CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216951Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	01/31/2023
Reviewer(s):	Orestis Panagiotou, MD, PhD Division of Epidemiology 1
Team Leader:	Fang Tian, PhD, MPH, MHS Division of Epidemiology 1
Associate Division Director:	Steven Bird, PhD, PharmD, MS Division of Epidemiology 1
OPE Director:	Judith Zander, MD Office of Pharmacovigilance and Epidemiology (OPE)
OSE Sentinel Team Leader:	Sarah Dutcher, PhD Regulatory Science Staff
OSE Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology (OSE)
Subject:	ARIA Sufficiency Memo: daprodustat and risk of malignancy
Drug Name(s):	Daprodustat (JESDUVROQ®)
Application Type/Number:	NDA 216951
Applicant/sponsor:	GSK
OSE RCM #:	2023-3279

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Daprodustat (JESDUVROQ®) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI). GSK submitted a New Drug Application (NDA 216951) for daprodustat for the indication of the treatment of anemia due to chronic kidney disease in adult patients on dialysis.

The efficacy and safety of daprodustat were evaluated in 5 global Phase III studies including 2 studies (ASCEND-ND/NCT02876835 and ASCEND-NHQ/NCT03409107) on non-dialysis patients and 3 studies (ASCEND-D/NCT02879305, ASCEND-ID/NCT03029208, and ASCEND-TD/NCT03400033) on dialysis patients.

Daprodustat (b) (4) product labeling will include the following limitation of use:

"Not been shown to improve quality of life, fatigue, or patient well-being.

Not indicated for use:

- *As a substitute for red blood cell transfusions in patients who require immediate correction of anemia.*

(b) (4)

1.2. Safety Concern

Daprodustat's mechanism of therapeutic action, which results in increased erythropoietin levels and activation of HIF-1, supports concerns about the post-market safety. Daprodustat is a reversible inhibitor of HIF-prolyl-4-hydroxylases (PH)1, PH2 and PH3 (IC50 in the nM range). This activity results in the stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes, including erythropoietin. It increases endogenous erythropoietin levels in a dose-dependent manner within 6 to 8 hours after administration. In turn, erythropoietin increases the expression of vascular and endothelial growth factors, promotes cell proliferation, and prevents apoptosis leading to increased levels of hemoglobin and hematocrit. In addition, increased levels of HIF-1 may be associated with unfavorable effects on cancer growth because they activate vascular endothelial growth factor (VEGF) which is a key mediator in tumor angiogenesis. Of note, no evidence of increased carcinogenicity was observed in animal studies.

Although no increased risk of malignancy was demonstrated in clinical studies comparing daprodustat to an ESA control, the incidence of treatment-emergent malignancies was sensitive to the systematic dosing frequency bias because the diagnosis of cancer was a reason for treatment discontinuation. Furthermore, the duration and size of these studies were not sufficient to fully characterize the potential for daprodustat to accelerate tumor growth and therefore, this remains an important potential risk.

The risk of malignancy is included as a Warning & Precaution in Section 5 of the proposed daprodustat label. The label further notes that use of daprodustat is not recommended in patients with active malignancy. In addition to biological plausibility linking HIF-1 activity and tumor growth, malignancy was identified as an adverse event of special interest (AESI) for daprodustat based on clinical experience with marketed ESAs (e.g., Epogen/Procrit, Aranesp) whose labels include an increased risk of tumor progression as a boxed warning). In the ASCEND-D trial, daprodustat was found to be non-inferior to the control ESA treatment; in this trial, the rates of cancer-related death, progression or recurrence were 3.2% in the daprodustat arm vs. 3.5% in the control arm. Considering that ESAs are known to increase cancer risk and their labeling includes a boxed warning for cancer risk, it is reasonable that daprodustat may increase the risk of malignancy outcomes as well.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of the desired post market study is to characterize the risk of malignancies, both solid and hematological ones, in dialysis-dependent (DD) patients receiving daprodustat, and to evaluate the causal effects of daprodustat on the risk of incident cancer as well as cancer progression. The regulatory goal is signal evaluation in the post-marketing setting.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Because ARIA is deemed insufficient in this memo to determine the risk of malignancy (both incident cancer and cancer progression), no sample size is projected for the evaluation of cancer risk.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population should include adult patients (18 years of age or older) with anemia due to chronic kidney disease who require chronic dialysis (including hemodialysis or peritoneal dialysis).

2.2 Is ARIA sufficient to assess the intended population?

Yes. ARIA can be used to identify the population of interest. There exist billing codes for anemia due to chronic kidney disease. The ICD-10-CM code is D63.1. In addition, CPT codes in the range 90935-90999 are used to reimburse for dialysis services and procedures. Validated

algorithms for identifying CKD and dialysis in claims data are available and can be implemented in ARIA.[1,2,3]

3 EXPOSURES

3.1 Treatment Exposure

The treatment exposure of interest is daprodustat, which is administered orally. National Drug Codes available in ARIA can be used to ascertain prescriptions.

3.2 Comparator Exposures

The comparator group of interest includes ESAs used for the treatment of anemia due to chronic kidney disease in DD patients. Eligible comparators will be epoetin alfa, epoetin alfa-epbx, darbepoetin, and methoxy polyethylene glycol-epoetin beta. These drugs are administered intravenously or subcutaneously and can be ascertained using Healthcare Common Procedure Coding System (J codes) or National Drug Codes.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. ARIA is deemed sufficient to capture both the treatment exposure (daprodustat) of interest and the comparator treatments (epoetin alfa, epoetin alfa-epbx, methoxy polyethylene glycol-epoetin beta, darbepoetin), based on Healthcare Common Procedure Coding System (J codes) or National Drug Codes that are available in ARIA's administrative claims and electronic health records. ARIA tools generate longitudinal records of outpatient pharmacy dispensings, which permit construction of patient-specific episodes of treatment with daprodustat.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcomes of interest are incident cancer and cancer progression. In particular, the interest is primary malignancies (hematological and non-hematological ones) among patients with no cancer history (including assessment by type and location), and the impact of daprodustat on progression-free survival and overall survival in patients with prior cancers.

The National Cancer Institute (NCI) defines malignancy as a disease "in which abnormal cells

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[1] Zou G, Liu H, Lin K, Zhu K, Hsieh TC. Trends and Outcomes of Hospitalized Influenza Patients With End-Stage Kidney Disease: Insights From the National Inpatient Sample 2010–2019. Cureus. 2022 Apr 25;14(4).
[2] Gibertoni D, Voci C, Iommi M, D'Ercole B, Mandreoli M, Santoro A, Mancini E. Developing and validating an algorithm to identify incident chronic dialysis patients using administrative data. BMC Medical Informatics and Decision Making. 2020 Dec;20(1):1-7.
[3] Clement FM, James MT, Chin R, Klarenbach SW, Manns BJ, Quinn RR, Ravani P, Tonelli M, Hemmelgarn BR. Validation of a case definition to define chronic dialysis using outpatient administrative data. BMC medical research methodology. 2011 Dec;11(1):1-6.

divide without control and can invade nearby tissues."[4] It also defines progression-free survival as "the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse"[5] and overall survival as "the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive."[6]

4.2 Is ARIA sufficient to assess the outcome of interest?

No. ARIA is not sufficient to identify incident cancer. To completely and accurately capture this outcome, a method for ascertaining tumor characteristics at the time of diagnosis is required, including site (e.g., cancer of the lung, lymphoma etc.), histology (e.g., non-small cell lung cancer), American Joint Committee on Cancer (AJCC)stage (i.e., stage I, II, III, or IV), and others. This ascertainment is feasible by linking electronic health records (EHR) or claims data to a population-based cancer registry such as the U.S. Surveillance, Epidemiology, and End Results (SEER) Program or state and territorial cancer registries funded through the CDC's National Program of Cancer Registries (NPCR). However, ARIA capabilities currently exclude linkages to such registries. Even though some Data Partners in ARIA may capture cancer-related information such as stage and histology in their EHR data, this information is not uniformly available given in a standardized format across partners. Similarly, diagnostics ICD-10 codes for various cancers lack high sensitivity and specificity for clinically relevant elements such as stage and histology.

ARIA is also not sufficient to identify cancer progression. To completely and accurately capture this outcome, it is necessary to establish when a patient is diagnosed with cancer and to describe their disease trajectory (e.g., when cancer progresses, additional sites of metastasis). Establishing when a cancer diagnosis occurs in ARIA is challenging considering the lack of linkage to a cancer registry. As outlined in the previous paragraph, diagnostic ICD-10 codes for various cancers lack high sensitivity and specificity for clinically relevant elements such as stage and histology. Importantly, even though some Data Partners in ARIA may capture cancer-related information such as stage and histology in their EHR data, using such data for the specific regulatory question under consideration will require a validated ascertainment for tumor progression for the progression-free-survival outcome.

Last, ARIA is not sufficient to identify any cancer-related outcome (either incidence, progression, or mortality) that is clinically manifested after more than 5 years, i.e., a period which is considered clinically and biologically relevant. The reason for the ARIA insufficiency is that in Sentinel Distributed Databases less than 25% of patients have continuous beyond 5 years;[7] the absolute sample size is expected to be even lower for patients on dialysis receiving

[4] National Cancer Institute, Dictionary of Cancer Terms. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/malignancy, Accessed January 13, 2023.
[5] National Cancer Institute, Dictionary of Cancer Terms. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/progression-free-survival. Accessed January 13, 2023.
[6] National Cancer Institute, Dictionary of Cancer Terms. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/overall-survival. Accessed January 13, 2023.
[7] See https://www.sentinelinitiative.org/about/key-database-statistics#length-of-member-enrollment-spans-in-the-sentinel-distributed-database

daprodustat for the treatment of anemia due to chronic kidney disease. This consideration is especially applicable to cancer incidence because from a pathophysiological aspect, cancer has a long latency period and is clinically manifested many years after exposure, thereby requiring long follow-up. It also applies to progression and mortality outcomes, especially for situations where treatments have led to considerable improvements in disease-specific and overall survival among cancer survivors. Hence, the poor patient retention in ARIA limits the usefulness of ARIA for long latency outcomes needed to assess the risk of malignancy due to daprodustat.

