https://doi.org/10.31925/farmacia.2026.5.23 **ORIGINAL ARTICLE**

DISPROPORTIONALITY SIGNALS AND DELAYED-ONSET ADVERSE EVENTS ASSOCIATED WITH DAPRODUSTAT IN FAERS: CLINICAL PRIORITIZATION AND TEMPORAL ONSET PROFILING ACROSS CARDIOVASCULAR, THROMBOTIC, HEMATOLOGIC AND NEOPLASTIC EVENTS

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Abstract

To characterize post-marketing safety signals and time-to-onset patterns of adverse events (AEs) associated with daprodustat using FAERS data from 2023 Q1 to 2025 Q4. A retrospective disproportionality analysis was performed using FAERS reports listing daprodustat as the primary suspect. FDA-recommended de-duplication was applied using CASEID, PRIMARYID and FDA_DT. AEs were analysed at MedDRA Preferred Term and System Organ Class levels. Signals were identified using predefined disproportionality thresholds of ROR > 3 with lower 95% CI > 1 and PRR > 2 with lower 95% CI > 1, while clinically relevant findings were interpreted using case counts, signal strength, seriousness outcomes, death reports and time-to-onset patterns. Overall, 1,436 primary-suspect reports were identified, and 1,301 unique cases were retained after de-duplication. Most reports originated from Japan (n = 1,296; 99.6%). A total of 3,773 daprodustat-associated events were analysed, of which 299 Preferred Terms met predefined disproportionality criteria. After excluding haemoglobin (Hb) increased and nephrogenic anaemia from primary AE interpretation as pharmacodynamic and indication-related terms, respectively, selected clinically interpretable signals included hospitalization, Hb decreased, deep vein thrombosis, renal failure and retinal haemorrhage. Complete time-to-onset data were limited, although several serious events were reported more than 91 days after onset. Daprodustat showed clinically relevant safety signals requiring cautious interpretation and further validation.

Rezumat

Studiul a urmărit caracterizarea semnalelor de siguranță și a intervalului până la apariția reacțiilor adverse (RA) asociate daprodustatului, utilizând datele FAERS din perioada trimestrul I 2023 – trimestrul IV 2025. A fost realizată o analiză retrospectivă de disproporționalitate a raportărilor în care daprodustatul a fost identificat drept medicament principal suspectat, cu eliminarea duplicatelor conform recomandărilor FDA, pe baza identificatorilor CASEID, PRIMARYID și FDA_DT. Reacțiile adverse au fost analizate conform clasificării MedDRA, la nivelul termenilor preferați și al claselor de aparate și sisteme. Semnalele au fost identificate utilizând pragurile ROR > 3 și PRR > 2, cu limita inferioară a intervalului de încredere de 95% > 1, iar relevanța clinică a fost evaluată în funcție de frecvența raportărilor, intensitatea semnalelor, gravitatea evenimentelor, decesele raportate și intervalul până la debut. Din 1.436 de raportări inițiale, au fost reținute 1.301 cazuri unice, majoritatea provenind din Japonia (99,6%). Au fost analizate 3.773 de evenimente asociate daprodustatului, dintre care 299 de termeni preferați au îndeplinit criteriile de disproporționalitate. Rezultatele evidențiază semnale de siguranță relevante clinic asociate daprodustatului, care necesită interpretare prudentă și validare suplimentară.

Keywords: pharmacovigilance, adverse drug reactions, daprodustat, time-to-onset, anaemia

Introduction

Daprodustat is a small-molecule, oral hypoxia-inducible factor (HIF) prolyl hydroxylase (PHD) inhibitor used for the treatment of anaemia associated with chronic kidney disease (CKD) in adults (1). The US Food and Drug Administration (FDA) approved daprodustat (Jesduvroq) on February 1, 2023 (2). Daprodustat appears to have 1000-fold or higher selectivity for the 3 prolyl hydroxylase domains (PHD1, PHD2, PHD3),

with a preference for PHD1 and PHD3 (1, 3, 4). By stabilizing HIF, daprodustat stimulates endogenous erythropoietin production and modulates iron metabolism, thereby mimicking the physiological hypoxia response (5). Daprodustat oral therapy offers advantages over injectable erythropoiesis-stimulating agents (ESAs) for CKD anaemia, and the ESA derivatives for the treatment of anaemia have been linked to a possibly increased risk of stroke, myocardial infarction and other adverse events (AEs) (6, 7). Daprodustat demonstrates significant efficacy in treating anaemia in CKD patients across both dialysis-dependent (DD) and non-dialysis-dependent (NDD) populations. In randomized controlled trials (RCTs), daprodustat significantly increased haemoglobin (Hb) levels compared with placebo and was noninferior to conventional ESAs such as darbepoetin alfa and recombinant human erythropoietin (8). Among Japanese haemodialysis patients, daprodustat maintained Hb levels within the target range (10.0 - 12.0 g/dL) with comparable efficacy to darbepoetin alfa (mean Hb 10.9 *vs.* 10.8 g/dL) (9). Additionally, daprodustat improved iron metabolism markers, such as reducing hepcidin levels and increasing total iron-binding capacity (TIBC), indicating enhanced iron utilization (10). Daprodustat demonstrates a favourable safety profile in patients with CKD, with adverse drug reactions comparable to those of ESAs. In RCTs, the incidence of major adverse cardiovascular events (MACE), thrombotic events and mortality was similar between daprodustat and ESA-treated groups (11). A subgroup analysis of the ASCEND-D trial in peritoneal dialysis (PD) patients reported no significant differences in treatment-emergent AEs or peritonitis rates between daprodustat and darbepoetin alfa (12). While some studies observed minor fluctuations in thyroid function markers (free T3, free T4, TSH) with HIF-PH inhibitors, these changes were not clinically significant (13). However, real-world evidence on the frequency and nature of these AEs remains limited.

Given the increasing use of daprodustat in clinical practice, a comprehensive pharmacovigilance assessment is necessary to characterize its safety profile outside of clinical trials. While RCTs provide high-quality evidence on efficacy and common AEs, they are often underpowered to detect rare but serious AEs. Although randomized trials have supported the efficacy and short-term tolerability of daprodustat, they are inherently limited in detecting uncommon, delayed, or population-specific AEs. Post-marketing pharmacovigilance using large spontaneous reporting systems can complement trial evidence by capturing real-world AE reports from broader, more heterogeneous patient populations. The current study is based on an FAERS-based signal detection study to identify disproportionate AE reporting for daprodustat, apply clinical prioritization to the detected signals, and describe their time-to-onset patterns.

Materials and Methods

Study design and data source

The study used a retrospective disproportionality analysis design. Individual case safety reports were obtained from the FAERS (14). Reported AEs were analysed using MedDRA Preferred Terms (PTs). System Organ Class (SOC)-level summaries were generated by mapping PTs to their corresponding primary MedDRA SOCs (15). Patient demographics, reporter characteristics, reporting country and reported outcomes were extracted when available. The study evaluated disproportionate reporting of AEs associated with daprodustat, including the brand name Jesduvroq.

