Received: 25 January 2022 | Revised: 9 March 2022 | Accepted: 16 March 2022

DOI: 10.1111/1744-9987.13839

ORIGINAL ARTICLE

Therapeutic Apheresis and Dialysis

WILEY

Safety of daprodustat in patients with anemia of chronic kidney disease: A pooled analysis of phase 3 studies in Japan

Masaomi Nangaku[1] | **Tadao Akizawa**[2] | **Takashi Nagakubo**[3] | **Taeko Yonekawa**[4] | **Toshifumi Kimura**[5] | **Yukihiro Endo**[4] | **Alexander Cobitz**[6]

[1]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan

[2]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

[3]Biostatistics, GlaxoSmithKline, Tokyo, Japan

[4]Medicines Development, GlaxoSmithKline, Tokyo, Japan

[5]Medical Affairs, GlaxoSmithKline, Tokyo, Japan

[6]Clinical Sciences, GlaxoSmithKline, Collegeville, Pennsylvania, USA

Correspondence
Toshifumi Kimura, Specialty Medical Affairs, GlaxoSmithKline, Akasaka Intercity AIR, 1-8-1 Akasaka, Minato-ku, Tokyo 107-0052, Japan.
Email: toshifumi.2.kimura@gsk.com

Funding information
Funding for this post hoc analysis study (NCT02791763, NCT02969655, NCT02829320) was provided by GlaxoSmithKline (GSK).

Abstract

Introduction: Daprodustat is an approved treatment for anemia of chronic kidney disease (CKD) in Japan.

Methods: This post hoc analysis evaluated pooled safety data for daprodustat from 3 phase 3 Japanese studies in dialysis-dependent and nondialysis patients with anemia of CKD.

Results: Median drug exposure duration was 365 days for both daprodustat ($N = 369$) and injectable erythropoiesis-stimulating agent (ESA, $N = 285$). The incidence per 100 patient-years of on-therapy adverse events (AEs) was 363.1 and 306.4 in the daprodustat and ESA groups, respectively. The incidence per 100 patient-years of thromboembolic and retinal events were 5.55 and 6.91 (daprodustat) and 6.28 and 7.46 (ESA), respectively. Cardiovascular and malignancy events were similar between groups, although analysis of these were limited by sample size and study duration.

Conclusion: The safety of daprodustat was comparable to ESA in this pooled analysis, although further large-scale research is needed to evaluate long-term risks including cardiovascular and malignancy events.

KEYWORDS

anemia, chronic kidney disease, daprodustat, dialysis, nondialysis, safety

1 | INTRODUCTION

Patients with chronic kidney disease (CKD) commonly develop anemia with inadequate erythropoietin production serving as a major driver. As kidney function deteriorates, incidence of anemia of CKD increases accordingly[1,2] and represents a significant burden for patients, including decreased quality of life and increased cardiovascular (CV) risk.[1,3] Injectable erythropoiesis-stimulating agents (ESAs) are the standard of care for the management of anemia of CKD, along with iron supplementation.[4] However, ESAs are associated with increased thromboembolic and CV risk, especially when treating to attain higher-than-recommended target

hemoglobin (Hgb) levels.[5] The cause of this risk remains unknown; possibilities include dose of ESA, achievement of higher- or lower-than-target Hgb levels, or the rate of Hgb rise.[6–9]

Daprodustat is an oral hypoxia-inducible factor-prolyl hydroxylase inhibitor (HIF-PHI) that has been approved for use in Japan and has completed five studies of the global phase 3 ASCEND program, (clinicaltrials.gov identification NCT03029208, NCT03400033, NCT02879305, NCT02876835, NCT03409107).[10–12] HIF-PHIs increase erythropoiesis within a physiological range through the inhibition of prolyl hydroxylase domain (PHD) enzymes and activation of hypoxia-inducible factors (HIFs), which regulate the body's response to hypoxia. HIFs also regulate the expression of vascular endothelial growth factor (VEGF) and certain genes involved directly or indirectly in iron uptake, mobilization, and transport, including duodenal cytochrome b (DCytb), divalent metal transporter 1 (DMT1), and transferrin.[13]

The mechanism-of-action of HIF-PHIs suggests several potential risks of their use. These risks include thromboembolic events, as observed with ESAs; ocular diseases, such as retinopathy; and tumor progression mediated by VEGF-induced angiogenesis or secondary to elevated HIF levels.[5,13,14] Studies have examined the safety of HIF-PHIs with regard to CV and thromboembolic risk with inconsistent results. In two large, international, randomized phase 3 trials, daprodustat was noninferior to ESAs with regard to change in hemoglobin and cardiovascular outcomes in both patients with CKD undergoing dialysis and not undergoing dialysis.[11,12] Conversely, in two pooled analyses of international phase 3 trials with large sample sizes, the HIF-PHI vadadustat was noninferior compared with ESA with respect to the relative risk of major adverse cardiovascular events (MACEs) in patients with CKD who were undergoing dialysis, but not patients who were not dialysis-dependent.[15,16] Recently, the US Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee has recommended against the use of another HIF-PHI, roxadustat, for both HD and ND patients due to an inadequate risk/benefit profile regarding thromboembolic risk;[17] however, roxadustat has been approved by the European Medicines Agency (EMA).[18]

In Japanese phase 3 studies, oral daprodustat 1–24 mg once daily achieved and maintained target Hgb levels in patients with CKD who underwent hemodialysis (HD), peritoneal dialysis (PD), or nondialysis (ND).[19–22] In these studies, daprodustat proved comparable to ESAs with regard to mean Hgb during weeks 40–52.[19,20] The 1-year safety evaluation in Japanese phase 3 studies showed that daprodustat was generally well tolerated in patients undergoing HD, PD, or ND. The resulting adverse event (AE) profile was comparable to ESA.[19,20] Due to small sample sizes, the data from these individual studies provide limited information on less frequent AEs, such as thromboembolism, MACEs, and ocular disorders. Furthermore, it has been reported that CV event rates in Japanese populations are much lower than in European and North American populations.[23] It is therefore crucial to address the safety profile of daprodustat in Japanese populations.

We conducted a post hoc pooled analysis of Japanese HD, ND, and PD patients with special focus on adverse events, including those linked to daprodustat's mechanism of action. The risk of additional thromboembolic or retinal events in patients with prior histories of thromboembolism or pre-existing retinal disease was also assessed.

2 | METHODS

2.1 | Studies included in pooled analysis

Data were pooled from a total of 3 trials: a 52-week randomized open-label phase 3 trial comparing daprodustat with epoetin beta pegol in Japanese ND patients,[19] which also included a PD cohort[22] (ClinicalTrials.gov Identifier: NCT02791763); a 52-week double-blind randomized active control study comparing daprodustat with darbepoetin alfa in Japanese HD patients[20] (ClinicalTrials.gov Identifier: NCT02969655); and a 24-week phase 3 open-label anemia correction study of daprodustat in Japanese HD patients[21] (ClinicalTrials.gov Identifier: NCT02829320) (Table S1)

2.2 | Safety outcomes

The measured safety outcomes included incidence of AEs and serious adverse events (SAEs). We also specifically analyzed AEs based on potential risks associated with daprodustat's mechanism of action (MOA) and the known safety profile of ESAs. These included thromboembolic events; MACEs, including all-cause mortality, myocardial infarction, and stroke; heart failure–related events; retinal events; and cancer-related mortality, tumor progression, and tumor recurrence.