5 COVARIATES

5.1 Covariates of Interest

The following covariates are necessary to account for in the design and/or analyses stages:

a. Demographics: age, sex, race/ethnicity
b. Clinical: body mass index, dialysis type (i.e., hemodialysis or peritoneal dialysis) for the DD population, time since initiation of dialysis, ESA hyporesponsiveness, smoking status, smoking intensity
c. Comorbid conditions: coronary artery disease, heart failure, angina, atrial fibrillation, myocardial infraction, stroke, transient ischemic attack, cardiac arrest, hypertension, prior cancer, diabetes, thromboembolic event
d. Laboratory values: hemoglobin levels, ferritin, hematocrit, hepcidin, iron, hs-CRP, electrolytes (e.g., potassium), albumin, creatinine, tumor-specific biomarkers

5.2 Is ARIA sufficient to assess the covariates of interest?

No. ARIA is not sufficient to assess a key covariate, i.e., prior cancer, which is necessary for determining the impact of daprodustat on cancer progression. While available diagnostic codes could be used to determine if a patient had been diagnosed with cancer prior to daprodustat initiation, these codes lack high sensitivity and specificity for clinically relevant elements such as stage and histology.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

ARIA might address the objectives for post-market assessment by conducting analyses in patient cohorts defined by age, index treatment for anemia due to chronic kidney disease, and pre-index medical history. The study should use a "new user with active comparator" design. Applicable ARIA analytic tools permit descriptive (Level 1) and comparative (Level 2) analysis, as indicated below.

Level 1 (Descriptive) Analysis

- To determine exposure (number of exposed patients and patient-years at risk).
- To calculate (background) incidence rates for the outcomes of interest.

Level 2 (Comparative) Analysis

- Covariate Stratification – to calculate incidence rates for the outcomes of interest in patient cohorts defined by exposure and other covariates (e.g., age, sex, cancer risk).
- Propensity Score Analysis – to estimate the causal effect of daprodustat compared to the comparison treatments. Methods available in ARIA for propensity score analysis include matching, stratification, inverse probability of treatment weighting (IPTW), and stratum weighting.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, we anticipate that ARIA design and analytic tools are sufficient to assess the questions of interest.

7 NEXT STEPS

DEPI-I has determined that the Sentinel ARIA system is **insufficient** to assess the risk of malignancy in dialysis-dependent patients receiving daprodustat for the treatment of anemia due to chronic kidney disease. DEPI recommends that DNH issues a PMR for conducting an observational study to further characterize and assess the risk of malignancies in dialysis-dependent patients receiving daprodustat for the treatment of anemia due to chronic kidney disease. The following PMR language is suggested:

"Conduct an observational study (at least 5 years follow up) to assess the risk for malignancy (hematological and non-hematological) in dialysis dependent chronic kidney disease adults with anemia treated with JESDUVROQ versus an erythropoiesis-stimulating agent (ESA) comparator arm. The study should include an assessment of primary malignancies among adults with no cancer history (including assessment by type and location), and the impact of JESDUVROQ on progression-free survival, and overall survival in adults with prior cancers."

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ORESTIS A PANAGIOTOU
01/31/2023 04:07:43 PM

FANG TIAN
01/31/2023 04:12:24 PM

STEVEN BIRD
01/31/2023 04:35:00 PM

JUDITH W ZANDER
01/31/2023 04:45:32 PM

SARAH K DUTCHER
01/31/2023 11:25:52 PM

ROBERT BALL
02/01/2023 07:36:36 AM

Department of Health and Human Services
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Epidemiology: ARIA Sufficiency Templates
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Associate Division Director:	Steven Bird, PhD, PharmD, MS Division of Epidemiology 1
OPE Director:	Judith Zander, MD Office of Pharmacovigilance and Epidemiology (OPE)
OSE Sentinel Team Leader:	Sarah Dutcher, PhD Regulatory Science Staff
OSE Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology (OSE)
Subject:	ARIA Sufficiency Memo for Safety Concerns: Major Adverse Cardiovascular Events, Venous Thromboembolism, Heart Failure, Serious Gastrointestinal Bleeding, and Eye Disorders
Drug Name(s):	Daprodustat (JESDUVROQ®)
Application Type/Number:	NDA 216951
Applicant/sponsor:	GSK
OSE RCM #:	2023-3279

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

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Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcomes of Interest	
Major adverse cardiovascular events	X
Venous thromboembolism	X
Heart failure	X
Serious gastrointestinal bleeding	X
Eye disorders (proliferative retinopathy)	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	X

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Daprodustat (JESDUVROQ®) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI) intended for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis. Daprodustat is currently undergoing FDA review with a PDUFA goal date of February 1, 2023.

The efficacy and safety of daprodustat in dialysis patients were evaluated in three global Phase III studies (ASCEND-D/NCT02879305, ASCEND-ID/NCT03029208, and ASCEND-TD/NCT03400033). Daprodustat (b) (4) product labeling will include the following limitation of use:

"Not been shown to improve quality of life, fatigue, or patient well-being.

Not indicated for use:

- *As a substitute for red blood cell transfusions in patients who require immediate correction of anemia.*

(b) (4)

1.2. Safety Concern

The following lines of evidence support concerns about the post-market safety of daprodustat: (1) randomized pre-market studies evaluated during the review process; (2) mechanism of therapeutic action (i.e., increases in erythropoietin and hemoglobin levels)

(1) Randomized pre-market studies

During the review of NDA 216951, safety concerns were raised for patients on dialysis (dialysis-dependent; DD).

In the DD population, notable risks included hospitalization for heart failure (HHF; particularly in patients with a history of heart failure) and bleeding gastric erosions. Daprodustat did not unacceptably increase the risk of major adverse cardiac events (MACE, defined as a composite of all-cause mortality, nonfatal myocardial infarction and nonfatal stroke) or other cardiovascular events compared to darbepoietin alfa or epoetin alfa in the DD population. Table 1 shows the hazard ratios for CV events in the DD population in the ASCEND-D trial comparing daprodustat to epoetin alfa (for patients on hemodialysis) or darbepoetin (for patients on peritoneal dialysis). However, epoetin alfa and darbepoetin are known to increase cardiovascular risk compared to placebo, and, with daprodustat being non-inferior to them, it is reasonable to expect increased absolute risks in patients receiving daprodustat as well.

Table 1. Adjudicated Cardiovascular Safety Endpoints, ASCEND-D

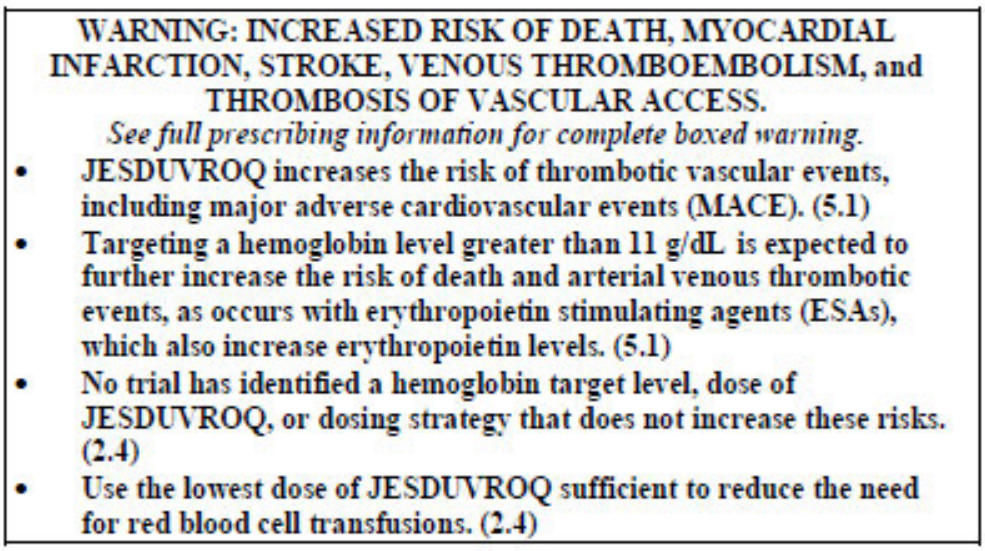
	Daprodustat N=1487	**Comparator* N=1477**	**Rate Difference per 100 PY (95% CI)**	**Hazard Ratio (95% CI)**
	Number of Events [Incidence Rate per 100 PY]			
Endpoint				
CV MACE	226 [6.7]	257 [7.7]	-1.0 (-2.3, 0.2)	0.86 (0.72, 1.03)
CV mortality	117 [3.3]	121 [3.5]	-0.2 (-1.0, 0.7)	0.95 (0.74, 1.23)
Fatal or nonfatal myocardial infarction	114 [3.3]	137 [4.1]	-0.7 (-1.7, 0.2)	0.81 (0.63, 1.04)
Fatal or nonfatal stroke	43 [1.2]	51 [1.9]	-0.2 (-0.8, 0.3)	0.84 (0.56, 1.25)
Hospitalization for heart failure	112 [3.3]	101 [3.0]	0.3 (-0.6, 1.1)	1.10 (0.84, 1.45)
Thromboembolic event	185 [5.7]	215 [6.75]	-1.1 (-2.3, 0.1)	0.84 (0.69, 1.02)
Vascular access thrombosis	164 [5.0]	201 [6.3]	-1.3 (-2.4, -0.1)	0.80 (0.65, 0.98)

** Comparator was epoetin alfa (for patients on hemodialysis) or darbepoetin (for patients on peritoneal dialysis).*

In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 g/dL to 14 g/dL) to lower targets (9 g/dL to 11.3 g/dL), erythropoietin stimulating agents (ESA) increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups. Daprodustat has been shown to be non-inferior to ESAs in terms of first occurrence of major adverse cardiovascular events (MACE) defined as all-cause mortality, non-fatal myocardial infarction and non-fatal stroke.