Time frame

FAERS data were collected from 2023-Q1 to 2025-Q4. Reports were eligible for inclusion if daprodustat or Jesduvroq was listed as the primary suspect drug. The analysis was first performed year by year to reduce the computational burden. Yearly outputs were then combined for the final analysis.

Data processing and deduplication

Data processing was conducted using the FAERS DEMO, DRUG, REAC, OUTC and THER files. The DEMO file was used for patient and report-level information. The DRUG file was used to identify daprodustat primary-suspect reports. The REAC file was used to extract reported AE PTs. The OUTC file was used to summarize seriousness outcomes. The THER file was used to assess time-to-onset when therapy start dates were available. Duplicate records were handled using key FAERS identifiers. Reports were processed separately for each year. Deduplication used CASEID, FDA_DT and PRIMARYID. For each duplicate CASEID, the report with the most recent FDA_DT was retained. When CASEID and FDA_DT were the same, the report with the highest PRIMARYID was retained. A final deduplication step was performed across years to retain one unique report *per* CASEID after yearly processing.

Inclusion and exclusion criteria

Reports were included if daprodustat or Jesduvroq was recorded as the primary suspect drug. Reports were excluded if daprodustat was listed only as a concomitant, secondary suspect, or interacting drug. Duplicate reports were excluded during the deduplication process described above. Administrative or product-use terms were not interpreted as clinical AE signals in the main PT-level signal table. These included product use issues, off-label use, prescribed underdose, product dose omission issues and intentional product use issues. Expected pharmacodynamic outcomes and indication-related disease terms were not interpreted as primary AE signals. Accordingly, increased Hb was treated as an expected pharmacodynamic outcome of daprodustat, and nephrogenic anaemia was treated as an indication-related term; both were summarized descriptively only. Death was

handled as a seriousness outcome rather than as a PT-level AE signal. Coronavirus infection and COVID-19 were excluded from the primary interpretation because they were considered likely study-period confounding terms without clear mechanistic plausibility as daprodustat-specific adverse reactions.

Comparator strategy

The primary disproportionality analysis used Japan-submitted FAERS reports as the comparator group because daprodustat reports were highly concentrated in Japan. This approach was selected to reduce geographic reporting bias. A global FAERS comparator analysis was also performed as a sensitivity analysis only. The primary Japan-comparator analysis was used to define retained signals. The global-comparator analysis was used to evaluate whether signal strength changed when the broader FAERS background was used. Terms that showed strong global-comparator signals but did not meet the Japan-comparator threshold were interpreted as sensitivity-only findings.

Signal detection

Disproportionality was assessed using the reporting odds ratio (ROR) and proportional reporting ratio (PRR) (16). For each PT, daprodustat-associated event counts were compared with those for the selected comparator. The primary analysis used Japan-submitted comparator events. A positive signal was defined using the predefined criteria of ROR > 3 with the lower limit of the 95% confidence interval greater than 1 and PRR > 2 with the lower limit of the 95% confidence interval greater than 1. PTs that met both criteria in the Japan comparator analysis were retained as primary signals. The same calculations were repeated using the global FAERS comparator to conduct a sensitivity analysis. SOC-level disproportionality was also assessed after mapping PTs to primary SOCs. SOC-level results were interpreted as supportive domain-level summaries. Clinical interpretation was based primarily on PT-level signals because SOC aggregation can dilute clinically specific signals.

Time-to-onset analysis

Time-to-onset (TTO) was assessed using therapy start dates from the THER file and event dates from the DEMO file. TTO was calculated as the difference between EVENT_DT and START_DT. Reports with missing, invalid, or negative TTO values were excluded from the TTO analysis. TTO results were summarized descriptively because complete timing data were available for only part of the dataset. The percentage of complete TTO reports was calculated using the total number of daprodustat-associated events for each PT as the denominator. Percentages within TTO windows were calculated using only complete TTO reports for that PT as the denominator. TTO windows were categorized as 0 - 7 days, 8 - 14 days, 15 - 21 days, 22 - 28 days, 29 - 60 days, 61 - 90 days and > 91 days. The 0 - 7 day category included events reported on day 0 when present. Temporal patterns were interpreted descriptively and were not used to establish causality (17). Mean, median and range were not used as primary TTO summaries because complete timing data were limited and unevenly distributed across PTs.

Outcome assessment

Reported seriousness outcomes were summarized using FAERS OUTC codes. These included death, hospitalization, life-threatening events, disability, required intervention and other serious outcomes. Outcome data were used to describe the seriousness profile of daprodustat reports. They were not treated as independent PT-level disproportionality signals.

Statistical analysis

All statistical analyses were performed using Python version 3.11. Descriptive variables were summarized as frequencies and percentages. Disproportionality analyses were based on 2 × 2 contingency tables constructed for each PT, where *a* represented daprodustat-associated reports with the PT, *b* represented daprodustat-associated reports with all other PTs, *c* represented comparator reports with the same PT, and *d* represented comparator reports with all other PTs.

$$ROR = \frac{a/b}{c/d} = \frac{ad}{bc},$$

$$PRR = \frac{a/(a+b)}{c/(c+d)}.$$

The 95% confidence interval for ROR was calculated using the standard log-linear method:

$$95\%\ CI_{ROR} = \exp\left[\ln(ROR) \pm 1.96 \times \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right].$$

The 95% confidence interval for PRR was calculated as:

$$95\%\ CI_{PRR} = \exp\left[\ln(PRR) \pm 1.96 \times \sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}\right].$$

A continuity correction of 0.5 was applied when any cell in the 2 × 2 table contained zero. No formal Bonferroni or Benjamini-Hochberg multiple-testing correction was applied because this was an exploratory pharmacovigilance signal-detection study rather than a confirmatory hypothesis-testing analysis. To reduce false-positive interpretation, retained signals were required to satisfy both ROR and PRR thresholds with lower 95% confidence interval limits greater than 1. No separate chi-square significance threshold was applied for PT-level or SOC-level signal retention.

Clinical trial number

Not applicable.

Results and Discussion

The current FAERS analysis identified 1,436 daprodustat primary-suspect reports from 2023-Q1 to 2025-Q4. The process of data extraction from the FAERS

database for Daprodustat is summarized in Figure 1. Final cross-year deduplication retained 1,301 unique cases for analysis. Reporting was highly concentrated in Japan. Japan accounted for 1,296 cases (99.6%), and the United States accounted for 5 cases (0.4%). This geographic concentration required the use of Japan-submitted FAERS reports as the primary comparator group. Most reports were submitted by physicians (n = 767; 59.0%) or pharmacists (n = 488; 37.5%). Age, sex and weight had substantial missing data. These demographic variables were therefore treated as descriptive only. No inference was made regarding sex or age predominance. The data on the demographic characteristics of reported cases are summarized in Table I.