2.3 | Evaluation procedure for potential AEs based on daprodustat MOA

For this post hoc analysis, Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) were used to identify thromboembolic events, MACEs, heart failure–related events, and retinal events. Comprehensive ophthalmologic exams (best corrected visual acuity,

TABLE 1 Baseline characteristics

	All		ND		HD		PD
	Daprodustat	ESA	Daprodustat	ESA	Daprodustat	ESA	Daprodustat
	(*N* = 369)	(*N* = 285)	(*N* = 149)	(*N* = 150)	(*N* = 164)	(*N* = 135)	(*N* = 56)
Sex, *n* (%)							
Male	256 (69)	181 (64)	96 (64)	92 (61)	116 (71)	89 (66)	44 (79)
Age (yrs), mean ± SD	66 ± 10.9	67 ± 10.4	68 ± 11.6	70 ± 9.1	64 ± 10.3	64 ± 10.5	64 ± 9.6
BMI (kg/m^2), mean ± SD	22.9 ± 3.67	23.6 ± 4.19	23.2 ± 3.43	24.2 ± 4.15	22.3 ± 3.83	23.0 ± 4.16	24.0 ± 3.55
Prior ESA use, *n* (%)							
ESA-naïve	122 (33)	91 (32)	91 (61)	91 (61)	28 (17)	0	3 (5)
User	247 (67)	194 (68)	58 (39)	59 (39)	136 (83)	135 (100)	53 (95)
Hemoglobin (g/dL), mean ± SD	10.5 ± 1.06	10.6 ± 0.93	10.3 ± 1.11	10.4 ± 1.04	10.6 ± 1.02	10.8 ± 0.73	10.8 ± 0.96
Iron parameters, mean ± SD							
TSAT (%)	30.9 ± 11.7	28.7 ± 10.1	31.8 ± 10.5	31.0 ± 10.6	27.9 ± 11.1	26.23 ± 8.9	37.3 ± 13.4
Ferritin (μg/L)	177.9 ± 154.2	173.4 ± 135.0	205.1 ± 147.3	198.2 ± 132.8	143.8 ± 160.2	146.0 ± 132.5	205.3 ± 135.9
Hypertension, *n* (%)	347 (94)	270 (95)	141 (95)	145 (97)	152 (93)	125 (93)	54 (96)
Hyperlipidemia, *n* (%)	195 (53)	165 (58)	91 (61)	105 (70)	70 (43)	60 (44)	34 (61)
Diabetes mellitus, *n* (%)	152 (41)	124 (44)	65 (44)	71 (47)	74 (45)	53 (39)	13 (23)
CV disease[a], *n* (%)	161 (44)	142 (50)	57 (38)	62 (41)	75 (46)	80 (59)	29 (52)
Disease-related thrombus/infarction/occlusion[b], *n* (%)	87 (24)	63 (22)	30 (20)	32 (21)	46 (28)	31 (23)	11 (20)
Eye diseases[c], *n* (%)	115 (31)	85 (30)	45 (30)	43 (29)	59 (36)	42 (31)	11 (20)

Abbreviations: BMI, body mass index; CV, cardiovascular; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; ND, nondialysis; PD, peritoneal dialysis; SD, standard deviation; TSAT, transferrin saturation.

[a]CV disease: angina pectoris, myocardial infarction, stroke, valvular heart disease, peripheral vascular disease, transient ischemic attack, cardiac arrest, coronary artery disease, congestive heart failure, arrhythmia, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, left ventricular hypertrophy, or non-ischemic cardiomyopathy.

[b]Thrombotic disease: myocardial infarction, stroke, transient ischemic attack, catheter thrombosis, arteriovenous graft thrombosis, arteriovenous fistula thrombosis, or retinal vein occlusion.

[c]Eye disease: age-related macular degeneration, retinal vein occlusion, macular edema, or diabetic retinopathy.

intraocular pressure, anterior segment examination, and funduscopic examination) using the Questions in Ophthalmologic Exam Assessment Worksheet (Table S2) were conducted by a study-designated ophthalmology specialist at baseline, week 12, and week 24 or 48.

An internal safety review team conducted periodic blinded case reviews to evaluate which events constituted potential cancer-related mortality and/or tumor progression and recurrence. Reviews were conducted without blinding in the single-arm 24 week HD trial and the open-label PD cohort.

2.4 | Statistical analyses

Adverse events were summarized by treatment group and expressed as exposure-adjusted event rates per 100 patient-years and frequency (%). Incidence of thromboembolic events by treatment group were stratified by baseline history of disease related to thromboembolism, infarction, and occlusion. A history of myocardial infarction, stroke, transient ischemic attack, catheter thrombosis, arteriovenous graft thrombosis, arteriovenous fistula thrombosis, and retinal vein occlusion were considered. Incidence of retinal events by treatment group were stratified by presence of eye diseases at baseline, including retinal vein occlusion, age-related macular degeneration, macular edema, or diabetic retinopathy. The adjusted frequency and relative risks (RRs) for AEs with 95% confidence interval were calculated using the Cochran–Mantel–Haenszel method and pooled data from the two randomized controlled trials that compared daprodustat with an injectable ESA.

3 | RESULTS

3.1 | Baseline characteristics

Patient characteristics were generally balanced between treatment groups in the pooled analysis. The majority of patients were men, the mean age was 66 years in the daprodustat group and 67 years in the ESA group, and mean body mass index (BMI) was 22.9 kg/m^2 in the daprodustat group and 23.6 kg/m^2 in the ESA group (Table 1). Sixty-seven percent of patients in the daprodustat group and 68% in the ESA group were treated with an ESA at baseline. The mean baseline Hgb was 10.5 g/dl (SD 1.06) in the daprodustat group and 10.6 g/dl (SD 0.93) in the ESA group. In the daprodustat and ESA groups, respectively, 347 of 369 (94%) and 270 of 285 (95%) patients had hypertension; 195 (53%) and 165 (58%) patients had hyperlipidemia; 152 (41%) and 124 (44%) patients had diabetes mellitus; 161 (44%) and 142 (50%) patients had CV disease; 87 (24%) and 63 (22%) patients had a history of disease-related thrombus/infarction/occlusion; and 115 (31%) and 85 (30%) patients had ocular disease at baseline.

3.2 | Daprodustat exposure

The median duration of exposure was 365 days for both the daprodustat group and the ESA group (range 6–372 days for daprodustat and 21–370 days for ESA). The median daily dose of daprodustat was 4.6 mg/day (range 1–18 mg).

3.3 | Summary of on-therapy AEs

In the overall pooled population, the incidence of on-therapy AEs was 363.1 per 100 patient-years in the daprodustat group and 306.4 per 100 patient-years in the ESA group (Table 2). The most frequent AEs were nasopharyngitis and gastrointestinal events in both groups.

There was no significant difference in RR for common AEs (those occurring in ≥5/100 patient-years) in the daprodustat group versus the ESA group, as the 95% CIs for all RRs included the point of null hypothesis (Figure S1).

