any food or drink at least 10 hours before dosing and 4 hours after dosing. No water was allowed within 2 hours before and after dosing, but it was allowed ad libitum at all other times. In part 2, participants fasted 10 hours before administration of a standard CKD meal or dosing. The standard CKD meal consisted of 500-700 kcal, 12-16 g of protein, greater than or equal to 1 g but less than 2 g of salt, and less than or equal to 500 mg of potassium based on the dietary recommendations for CKD patients.[9] Study participants who were in

the fed state consumed a standard CKD meal in 20 minutes or less as breakfast, and the drug product was administered 30 minutes after the end of the meal. No water was allowed until 2 hours after dosing, but it was allowed ad libitum at all other times.

Healthy Japanese male participants aged between 20 and 55 years with a body weight ≥ 50 kg and a body mass index between 18.5 and 24.9 kg/m^2 were eligible to participate in this study. Participants were healthy, as determined by the investigator at the screening evaluation, which included assessment of concurrent conditions, medical history, concomitant medications, alcohol and smoking habits, allergies, and presence of infectious diseases, as well as physical examination, laboratory tests, and a 12-lead electrocardiogram (ECG).

Table 1. Summary of Demographic Characteristics

Demographics	Part 1 n = 52	Part 2 n = 12
Age (years), mean (SD)	27.9 (6.9)	30.0 (7.5)
Sex, n (%)		
Male	52 (100)	12 (100)
Female	0	0
BMI (kg/m^2), mean (SD)	21.38 (1.66)	20.58 (1.56)
Height (cm), mean (SD)	170.2 (5.05)	171.0 (5.09)
Weight (kg), mean (SD)	61.97 (5.33)	60.13 (4.24)

BMI, body mass index.

Pharmacokinetic Sample Collection and Bioanalytical Methods

Blood samples were collected for the measurement of daprodustat concentrations predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours following daprodustat administration in parts 1 and 2. Samples were collected at nominal times relative to the proposed time of daprodustat dosing.

The blood samples were taken via an indwelling cannula (or by direct venipuncture), collected in a blood collection tube containing ethylenediaminetetraacetic acid dipotassium. The tube was immediately inverted 10 times and was placed on water ice until centrifugation, which should occur within 1 hour of sample collection (3000 rpm, 4°C, 10 minutes). Supernatant plasma was transferred to a 2.0-mL polypropylene tube and stored at -20°C before shipment. Samples were shipped frozen on dry ice at agreed times throughout the study to a bioanalytical facility (PPD, Middleton, Wisconsin).

The bioanalytical method for the daprodustat analysis in plasma was validated by PPD. The concentration of daprodustat was analyzed by high-performance liquid chromatography-tandem mass spectrometry with negative ion mode. The analytical system consisted of a Series 1100 HPLC system (Agilent, Santa Clara, California), XBridge Phenyl analytical column (2.1 × 30 mm, 3.5 μm; Waters, Milford, Massachusetts), and an API6500 mass spectrometer (Sciex, Framingham, Massachusetts). Daprodustat was extracted from a 250-μL aliquot of plasma by solid-phase extraction using Evolute ABN (30 μm, 25 mg 96-well plate; Biotage, Charlotte, North Carolina) with isotopically labeled internal standard ([$^{13}C_5$ ^{15}N]-daprodustat). Mobile phases consisted of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B). Extracts were separated under the following gradient conditions: 1-minute gradient from 50% to 95% (B) with a flow rate of 0.4 mL/min and kept from 1 to 2 minutes, washing using 95% (B) from 2.1 to 2.5 minutes with a flow rate of 0.6 mL/min, and gradient down from 95% to 50% (B) from 2.5 to 2.6 minutes with 0.6 mL/min, then 50% (B) at 3 to 3.5 minutes with a flow rate of 0.4 mL/min. The transition mass for daprodustat and the internal standard was 392 to 291 and 398 to 294, respectively. The lower and higher limits of quantification were 5 and 2500 pg/mL, respectively. The applicable analytical run for study samples met all predefined acceptance criteria, whereas bias and precision of quality control samples analyzed with study samples were within ±15% and under 15%, respectively.