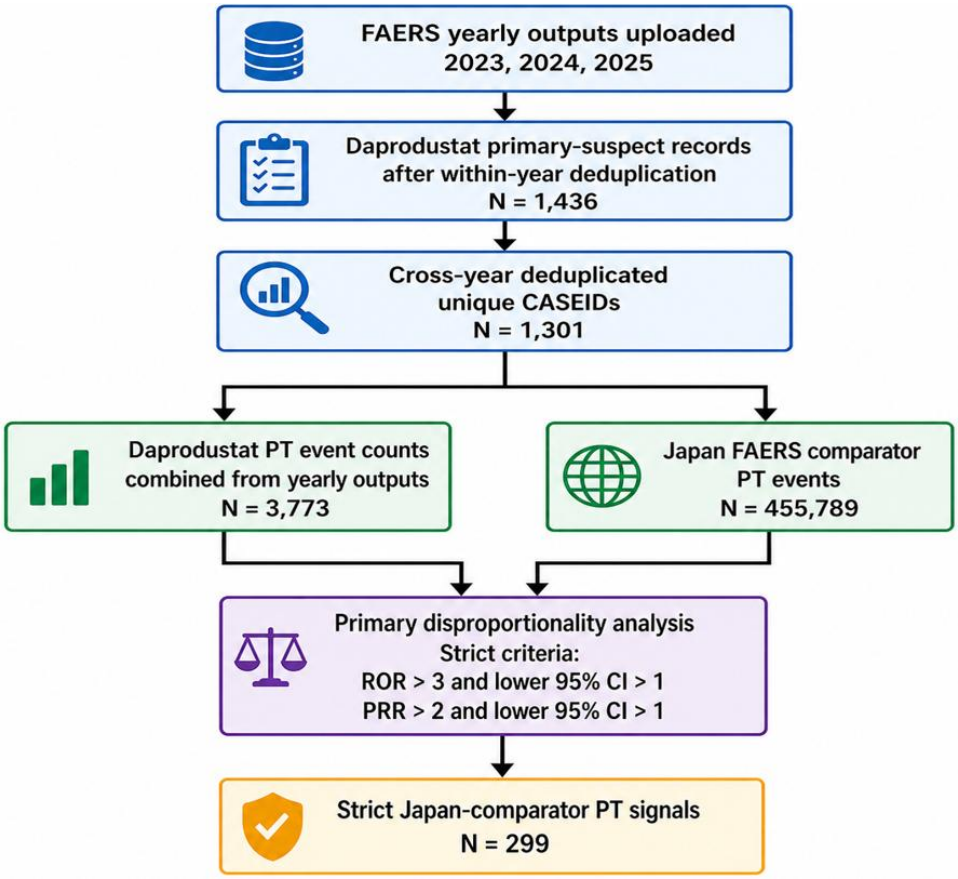


Figure 1.
FAERS case selection and Japan-comparator signal detection workflow
The figure was designed using Microsoft Publisher for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA)

Table I
Demographic and clinical characteristics of adverse event reports for daprodustat from the FAERS database

Characteristics	Frequency	Percentage
Total reports		
Final deduplicated daprodustat primary-suspect cases	1301	—
Year of retained latest report		
2023	440	33.8
2024	399	30.7
2025	462	35.5
Age		
Available	122	9.4
Missing	1179	90.6
Gender		
Available	168	12.9
Missing/ Unknown	1133	87.1
Male	104	61.9
Female	64	38.1

Characteristics	Frequency	Percentage
Reporter qualification		
Physician	767	59.0
Pharmacist	488	37.5
Other Health Personnel	28	2.2
Consumer	3	0.2
Missing	15	1.2
Occurring country		
Japan	1296	99.6
United States	5	0.4

SOC safety signal profile

Table II presents the revised SOC-level disproportionality analysis using the Japan-submitted FAERS comparator. After completion of PT-to-SOC mapping, all 3,773 daprodustat-associated PT events were assigned to a SOC. The most frequent SOCs were general disorders and administration site conditions (n = 586), surgical and medical procedures (n = 326), product issues (n = 313), investigations (n = 297), neoplasms benign, malignant and unspecified (n = 243) and gastrointestinal disorders (n = 243). Only surgical and medical procedures met the predefined strict SOC-level signal criteria, with an ROR of 10.04 (95% CI 8.93–11.29) and PRR of 9.26 (95% CI 8.31–10.31). Other clinically relevant SOCs showed modest disproportionality but did not meet the strict threshold, including cardiac disorders, metabolism and nutrition disorders, vascular disorders, renal and urinary disorders and eye disorders.

Table II

Disproportionality analysis of adverse events associated with daprodustat by SOC

SOC	Frequency	ROR (95% CI)	PRR (95% CI)
General disorders and administration site conditions	586	0.85 (0.78–0.93)	0.87 (0.81–0.94)
Surgical and medical procedures	326	10.04 (8.93–11.29)	9.26 (8.31–10.31)
Product issues	313	1.66 (1.48–1.86)	1.60 (1.44–1.78)
Investigations	297	0.89 (0.79–1.00)	0.90 (0.81–1.00)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	243	1.09 (0.95–1.24)	1.08 (0.96–1.22)
Gastrointestinal disorders	243	0.82 (0.72–0.93)	0.83 (0.73–0.94)
Nervous system disorders	233	1.01 (0.89–1.16)	1.01 (0.89–1.15)
Cardiac disorders	205	1.74 (1.51–2.00)	1.70 (1.49–1.94)
Metabolism and nutrition disorders	203	1.50 (1.30–1.73)	1.47 (1.29–1.68)
Infections and infestations	177	0.57 (0.49–0.66)	0.59 (0.51–0.68)
Renal and urinary disorders	167	1.32 (1.13–1.54)	1.31 (1.13–1.52)
Injury, poisoning and procedural complications	137	1.33 (1.12–1.58)	1.32 (1.12–1.56)
Blood and lymphatic system disorders	135	0.97 (0.81–1.15)	0.97 (0.82–1.14)
Vascular disorders	133	1.49 (1.25–1.77)	1.47 (1.24–1.74)
Respiratory, thoracic and mediastinal disorders	117	0.61 (0.50–0.73)	0.62 (0.52–0.74)
Eye disorders	64	1.42 (1.11–1.82)	1.41 (1.11–1.80)
Hepatobiliary disorders	47	0.50 (0.37–0.67)	0.51 (0.38–0.67)
Musculoskeletal and connective tissue disorders	39	0.47 (0.34–0.65)	0.48 (0.35–0.65)
Skin and subcutaneous tissue disorders	36	0.23 (0.16–0.32)	0.24 (0.17–0.33)
Endocrine disorders	34	0.51 (0.36–0.71)	0.51 (0.37–0.72)
Psychiatric disorders	11	0.28 (0.16–0.51)	0.29 (0.16–0.52)
Immune system disorders	9	0.13 (0.07–0.26)	0.14 (0.07–0.26)
Social circumstances	9	1.78 (0.92–3.43)	1.77 (0.92–3.42)
Reproductive system and breast disorders	4	0.86 (0.32–2.29)	0.86 (0.32–2.29)
Ear and labyrinth disorders	4	0.63 (0.24–1.68)	0.63 (0.24–1.68)
Congenital, familial and genetic disorders	1	0.24 (0.03–1.74)	0.24 (0.03–1.74)
Pregnancy, puerperium and perinatal conditions	0	0.03 (0.00–0.45)	0.03 (0.00–0.45)