Currently, the proposed label includes a boxed warning regarding the increased risk of thrombotic vascular events including death, myocardial infraction, stroke and thromboembolism (Figure 1).

Figure 1. Proposed Boxed Warning in the USPI Label of Daprodustat



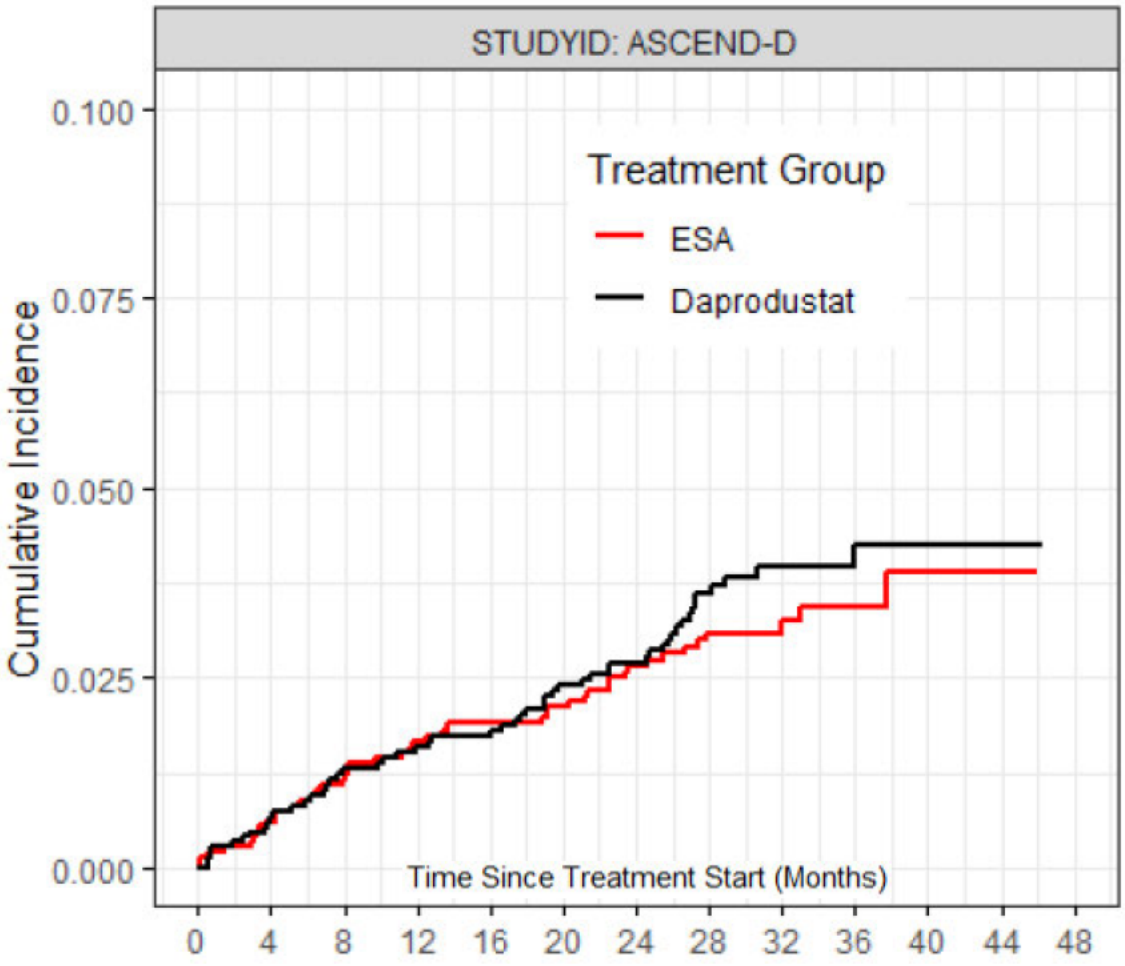
WARNING: INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, and THROMBOSIS OF VASCULAR ACCESS.

See full prescribing information for complete boxed warning.

- **JESDUVROQ increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE). (5.1)**
- **Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial venous thrombotic events, as occurs with erythropoietin stimulating agents (ESAs), which also increase erythropoietin levels. (5.1)**
- **No trial has identified a hemoglobin target level, dose of JESDUVROQ, or dosing strategy that does not increase these risks. (2.4)**
- **Use the lowest dose of JESDUVROQ sufficient to reduce the need for red blood cell transfusions. (2.4)**

In DD patients, there was a higher number of adverse events of special interest (AESI) for serious gastric/esophageal erosions reported in the daprodustat arm compared to control arm (HR [95% CI]: 1.16 [0.78, 1.73] in ASCEND-D). The risk appears to accumulate constantly over time (i.e., there is not an apparent delay), and is driven by treatment differences in serious hemorrhages, rather than ulcerations (Figure 2).

Figure 2. Time to First Treatment-Emergent Serious Adverse Event for Gastrointestinal Bleed in the ASCEND-D trial



Source: FDA Briefing Document for NDA 216951 (Drug Name: Daprodustat; Applicant: GlaxoSmithKline (GSK) Intellectual Property (No. 2) Limited England) for the Cardiovascular and Renal Drugs Advisory Committee Meeting on October 26, 2022.

Analysis Source: Clinical Reviewer, ADAE.xpt, ADSL.xpt, R Version 4.2, ITT population.

Abbreviations: ESA, erythropoiesis-stimulating agent; ITT, intention-to-treat. This analysis treats deaths and administrative censoring the same.

(2) Mechanism of therapeutic action

Daprodustat is a reversible inhibitor of HIF-prolyl-4-hydroxylases (PH)1, PH2 and PH3 (IC50 in the nM range). This activity results in the stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes, including erythropoietin. It increases endogenous erythropoietin levels in a dose-dependent manner within 6 to 8 hours after administration. In turn, erythropoietin increases the expression of vascular and endothelial growth factors, promotes cell proliferation, and prevents apoptosis leading to increased levels of hemoglobin and hematocrit. These

pathophysiological alterations create a prothrombotic environment due to increased blood viscosity and peripheral vascular resistance that may be clinically manifested as myocardial infraction, stroke, other thrombotic events, and even death.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of this ARIA memo is to discuss whether ARIA is sufficient to characterize the long-term safety (i.e., at least 5 years) of daprodustat in DD CKD patients with anemia. The long-term safety outcomes include the risks of major adverse cardiovascular events (MACE), defined both as non-fatal stroke, non-fatal myocardial infraction, and cardiovascular death and as non-fatal stroke, non-fatal myocardial infraction, and all-cause death; hospitalization for heart failure; thromboembolic disease to include vascular access thrombosis; serious gastrointestinal bleeding, and eye disorders (proliferative retinopathy). The regulatory goal is signal refinement in the post-marketing setting.

1.5. Effect Size of Interest or Estimated Sample Size Desired

This is a single arm prospective study to better characterize the safety of daprodustat. No sample size has been specified.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The study population should include adult patients (18 years of age or older) with anemia due to chronic kidney disease who undergo dialysis (including hemodialysis or peritoneal dialysis). The study population should also include patients previously treated with ESAs and patients naïve to ESAs.

2.2 Is ARIA sufficient to assess the intended population?

Yes. ARIA can be used to identify the population of interest. There exist billing codes for anemia in / due to chronic kidney disease. The ICD-10-CM code is D63.1. In addition, CPT codes in the range 90935-90999 are used to reimburse for dialysis services and procedures.

Moreover, there exist validated algorithms for identifying CKD and dialysis in claims data,[1,2,3] which can be implemented in ARIA.

3 EXPOSURES

3.1 Treatment Exposure

The treatment exposure of interest is daprodustat, which is administered orally. National Drug Codes available in ARIA can be used to ascertain prescriptions.

3.2 Comparator Exposures

Comparator exposures are not applicable. The review Division is interested in a prospective, single-arm, non-interventional study which will not contrast daprodustat against other ESAs.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. ARIA is deemed sufficient to capture exposure to daprodustat based on Healthcare Common Procedure Coding System (J codes) or National Drug Codes that are available in ARIA's administrative claims and electronic health records. ARIA tools generate longitudinal records of outpatient pharmacy dispensings, which permit construction of patient-specific episodes of treatment with daprodustat.

4 OUTCOME(S)

4.1 Outcomes of Interest

The primary outcomes of interest are myocardial infraction, stroke, all-cause death, hospitalization for heart failure, thromboembolic disease, vascular access thrombosis, major gastric bleeding, and eye disorders (proliferative retinopathy). A composite outcome to capture MACE is also of interest and is defined as non-fatal stroke, non-fatal myocardial infraction, or all-cause death. Defining MACE using cardiovascular death instead of all-cause mortality will also be implemented.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is not sufficient to assess the outcomes of interest.