Safety Assessments

Safety was assessed in all participants by monitoring adverse events (AEs), clinical laboratory tests (hematology, chemistry, and urinalysis), vital signs (blood pressure, heart rate, and body temperature), 12-lead ECGs, and physical examinations. AEs were collected from the start of treatment until the follow-up visit. Clinical laboratory tests were performed predose, 24 hours postdose, and at follow-up. Vital signs, 12-lead ECGs, and physical examinations were performed predose, 3 and 24 hours postdose, and at follow-up.

Pharmacokinetic Analyses

Plasma daprodustat concentration-time data were analyzed by noncompartmental methods using Phoenix WinNonlin version 6.3 (Certara L.P., St. Louis, Missouri).

The plasma concentration-time data were used to determine the following PK parameters: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, %AUCex, CL/F, kel, and correlation coefficient between time and log concentration of daprodustat for the points used in estimation of kel. The calculations were based on the actual sampling times recorded during the study.

Statistical Analyses

In part 1, the number of participants was determined based on statistical considerations. According to the

regulatory definition of BE criteria; the 90% confidence interval (CI) of the ratio for $AUC_{0\text{-}t}$ and C_{max} between tablet strengths (2 mg × 2 versus 4 mg × 1) should lie within the range of 0.80-1.25. Assuming the true ratio was 1.0 and the coefficient of variation within subject (%CVw) was 35%, in a 2-way crossover design 52 participants in total (ie, 26 participants for each group) were randomized to achieve at least 90% power for meeting the BE criteria. In part 2, the number of participants was determined based on feasibility rather than statistical considerations. A total of 12 participants (ie, 6 participants for each group) were randomized in a 2-way crossover design.

The safety population was defined as all participants who received at least 1 dose of the study medication. The PK population was defined as all participants who received at least 1 dose of the study medication from whom a PK sample was obtained and analyzed.

For part 1, the $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of daprodustat were separately analyzed following the log-transformation of PK parameters of daprodustat. The model included tablet strength, period, and group as fixed effects, whereas subject was a random effect. The estimates of least-squares means for each tablet strength and the treatment difference was exponentially back-transformed to obtain adjusted geometric means of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} for each tablet strength and adjusted geometric mean ratios (test/reference) along with the associated 90%CIs. Two treatments were considered bioequivalent if the 90%CI of the geometric mean ratio of the $AUC_{0\text{-}t}$ and C_{max} was within the acceptable range of 0.80-1.25.

For part 2, the effect of food on the PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}) was assessed using the same mixed-effects model as part 1, with feeding condition (fasted or fed) instead of tablet strength effect. The formal test of bioequivalence was not performed for part 2.