The incidence of on-therapy SAEs and AEs leading to discontinuation of study treatment was similar between the two treatment groups. The incidence of on-therapy drug-related AEs was numerically higher in the daprodustat group than in the ESA group, though this affected fewer than 10% of patients in either group: 7%, or 8.83 per 100 patient-years in the daprodustat group and 4%, or 4.28 per 100 patient-years in the ESA group (Table S3).

Three fatal on-therapy AEs were reported in the overall pooled population: 1 of 369 (0.3%) patients in the daprodustat group and 2 of 285 (0.7%) patients in the ESA group. The patient in the daprodustat group died of hemorrhagic shock. In the ESA group, 1 patient died of an arrhythmia, and 1 patient died of an aortic dissection. The incidence of fatality was 0.32 per 100 patient-years in the daprodustat group and 0.77 per 100 patient-years in the ESA group. The incidences of both AEs and drug-related AEs did not show a clear relationship with daprodustat dosage or exposure duration (Table S4 and Table S5).

3.4 | Potential adverse events based on daprodustat MOA

3.4.1 | Thromboembolic events

The incidence per 100 patient-years of thromboembolic events was similar in the daprodustat and ESA groups, 5.55 and 6.28, respectively (Table 3). The RR of thromboembolic events in the daprodustat group versus the ESA group was 0.68 (95% CI: 0.33, 1.44) (Figure S2). The most common thromboembolic event in the overall pooled population was shunt occlusion (1.28 and 2.32 per 100 patient-years in the daprodustat and ESA groups, respectively) (Table 3).

In a subgroup analysis of patients based on thromboembolic disease status at baseline, there was no difference in the frequency of thromboembolism in patients treated with daprodustat who had a history of disease-related thrombus, infarction, or occlusion at baseline (5.45 per 100 patient-years) compared to patients without a history of disease-related thrombus, infarction, or occlusion at baseline (5.59 per 100 patient-years) (Table 4).

Two events of thrombosis and/or tissue ischemia secondary to excessive erythropoiesis (Hgb values exceeded 13 g/dl within a period of −30 to +15 days of the day of onset) were observed in the daprodustat group (deep vein thrombosis, exceeded target with Hgb 13.1 g/dl, and myocardial infarction, exceeded target with Hgb 13.3 g/dl). Both occurred in the open-label PD cohort. No events were observed in the ESA group.

3.4.2 | Cardiovascular events

The incidence of MACE was similar in patients treated with daprodustat (2.58 per 100 patient-years) and an ESA (2.70 per 100 patient-years) (Table 5). The RR for MACE in the daprodustat versus ESA groups was 0.86 (95% CI: 0.29, 2.52) (Figure S2). The most common MACE was

TABLE 2 Common AEs (≥5/100 patient-years in any group for the overall pooled population)

	All				ND				HD				PD	
	Daprodustat ($N = 369$)		ESA ($N = 285$)		Daprodustat ($N = 149$)		ESA ($N = 150$)		Daprodustat ($N = 164$)		ESA ($N = 135$)		Daprodustat ($N = 56$)	
Frequently reported AE	***n* (%)**	**Rate[a]**	***n* (%)**	**Rate[a]**	***n* (%)**	**Rate[a]**	***n* (%)**	**Rate[a]**	***n* (%)**	**Rate[a]**	***n* (%)**	**Rate[a]**	***n* (%)**	**Rate[a]**
Any event	**342 (93)**	**363.1**	**265 (93)**	**306.4**	**137 (92)**	**310.3**	**134 (89)**	**250.4**	**151 (92)**	**420.7**	**131 (97)**	**397.2**	**54 (96)**	**381.8**
Nasopharyngitis	131 (36)	54.78	129 (45)	68.56	49 (33)	49.86	56 (37)	56.83	66 (40)	64.56	73 (54)	81.44	16 (29)	41.43
Diarrhea	33 (9)	11.25	19 (7)	7.54	5 (3)	3.97	7 (5)	5.35	20 (12)	16.12	12 (9)	9.90	8 (14)	18.38
Constipation	20 (5)	6.56	24 (8)	9.51	10 (7)	7.99	18 (12)	14.18	8 (5)	6.07	6 (4)	4.79	2 (4)	4.19
Vomiting	24 (7)	7.96	15 (5)	5.92	5 (3)	3.92	4 (3)	3.03	16 (10)	12.57	11 (8)	9.06	3 (5)	6.39
Nausea	15 (4)	4.92	16 (6)	6.30	0	–	4 (3)	3.04	9 (5)	6.84	12 (9)	9.81	6 (11)	13.31
Contusion	24 (7)	7.90	19 (7)	7.59	5 (3)	3.91	8 (5)	6.24	17 (10)	13.19	11 (8)	9.01	2 (4)	4.25
Shunt stenosis	21 (6)	6.97	20 (7)	7.99	0	–	0	–	21 (13)	16.84	20 (15)	17.03	0	–
Back pain	24 (7)	7.95	21 (7)	8.38	12 (8)	9.89	11 (7)	8.65	7 (4)	5.25	10 (7)	8.09	5 (9)	10.59
Arthralgia	12 (3)	3.91	14 (5)	5.46	3 (2)	2.36	4 (3)	3.03	6 (4)	4.49	10 (7)	8.04	3 (5)	6.51
Pruritus	17 (5)	5.56	8 (3)	3.10	12 (8)	9.72	5 (3)	3.81	3 (2)	2.22	3 (2)	2.36	2 (4)	4.21
Hyperkalaemia	17 (5)	5.55	10 (4)	3.89	12 (8)	9.66	8 (5)	6.18	4 (2)	2.98	2 (1)	1.57	1 (2)	2.09
Renal impairment	9 (2)	2.90	13 (5)	5.03	9 (6)	7.15	13 (9)	10.00	0	–	0	–	0	–
Hypertension	14 (4)	4.59	16 (6)	6.30	4 (3)	3.18	8 (5)	6.20	5 (3)	3.72	8 (6)	6.41	5 (9)	11.21

Note: Bold values indicate the parent categories.

Abbreviations: AE, adverse event; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; ND, nondialyisis; PD, peritoneal dialysis.

[a]Number of patients with adverse events per 100 patient-years.

TABLE 3 Thromboembolic events

	All				ND				HD				PD	
	Daprodustat ($N = 369$)		ESA control ($N = 285$)		Daprodustat ($N = 149$)		ESA control ($N = 150$)		Daprodustat ($N = 164$)		ESA control ($N = 135$)		Daprodustat ($N = 56$)	
MedDRA preferred term[a]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]
Thromboembolism, any event	**17 (5)**	**5.55**	**16 (6)**	**6.28**	**2 (1)**	**1.56**	**4 (3)**	**3.03**	**11 (7)**	**8.39**	**12 (9)**	**9.77**	**4 (7)**	**8.47**
Shunt occlusion	4 (1)	1.28	6 (2)	2.32	0	–	1 (<1)	0.75	4 (2)	2.96	5 (4)	3.97	0	–
Shunt thrombosis	2 (<1)	0.64	1 (<1)	0.38	0	–	0	–	2 (1)	1.48	1 (<1)	0.78	0	–
Transient ischemic attack	2 (<1)	0.64	3 (1)	1.15	0	–	2 (1)	1.51	1 (<1)	0.74	1 (<1)	0.78	1 (2)	2.08
Cerebral infarction	2 (<1)	0.64	2 (<1)	0.77	1 (<1)	0.78	1 (<1)	0.75	1 (<1)	0.74	1 (<1)	0.78	0	–
Deep vein thrombosis	2 (<1)	0.64	0	–	1 (<1)	0.78	0	–	0	–	0	–	1 (2)	2.08
Peripheral arterial occlusive disease	1 (<1)	0.32	1 (<1)	0.38	0	–	0	–	0	–	1 (<1)	0.78	1 (2)	2.11
Peripheral artery occlusion	0	–	1 (<1)	0.38	0	–	0	–	0	–	1 (<1)	0.78	0	–
Venous occlusion	1 (<1)	0.32	0	–	0	–	0	–	1 (<1)	0.74	0	–	0	–
Retinal vein occlusion	2 (<1)	0.64	1 (<1)	0.38	0	–	0	–	2 (1)	1.47	1 (<1)	0.78	0	–
Retinal artery occlusion	0	–	1 (<1)	0.38	0	–	0	–	0	–	1 (<1)	0.78	0	–
Myocardial infarction	1 (<1)	0.32	0	–	0	–	0	–	0	–	0	–	1 (2)	2.08
Pulmonary embolism	1 (<1)	0.32	0	–	0	–	0	–	0	–	0	–	1 (2)	2.08