SOC = System organ class; PT = Preferred term; ROR = reporting odds ratio; PRR = proportional reporting ratio; CI = confidence interval

Disproportionality signals at the PT level

The Japan-comparator analysis identified 299 retained preferred-term signals using the predefined signal criteria. Hb increased, and nephrogenic anaemia also met the statistical thresholds but were excluded from primary AE signal interpretation because Hb elevation is an expected pharmacodynamic outcome of daprodustat and nephrogenic anaemia represents the treatment indication. These two PTs were therefore summarized descriptively only. The main retained signals were clinically concentrated in hematologic, nutritional, metabolic, thrombotic, renal,

ocular and neoplastic categories. The most frequent retained signal was hospitalization (n = 255; ROR 14.90, 95% CI 13.04–17.04). Other frequent clinically interpretable signals included decreased Hb (n = 82; ROR 16.36, 95% CI 12.97–20.65), dysphagia (n = 65; ROR 8.70, 95% CI 6.75–11.21) and marasmus (n = 55; ROR 19.14, 95% CI 14.38–25.48). Clinically important thrombotic, renal and ocular signals were also retained. These included deep vein thrombosis (n = 31; ROR 8.46, 95% CI 5.87–12.19), renal failure (n = 25; ROR 4.90, 95% CI 3.28–7.31) and retinal haemorrhage (n = 18; ROR 12.62, 95% CI 7.76–20.53). Selected neoplastic terms also met the signal criteria. These included myelodysplastic syndrome, colon cancer, gastric cancer, malignant neoplasm and malignant lung neoplasm. Table III presents selected clinically relevant PT-level signals from the 299 retained signals. These signals were selected for main-text display based on event frequency, signal strength, clinical relevance and representation of key safety domains, including hematologic, thrombotic, renal, ocular, nutritional/metabolic and neoplastic events. The complete list of all 299 retained PT-level signals is provided in Supplementary Table S1. These findings should be interpreted cautiously because FAERS signal detection identifies reporting disproportionality and does not establish causality.

Table III

Selected clinically relevant disproportionality signals for daprodustat-associated AEs at the SOC and PT level

SOC	PT	N	Japan comparator events (c)	ROR (95% CI)	PRR (95% CI)
Surgical and medical procedures	Hospitalisation	255	2206	14.90 (13.04 - 17.04)	13.96 (12.32 - 15.83)
	Dialysis	25	85	35.76 (22.87 - 55.92)	35.53 (22.77 - 55.43)
Investigations	Haemoglobin decreased	82	618	16.36 (12.97 - 20.65)	16.03 (12.76 - 20.14)
	Haemoglobin increased	66	40	202.86 (136.79 - 300.84)	199.32 (134.76 - 294.82)
	Fibrin D dimer increased	11	141	9.45 (5.11 - 17.47)	9.42 (5.11 - 17.39)
	Haemoglobin abnormal	10	12	100.93 (43.58 - 233.76)	100.67 (43.52 - 232.86)
Metabolism and nutrition disorders	Marasmus	55	352	19.14 (14.38 - 25.48)	18.88 (14.23 - 25.03)
	Hypophagia	16	351	5.53 (3.34 - 9.13)	5.51 (3.34 - 9.08)
	Feeding disorder	16	382	5.08 (3.08 - 8.38)	5.06 (3.07 - 8.33)
	Malnutrition	10	120	10.09 (5.29 - 19.25)	10.07 (5.29 - 19.17)
Neoplasms benign, malignant and unspecified	Myelodysplastic syndrome	21	508	5.02 (3.24 - 7.77)	4.99 (3.23 - 7.72)
	Colon cancer	20	589	4.12 (2.63 - 6.44)	4.10 (2.63 - 6.40)
	Gastric cancer	16	351	5.53 (3.34 - 9.13)	5.51 (3.34 - 9.08)
	Neoplasm malignant	16	525	3.69 (2.24 - 6.08)	3.68 (2.24 - 6.05)
	Lung neoplasm malignant	16	580	3.34 (2.03 - 5.50)	3.33 (2.03 - 5.47)
Gastrointestinal disorders	Dysphagia	65	917	8.70 (6.75 - 11.21)	8.56 (6.67 - 10.99)
Blood and lymphatic system disorders	Nephrogenic anaemia	46	98	57.39 (40.37 - 81.59)	56.70 (40.00 - 80.37)
	Iron deficiency anaemia	12	149	9.76 (5.41 - 17.58)	9.73 (5.41 - 17.50)
Renal and urinary disorders	Renal failure	25	620	4.90 (3.28 - 7.31)	4.87 (3.27 - 7.26)
	Chronic kidney disease	20	301	8.06 (5.12 - 12.69)	8.03 (5.11 - 12.61)
	End-stage renal disease	10	63	19.22 (9.86 - 37.49)	19.18 (9.85 - 37.34)
General disorders and administration site conditions	Therapeutic response decreased	25	579	5.24 (3.51 - 7.84)	5.22 (3.50 - 7.77)
	General physical health deterioration	20	762	3.18 (2.04 - 4.97)	3.17 (2.04 - 4.94)
Vascular disorders	Deep vein thrombosis	31	446	8.46 (5.87 - 12.19)	8.40 (5.84 - 12.07)
	Thrombosis	14	384	4.42 (2.59 - 7.54)	4.40 (2.59 - 7.50)
Injury, poisoning and procedural complications	Fracture	31	1232	3.06 (2.14 - 4.37)	3.04 (2.13 - 4.34)
Eye disorders	Retinal haemorrhage	18	173	12.62 (7.76 - 20.53)	12.57 (7.74 - 20.40)
Infections and infestations	Peritonitis	14	425	3.99 (2.34 - 6.80)	3.98 (2.34 - 6.77)
Nervous system disorders	Dementia	13	470	3.35 (1.93 - 5.82)	3.34 (1.93 - 5.79)
Cardiac disorders	Cardiac failure congestive	12	415	3.50 (1.97 - 6.22)	3.49 (1.97 - 6.20)

SOC groups are ordered by cumulative A across retained PT signals within each SOC. The table includes retained PT-level signals that meet the predefined criteria: ROR > 3 with lower 95% CI > 1 and PRR > 2 with lower 95% CI > 1, using Japan-submitted FAERS reports as the comparator. The table presents selected PT-level signals from the 299 retained signals and is not intended to represent the complete list of signals. The complete list is provided in Supplementary Table S1

Comparator sensitivity analysis

The sensitivity analysis summarized in Table IV showed that comparator selection influenced the magnitude of several signals. Marasmus had a higher ROR value with the global FAERS comparator than with the Japan comparator. This finding supports using Japan-submitted reports as the primary comparator group. Cardiac failure, cerebral infarction, renal impairment and dehydration also showed stronger signals in the global analysis. These events did not meet the strict Japan-comparator threshold. Cardiac failure came close to the primary threshold (n = 73; Japan-comparator ROR 2.99, 95% CI 2.37–3.78). Cerebral infarction (n = 44; ROR 2.40, 95% CI 1.78–3.25) and renal impairment (n = 61; ROR 1.57, 95% CI 1.22–2.03) were weaker in the Japan-comparator analysis. These events were not classified as primary retained signals. They were kept as clinically relevant sensitivity findings because of their seriousness and stronger global-comparator estimates. The comparator sensitivity analysis is illustrated in Figure 2. The figure highlights the largest comparator-dependent shifts, especially for marasmus, cerebral infarction and cardiac failure.