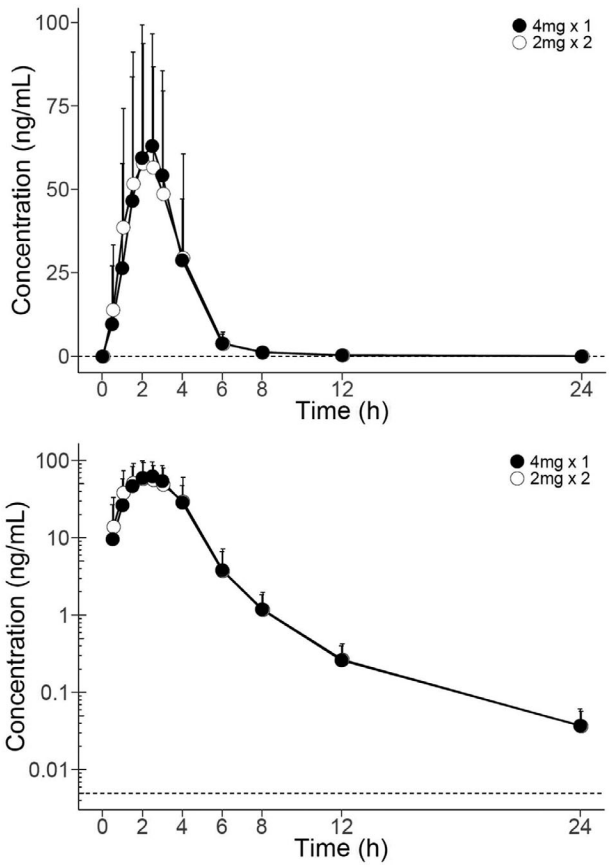
Results

Participant Disposition and Demographics

A total of 64 healthy Japanese male participants were enrolled. In part 1, all 52 participants received the study drug, and 51 participants completed the study. One participant who completed treatment in period 1 was withdrawn from the study because of the participant's inconvenience of the subsequent study schedule. In part 2, all 12 participants received the study drug and completed the study. The demographic characteristics of the participants are summarized in Table 1.

Pharmacokinetics

Mean daprodustat plasma concentration-time profiles categorized by strength or food effect are displayed in Figures 1 and 2. Daprodustat PK parameters in part 1 and part 2 are summarized in Table 2. The results of the statistical analysis for both parts are presented in Table 3.

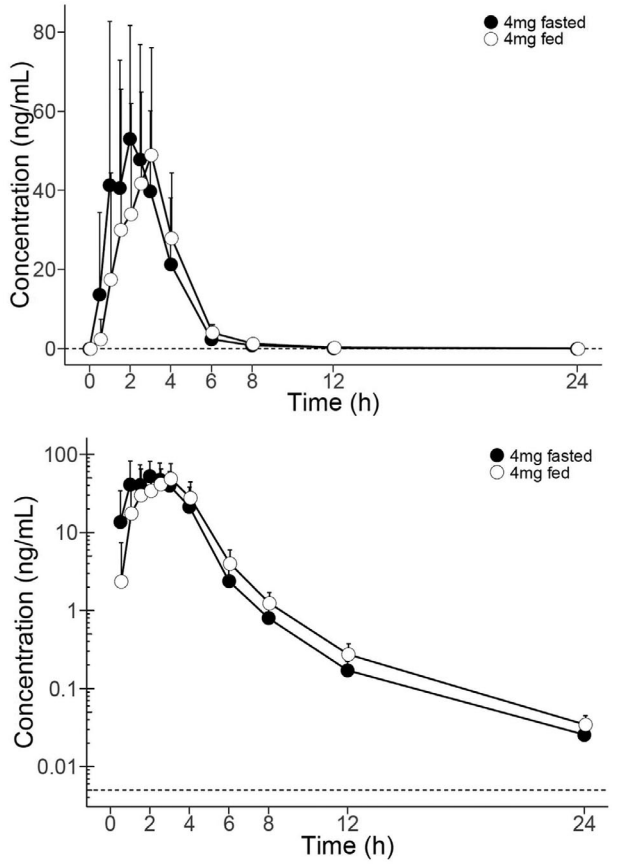


Note: Dashed line: LLQ = 0.005 ng/mL

Figure 1. Part 1: mean ± SD daprodustat plasma concentration-time profiles following single doses of 4 mg daprodustat using different tablet strengths (n = 52 in 4-mg tablet × 1, n = 51 in 2-mg tablet × 2).

Following the single oral 4-mg daprodustat dose (2-mg tablet × 2 or 4-mg tablet × 1) in part 1, daprodustat plasma concentration reached a peak at 2.0 hours (median) after dosing and was rapidly eliminated. The $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} were similar in participants dosed with 2 daprodustat 2-mg tablets and 1 daprodustat 4-mg tablet. The T_{max} was identical for both tablet strengths, and the $t_{1/2}$ values were also similar. The mean percent $AUC_{0\text{-}inf}$ extrapolated was <20%. The 90%CIs for the adjusted geometric mean ratios for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} for 2 daprodustat 2-mg tablets compared with 1 daprodustat 4-mg tablet were within the predefined bioequivalence range of 0.80-1.25.