ARIA is not sufficient to identify the outcome of eye disorders (proliferative retinopathy). This will require prospective collection of data from serial retinal exams to study. The need to

[1] Zou G, Liu H, Lin K, Zhu K, Hsieh TC. Trends and Outcomes of Hospitalized Influenza Patients With End-Stage Kidney Disease: Insights From the National Inpatient Sample 2010–2019. Cureus. 2022 Apr 25;14(4).
[2] Gibertoni D, Voci C, Iommi M, D'Ercole B, Mandreoli M, Santoro A, Mancini E. Developing and validating an algorithm to identify incident chronic dialysis patients using administrative data. BMC Medical Informatics and Decision Making. 2020 Dec;20(1):1-7.
[3] Clement FM, James MT, Chin R, Klarenbach SW, Manns BJ, Quinn RR, Ravani P, Tonelli M, Hemmelgarn BR. Validation of a case definition to define chronic dialysis using outpatient administrative data. BMC medical research methodology. 2011 Dec;11(1):1-6.

prospectively identify this outcome in a non-select real-world population is a key aspect to this post-market prospective clinical study. A prospective study is needed to fully characterize safety outcomes, in particular proliferative retinopathy. ARIA's retrospective design does not meet the requirements to prospectively evaluate the risks of interest.

For the outcomes of hospitalization for heart failure, myocardial infraction, stroke, VTE, and vascular access thrombosis, validated claims-based algorithms with high sensitivity and specificity exist. A subset of Sentinel Data Partners have access to all-cause-mortality and cardiovascular mortality necessary for the MACE endpoint. However, ARIA is not sufficient to identify any outcomes that are clinically manifested after more than 5 years, i.e., a period which is considered clinically and biologically relevant. The reason for the ARIA insufficiency is that in Sentinel Distributed Databases less than 25% of patients have continuous beyond 5 years;[4] the absolute sample size is expected to be even lower for patients on dialysis receiving daprodustat for the treatment of anemia due to chronic kidney disease. Since the long-term effects of daprodustat after 5 years are of interest for all outcomes, ARIA is not sufficient to assess the long-term safety of daprodustat on any outcome.

5 COVARIATES

5.1 Covariates of Interest

The following covariates are necessary to account for in the design and/or analyses stages:

a. Demographics: age, sex, race/ethnicity
b. Clinical: body mass index, dialysis type (i.e., hemodialysis or peritoneal dialysis) for the DD population, time since initiation of dialysis, ESA hyporesponsiveness, chronic kidney disease stage (for NDD patients), blood pressure levels
c. Comorbid conditions: coronary artery disease, heart failure, angina, atrial fibrillation, myocardial infraction, stroke, transient ischemic attack, cardiac arrest, hypertension, cancer, diabetes, thromboembolic event
d. Laboratory values: hemoglobin levels, ferritin, hematocrit, hepcidin, iron, hs-CRP, electrolytes (e.g., potassium), albumin, creatinine, lipid and cholesterol levels (to account for differences in cardiovascular risk)
e. Prior treatment history with ESAs including epoetin alfa, epoetin alfa-epbx, methoxy polyethylene glycol-epoetin beta, darbepoetin

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes, ARIA is sufficient to assess to assess covariates of interest. Sentinel data partners can capture demographic characteristics (e.g., age, sex, race/ethnicity), clinical information (e.g., past medical history, comorbidities), laboratory values (e.g., hemoglobin levels, hematocrit, creatinine, cardiovascular risk factors), and prior ESA use.

[4] See https://www.sentinelinitiative.org/about/key-database-statistics#length-of-member-enrollment-spans-in-the-sentinel-distributed-database

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

ARIA might address the objectives for post-market assessment by conducting analyses in patient cohorts defined by age, index treatment for anemia due to chronic kidney disease, and pre-index medical history. Applicable ARIA analytic tools permit descriptive (Level 1) and comparative (Level 2) analysis, as indicated below.

Level 1 (Descriptive) Analysis

- To determine exposure (number of exposed patients and patient-years at risk).
- To calculate (background) incidence rates for the outcomes of interest.

Level 2 (Comparative) Analysis

- Covariate Stratification – to calculate incidence rates for the outcomes of interest in patient cohorts defined by exposure and other covariates (e.g., age, sex, cardiovascular risk, prior ESA use).

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, ARIA's design and analytic tools are expected to be sufficient to assess the question of interest.

7 NEXT STEPS

DEPI-I has determined that the Sentinel ARIA system is **insufficient** to assess the risk of major adverse cardiovascular events, VTE, Heart Failure, serious GI bleeding, and eye disorders in dialysis-dependent patients receiving daprodustat for the treatment of anemia due to chronic kidney disease. DEPI recommends that DNH issues a PMR for conducting a prospective non-interventional study to further characterize and assess these risks. The following PMR language is suggested:

"Conduct a prospective observational study to characterize the long-term safety (at least 5 years follow up) of JESDUVROQ in adults with dialysis dependent chronic kidney disease treated with the approved dosing regimen of JESDUVROQ in the United States (US). Specific safety outcomes of interest include: the risk of major adverse cardiovascular events (MACE) defined as all-cause mortality, non-fatal myocardial infarction and non-fatal stroke; thrombotic vascular events to include vascular access thrombosis; hospitalization for heart failure; serious gastrointestinal bleeds and eye disorders (proliferative retinopathy). The study population should include adults previously treated with erythropoiesis-stimulating agents (ESAs) and adults naïve to ESAs. The effect of baseline and maximum achieved hemoglobin on the specified safety outcomes should be evaluated.."

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	January 31, 2023
Reviewer(s):	Kate Gelperin, MD, MPH Division of Epidemiology 1
Team Leader:	Fang Tian, PhD, MPH, MHS Division of Epidemiology 1
Associate Division Director:	Steven Bird, PhD, PharmD, MS Division of Epidemiology 1
OPE Director:	Judith Zander, MD Office of Pharmacovigilance and Epidemiology (OPE)
Sentinel Team Leader:	Sarah Dutcher, PhD Regulatory Science Staff
OSE Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology (OSE)
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name(s):	Daprodustat (JESDUVROQ)
Application Type/Number:	NDA 216951
Applicant/sponsor:	GlaxoSmithKline (GSK)
OSE RCM #:	TTT 2022-3072

A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Daprodustat (JESDUVROQ) is an oral hypoxia inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) that, when approved, will be indicated "for the treatment of anemia due to chronic kidney disease in adults on dialysis." The currently proposed labeling for JESDUVROQ as of January 18, 2023 includes a boxed warning stating "INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, and THROMBOSIS OF VASCULAR ACCESS."

The currently proposed labeling for JESDUVROQ as of January 18, 2023, also includes a Limitation of Use stating JESDUVROQ is "Not indicated for use:

- As a substitute for red blood cell transfusions in patients who require immediate correction of anemia.

(b) (4)

The currently proposed labeling for JESDUVROQ as of January 18, 2023, states in HIGHLIGHTS OF PRESCRIBING INFORMATION, USE IN SPECIFIC POPULATIONS:

- "Pregnancy: May cause fetal harm (8.1)"

Daprodustat is a new molecular entity (NME) and will be the first of this class to be approved in the US. Two prior HIF-PHI NDAs were issued Complete Response (CR) by FDA (roxadustat (b) (4) and vadadustat (b) (4) due to thrombosis and thromboembolic risk above standard of care (ESAs), and other safety issues including liver injury with vadadustat. HIF-PHIs have been approved in Japan (roxadustat, daprodustat) and EU (roxadustat).

1.2. Describe the Safety Concern

The mechanism of action of daprodustat and findings from animal studies suggest the potential for maternal and fetal toxicity from exposure to daprodustat. Nine pregnancies occurred in patients exposed to daprodustat identified in clinical trials. The outcomes for these pregnancies suggest an elevated risk of spontaneous abortions (SAB). Pregnancy outcomes included: seven SAB at ages 6-19 weeks gestation (including both fetuses of one twin pregnancy); two elective abortions; and one normal live birth. These nine exposed pregnancies were reviewed by DPMH[1] as follows: "Though obviously a small sample size, these findings suggest an elevated risk of SAB which does align with the findings seen in animal studies and is consistent with the division's concerns regarding the

[1] DPMH Review; Liedtka, J. Pregnancy and Lactation Labeling NDA 216951; DARRTS REF ID# 5086969.

mechanism of action of daprodustat as having the potential to cause fetal harm. There are confounders, however, such as the fact that 3 of the women had a personal history of SAB, that the

underlying disease of CKD can predispose to SAB, and that 5 of the women were 35 or older at the time of pregnancy, another risk factor for SAB." DPMH concluded that the available data for daprodustat use in pregnant women are "insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes." DPMH further concluded that "Pregnancy would be expected to be uncommon in women on dialysis (the indicated population) and a traditional pregnancy registry or a claims database study would likely be unsuccessful due to low enrollment. Therefore, DPMH recommends a postmarketing requirement (PMR) Descriptive Pregnancy Safety Study to follow-up on maternal and infant outcomes of pregnancies that do occur. Additionally, DPMH recommends that the applicant submit annual reports of daprodustat utilization rates amongst females of reproductive potential (females aged 15 to 50 years) calculated cumulatively from the time of initial approval. If there appears to be substantial use of daprodustat in females of reproductive potential, then this would be considered new safety information that would trigger FDAAA and would result in the Agency issuing a PMR for pregnancy registry study at that time."