Table IV

Sensitivity analysis comparing Japan-submitted FAERS comparator results with the global FAERS comparator

PT	N	Japan ROR (95% CI)	Japan PRR (95% CI)	Global ROR (95% CI)	Global PRR (95% CI)
Hospitalisation*	255	14.90 (13.04–17.04)	13.96 (12.32–15.83)	23.80 (20.95–27.03)	22.26 (19.76–25.07)
Haemoglobin decreased*	82	16.36 (12.97–20.65)	16.03 (12.76–20.14)	15.68 (12.59–19.52)	15.36 (12.39–19.03)
Dysphagia*	65	8.70 (6.75–11.21)	8.56 (6.67–10.99)	12.48 (9.77–15.96)	12.29 (9.65–15.64)
Marasmus*	55	19.14 (14.38–25.48)	18.88 (14.23–25.03)	484.92 (365.89–642.67)	477.87 (361.90–631.01)
Deep vein thrombosis*	31	8.46 (5.87–12.19)	8.40 (5.84–12.07)	15.84 (11.12–22.57)	15.72 (11.06–22.34)
Fracture*	31	3.06 (2.14–4.37)	3.04 (2.13–4.34)	32.23 (22.60–45.96)	31.97 (22.49–45.46)
Dialysis*	25	35.76 (22.87–55.92)	35.53 (22.77–55.43)	48.93 (32.94–72.68)	48.61 (32.81–72.03)
Therapeutic response decreased*	25	5.24 (3.51–7.84)	5.22 (3.50–7.77)	6.74 (4.54–9.98)	6.70 (4.53–9.90)
Renal failure*	25	4.90 (3.28–7.31)	4.87 (3.27–7.26)	5.08 (3.43–7.53)	5.05 (3.42–7.47)
Myelodysplastic syndrome*	21	5.02 (3.24–7.77)	4.99 (3.23–7.72)	30.72 (19.97–47.25)	30.56 (19.91–46.89)
Chronic kidney disease*	20	8.06 (5.12–12.69)	8.03 (5.11–12.61)	6.96 (4.48–10.80)	6.92 (4.47–10.72)
Colon cancer*	20	4.12 (2.63–6.44)	4.10 (2.63–6.40)	28.70 (18.47–44.61)	28.55 (18.41–44.28)
General physical health deterioration*	20	3.18 (2.04–4.97)	3.17 (2.04–4.94)	2.41 (1.55–3.73)	2.40 (1.55–3.71)
Retinal haemorrhage*	18	12.62 (7.76–20.53)	12.57 (7.74–20.40)	56.52 (35.45–90.10)	56.25 (35.36–89.48)
Gastric cancer*	16	5.53 (3.34–9.13)	5.51 (3.34–9.08)	24.25 (14.82–39.68)	24.15 (14.79–39.44)
Hypophagia*	16	5.53 (3.34–9.13)	5.51 (3.34–9.08)	11.36 (6.94–18.57)	11.31 (6.93–18.46)
Feeding disorder*	16	5.08 (3.08–8.38)	5.06 (3.07–8.33)	9.57 (5.85–15.64)	9.53 (5.84–15.55)
Neoplasm malignant*	16	3.69 (2.24–6.08)	3.68 (2.24–6.05)	4.09 (2.50–6.68)	4.08 (2.50–6.65)
Lung neoplasm malignant*	16	3.34 (2.03–5.50)	3.33 (2.03–5.47)	11.65 (7.13–19.05)	11.61 (7.11–18.94)
Thrombosis*	14	4.42 (2.59–7.54)	4.40 (2.59–7.50)	3.64 (2.15–6.15)	3.63 (2.15–6.12)
Peritonitis*	14	3.99 (2.34–6.80)	3.98 (2.34–6.77)	18.31 (10.82–30.98)	18.24 (10.80–30.81)
Dementia*	13	3.35 (1.93–5.82)	3.34 (1.93–5.79)	6.93 (4.02–11.95)	6.91 (4.01–11.89)
Iron deficiency anaemia*	12	9.76 (5.41–17.58)	9.73 (5.41–17.50)	23.73 (13.44–41.90)	23.66 (13.43–41.70)
Cardiac failure congestive*	12	3.50 (1.97–6.22)	3.49 (1.97–6.20)	6.70 (3.80–11.81)	6.68 (3.80–11.76)
Fibrin d dimer increased*	11	9.45 (5.11–17.47)	9.42 (5.11–17.39)	55.48 (30.57–100.69)	55.33 (30.54–100.23)
Haemoglobin abnormal*	10	100.93 (43.58–233.76)	100.67 (43.52–232.86)	22.37 (12.00–41.68)	22.31 (11.99–41.50)
End-stage renal disease*	10	19.22 (9.86–37.49)	19.18 (9.85–37.34)	17.10 (9.18–31.86)	17.06 (9.18–31.73)
Malnutrition*	10	10.09 (5.29–19.25)	10.07 (5.29–19.17)	14.68 (7.88–27.33)	14.64 (7.88–27.22)
Cardiac failure†	73	2.99 (2.37–3.78)	2.95 (2.35–3.71)	17.63 (13.98–22.23)	17.31 (13.78–21.73)
Cerebral infarction†	44	2.40 (1.78–3.25)	2.39 (1.77–3.21)	42.21 (31.31–56.91)	41.73 (31.06–56.07)
Renal impairment†	61	1.57 (1.22–2.03)	1.56 (1.22–2.01)	12.08 (9.37–15.56)	11.90 (9.27–15.27)
Dehydration†	24	1.96 (1.31–2.94)	1.96 (1.31–2.92)	3.79 (2.54–5.66)	3.77 (2.53–5.62)
Death‡	97	1.77 (1.44–2.17)	1.75 (1.44–2.13)	2.19 (1.79–2.68)	2.16 (1.77–2.63)
Coronavirus infection§	18	3.38 (2.11–5.40)	3.37 (2.11–5.37)	27.32 (17.16–43.47)	27.19 (17.12–43.18)