Note: Bold values indicate the parent categories.

Abbreviations: ESA, erythropoiesis-stimulating agent; HD, hemodialysis; MedDRA, Medical Dictionary for Regulatory Activities; ND, nondialysis; PD, peritoneal dialysis.

[a]Thromboembolic events were identified based on Standardized MedDRA Query "Embolic and Thrombotic events_narrow."

[b]Number of patients with adverse events per 100 patient-years.

TABLE 4 Incidence of on-therapy thromboembolic events by disease-related thrombus/infarction/occlusion at baseline

	History of disease-related thrombus/infarction/occlusion at baseline:[b] yes				History of disease-related thrombus/infarction/occlusion at baseline:[b] no			
	Daprodustat ($N = 87$)		ESA control ($N = 63$)		Daprodustat ($N = 282$)		ESA control ($N = 222$)	
MedDRA preferred term[a]	*n* (%)	Rate[c]	*n* (%)	Rate[c]	*n* (%)	Rate[c]	*n* (%)	Rate[c]
Any event	**4 (5)**	**5.45**	**6 (10)**	**11.48**	**13 (5)**	**5.59**	**10 (5)**	**4.94**
Shunt occlusion	0	–	1 (2)	1.86	4 (1)	1.69	5 (2)	2.44
Shunt thrombosis	1 (1)	1.35	0	–	1 (<1)	0.42	1 (<1)	0.48
Transient ischemic attack	0	–	2 (3)	3.78	2 (<1)	0.84	1 (<1)	0.48
Cerebral infarction	1 (1)	1.35	1 (2)	1.87	1 (<1)	0.42	1 (<1)	0.48
Deep vein thrombosis	0	–	0	–	2 (<1)	0.84	0	–
Peripheral arterial occlusive disease	0	–	1 (2)	1.86	1 (<1)	0.42	0	–
Peripheral artery occlusion	0	–	0	–	0	–	1 (<1)	0.48
Venous occlusion	0	–	0	–	1 (<1)	0.42	0	–
Retinal artery occlusion	0	–	0	–	0	–	1 (<1)	0.48
Retinal vein occlusion	1 (1)	1.33	1 (2)	1.86	1 (<1)	0.42	0	–
Pulmonary embolism	0	–	0	–	1 (<1)	0.42	0	–
Myocardial infarction	1 (1)	1.33	0	–	0	–	0	–

Note: Bold values indicate the parent categories.

Abbreviations: ESA, erythropoiesis-stimulating agent; MedDRA, Medical Dictionary for Regulatory Activities.

[a]Thromboembolic events were identified based on Standardized MedDRA Query "Embolic and Thrombotic events_narrow."

[b]Disease related to thrombus/infarction/occlusion: Myocardial infarction, stroke, transient ischemic attack, catheter thrombosis, arteriovenous graft thrombosis, arteriovenous fistula thrombosis, or retinal vein occlusion.

[c]Number of patients with adverse events per 100 patient-years.

stroke, which was reported with a similar incidence in the daprodustat and ESA groups (Table 5).

The incidence of cardiac failure events was nominally lower in the daprodustat group than the ESA group, 1.94 per 100 patient-years and 3.87 per 100 patient-years, respectively. The RR for cardiac failure in the daprodustat versus ESA groups was 0.2 (95% CI: 0.04, 0.91) (Figure S2). The most common cardiac failure event in the overall pooled population was congestive heart failure in both the daprodustat and ESA groups (Table 5).

3.4.3 | Retinal events

The incidence of retinal AEs was similar between the daprodustat group and the ESA group (6.91 per 100 patient-years and 7.46 per 100 patient-years in the daprodustat and ESA groups, respectively) (Table 6). The RR of an on-therapy retinal event was 0.84 (95% CI: 0.44, 1.6) for daprodustat versus ESA (Figure S2). The common on-therapy retinal events in the overall pooled population were retinal hemorrhage (2.90 and 3.49 per 100 patient-years in the daprodustat and ESA groups, respectively); macular edema (1.92 and 2.32 per 100 patient-years in the daprodustat and ESA groups, respectively); and diabetic retinopathy (1.29 and 0.77 per 100 patient-years in the daprodustat and ESA groups, respectively) (Table 6). When patients were stratified by the presence of ocular disease at baseline, patients in the daprodustat group who had ocular disease at baseline had a similar incidence of on-therapy retinal events (7.05 per 100 patient-years) as patients with no ocular disease at baseline (6.84 per 100 patient-years) (Table 7).

Based on ophthalmic examination using the Ophthalmologic Exam Assessment Worksheets, 47 (13%) of the 369 patients in the daprodustat group and 32 of 280 (11%) patients in the ESA group who had a response to any question on the worksheet had an abnormal finding (Table S6). For the daprodustat group, an abnormal finding was reported for any question on the worksheet in 29 of 253 (11%) patients with no ocular disease at baseline and 18 of 114 (16%) patients with ocular disease at baseline (Table S7).

3.4.4 | Cancer-related mortality and tumor progression and recurrence

In the overall pooled population, the incidence per 100 patient-years of cancer-related events was 1.28 in the

TABLE 5 Cardiovascular events[a]