Pregnancy among women with end stage kidney disease (ESKD) on dialysis in the United States was reported to be uncommon in a recent retrospective cohort study using data from the United States Renal Data System with Medicare as primary payer (Shah 2019).[2] Pregnancy rate was 17.8 per thousand person years (PTPY) with the highest rate in women aged 20–24 (40.9 PTPY). Overall, 2352 pregnancies were identified in 2008 women. The percentages of fetal outcomes were as follows: live birth (27.1%, n=637), stillbirth (2.6%, n=60), spontaneous abortion (29.4%, n=691), therapeutic abortion (7.6%, n=178), ectopic/trophoblastic pregnancies (2.7%, n=63), and unknown outcome (31.0%, n=730).

Reviewer Comment: DEPI concurs with DPMH that pregnancy in women with ESKD on dialysis is uncommon and a traditional pregnancy registry or claims database study are unlikely to be feasible in this population. However, the potential for off-label use in females of reproductive potential not on dialysis may be a concern and would represent new safety information if this is identified.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

[2] Shah S, Christianson AL, Meganathan K, Leonard AC, Schauer DP, Thakar CV. Racial Differences and Factors Associated with Pregnancy in ESKD Patients on Dialysis in the United States. J Am Soc Nephrol. 2019 Dec;30(12):2437-2448. doi: 10.1681/ASN.2019030234. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6900804/

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☒ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☐ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Descriptive pregnancy safety study, which enrolls exposed pregnancies from worldwide sources into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including infant outcomes through at least the first year of life. The study is not expected to have sufficient sample size to support inferential analyses. A single-arm pregnancy safety study is appropriate because use of this drug among pregnant women is expected to be uncommon.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: The PMR specifies worldwide safety data collection, however the ARIA study population is limited to United States only.

Outcomes: 1) ARIA lacks capacity to identify spontaneous abortion with sufficient sensitivity. Because the management of spontaneous abortions and terminations can occur exclusively in an outpatient setting, claims-based algorithms may under ascertain these outcomes.[3] 2) ARIA lacks access to detailed narratives. The study being considered for broad-based surveillance is descriptive without comparison group(s). Thus, detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and assess causality.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy study being considered would collect detailed narratives with information on potential covariates, such as lifestyle factors (drugs of abuse or alcohol), prenatal supplement use (folic acid).

Analytic tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

2.5. Please include the proposed PMR language in the approval letter.

"Conduct a worldwide descriptive study to collect prospective and retrospective data on women exposed to daprodustat during pregnancy to assess the risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol."

[3] Zhu Y, Bateman BT, Hernandez-Diaz S, et al. Validation of claims-based algorithms to identify non-live birth outcomes. Pharmacoepidemiol Drug Saf. 2022 Nov 24. PMID: 36420643.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 23, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216951
Product Name and Strength:	Jesduvroq (daprodustat) tablets, 1 mg, 2 mg, 4 mg, 6 mg and 8 mg
Applicant/Sponsor Name:	GlaxoSmithKline Intellectual Property (No. 2) Limited England (GSK)
OSE RCM #:	2022-1899-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

GlaxoSmithKline Intellectual Property (No. 2) Limited England (GSK) submitted revised 30 count container labels [redacted] (b) (4) on January 23, 2023 for Jesduvroq (daprodustat) tablets under NDA 216951. We reviewed the revised 30 count container labels [redacted] (b) (4) for Jesduvroq (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a], and via email on January 18, 2023 and January 20, 2023.

2 CONCLUSION

GSK implemented all of our recommendations and we have no additional recommendations at this time. [redacted] (b) (4)

[a] Kane, D. Label and Labeling Review for Jesduvroq (NDA 216951). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 JAN 05. RCM No.: 2022-1899.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 5, 2023
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH)
Application Type and Number:	NDA 216951
Product Name, Dosage Form, and Strength:	Jesduvroq (daprodustat) tablets, 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKline Intellectual Property (No. 2) Limited England (GSK)
FDA Received Date:	February 1, 2022 and June 15, 2022
TTT ID #:	2022-1899
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

GlaxoSmithKline Intellectual Property (No. 2) Limited England (GSK) submitted NDA 216951 Jesduvroq (daprodustat) tablets on February 1, 2022. Jesduvroq is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI) proposed for the treatment of anemia due to chronic kidney disease in adults on dialysis and not on dialysis. We evaluated the proposed Jesduvroq prescribing information, medication guide, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

GlaxoSmithKline Intellectual Property (No. 2) Limited England (GSK) submitted a 505(b)(1) application to obtain marketing approval of Jesduvroq (daprodustat) tables. (b) (4)

(b) (4)

We performed a risk assessment of the proposed prescribing information (PI), medication guide, and container labels for Jesduvroq to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI, medication guide, and container labels for Jesduvroq identified areas of vulnerability that may lead to medication errors. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Jesduvroq prescribing information (PI), medication guide, 30 count container labels, (b) (4) identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to GlaxoSmithKline Intellectual Property (No. 2) Limited England so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We recommend referring the practitioner to the full prescribing information for the dosage as it is dependent on several factors and thus not included in this section. We recommend revising the first sentence to read "See Full Prescribing Information for starting dosage based on patient dialysis status and hemoglobin level.".

b. We note the Highlights of Dosage and Administration lacks the route of administration. We recommend adding a second bullet to the Highlights of Dosage and Administration that states "Take JESDUVROQ orally once daily with or without food".

B. Prescribing Information

1. Section 2: Dosage and Administration

a. We note Jesduvroq is to be swallowed whole. We recommend including this information as part of Section 2.2 Initial Dose of Jesduvroq. We recommend including the statement "Swallow tablets whole. Do not cut, crush, or chew the tablet." to the end of the second paragraph of information.

b. As currently presented Table 4 includes the abbreviations for the routes of administration for the Erythropoiesis-Stimulating Agents. We recommend spelling out the routes of administration and removing the use of the abbreviations. In addition, information on the conversion from

the subcutaneous route of Epoetin alfa should also be included as currently presented it is missing.

c. As currently presented, Table 5 includes the row headers "Dose of Jesduvroq (once daily)". We recommend revising the row headers to read "Once daily dose of JESDUVROQ".

2. Section 3: Dosage Forms and Strengths

a. As currently presented, the Jesduvroq dosage form is not presented at the beginning of Section 3 Dosage Forms and Strengths. We recommend including the dosage at the beginning of Section 3 Dosage Forms and Strengths. Add "Tablets:" to the beginning of Section 3.

3. Section 16: How Supplied/Storage and Handling

a. As currently presented, all of the information presented in Section 16 How Supplied/Storage and Handling is presented without the use of subheadings. We recommend including subheadings in Section 16 in order to increase the readability of Section 16. We recommend including one subheading for "How Supplied" and a second subheading for "Storage and Handling".

b. We note there are 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablet strengths proposed for Jesduvroq. Additionally, we note the proposed PI presents each of the tablet descriptions and configurations in paragraph format. We recommend presenting the tablet descriptions and package configurations in a table in order to increase readability of the important information. We recommend including the table below in Section 16:

Tablet Strength	Package Configuration and NDC Number	Tablet Description and Markings
1 mg	30 count bottle (NDC 0173-0897-13) (b) (4)	Round, gray, biconvex, film-coated tablets debossed with "GS KF" on one side
2 mg	30 count bottle (NDC 0173-0903-13) (b) (4)	Round, yellow, biconvex, film-coated tablets debossed with "GS V7" on one side
4 mg	30 count bottle (NDC 0173-0906-13) (b) (4)	Round, white, biconvex, film-coated tablets

		debossed with “GS 13” on one side
6 mg	30 count bottle (NDC 0173-0911-13) (b) (4)	Round, pink, biconvex, film-coated tablets debossed with “GS IM” on one side
8 mg	30 count bottle (NDC 0173-0914-13) (b) (4)	Round, orange, biconvex, film-coated tablets debossed with “GS 5E” on one side

C. Medication Guide

1. We note the Jesduvroq tablets are to be swallowed whole. We recommend adding the statement “Do not cut, crush or chew the tablet.” to the end of the fourth bullet under “How Should I take Jesduvroq”.

4.2 RECOMMENDATIONS FOR GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO. 2) LIMITED ENGLAND

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. As currently presented, the dosage form on the proposed container labels is included after the established name in parentheses. We recommend including the dosage form inside of the parentheses in order to align with the presentation used in the Prescribing Information.
2. We note the (b) (4) font color for the proprietary name is similar to the (b) (4) font color used to highlight the 4 mg strength. The use of the same colors for the font of the proprietary name and to highlight one of the strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors. We recommend revising the font color of the proprietary name or the color box on the 4 mg strength so they do not overlap with any of the colors utilized.
3. As currently presented, the proposed container labels state “See prescribing information for dosage information. Warning: See full prescribing information for complete boxed warning.”. We recommend revising these statements as they are redundant and replacing with “Recommended Dosage: See Prescribing Information.”.

4. We note Jesduvroq is to be dispensed with a Medication Guide. Additionally, we note the proposed container labels do not contain a statement regarding dispensing Jesduvroq with the Medication Guide. We recommend including the statement "Dispense the enclosed Medication Guide to each patient" or a similar statement in accordance with 21 CFR 208.24(d) on each of the container labels.
5. As currently presented, the proposed container labels contain the statement [redacted] (b) (4) We recommend removing this statement from the container labels as for oral products this statement is not necessary.
6. The Rx Only statement appears prominent on the principal display panel. We recommend decreasing the prominence by debolding the Rx Only statement.
7. We note the storage information for Jesduvroq has been revised in the PI. Revise the storage information on the proposed container labels to align with the storage information presented in the PI.
8. We recommend including the statement "Swallow tablets whole. Do not cut, crush or chew the tablet" on the principal display panel to mitigate product administration errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jesduvroq received on February 1, 2022 from GlaxoSmithKline Intellectual Property (No. 2) Limited England.