The Japan-submitted FAERS comparator was used as the primary analysis because daprodustat reports were geographically concentrated in Japan. The global FAERS comparator was retained only for sensitivity analysis. *Primary retained Japan-comparator signals met the predefined criteria of ROR > 3 with lower 95% CI > 1 and PRR > 2 with lower 95% CI > 1. †Sensitivity-only findings were clinically relevant terms that did not meet the strict Japan-comparator threshold but showed stronger disproportionality in the global-comparator analysis. ‡Death was handled as a seriousness outcome rather than a PT-level AE signal. §Coronavirus infection was excluded from primary interpretation because of likely study-period confounding and limited mechanistic plausibility. Haemoglobin increased (n = 66; ROR 202.86, 95% CI 136.79–300.84; PRR 199.32, 95% CI 134.76–294.82) and nephrogenic anaemia (n = 46; ROR 57.39, 95% CI 40.37–81.59; PRR 56.70, 95% CI 40.00–80.37) met statistical disproportionality criteria but were excluded from primary AE signal interpretation because they represent an expected pharmacodynamic outcome and an indication-related term, respectively

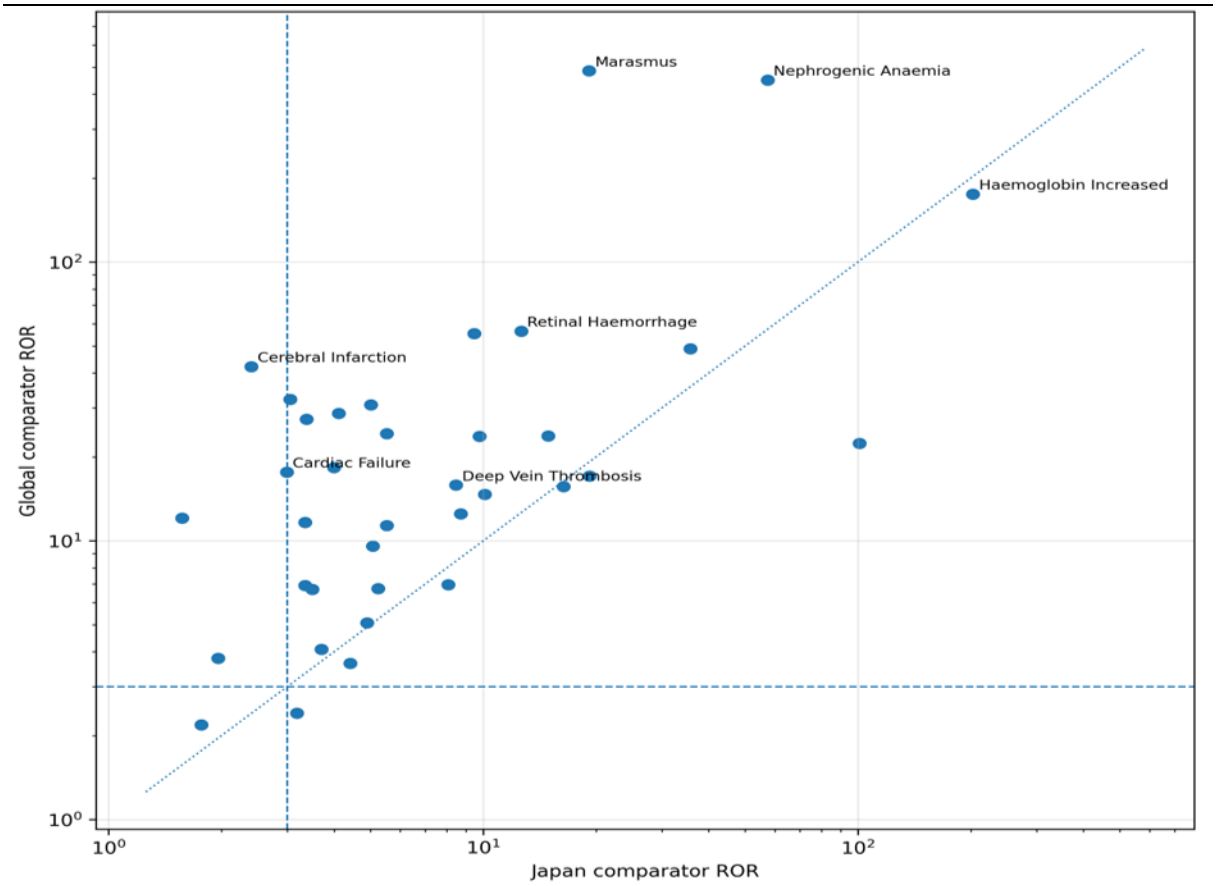


Figure 2.
Comparator sensitivity plot showing differences between Japan-comparator and global-comparator ROR estimates for selected preferred terms

TTO patterns and temporal risk windows

The TTO analysis is summarized in Table V. Complete TTO data were available for only part of the dataset. For this reason, the temporal results were interpreted descriptively. Among retained hematologic signals, Hb decreased had complete TTO data in 22 of 82 events (26.8%). The reports were spread across early, intermediate and delayed periods. Seven reports occurred after 91 days (31.8%). Marasmus showed delayed reporting in 55.6% of complete reports. Deep vein thrombosis was reported across several time windows, including 29 - 60 days and > 91 days. This pattern was treated descriptively rather than as evidence of a statistically established bimodal distribution. Delayed reporting was also observed for selected neoplastic and ocular signals, including myelodysplastic syndrome, gastric cancer, colon cancer and retinal haemorrhage. Although cardiac failure and cerebral infarction were not retained as primary Japan-comparator signals, their TTO profiles remained clinically notable. Delayed reporting after 91 days occurred in 50.0% of complete cardiac failure reports and 40.0% of complete cerebral infarction reports. The TTO distribution across retained PT signals is illustrated in Figure 3.

This FAERS pharmacovigilance analysis of daprodustat from 2023-Q1 to 2025-Q4 identified 1,301 unique primary-suspect cases after cross-year deduplication. The analysis revealed clinically important reporting signals across hematologic, renal, vascular, ocular, nutritional/metabolic and neoplastic domains. Using Japan-submitted FAERS reports as the primary comparator, 299 preferred-term signals met the predefined disproportionality criteria. The most frequent retained signal was hospitalization (n = 255; ROR 14.90). After excluding Hb increased and nephrogenic anaemia from primary AE interpretation, the main clinically interpretable hematologic signal was Hb decreased (n = 82; ROR 16.36). Clinically relevant non-hematologic signals included deep vein thrombosis (n = 31; ROR 8.46), renal failure (n = 25; ROR 4.90), retinal haemorrhage (n = 18; ROR 12.62) and marasmus (n = 55; ROR 19.14). Selected neoplastic terms also met the signal criteria, including myelodysplastic syndrome, colon cancer, gastric cancer, malignant neoplasm and malignant lung neoplasm. Post-marketing monitoring of daprodustat should therefore prioritize clinically interpretable hematologic abnormalities, thrombotic events, renal deterioration, ocular bleeding, nutritional decline and delayed serious events.