	All				ND				HD				PD	
	Daprodustat ($N = 369$)		ESA control ($N = 285$)		Daprodustat ($N = 149$)		ESA control ($N = 150$)		Daprodustat ($N = 164$)		ESA control ($N = 135$)		Daprodustat ($N = 56$)	
MedDRA preferred term[a]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]
MACE, any event	**8 (2)**	**2.58**	**7 (2)**	**2.70**	**4 (3)**	**3.13**	**5 (3)**	**3.79**	**2 (1)**	**1.48**	**2 (1)**	**1.57**	**2 (4)**	**4.16**
Death, any event	**1 (<1)**	**0.32**	**2 (<1)**	**0.77**	**1 (<1)**	**0.78**	**2 (1)**	**1.51**	**0**	–	**0**	–	**0**	–
Aortic dissection	0	–	1 (<1)	0.38	0	–	1 (<1)	0.75	0	–	0	–	0	–
Arrhythmias	0	–	1 (<1)	0.38	0	–	1 (<1)	0.75	0	–	0	–	0	–
Hemorrhagic shock	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Myocardial infarction, any event	**2 (<1)**	**0.64**	**0**	–	**1 (<1)**	**0.78**	**0**	–	**0**	–	**0**	–	**1 (2)**	**2.08**
Unstable angina	1 (<1)	0.32	0	–	0	–	0	–	0	–	0	–	1 (2)	2.08
Blood creatinine phosphokinase increased	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Myocardial infarction	1 (<1)	0.32	0	–	0	–	0	–	0	–	0	–	1 (2)	2.08
Stroke, any event	**5 (1)**	**1.61**	**5 (2)**	**1.93**	**2 (1)**	**1.56**	**3 (2)**	**2.27**	**2 (1)**	**1.48**	**2 (1)**	**1.57**	**1 (2)**	**2.08**
Transient ischemic attack	2 (<1)	0.64	3 (1)	1.15	0	–	2 (1)	1.51	1 (<1)	0.74	1 (<1)	0.78	1 (2)	2.08
Cerebral infarction	2 (<1)	0.64	2 (<1)	0.77	1 (<1)	0.78	1 (<1)	0.75	1 (<1)	0.74	1 (<1)	0.78	0	–
Carotid artery stenosis	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Heart failure, any event	**6 (2)**	**1.94**	**10 (4)**	**3.87**	**1 (<1)**	**0.78**	**6 (4)**	**4.59**	**1 (<1)**	**0.73**	**4 (3)**	**3.14**	**4 (7)**	**8.79**
Congestive heart failure	4 (1)	1.29	7 (2)	2.70	1 (<1)	0.78	5 (3)	3.82	0	–	2 (1)	1.56	3 (5)	6.46
Heart failure	2 (<1)	0.64	1 (<1)	0.38	0	–	1 (<1)	0.75	1 (<1)	0.73	0	–	1 (2)	2.12
Pulmonary edema	0	–	2 (<1)	0.77	0	–	0	–	0	–	2 (1)	1.57	0	–

Note: Bold values indicate the parent categories.

Abbreviations: ESA, erythropoiesis-stimulating agent; HD, hemodialysis; MACE, major adverse cardiac event; MedDRA, Medical Dictionary for Regulatory Activities; ND, nondialysis; PD, peritoneal dialysis; SMQ, Standardized MedDRA Query.

[a]Death was identified as a fatal adverse event. Myocardial infarction and heart failure were identified based on SMQs "Myocardial infarction_broad" or "Cardiac Failure_narrow", respectively. Stroke was identified based on SMQ "Ischemic central nervous system vascular conditions_narrow" and additional preferred terms.

[b]Number of patients with adverse events per 100 patient-years.

TABLE 6 Retinal events

	All				ND				HD				PD	
	Daprodustat ($N = 369$)		ESA ($N = 285$)		Daprodustat ($N = 149$)		ESA ($N = 150$)		Daprodustat ($N = 164$)		ESA ($N = 135$)		Daprodustat ($N = 56$)	
MedDRA preferred term[a]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]	***n*** **(%)**	**Rate**[b]
Any event	**21 (6)**	**6.91**	**19 (7)**	**7.46**	**9 (6)**	**7.26**	**10 (7)**	**7.76**	**8 (5)**	**5.95**	**9 (7)**	**7.15**	**4 (7)**	**8.78**
Retinal hemorrhage	9 (2)	2.90	9 (3)	3.49	2 (1)	1.56	4 (3)	3.05	5 (3)	3.69	5 (4)	3.95	2 (4)	4.25
Macular edema	6 (2)	1.92	6 (2)	2.32	3 (2)	2.34	4 (3)	3.05	2 (1)	1.47	2 (1)	1.57	1 (2)	2.10
Diabetic retinopathy	4 (1)	1.29	2 (<1)	0.77	3 (2)	2.37	1 (<1)	0.75	1 (<1)	0.73	1 (<1)	0.78	0	–
Vitreous floaters	3 (<1)	0.97	0	–	1 (<1)	0.78	0	–	1 (<1)	0.74	0	–	1 (2)	2.12
Retinal vein occlusion	2 (<1)	0.64	1 (<1)	0.38	0	–	0	–	2 (1)	1.47	1 (<1)	0.78	0	–
Retinal exudates	2 (<1)	0.64	0	–	0	–	0	–	1 (<1)	0.73	0	–	1 (2)	2.08
Dry age–related macular degeneration	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Neovascular age-related macular degeneration	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Retinal disorder	1 (<1)	0.32	0	–	0	–	0	–	0	–	0	–	1 (2)	2.08
Serous retinal detachment	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Retinal artery occlusion	0	–	1 (<1)	0.38	0	–	0	–	0	–	1 (<1)	0.78	0	–
Retinal cyst	0	–	1 (<1)	0.38	0	–	1 (<1)	0.76	0	–	0	–	0	–
Retinal drusen	0	–	1 (<1)	0.38	0	–	1 (<1)	0.75	0	–	0	–	0	–
Retinal tear	0	–	1 (<1)	0.38	0	–	1 (<1)	0.76	0	–	0	–	0	–
Visual field test abnormal	0	–	1 (<1)	0.38	0	–	0	–	0	–	1 (<1)	0.78	0	–

Note: Bold values indicate the parent categories.

Abbreviations: ESA, erythropoiesis-stimulating agent; HD, hemodialysis; MedDRA, Medical Dictionary for Regulatory Activities; ND, nondialysis; PD, peritoneal dialysis; SMQ, Standardized MedDRA Query.

[a]Retinal events were identified based on SMQ "Retinal disorders_narrow."

[b]Number of patients with adverse events per 100 patient-years.

TABLE 7 Incidence of on-therapy retinal events by history of ocular disease

	Ocular diseases at baseline:yes[a]				Ocular diseases at baseline:no[a]			
	Daprodustat ($N = 115$)		ESA control ($N = 85$)		Daprodustat ($N = 254$)		ESA control ($N = 200$)	
MedDRA preferred term[b]	***n* (%)**	**Rate[c]**	***n* (%)**	**Rate[c]**	***n* (%)**	**Rate[c]**	***n* (%)**	**Rate[c]**
Any event	**7 (6)**	**7.05**	**9 (11)**	**12.54**	**14 (6)**	**6.84**	**10 (5)**	**5.47**
Macular edema	3 (3)	2.95	5 (6)	6.80	3 (1)	1.42	1 (<1)	0.54
Retinal hemorrhage	2 (2)	1.98	4 (5)	5.40	7 (3)	3.34	5 (3)	2.72
Diabetic retinopathy	3 (3)	2.98	1 (1)	1.31	1 (<1)	0.48	1 (<1)	0.54
Retinal artery occlusion	0	–	1 (1)	1.32	0	–	0	–
Retinal cyst	0	–	1 (1)	1.32	0	–	0	–
Retinal drusen	0	–	1 (1)	1.31	0	–	0	–
Retinal vein occlusion	1 (<1)	0.98	0	–	1 (<1)	0.47	1 (<1)	0.54
Vitreous floaters	0	–	0	–	3 (1)	1.44	0	–
Retinal exudates	0	–	0	–	2 (<1)	0.95	0	–
Dry age–related macular degeneration	0	–	0	–	1 (<1)	0.48	0	–
Neovascular age–related macular degeneration	0	–	0	–	1 (<1)	0.47	0	–
Retinal disorder	0	–	0	–	1 (<1)	0.47	0	–
Retinal tear	0	–	0	–	0	–	1 (<1)	0.54
Serous retinal detachment	0	–	0	–	1 (<1)	0.47	0	–
Visual field tests abnormal	0	–	0	–	0	–	1 (<1)	0.54

Note: Bold values indicate the parent categories.
Abbreviations: ESA, erythropoiesis-stimulating agent; HD, hemodialysis; MedDRA, Medical Dictionary for Regulatory Activities; ND, nondialysis; PD, peritoneal dialysis; SMQ, Standardized MedDRA Query.
[a]Ocular diseases: age-related macular degeneration, retinal vein occlusion, macular edema, or diabetic retinopathy.
[b]Retinal events were identified based on SMQ "Retinal disorders_narrow."
[c]Number of patients with adverse events per 100 patient-years.