Table 2. Relevant Product Information for Jesduvroq	
Initial Approval Date	N/A
Active Ingredient	daprodustat
Indication	Jesduvroq is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI), is indicated for the treatment of anemia due to chronic kidney disease in adults on dialysis and not on dialysis.
Route of Administration	Oral
Dosage Form	tablets
Strength	1 mg, 2 mg, 4 mg, 6 mg, and 8 mg
Dose and Frequency	The starting dose of JESDUVROQ is based on the patient's dialysis status and hemoglobin level. For those switching from an erythropoiesis stimulating agent (ESA) to JESDUVROQ, the dose is based on their existing ESA dose.
How Supplied	• JESDUVROQ tablets, 1 mg, are round, gray, biconvex, film-coated tablets debossed with "GS KF" on one face, packaged in bottles of 30 (NDC 0173-0897-13) (b) (4) . • JESDUVROQ tablets, 2 mg, are round, yellow, biconvex, film-coated tablets debossed with "GS V7" on one face, packaged in bottles of 30 (NDC 0173-0903-13) (b) (4) • JESDUVROQ tablets, 4 mg, are round, white, biconvex, film-coated tablets debossed with "GS 13" on one face, packaged in bottles of 30 (NDC 0173-0906-13) (b) (4) • JESDUVROQ tablets, 6 mg, are round, pink, biconvex, film-coated tablets debossed with "GS IM" on one face, packaged in bottles of 30 (NDC 0173-0911-13) (b) (4) • JESDUVROQ tablets, 8 mg, are round, orange, biconvex, film-coated tablets debossed with "GS 5E" on one face, packaged in bottles of 30 (NDC 0173-0914-13) (b) (4)
Storage	Store below 30°C (86°F).

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Jesduvroq labels and labeling submitted by GlaxoSmithKline Intellectual Property (No. 2) Limited England.

- 30 Count Container label received on February 1, 2022 and June 15, 2022

(b) (4)

- Prescribing Information and Medication Guide (Image not shown) received on February 1, 2022, available from \\CDSESUB1\evsprod\nda216951\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf

G.2Label and Labeling Images

(b) (4)

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 5, 2023

To: Caden Brennen, MS, Regulatory Project Manager
Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling
(DNH)

From: Melissa Khashei, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader
(OPDP)

Subject: OPDP Labeling Comments for JESDUVROQ (daprodustat tablets), for oral use

NDA: 216951

Background:
In response to DNH's consult request dated February 3, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), and carton and container labeling for the original NDA submission for JESDUVROQ (daprodustat tablets), for oral use.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 22, 2022 and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on January 2, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on February 2, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or Melissa.Khashei@fda.hhs.gov.

49 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MELISSA KHASHEI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 30, 2022
To:	Caden Brennen, MS Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Melissa Khashei, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide
Drug Name (established name):	JESDUVROQ (daprodustat)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216951
Applicant:	GlaxoSmithKline Intellectual Property (No. 2) Limited England C/O GlaxoSmithKline

1 INTRODUCTION

On February 1, 2022, GlaxoSmithKline Intellectual Property (No. 2) Limited England C/O GlaxoSmithKline submitted for the Agency's review an original New Drug Application (NDA) 216951 for JESDUVROQ (daprodustat) tablets. The proposed indication is for the treatment of anemia due to chronic kidney disease in adults patients on dialysis and not on dialysis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Non-Malignant Hematology (DNH) on February 3, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for JESDUVROQ (daprodustat) tablets.

2 MATERIAL REVIEWED

- Draft JESDUVROQ (daprodustat) tablets MG received on February 1, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 22, 2022.
- Draft JESDUVROQ (daprodustat) tablets Prescribing Information (PI) received on February 1, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 22, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MELISSA KHASHEI
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BARBARA A FULLER
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 9, 2022

TO: Ann T. Farrell, Ph.D.
Director
Division of Non-Malignant Hematology
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Routine inspection of clinical sites supporting clinical PK Study 213022 (NDA 216951).

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged the inspection of study 213022 (NDA 216951) conducted at Altasciences Clinical Kansas, Inc. and PPD Development, L.P.

At Altasciences Clinical Kansas, Inc, a Form FDA 483 was not issued at the close-out of the inspection. However, there was verbal discussion with site's management regarding the maintenance of blinding codes onsite. The discussion item did not impact the reliability of the data from the audited study.

At PPD Development, L.P., no objectionable conditions were observed, and a Form FDA 483 was not issued at its inspection close-out.

After reviewing the inspectional findings, I conclude that the data for study 213022 from both clinical sites are reliable.

2. Inspected Study:

NDA 216951
Study Number: 213022
Study Title: "A Two-Part, Randomized, Double-Blind, Single-Dose, Crossover Study to Compare Daprodustat Formulations Produced by Two Methods of Manufacture for Bioequivalence and Dissolution in Healthy Adult Volunteers"
Dates of conduct: 12/18/2020 (initiation) – 5/18/2021 (completion)

Site A:
Altasciences Clinical Kansas, Inc.
10330 Old Olive Street Rd (physical address)
10103 Metcalf Avenue (mailing address)
Overland Park, KS 66212
Investigator: Martin K. Kankam, MD, PhD, MPH, FAPCR

Site B:
PPD Development, L.P.
8285 West Arby Avenue, Suite 331
Las Vegas, NV 89113
Investigator: Darin B. Brimhall, DO, FACP

3. Inspectional Findings

Altasciences Clinical Kansas, Inc., Overland Park, KS

ORA investigator Carmen Y. Fisher inspected Altasciences Clinical Kansas, Inc., Overland Park, KS from October 7-12, 2022.

The previous OSIS inspection of Altasciences Clinical Kansas, Inc. was conducted from June 3-7, 2019. At the conclusion of the inspection, Form FDA 483 was not issued. The final inspection classification was NAI.

The current inspection included auditing the following items:

-Electronic case report forms (eCRFs) & paper source records
-Informed consent process
-Protocol adherence and deviations
-Institutional review board approvals & monitoring reports
-Site staff responsibility & training logs
-Test article accountability and storage
-Randomization schedule & blinding codes
-Reserve samples
-Adverse events

At the conclusion of the inspection, investigator Carmen Y. Fisher did not issue Form FDA 483 to the clinical site. However, the investigator had verbal discussion with management regarding the site not maintaining the blinding codes for the 8 mg dose investigational drug products (IPs) onsite.

The discussion item, the firm's response (during the inspection) which was documented in the EIR's Exhibit 5 (provided as Attachment 1), and my evaluation are presented below.

Discussion Item 1:
Upon the ORA investigator's request for review, the firm was unable to locate the blinding codes for the 8 mg dose IPs at the Altasciences Clinical facility in Kansas.

Firm's Response:
During the inspection, the firm provided explanation regarding the absence of the blinding codes at the site. According to the site's management, Altasciences was originally contracted to perform the clinical study for the 4 mg dosage IP only. Thus, they received the blinding codes for the 4 mg IP only, which was maintained onsite. Altasciences was later onboarded to also perform the study for the 8 mg dosage IP. The 8 mg IP was shipped to the Altasciences Clinical facility in Kansas, but the blinding codes for these IPs were not provided to the Altasciences facility. The site stated after their investigation it was determined that the blinding codes for the 8 mg dosage IPs were located and available at PPD Development, LP (Austin, TX), which was the clinical site originally contracted to conduct the clinical study for the 8 mg IP formulation.

OSIS Evaluation:
The blinding codes are expected to be maintained onsite during study conduct because, in the event of serious adverse events, breaking the blind for a subject may be deemed necessary for a subject's care. In this case, the site failed to maintain the blinding codes for the 8 mg dosage IP.

The blinding in this study protocol was for different manufacturing processes (twin screw granulation vs. high shear wet granulation) of the same IP formulation manufactured at two different manufacturing facilities. The lack of availability of the blinding codes onsite for the 8 mg formulation does not impact on subject safety because the IPs tested in the audited BE study have the same formulation and same dosage (8 mg) within the cohort. In addition, I reviewed the Safety Data Source Tables within the clinical study report and confirmed for 8 mg dosage study cohort that there were no severe, treatment-

emergent adverse events that would require the site's staff to break the blinds for the study.

Per the study protocol, the site pharmacist who is dispensing the drug is unblinded to the manufacturing process of the 8 mg IPs used in the study. EIR states that ORA investigator verified the randomization schedule maintained on-site and the blinding information regarding the identity of the drug treatments (i.e., IP with Process 1 or Process 2).

Therefore, I conclude that the discussion item does not impact the subject safety nor data reliability.

PPD Development, L.P., Las Vegas, NV

ORA investigator Rebecca Teves Davis inspected PPD Development, L.P., Las Vegas, NV from October 4-7, 2022.

This was the first OSIS inspection of PPD Development, L.P. under the BA/BE program.