In part 2, the exposure of daprodustat in the fed state was slightly lower than in the fasted state. The ratio of fed/fasted for $AUC_{0\text{-}t}$ was 0.91, indicating that



Note: Dashed line: LLQ = 0.005 ng/mL

Figure 2. Part 2: mean ± SD daprodustat plasma concentration-time profiles following single doses of 4 mg daprodustat in fed or fasted state (n = 12).

$AUC_{0\text{-}t}$ in the fed state was 9% lower than in the fasted state. Similarly, the ratio of fed/fasted for C_{max} was 0.89, indicating that C_{max} in the fed state was 11% lower compared with the fasted state. The median T_{max} was delayed from 1.75 to 2.75 hours when administering daprodustat with a standard CKD meal. There was no apparent difference in $t_{1/2}$ between fed and fasted states.

Safety

During part 1 of the study, 4 of the 52 participants (8%) experienced AEs, and no AE was reported in part 2 of the study. All 4 AEs were considered by the investigator to be moderate in intensity (Table 4), unrelated to treatment with study medication, and resolved by the end of the study. No serious adverse events (SAEs) or deaths were reported during this study. No participant was withdrawn from the study because of an AE. In addition, no safety signals were identified via vital signs, 12-lead ECGs, or clinical laboratory parameters. Overall daprodustat was generally well tolerated in healthy Japanese male participants following administration of a single oral dose of daprodustat 4 mg in the fed and fasted states.

Discussion

This study was conducted to evaluate the BE between daprodustat tablet strengths (2 versus 4 mg) in healthy Japanese male participants and to evaluate the food effect on the PK of daprodustat in healthy Japanese male participants.

In part 1, the BE of daprodustat tablet strengths (2-mg tablet × 2 versus 4-mg tablet × 1) was investigated. The 90%CIs for the adjusted geometric mean ratios for $AUC_{0\text{-}t}$ and C_{max} for 2 daprodustat 2-mg tablets compared with 1 daprodustat 4-mg tablet under fasted states were within the predefined BE range of 0.80-1.25. Therefore, BE was demonstrated between the daprodustat 2-mg tablet and the daprodustat 4-mg tablet used in this study. For other PK parameters, the 90%CI for the adjusted geometric mean ratios for $AUC_{0\text{-}inf}$ was also contained within the 0.80-1.25 ranges for BE. In part 2, the effect of administration with a standard CKD meal (fed versus fasted) was investigated following a single oral dose of 4-mg daprodustat. The

Table 2. Summary of Daprodustat Pharmacokinetic Parameters

	Part 1		Part 2	
	2-mg Tablet × 2 (n = 51)	4-mg Tablet × 1 (n = 52)	4 mg, Fed (n = 12)	4 mg, Fasted (n = 12)
C_{max} (ng/mL)	94.2 (30.6)	90.0 (27.7)	69.9 (17.6)	79.3 (23.6)
T_{max} (h)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	2.75 (1.0, 3.0)	1.75 (1.0, 4.0)
$AUC_{0\text{-}t}$ (ng·h/mL)	190.8 (55.1)	187.8 (58.1)	145.0 (25.6)	159.0 (29.8)
$AUC_{0\text{-}inf}$ (ng·h/mL)	191.0 (55.2)	187.9 (58.2)	145.2 (25.6)	159.1 (29.8)
$t_{1/2}$ (h)	3.27 (0.42)	3.28 (0.43)	3.23 (0.32)	3.25 (0.26)
CL/F (L/h)	22.9 (7.43)	23.2 (6.79)	28.4 (5.11)	26.0 (4.98)

T_{max} is median (min, max); other PK parameters are arithmetic mean (SD).