Table V

TTO analysis of daprodustat-associated adverse events

PT	Total PT events	Complete TTO, n (%)	0 - 7 days n (%)	8 - 14 days n (%)	15 - 21 days n (%)	22 - 28 days n (%)	29 - 60 days n (%)	61 - 90 days n (%)	91 days n (%)
Hospitalisation	255	5 (2.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	1 (20.0%)
Haemoglobin decreased	82	22 (26.8%)	4 (18.2%)	5 (22.7%)	0 (0.0%)	1 (4.5%)	4 (18.2%)	1 (4.5%)	7 (31.8%)
Haemoglobin increased	66	15 (22.7%)	2 (13.3%)	3 (20.0%)	0 (0.0%)	2 (13.3%)	4 (26.7%)	2 (13.3%)	2 (13.3%)
Dysphagia	65	6 (9.2%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	2 (33.3%)	1 (16.7%)
Marasmus	55	9 (16.4%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (11.1%)	5 (55.6%)
Nephrogenic anaemia	46	12 (26.1%)	3 (25.0%)	2 (16.7%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	0 (0.0%)	5 (41.7%)
Deep vein thrombosis	31	14 (45.2%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	4 (28.6%)	2 (14.3%)	4 (28.6%)
Dialysis	25	2 (8.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Therapeutic response decreased	25	2 (8.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Renal failure	25	9 (36.0%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	2 (22.2%)	3 (33.3%)	2 (22.2%)
Myelodysplastic syndrome	21	4 (19.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (100.0%)
Chronic kidney disease	20	12 (60.0%)	4 (33.3%)	1 (8.3%)	0 (0.0%)	1 (8.3%)	1 (8.3%)	0 (0.0%)	5 (41.7%)
Colon cancer	20	8 (40.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	4 (50.0%)
General physical health deterioration	20	8 (40.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	2 (25.0%)	2 (25.0%)
Retinal haemorrhage	18	5 (27.8%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	3 (60.0%)
Gastric cancer	16	9 (56.2%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	7 (77.8%)
Hypophagia	16	9 (56.2%)	1 (11.1%)	1 (11.1%)	1 (11.1%)	0 (0.0%)	3 (33.3%)	0 (0.0%)	3 (33.3%)
Feeding disorder	16	7 (43.8%)	2 (28.6%)	1 (14.3%)	0 (0.0%)	1 (14.3%)	2 (28.6%)	0 (0.0%)	1 (14.3%)
Neoplasm malignant	16	2 (12.5%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Lung neoplasm malignant	16	6 (37.5%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	2 (33.3%)	1 (16.7%)
Thrombosis	14	6 (42.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	4 (66.7%)
Peritonitis	14	5 (35.7%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (60.0%)
Iron deficiency anaemia	12	6 (50.0%)	2 (33.3%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	3 (50.0%)
Cardiac failure congestive	12	5 (41.7%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (20.0%)	0 (0.0%)	2 (40.0%)
Fibrin D dimer increased	11	2 (18.2%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
End stage renal disease	10	2 (20.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Malnutrition	10	2 (20.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Cardiac failure	73	14 (19.2%)	1 (7.1%)	2 (14.3%)	1 (7.1%)	0 (0.0%)	1 (7.1%)	2 (14.3%)	7 (50.0%)
Cerebral infarction	44	15 (34.1%)	3 (20.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	3 (20.0%)	1 (6.7%)	6 (40.0%)
Renal impairment	61	20 (32.8%)	0 (0.0%)	4 (20.0%)	2 (10.0%)	2 (10.0%)	6 (30.0%)	1 (5.0%)	5 (25.0%)
Dehydration	24	12 (50.0%)	2 (16.7%)	2 (16.7%)	0 (0.0%)	2 (16.7%)	3 (25.0%)	1 (8.3%)	2 (16.7%)
Death	97	9 (9.3%)	1 (11.1%)	1 (11.1%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	5 (55.6%)
Coronavirus infection	18	3 (16.7%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)

The complete TTO percentages use total PT events as the denominator. Window percentages use complete TTO reports for that PT as the denominator. The 0 - 7-day category includes day 0 when it is present in the uploaded TTO output

The disproportionality analysis identified clinically meaningful PT-level signals rather than a dominant reproductive or congenital safety pattern. Only surgical and medical procedures met the strict SOC-level signal threshold (ROR 10.04, 95% CI 8.93–11.29; PRR 9.26, 95% CI 8.31–10.31). At the PT level, the strongest clinically interpretable signals included Hb decreased (n = 82; ROR 16.36, 95% CI 12.97–20.65), retinal haemorrhage (n = 18; ROR 12.62, 95% CI 7.76–20.53), deep vein thrombosis (n = 31; ROR 8.46, 95% CI 5.87–12.19) and renal failure (n = 25; ROR 4.90, 95% CI 3.28–7.31). The hematologic pattern is biologically plausible because daprodustat is a HIF-prolyl hydroxylase inhibitor

that stimulates erythropoiesis and modifies iron handling in CKD-related anaemia. In phase 3 trials, daprodustat maintained Hb efficacy comparable to darbepoetin alfa in both non-dialysis and incident dialysis CKD populations (18). Real-world cardiovascular pharmacovigilance data from JADER also support continued attention to thrombotic and cardiac outcomes with HIF-PH inhibitors, as embolic/thrombotic events (ROR 6.66) and cardiac failure (ROR 3.86) showed positive signals in that database (19).

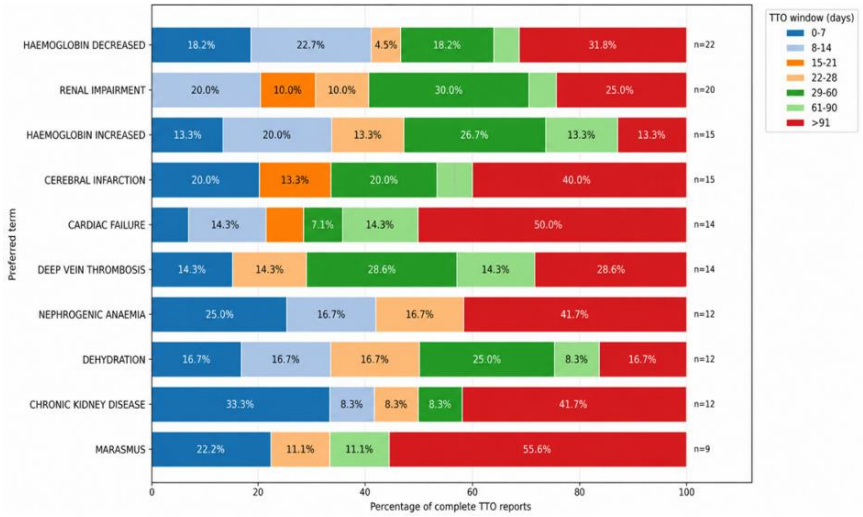


Figure 3.