TABLE 8 Cancer-related mortality and tumor progression and recurrence

	All				ND				HD				PD	
	Daprodustat ($N = 369$)		ESA ($N = 285$)		Daprodustat ($N = 149$)		ESA ($N = 150$)		Daprodustat ($N = 164$)		ESA ($N = 135$)		Daprodustat ($N = 56$)	
MedDRA preferred terma	***n* (%)**	**Rateb**	***n* (%)**	**Rateb**	***n* (%)**	**Rateb**	***n* (%)**	**Rateb**	***n* (%)**	**Rateb**	***n* (%)**	**Rateb**	***n* (%)**	**Rateb**
Any Event	**4 (1)**	**1.28**	**4 (1)**	**1.53**	**3 (2)**	**2.34**	**3 (2)**	**2.26**	**0**	**–**	**1 (<1)**	**0.78**	**1 (2)**	**2.10**
Lung neoplasm malignant	1 (<1)	0.32	1 (<1)	0.38	1 (<1)	0.78	1 (<1)	0.75	0	–	0	–	0	–
Breast cancer	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Clear cell renal cell carcinoma	1 (<1)	0.32	0	–	0	–	0	–	0	–	0	–	1 (2)	2.10
Metastases to skin	0	–	1 (<1)	0.38	0	–	1 (<1)	0.75	0	–	0	–	0	–
Ovarian cancer	1 (<1)	0.32	0	–	1 (<1)	0.78	0	–	0	–	0	–	0	–
Pancreatic carcinoma	0	–	1 (<1)	0.38	0	–	0	–	0	–	1 (<1)	0.78	0	–
Rectal cancer	0	–	1 (<1)	0.38	0	–	1 (<1)	0.75	0	–	0	–	0	–
Renal cancer	0	–	1 (<1)	0.38	0	–	1 (<1)	0.75	0	–	0	–	0	–

Note: Bold values indicate the parent categories.
Abbreviations: ESA, erythropoiesis-stimulating agent; HD, hemodialysis; MedDRA, Medical Dictionary for Regulatory Activities; ND, nondialysis; PD, peritoneal dialysis.
[a]MedDRA/J ver. 21.1.
[b]Number of patients with adverse events per 100 patient-years.

daprodustat group and 1.53 in the ESA group (Table 8). The RR for cancer-related events in the daprodustat versus ESA groups was 0.75 (95% CI: 0.17, 3.32) (Figure S2). No cancer-related AEs were reported in more than 1 patient in any treatment group or patient population (ND, HD, PD) per MedDRA preferred term, and there were no trends identified in the types or locations of cancer (Table 8).

4 | DISCUSSION

In this post hoc pooled analysis of Japanese phase 3 trials, daprodustat was generally well tolerated in patients with anemia of CKD undergoing HD, PD, or ND, and the AE profile was comparable for daprodustat and injectable ESA. No new safety signals were identified, and the safety profile for daprodustat was similar to previous international phase 2 studies and consistent with AEs typical in a CKD patient population.[24,25]

Our study showed a similar incidence of thromboembolic events between the pooled daprodustat and injectable ESA groups, with similar incidence regardless of baseline history of disease-related thrombus, infarction, or occlusion in the daprodustat group. Although the cause of increased thromboembolic risk observed with ESA treatment has not been elucidated, a rapid increase in Hgb (>2.0 g/dl/4 weeks) and iron deficiency have been proposed as contributing factors.[26,27] In terms of these potential risks, the ESA-naïve patients in the ND and HD groups in our study both had mean Hgb increases of 0.8 g/dl at 4 weeks; only one patient had a hemoglobin increase >2.0 g/dl after 4 weeks.[19,21] In addition, inclusion criteria included transferrin saturation >20% or ferritin >100 ng/ml at screening, and iron supplementation was provided when indicated. The Japanese phase 3 studies in our pooled analysis were designed to minimize thromboembolic risks, resulting in a low number of events in both the daprodustat and ESA groups; however, they did not include placebo comparators. Recently, the FDA Advisory Committee on Cardiovascular and Renal Drugs recently found that roxadustat posed a higher risk of thromboembolism versus placebo in both ND and HD patients;[28] however, roxadustat has been approved by the EMA.[18]

Data on CV safety with HIF-PHIs is limited, with inconsistent results for different HIF-PHIs. A recent pooled analysis of global CV outcome trials of roxadustat for the treatment of anemia in dialysis-dependent and nondialysis CKD patients found a comparable risk of MACE and MACE+ (composite of MACE plus unstable angina or congestive heart failure requiring hospitalization) in patients treated with roxadustat versus epoetin alpha and placebo, respectively.[29] Two recent global CV outcomes trials of vadadustat demonstrated noninferiority to darbepoetin alpha regarding risk of MACE in dialysis-dependent but not in nondialysis CKD patients.[15,16] Although we did not adjudicate MACE in the studies in our pooled analysis, the incidence of MACE was similar between the daprodustat and ESA groups, but it should be noted that the reported number of MACE events overall were very few. Moreover, the studies included in our pooled analysis had short treatment periods (<1 year) and enrolled a relatively small number of patients. In addition, these studies were conducted in Japan, which has a lower overall incidence of MACE compared to the United States and European countries.[19–21,23] Two recently completed large CV outcome trials, ASCEND-D and ASCEND-ND, have demonstrated that daprodustat posed no increased risk of MACE when compared with ESA.[11,12]

Retinal AEs also represent a potential risk for patients treated with HIF-PHIs due to the role of HIF in regulating VEGF.[30] Increases in local VEGF production have been linked to the retinal neovascularization observed in diabetic proliferative retinopathy, and anti-VEGF agents are effective treatments for diabetic retinopathy.[30,31] VEGF has also been implicated in the choroidal leakage, edema, and neovascularization seen in age-related macular degeneration.[32] Conversely, animal studies have shown that PHD inhibition and HIF-1α upregulation may actually serve to prevent oxygen-induced retinopathy.[33]

In a Japanese phase 2 study, Akizawa et al found that patients treated with 4–10 mg daprodustat once daily had no changes in circulating VEGF levels.[34] In our pooled analysis, the overall frequency of retinal AEs in the daprodustat group was similar to the ESA group. Because our phase 3 trials included patients with retinal vascular disorders, we were able to evaluate whether treatment with daprodustat aggravated symptoms in patients with pre-existing ocular diseases such as age-related macular degeneration, retinal vein occlusion, macular edema, and diabetic retinopathy, compared to patients without ocular disease. Post hoc analysis showed that there was no difference in the frequency of retinal events in patients with or without ocular disease at baseline for the daprodustat-treated group. This finding suggests that treatment with daprodustat for up to 1 year poses a low risk of retinal events, but further research is needed to understand fully the risk of retinal diseases associated with HIF-PHI–targeted therapies.