Table 3. Summary of Bioequivalence and Food Effect for Pharmacokinetic Parameters

Parameter	Treatment	n	Adjusted Geometric Mean	Ratio	90%CI
Part 1					
$AUC_{0\text{-}t}$ (ng·h/mL)	2-mg tablet × 2	51	182.6	1.02	(0.97-1.07)
	4-mg tablet × 1	52	179.7		
$AUC_{0\text{-}inf}$ (ng·h/mL)	2-mg tablet × 2	51	182.8	1.02	(0.97-1.07)
	4-mg tablet × 1	52	179.9		
C_{max} (ng/mL)	2-mg tablet × 2	51	88.93	1.04	(0.97-1.12)
	4-mg tablet × 1	52	85.14		
Part 2					
$AUC_{0\text{-}t}$ (ng·h/mL)	4-mg fed	12	143.0	0.91	(0.82-1.01)
	4-mg fasted	12	156.4		
$AUC_{0\text{-}inf}$ (ng·h/mL)	4-mg fed	12	143.1	0.91	(0.82-1.01)
	4-mg fasted	12	156.6		
C_{max} (ng/mL)	4-mg fed	12	67.82	0.89	(0.73-1.08)
	4-mg fasted	12	76.19		

Adjusted geometric mean ratio for AUC or C_{max} is 2-mg tablet × 2/4-mg tablet × 1 (part 1). Adjusted geometric mean ratio for AUC or C_{max} is fed/fasted (part 2).

Table 4. All Adverse Events (Part 1)

Preferred Term	Daprodustat 2-mg Tablet ×2 (n = 51)	Daprodustat 4-mg Tablet ×1 (n = 52)	Total (n = 52)
Any event, n (%)	3 (6%)	1 (2%)	4 (8%)
Tonsillitis	2 (4%)	0	2 (4%)
Nasopharyngitis	1 (2%)	0	1 (2%)
Pharyngitis	0	1 (2%)	1 (2%)

No AEs were reported in part 2.

exposures ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}) of daprodustat in the fed state were slightly lower (9%, 9%, and 11%, respectively) than those in the fasted state. However, there was considerable overlap in the 95%CIs of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} in the fed and fasted states. The median of T_{max} was delayed from 1.75 to 2.75 hours when administering daprodustat with a standard CKD meal. However, there was considerable overlap in the range of T_{max} values in the fed and fasted states. There was no apparent difference in $t_{1/2}$ between the fed and fasted states. These data indicated that a standard CKD meal did not have a large effect on the PK parameters of daprodustat after a single oral dose of 4 mg daprodustat. The use of daprodustat for renal anemia may require individual dose adjustments, and until the clinical relevance of this change in exposure can be determined, within-subject variability in plasma exposure of daprodustat may be minimized by consistently taking daprodustat either with or without food. These results are consistent with the previous study in which the effect of a high-fat/-calorie meal was investigated in non-Japanese.[4]

Following a single oral dose of 4 mg daprodustat in healthy Japanese male participates, there were no drug-related AEs or SAEs or deaths. In addition, no safety signals were identified via vital signs, 12-lead ECGs, or clinical laboratory parameters. Overall daprodustat was generally well tolerated in healthy Japanese male participants following administration of a single oral dose of daprodustat 4 mg in the fed and fasted states.

Conclusion

Bioequivalence was demonstrated between the daprodustat 2-mg tablet and the daprodustat 4-mg tablet. A standard CKD meal did not have a large effect on the PK parameters of daprodustat after a single oral dose of daprodustat 4 mg. Administration of single oral doses of daprodustat 4 mg was generally well tolerated in the healthy Japanese participants, and no new safety signals were identified.

Acknowledgments

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Conflicts of Interest

At the time this study was conducted, all the authors were employees of GlaxoSmithKline (GSK), and Akira Wakamatsu was a shareholder of GSK.

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Data-Sharing Statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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