The current inspection included auditing the following items:

-Electronic case report forms (eCRFs) & source documentation
-Informed consent forms
-Institutional review board approvals
-Protocol compliance
-Concomitant medications
-Test article accountability and storage
-Randomization schedule
-Subject eligibility determination
-Adverse event reporting
-Applicable standard operating procedures (SOPs)
-Correspondence between sponsor and investigator

At the conclusion of the inspection, investigator Rebecca Teves Davis did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Draft: MCD 12/5/2022, 12/6/2022, 12/7/2022, 12/9/2022
Edit: HI 12/5/2022, 12/7/2022; JC 12/6/2022, 12/7/2022, 12/9/2022

OSIS File #: BE 9475

eNSpect Assignment ID: 199566
eNSpect OpID: 225339 (Altasciences Clinical Kansas, Inc)
225340 (PPD Development, L.P.)

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: 12/1/22 **Date Consulted:** 3/2/22

From: Jane Liedtka, M.D., Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Caden Brennen, Regulatory Project Manager (RPM)
Division of Non-Malignant Hematology (DNH)

Drug: Daprodustat

NDA: 216951

Indication: For the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis and not on dialysis

Applicant: GlaxoSmithKline (GSK) Intellectual Property (No. 2) Limited England

Subject: Pregnancy and Lactation Labeling [Original New Drug Application (NDA), New Medical Entity (NME)]

Materials Reviewed:

- Applicant's submission dated 2/1/22
- DPMH review of Epogen/Procrit (epoetin alfa), BLA 103234. Tamara Johnson, MD, MS. 5/26/17. Darrts Reference ID # 4104111.[1]

[1] DPMH review of Epogen/Procrit, BLA 103234. Tamara Johnson, MD, MS. 5/26/17. Darrts Reference ID # 4104111.

Consult Question: Please review the pregnancy and lactation information submitted and provide advice on labeling text for sections 8.1-8.3.

INTRODUCTION AND BACKGROUND

- On 2/1/22, GSK submitted original NDA 216951for daprodustat to DNH for the indication of the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis and not on dialysis.
- On 3/2/22, DNH consulted DPMH to assist with the proposed labeling language for Section 8 for NDA 216951.
- Daprodustat, an NME, belongs to a new class of agents known as hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs). Daprodustat received approval in Japan on 6/29/20 for the same indication. (b) (4)
- The starting dose of daprodustat is based on the patient's dialysis status and hemoglobin level. For those switching from an erythropoiesis stimulating agent (ESA) to daprodustat, the dose is based on their existing ESA dose.

Table 1: Drug Characteristics[2]

	DAPRODUSTAT
Mechanism of Action	Daprodustat is a reversible inhibitor of HIF-prolyl-4-hydroxylases (PHD)1, PHD2 and PHD3. This activity results in the stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes, including erythropoietin and transferrin.
Half-life	The terminal elimination half-life of daprodustat is approximately 1-4 hours.
Molecular weight	The molecular mass of daprodustat is approximately 393 Daltons.
Protein-binding	In vitro, plasma protein binding of daprodustat is >99%.
Bioavailability	The absolute bioavailability of daprodustat is 65%.
Adverse Reactions	Most common adverse reactions (incidence ≥5%) are hypertension, thrombotic vascular events, peripheral edema, constipation, abdominal pain, and hypersensitivity reactions.

Source: Reviewer's Table

Current Labeling for Products with Similar Indications

There have been two previously proposed oral HIF-PHIs submitted to DNH for the indication of the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis and not on dialysis, roxadustat (b) (4) and vadadustat (b) (4) In both cases, it was determined that the benefits did not outweigh the risks for the treatment of anemia of chronic kidney disease due to concerns regarding adjudicated major adverse cardiac events (MACE) and adjudicated thromboembolic (TE) events. Labeling negotiations were not conducted for these products.

There are currently two products [in a different class, erythropoiesis-stimulating agents (ESA)] approved for the same indication as that proposed for daprodustat, that of "treatment

[2] Proposed labeling for daprodustat confirmed by Divisional Team.

of anemia due to CKD on dialysis and not on dialysis", epoetin alfa and darbepoetin. As a class, the ESA's carry a Boxed Warning for increased "risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence". See Attachment A for relevant excerpts from the currently approved labeling for Procrit (epoetin alfa) injection[3] and Aranesp (darbepoetin alfa) injection[4] for Section 8.

Reviewer's Comments

Discussions with the divisional team revealed that HIF-PHIs as a class share the spectrum of adverse events seen with the ESA's and if daprodustat is approved it is likely to have a similar boxed warning to that seen with the approved ESAs. This will need to be considered when assessing the risk benefit analysis for use of these products in pregnant or lactating women.

Pregnancy and Anemia and Chronic Kidney Disease

Anemia in pregnancy is most commonly due to iron deficiency or acute blood loss during the peripartum period.[5] Adverse pregnancy outcomes related to iron-deficiency have included low birthweight and preterm delivery.[6] The American Congress of Obstetricians and Gynecologists (ACOG) practice guidelines recommend screening all pregnant women for iron deficiency and those identified with the condition to receive iron supplementation. For acute blood loss peripartum, transfusion is recommended, especially because "Severe anemia with maternal Hgb levels less than 6 g/dL has been associated with abnormal fetal oxygenation resulting in non-reassuring fetal heart rate patterns, reduced amniotic fluid volume, fetal cerebral vasodilatation, and fetal death."[1]

In chronic kidney disease, anemia is further associated with adverse pregnancy and fetal outcomes including hypertension, pre-eclampsia, premature birth, low-birth weight, polyhydramnios, and intrauterine growth restriction.[7,8] In a retrospectuive cohort study published in 2019[9], 48,000 women on dialysis between 2005 and 2013 were analyzed and showed that 18 of every 1,000 women became pregnant while on dialysis. However, fewer than 30% of women who became pregnant during the study had a live born infant. The rate of miscarriage was ≈ 29% and there were a high percentage (30%) of unknown outcomes.

[3] Procrit Label from July 2018.
[4] Aranesp Label from 2019.
[5] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 95: Anemia in pregnancy. Obstet Gynecol. 2008 Jul;112(1):201–7. [Reaffirmed 2015]
[6] Rogers VL, Worley KC. Obstetrics & Obstetric Disorders. In: Papadakis MA, McPhee SJ, Rabow MW. eds. Current Medical Diagnosis & Treatment 2017 New York, NY: McGraw-Hill.
[7] Renal and Urinary Tract Disorders. In: Cunningham F, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. eds. Williams Obstetrics, Twenty-Fourth Edition New York, NY: McGraw-Hill; 2013.
[8] Anantharaman P, Schmidt RJ, Holley JL. Chapter 55. Pregnancy & Renal Disease. In: Lerma EV, Berns JS, Nissenson AR. eds. CURRENT Diagnosis & Treatment: Nephrology & Hypertension New York, NY: McGraw-Hill; 2009.
[9] Shah S et al. Racial Differences and Factors Associated with Pregnancy in ESKD Patients on Dialysis in the United States. J of the American Society of Nephrology. 2019; 30: 2437–2448.

REVIEW

Pregnancy

Nonclinical Experience

Daprodustat was orally administered to pregnant rats at 0.5, 7, or 60 mg/kg/day from gestation day 6 to gestation day 17 during the period of organogenesis. No adverse effects were observed at doses less than or equal to 7 mg/kg/day (3 times the MRHD based on body surface area). Daprodustat administration resulted in post-implantation loss, increased embryofetal death, and reduction in skeletal ossification in rats at a dose of 60 mg/kg/day (24 times the MRHD based on body surface area), which was associated with maternal toxicity (reduced body weight gain or weight loss). Maternal toxicity occurred at doses associated with daprodustat-related polycythemia in non-pregnant rats. Daprodustat was orally administered to pregnant rabbits at doses of 4, 30, or 60 mg/kg/day from gestation day 7 until gestation day 19 during the period of organogenesis. No adverse effects were observed at doses less than or equal to 30 mg/kg/day (24 times the MRHD based on body surface area). Daprodustat administration was associated with low incidence of abortions and fetal skeletal malformations (irregularly shaped anterior fontanelle, manubrium, fused sternal centra, and microphthalmia) at a dose of 60 mg/kg/day (49 times the MRHD based on body surface area) in the presence of maternal toxicity.

In a pre- and postnatal development study, pregnant rats were dosed orally with daprodustat from implantation until weaning (gestation day 6 to lactation day 21) at 0.8, 7, or 40 mg/kg/day concomitantly along with 3 major human metabolites of daprodustat. No adverse effects were observed at doses less than or equal to 7 mg/kg/day (3 times the MRHD based on body surface area). Maternal toxicity was noted at 40 mg/kg/day, which represents 16-times the MRHD based on body surface area, which was associated with dystocia and increased pup deaths and decreased pup weights.

Applicant's Review of Literature

Since daprodustat is an NME, no review of the literature was requested from the applicant.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed on 7/11/22 using the search terms "daprodustat AND pregnancy," "daprodustat and pregnancy and birth defects," "daprodustat and pregnancy and congenital malformations," "daprodustat and pregnancy and stillbirth," "daprodustat and spontaneous abortion" daprodustat AND teratogenicity" and "daprodustat and pregnancy and miscarriage." No reports of adequate and well-controlled studies of daprodustat use in pregnant women were identified. No case reports for daprodustat exposure during pregnancy were identified.

No entry for daprodustat was found in Micromedex[10] or in Briggs and Freeman's *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* [11].

[10] https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed July 8, 2021

[11] Briggs GG and Freeman RK. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.