HIF-PHIs also carry a potential risk of cancer-related mortality, and tumor progression or recurrence as a result of HIF-induced upregulation of VEGF, which is a key mediator in tumor angiogenesis.[30] Elevated expression of both HIF-1α and HIF-2α has been associated with

poor prognosis in a broad range of human cancers.[35] In addition, HIF-2α has been identified as a key driver of renal cell carcinoma progression, and HIF-2α inhibitors for renal cell carcinoma are under development.[36] Inactivation of the von Hippel–Lindau (VHL) tumor suppressor gene in VHL diseases, which are characterized by frequent development of benign and malignant tumors, including clear cell renal cell carcinoma is also associated with aberrant stabilization of HIF-1α and HIF-2α.[37] Somatic biallelic inactivation of VHL also occurs in most sporadic clear cell renal cell carcinomas.[37] Thus, a potential risk of tumorigenesis by HIF-PHIs is based on considerations of HIF-related biology.

Our analyses revealed that the incidence of cancer-related AEs was similar between the daprodustat group (1.28 per 100 patient-years) and the ESA control group (1.53 per 100 patient-years), and that there was no pattern linked to the types or location of cancer in either treatment group. These results are consistent with the finding of Akizawa et al that serum VEGF levels did not increase in HD patients treated within the clinically approved dose range of daprodustat.[34] In addition, no daprodustat treatment-related neoplastic findings were observed in 2-year rat (daprodustat alone) or mouse (oral daprodustat in combination with subcutaneous administration of the 3 major circulating human metabolites) carcinogenicity studies.[38] These findings are also consistent with previous in vitro human research on Chuvash polycythemia, which showed that VHL inactivation alone is not sufficient for spontaneous tumorigenesis. In a mouse model, homozygosity for the VHL R200W mutation induced the upregulation of HIF signaling, which resulted in polycythemia but no increased risk of cancer.[39,40]

Overall, limitations of this study include a short duration of 1 year and a small sample size. The trials in this pooled analysis did not include exclusion criteria related to eye disease. Therefore, patients with eye disease, regardless of activity and severity level, were eligible for enrollment in each clinical study. However, baseline activity and severity of eye disease were not evaluated in these studies. Further studies are needed to address the impact of baseline eye disease activity and severity on eye disease risk after daprodustat treatment. The current dataset is not sufficient to definitively characterize or refute the potential risk of malignancy posed by treatment with daprodustat. In addition, patients with a history of malignancy within 2 years of screening, or who were currently receiving treatment for cancer or complex kidney cysts, were excluded. We were also unable to conclusively evaluate CV AEs. Postmarketing surveillance is ongoing to evaluate the overall safety risk of daprodustat in routine clinical practice in Japan.

5 | CONCLUSION

The safety profile of daprodustat in patients undergoing HD, PD, or ND was comparable to injectable ESA in a pooled analysis of three Japanese phase 3 studies, and no new safety signals were identified. Further large-scale research is needed to evaluate long-term risk, including CV events and malignancy.

ACKNOWLEDGMENTS

All listed authors meet the criteria set forth by the International Committee for Medical Journal Editors. Medical editorial support (assembling tables and figures, collating author comments, copyediting, fact checking, and referencing) was provided by Nancy Robinson, DVM, and Sarah Hummasti, PhD, and graphic services were provided by AOIC, LLC and were funded by GSK.

CONFLICT OF INTEREST

Masaomi Nangaku: has received grants and personal fees from Astellas Pharma Inc. (Astellas), Chugai Pharmaceutical Co., Ltd. (Chugai), Daiichi Sankyo Co., Ltd., GlaxoSmithKline (GSK), Kyowa Kirin Co., Ltd. (KKC), Mitsubishi Tanabe Pharma, and Torii Pharmaceutical Co., Ltd. (Torii); grants from Bayer Yakuhin, Ltd. (Bayer), Ono Pharmaceutical Co., Ltd. (Ono), and Takeda Pharmaceutical Company Ltd. (Takeda); and personal fees from AstraZeneca and JT Pharmaceuticals. Tadao Akizawa: has received personal fees from Astellas, Bayer, Chugai, Fuso, GSK, JT Pharmaceuticals, KKC, Kissei, Nipro Corporation, Ono, Otsuka, Torii, Mitsubishi Tanabe Pharma, and Sanwa Chemical Industrial Co., Ltd. Y.T. has received personal fees from Chugai, GSK, KKC, and Torii. Takashi Nagakubo, Toshifumi Kimura, Yukihiro Endo, and Alexander Cobitz are employees and stockholders in GSK. Taeko Yonekawa is an employee of GSK.

AUTHOR CONTRIBUTIONS

MN, TA, TY, YE, and AC contributed to the conception or design of the study; MN, TA, TN, TY, TK, YE, and AC contributed to the data analysis or interpretation; all authors provided critical review and final approval of the publication.

ETHICS APPROVAL

All three studies were approved by the ethics committee at every participating institution and were conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki.

PATIENT CONSENT

All patients from all three studies provided written informed consent to participate in the studies.

DATA SHARING STATEMENT

The data that report the findings of this study such as anonymized individual participant data and study documents, can be requested for further research from www.clinicalstudydatarequest.com.

CLINICAL TRIAL REGISTRATION

This is a pooled post hoc analysis of registered study results. Registered on Clinicaltrials.gov. NCT02791763, NCT02969655, and NCT02829320.

ORCID

Tadao Akizawa https://orcid.org/0000-0002-6150-9201
Toshifumi Kimura https://orcid.org/0000-0001-8831-7659