TTO distribution across selected preferred terms, emphasizing immediate and delayed reporting windows

Hb decreased remained clinically interpretable as a reported AE term. In contrast, increased Hb was not interpreted as an AE signal because elevation of Hb reflects the expected pharmacodynamic effect of daprodustat. Nephrogenic anaemia was also excluded from primary AE interpretation because it reflects the treatment indication rather than a suspected drug-induced event. Hb increased showed the highest ROR among frequently retained PTs (ROR 202.86, 95% CI 136.79–300.84), while Hb decreased was also retained as a frequent signal (n = 82; ROR 16.36, 95% CI 12.97–20.65). This bidirectional Hb signal pattern suggests instability of Hb control in real-world use rather than a single direction of effect. Daprodustat and other HIF-PH inhibitors are known to regulate erythropoietin production and iron metabolism through HIF-mediated pathways. They can reduce hepcidin and improve iron availability for erythropoiesis, but this same pharmacologic pathway may contribute to clinically relevant shifts in Hb and iron indices in susceptible patients (20).

Nutritional deterioration is common in advanced CKD and dialysis populations. It may reflect frailty, inflammation, reduced oral intake, dialysis-related catabolism and comorbidity burden rather than a single drug effect. Protein-energy wasting is a recognized CKD-related syndrome and is associated with adverse outcomes (21). Severe protein-energy malnutrition has also been reported in approximately 6 - 8% of dialysis patients (22). This background is important when interpreting nutritional events in FAERS. In the present analysis, nutritional and metabolic PTs were retained as signals, including marasmus (n = 55; ROR 19.14, 95% CI 14.38–25.48), hypophagia (n = 16; ROR 5.53, 95% CI 3.34–9.13), feeding disorder (n = 16; ROR 5.08, 95% CI 3.08–8.38) and malnutrition (n = 10; ROR 10.09, 95% CI 5.29–19.25). These signals should be considered hypothesis-generating and should prompt attention to appetite, weight change, dietary intake, inflammation and frailty during daprodustat therapy.

Cardiovascular and thrombotic events remain important safety concerns in CKD patients receiving anaemia therapy. In phase 3 daprodustat trials, major cardiovascular outcomes were generally comparable with ESA therapy, but heart failure and thrombotic events remained clinically relevant safety endpoints (10, 18, 23). A recent Japanese pharmacovigilance study also reported positive signals for embolic and thrombotic events (ROR = 6.66) and cardiac failure (ROR = 3.86) with HIF-PH inhibitors (Wu *et al.*, 2025). In the present analysis, deep vein thrombosis was retained as a primary Japan-comparator signal (n = 31; ROR 8.46, 95% CI: 5.87–12.19). Thrombosis was also retained (n = 14; ROR 4.42, 95% CI: 2.59–7.54). Cardiac failure did not meet the strict Japan comparator threshold but came close (n = 73; ROR 2.99, 95% CI 2.37–3.78). Cerebral infarction was also weaker in the Japan-comparator analysis (n = 44; ROR 2.40, 95% CI: 1.78–3.25). Both cardiac failure and cerebral infarction showed stronger global-comparator estimates and were therefore retained as clinically relevant sensitivity findings.

Renal, ocular and neoplastic findings also require cautious clinical interpretation. Daprodustat is used in patients with CKD, so renal AE terms may partly reflect disease progression, dialysis transition, or baseline renal vulnerability. In the present analysis, renal failure was retained as a primary signal (n = 25; ROR 4.90, 95% CI: 3.28–7.31). CKD (n = 20; ROR 8.06, 95% CI: 5.12–12.69) and end-stage renal disease (n = 10; ROR 19.22, 95% CI: 9.86–37.49) were also retained, but these terms should be interpreted in the context of the treated population. Retinal haemorrhage was retained as an ocular signal (n = 18; ROR 12.62, 95% CI: 7.76–20.53). This may be clinically relevant in patients with CKD, diabetes, hypertension, or Hb fluctuation. Several malignancy-related terms also met the signal criteria, including myelodysplastic syndrome, colon cancer, gastric cancer, malignant neoplasm and malignant lung neoplasm. However, trial-based evidence has not established a clear carcinogenic risk for daprodustat (24), and spontaneous reporting data cannot prove causality (25). These oncologic signals should therefore be treated as surveillance findings that require confirmation in controlled observational studies.

TTO findings provided clinical context beyond disproportionality estimates. The Jesduvroq prescribing information recommends Hb monitoring every 2 weeks during the first month after treatment initiation or dose adjustment and every 4 weeks thereafter (26, 27). The information also warns that rapid Hb rise and Hb targets above 11 g/dL may increase the risk of death and thrombotic vascular events. This label guidance is relevant to our TTO findings. Hb decreased had complete TTO data in 22 of 82 events. Seven of these reports occurred after 91 days (31.8%). The label also highlights thrombotic vascular events, heart failure hospitalization, gastrointestinal bleeding and malignancy as important safety concerns. In our analysis, marasmus was reported with a delay in 55.6% of complete reports. Retinal haemorrhage and selected neoplastic terms also showed delayed reporting. Cardiac failure and cerebral infarction were not primary Japan-comparator signals, but delayed reporting after 91 days occurred in 50.0% and 40.0% of their complete reports. The temporal pattern suggests that daprodustat monitoring should not be limited to treatment initiation. Follow-up should remain attentive to Hb decrease, thrombotic events, ocular bleeding, nutritional decline and delayed serious events over longer treatment periods.

This study has several strengths and limitations. The analysis used FAERS data through 2025-Q4 and applied year-wise processing, followed by final cross-year deduplication. The Japan-submitted comparator reduced geographic reporting bias because almost all daprodustat reports originated from Japan. The study also used strict predefined ROR and PRR criteria and excluded administrative terms, non-specific outcome terms and likely study-period confounding terms from the main signal interpretation. However, FAERS is a spontaneous reporting system and is affected by underreporting, reporting delays, duplicate submissions, incomplete clinical information and variable coding quality. The analysis could not adjust for CKD stage, dialysis status, dose changes, Hb targets, comorbidities, or concomitant medications.

Conclusions

This current FAERS analysis identified clinically relevant daprodustat-associated reporting signals from 2023-Q1 to 2025-Q4. After use of the Japan-submitted comparator, the main retained signals involved Hb abnormalities, nephrogenic anaemia, deep vein thrombosis, renal failure, retinal haemorrhage, nutritional decline and selected malignancy-related terms. Cardiac failure, cerebral infarction, renal impairment and dehydration showed stronger estimates in the global-comparator analysis but did not meet the strict Japan-comparator threshold. These events should be interpreted as clinically relevant sensitivity findings. TTO results suggested that some serious events were reported after longer treatment periods, although timing data were incomplete. The daprodustat therapy requires careful post-marketing surveillance with attention to Hb stability, thrombotic risk, renal status, ocular bleeding, nutritional deterioration and delayed serious outcomes.

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Availability of data and materials

All the data referenced in this study were drawn from publicly available databases, and references to available data can be accessed at: [https://open.fda.gov/data/faers/].

Ethics approval and consent to participate

This study conducts a secondary analysis of publicly available data from the FAERS database and does not require ethical approval.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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