REFERENCES

1. Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: core curriculum 2018. Am J Kidney Dis. 2018;71(3):423–35.
2. Del Vecchiol L, Minutolo R. ESA, iron therapy and new drugs: are there new perspectives in the treatment of Anaemia? J Clin Med. 2021;10(4):839.
3. Moisi MI, Bungau SG, Vesa CM, Diaconu CC, Behl T, Stoicescu M, et al. Framing cause-effect relationship of acute coronary syndrome in patients with chronic kidney disease. Diagnostics (Basel). 2021;11(8):1518.
4. Yamamoto H, Shinichi N, Tadashi T, Ikuto M, Kazuhide S, Masaomi N, et al. 2015 Japanese Society for Dialysis Therapy: guidelines for renal anemia in chronic kidney disease. Ren Replace Ther. 2017;3(1):1–46.
5. Locatelli F, Fishbane S, Block GA, Macdougall IC. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. Am J Nephrol. 2017;45(3):187–99.
6. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–32.
7. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085–98.
8. Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363(12):1146–55.
9. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008;74(6):791–8.
10. GlaxoSmithKline. GSK announces positive headline results from five Phase 3 studes of daprodustat for patients with anemia due to chronic kidney disease. GlaxoSmithKline; 16 Jul 2021. Available from: https://www.gsk.com/en-gb/media/press-releases/gsk-announces-daprodustat-phase-3-headline-results/
11. Singh AK, Carroll K, McMurray JJV, Solomon S, Jha V, Johansen KL, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. N Engl J Med. 2021;385(25):2313–24. https://doi.org/10.1056/NEJMoa2113380
12. Singh AK, Carroll K, Perkovic V, Solomon S, Jha V, Johansen KL, et al. Daprodustat for the treatment of anemia in patients undergoing dialysis. N Engl J Med. 2021;385(25):2325–35. https://doi.org/10.1056/NEJMoa2113379
13. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD. Am J Kidney Dis. 2017;69(6):815–26.
14. Del Vecchio L, Locatelli F. Investigational hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) for the treatment of anemia associated with chronic kidney disease. Expert Opin Investig Drugs. 2018;27(7):613–21.
15. Eckardt KU, Agarwal R, Aswad A, Awad A, Block GA, Bacci MR, et al. Safety and efficacy of Vadadustat for anemia in patients undergoing dialysis. N Engl J Med. 2021;384(17):1601–12.
16. Chertow GM, Pergola PE, Farag YMK, Agarwal R, Arnold S, Bako G, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. N Engl J Med. 2021;384(17):1589–600.
17. AstraZeneca. Status on FDA Advisory Committee vote on roxadustat in anaemia of chronic kidney disease [Internet]. Astrazeneca; 16 Jul 2021. Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/status-on-us-fda-advisory-committee-for-roxadustat.html
18. Evrenzo [Internet]. European Medicines Agency; 2021. Roxadustat. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/evrenzo
19. Nangaku M, Hamano T, Akizawa T, Tsubakihara Y, Nagai R, Okuda N, et al. Daprodustat compared with Epoetin Beta Pegol for anemia in Japanese patients not on dialysis: a 52-week randomized open-label phase 3 trial. Am J Nephrol. 2021;52(1):26–35.
20. Akizawa T, Nangaku M, Yonekawa T, Okuda N, Kawamatsu S, Onoue T, et al. Efficacy and safety of Daprodustat compared with Darbepoetin Alfa in Japanese hemodialysis patients with anemia: a randomized, double-blind, phase 3 trial. Clin J Am Soc Nephrol. 2020;15(8):1155–65.
21. Tsubakihara Y, Akizawa T, Nangaku M, Onoue T, Yonekawa T, Matsushita H, et al. A 24-week anemia correction study of Daprodustat in Japanese dialysis patients. Ther Apher Dial. 2020;24(2):108–14.
22. Kanai H, Nangaku M, Nagai R, Okuda N, Kurata K, Nagakubo T, et al. Efficacy and safety of Daprodustat in Japanese peritoneal dialysis patients. Ther Apher Dial. 2021;25(6):979–87. https://doi.org/10.1111/1744-9987.13686
23. Stirnadel-Farrant HA, Karaboyas A, Cizman B, Bieber BA, Kler L, Jones D, et al. Cardiovascular event rates among hemodialysis patients across geographical regions-a snapshot from the dialysis outcomes and practice patterns study (DOPPS). Kidney Int Rep. 2019;4(6):864–72.
24. Holdstock L, Cizman B, Meadowcroft AM, Biswas N, Johnson BM, Jones D, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants with chronic kidney disease. Clin Kidney J. 2019;12(1):129–38.
25. Meadowcroft AM, Cizman B, Holdstock L, Biswas N, Johnson BM, Jones D, et al. Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants on hemodialysis. Clin Kidney J. 2019;12(1):139–48.

26. Uchida KN, Nangaku M, Abe M, Okada H, Takeda N, Hanafusa N, et al. Recommendation on the appropriate use of HIF-PH inhibitors. Japanese Journal of Nephrology. 2020; 62(7):711–6. (in Japanese).
27. Yap DYH, McMahon LP, Hao CM, Hu N, Okada H, Suzuki Y, et al. Recommendations by the Asian Pacific society of nephrology (APSN) on the appropriate use of HIF-PH inhibitors. Nephrology (Carlton). 2021;26(2):105–18.
28. U.S. Food and Drug Administration Office of New Drugs, Center for Drug Development & Research. Cardiovascular and Renal Drugs Advisory Committee Meeting July 15, 2021 Roxadustat—FDA Roxadustat Briefing Document: Roxadustat; NDA 213805. Accessed September 23, 2021. Available from: https://www.fda.gov/media/150728/download
29. Provenzano R, Szczech L, Leong R, Saikali KG, Zhong M, Lee TT, et al. Efficacy and cardiovascular safety of Roxadustat for treatment of anemia in patients with non-dialysis-dependent CKD: pooled results of three randomized clinical trials. Clin J Am Soc Nephrol. 2021;16(8):1190–200.
30. Apte R, Chen D, Ferrara N. VEGF in signaling and disease: beyond discovery and development. Cell. 2019;176(6): 1248–64.
31. Wang X, Wang G, Wang Y. Intravitreous vascular endothelial growth factor and hypoxia-inducible factor 1a in patients with proliferative diabetic retinopathy. Am J Ophthalmol. 2009; 148(6):883–9.
32. Campochiaro PA. Ocular versus extraocular neovascularization: mirror images or vague resemblances. Invest Ophthalmol Vis Sci. 2006;47(2):462–74.
33. Gunton JE. Hypoxia-inducible factors and diabetes. J Clin Invest. 2020;130(10):5063–73.
34. Akizawa T, Tsubakihara Y, Nangaku M, Endo Y, Nakajima H, Kohno T, et al. Effects of Daprodustat, a novel hypoxia-inducible factor prolyl hydroxylase inhibitor on anemia Management in Japanese Hemodialysis Subjects. Am J Nephrol. 2017;45(2):127–35.
35. Keith B, Johnson RS, Simon M. HIF1α and HIF2α: sibling rivalry in hypoxic tumour growth and progression. Nat Rev Cancer. 2011;12(1):9–22.
36. Yu Y, Yu Q, Zhang X. Allosteric inhibition of HIF-2α as a novel therapy for clear cell renal cell carcinoma. Drug Discov Today. 2019;24(12):2332–40.
37. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. Nature Rev Cancer. 2015;15(1):55–64.
38. Adams DF, Watkins MS, Durette L, Laliberte J, Goulet F, Debien E, et al. Carcinogenicity assessment of Daprodustat (GSK1278863), a hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitor. Toxicol Pathol. 2020;48(2):362–78.
39. Gordeuk VR, Sergueeva AI, Miasnikova GY, Okhotin D, Voloshin Y, Choyke PL, et al. Congenital disorder of oxygen sensing: association of the homozygous Chuvash polycythemia VHL mutation with thrombosis and vascular abnormalities but not tumors. Blood. 2004;103(10):3924–32.
40. Hickey MM, Lam JC, Bezman NA, Rathmell WK, Simon M. von Hippel-Lindau mutation in mice recapitulates Chuvash polycythemia via hypoxia-inducible factor-2alpha signaling and splenic erythropoiesis. J Clin Invest. 2007;117(12):3879–89.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Nangaku M, Akizawa T, Nagakubo T, Yonekawa T, Kimura T, Endo Y, et al. Safety of daprodustat in patients with anemia of chronic kidney disease: A pooled analysis of phase 3 studies in Japan. Ther Apher Dial. 2022;26: 1065–78. https://doi.org/10.1111/1744-9987.13839