GSK Pharmacovigilance Database (PVDB)

There were 9 pregnancies exposed to daprodustat identified in the clinical trials, details on these pregnancies are summarized in Table 2 below. The outcomes for these 9 pregnancies were as follows

- 7 spontaneous abortions (SABs) at ages 6-19 weeks gestation (including both fetuses of one twin pregnancy)
- 2 elective abortions
- One normal live birth

Reviewer's Comments

Though obviously a small sample size, these findings suggest an elevated risk of spontaneous abortion (SAB) which does align with the findings seen in animal studies and is consistent with the division's concerns regarding the mechanism of action of daprodustat as having the potential to cause fetal harm. There are confounders, however, such as the fact that 3 of the women had a personal history of SAB, that the underlying disease of CKD can predispose to SAB, and that 5 of the women were 35 or older at the time of pregnancy, another risk factor for SAB.

Table 2: Pregnancies Reported in the Daprodustat Development Program

Participant ID/ Study	Country	Maternal Age (years)	Relevant Medical/ Pregnancy History	Relevant Concomitant Meds	Perinatal complications	Treatment/ Dose/ Frequency	Timing of drug exposure[1] in relation to the gestational age[2]	Pregnancy Outcome	Adverse infant outcomes observed
1) (b) (6) 113747	Russia	37	Pregnancy: 2 prior full term normal births	Medications: 2 phytotherapeutics: -Canephron (herbals) -Ursolean (herbals)	No reported pregnancy complications	Erythropoietin/ 30 ug/ Every 4 weeks	140 days after the first dose and 63 days after the most recent dose of erythropoietin, the participant underwent an elective abortion (gestational age at the time of elective abortion: approximately 9 weeks).	Elective abortion	None reported
2) (b) (6) 204837	US	42	Medical: Hemodialysis (HD) Pregnancy: 6 past pregnancies: 1 live birth, full-term infant, 1 stillbirth, and 4 miscarriages (most recent at 27 weeks)	Medications: hydralazine	No reported pregnancy complications	Epoetin alfa/ 5000 units/ Weekly	2 months 7 days after the first dose and 38 days after the most recent dose, the participant experienced an event of spontaneous abortion (gestational age at the time of spontaneous abortion: 13 weeks).	Spontaneous abortion	Congenital anomaly was present (additional details not provided)
3) (b) (6) 200807	Brazil	32	Medical: On HD Pregnancy: 2 prior miscarriages, one complicated by pre-eclampsia in 2013	Contraception: Oral contraceptive Medications: Diazepam	Twin pregnancy	Epoetin alfa/ 10000 U/ Weekly	1 year and or 49 days after the first dose and 98 days after the most recent dose, the participant experienced an event of spontaneous abortion (gestational age at the time of spontaneous abortion: 19[3] weeks).	Spontaneous abortion of both fetuses	None reported

Participant ID/ Study	Country	Maternal Age (years)	Relevant Medical/ Pregnancy History	Relevant Concomitant Meds	Perinatal complications	Treatment/ Dose/ Frequency	Timing of drug exposure[1] in relation to the gestational age[2]	Pregnancy Outcome	Adverse infant outcomes observed
4) (b) (6) 200807	Argentina	35	Medical: On HD for 12 years Pregnancy: No prior abortions	Contraception: drospirenone/ ethinylestradiol (non- compliant)	Intermittent metrorrhagia from the beginning of pregnancy	Daprodustat/ 2 mg QD	284 days after the first dose and 22 days after the most recent dose of daprodustat the participant experienced an event of spontaneous abortion (approximate gestational age at the time of spontaneous abortion:8 weeks).	Spontaneous abortion	None reported
5) (b) (6) 200807	US	31	Medical: On HD, History of DVT Pregnancy: 1-Full term pregnancy (normal birth)	Contraception: oral contraceptive pills (non-compliant) Medications: -warfarin -enoxaparin -gentamicin -Buproprion	HCG was abnormal on initial and additional testing. Subsequent US did not reveal a viable fetus. Anemia	Daprodustat/ 4 mg/ QD	1 year and 32 days after the first dose of daprodustat and 19 days since last dose the participant experienced an event of spontaneous abortion (gestational age at the time of spontaneous abortion: 10 gestational weeks). 8 days later participant presented with heavy vaginal bleeding from missed miscarriage. Hgb nadir of 4.9. Transfused 3 units PRBCs. Required D&C and surgical intervention for hemostasis.	Spontaneous abortion	None reported
6) (b) (6) 200807	South Africa	29	Medical: On HD Chronic glomerulonephritis, status post kidney transplant with chronic allograft rejection Recurrent UTIs of graft, Pregnancy: Spontaneous abortion	Contraception: medroxyprogesterone acetate (intra-muscular) Medications: enalapril, mycophenolate mofetil, allopurinol.	No reported pregnancy complications	Daprodustat/ 4 mg/ QD	3 months and 15 days after the first dose and 24 days after the most recent dose of daprodustat, the participant experienced an event of spontaneous abortion (gestational age at the time of spontaneous abortion: 12 weeks).	Spontaneous abortion	None reported

Participant ID/ Study	Country	Maternal Age (years)	Relevant Medical/ Pregnancy History	Relevant Concomitant Meds	Perinatal complications	Treatment/ Dose/ Frequency	Timing of drug exposure[1] in relation to the gestational age[2]	Pregnancy Outcome	Adverse infant outcomes observed
7) (b) (6) 200808	Ukraine	42	Medical: No relevant medical history. Pregnancy: 1 normal birth	Contraception: abstinence Medications: enalapril	No reported pregnancy complications	Daprodustat/ 2 mg/ QD	Unknown Date of LMP: (b) (6) participant had 1st dose (b) (6) and last dose (b) (6) Maximum gestational exposure 12 weeks[4]	Elective abortion	None reported
8) (b) (6) 213022	US	35	Pregnancy: 2 prior full term normal births	Contraception: none	No reported pregnancy complications	Daprodustat/ 2 mg/ QD	The participant's LMP was on (b) (6). Negative pregnancy test on (b) (6). Positive pregnancy test on (b) (6). Study treatment was already completed when the pregnancy was discovered.	Normal birth	None reported[5]
9) (b) (6) 213022	US	26	None	Contraception: condoms with spermicide (non-compliant)	No reported pregnancy complications	Daprodustat/ 4 mg/ QD Single dose - daprodustat 4 mg (b) (6) Withdrawn from the study [physician decision] on (b) (6) due to pregnancy and did not receive daprodustat in Period 2	20 days after the first dose and last dose of daprodustat, the participant experienced an event of spontaneous abortion (gestational age approximately 6 weeks).	Spontaneous abortion	None reported

Source:
GSK Safety database
Narratives: m5.3.5.1 Study PHI113747 CSR Section 11, Study 204837 CSR Section 14, Study 200807 CSR Section 15.3, Study 200808 CSR Section 15.3, m5.3.1.2 Study 213022
CSR Section 17
Participant Exposure (Treatment, Dose Frequency): m5.3.5.1 Study PHI113747 CSR Listing 8.02, Study 204837 CSR Listing 1.012, Study 200808 CSR Listing 1.011, Study 200807 CSR Listing 1.011, m5.3.1.2 Study 213022 CSR Listing 1.23

Abbreviations: CKD=chronic kidney disease; CRF=case report form; D&C=dilatation and curettage; DVT=deep venous thrombosis; HCG=Human Chorionic Gonadotropin; HD=hemodialysis; LMP=last menstrual period; nos=not otherwise specified; PRBC=packed red blood cells; QD=once daily; US=ultrasound; UTI=urinary tract infection.

1 Timing of drug exposure in relation to gestational age reflects information provided in the narrative. There may be minor discrepancies between narrative and listings.
2 Gestational age reflects information provided in the narrative. If gestational age was not provided, the date of the Last Menstrual Period (LMP) and Event date were used to calculate gestational age.
3 CRF states 16 weeks gestational age for Participant (b) (6)
4 CRF notes 18 weeks gestational age for Participant
5 Email communication from site confirmed live normal birth (b) (6) (baby healthy and doing well). The participant will need to sign a new pregnancy reporting informed consent form to obtain additional details on the case. Information will be provided if it becomes available.

Lactation

Nonclinical Experience
In a pre-and postnatal development study in rats, when daprodustat was orally administered to maternal rats during the lactation period, the drug was detected in plasma of suckling pups on postnatal day 10. The plasma concentration of daprodustat in pups was 2.3-3.7 % of daprodustat detected in the plasma of dams when dosed at 40 mg/kg/day.

Applicant's Review of Literature
Since daprodustat is an NME, no review of the literature was requested from the applicant.

DPMH Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[12], the Drugs and Lactation Database (LactMed),[13] Micromedex[11], and of published literature in PubMed using the search terms "daprodustat and lactation" and "daprodustat and breastfeeding." No reports of adequate and well-controlled studies or case reports of daprodustat use in lactating women were found. Daprodustat is not referenced in *Medications and Mother's* Milk[7]or in LactMed[8].

Reviewer's Comments
Pharmacokinetic parameters such as low molecular weight (393 Da) and the presence of daprodustat in rat milk suggest it is likely that daprodustat will be present in human milk. The high protein binding (99%) suggest that the amount present is likely to be low. Given the spectrum of serious adverse events that can be seen with daprodustat in adults, such as thrombotic vascular events, hypertension, hypersensitivity reactions and malignancy, breastfeeding is not recommended during treatment with daprodustat, and for one month after the last dose. According to the pharmacology-toxicology reviewer the reason one month is proposed (not the usual 5X half-life) is because "It is consistent with the Reproductive toxicology guidance (Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry), due to the risk of malignancy, mechanism of action, and potential drug class effects, we would recommend one month".

Use in Females and Males of Reproductive Potential

Nonclinical Experience
Daprodustat was not carcinogenic in two-year carcinogenicity studies when administered orally at doses of 0.02, 0.1, 0.8, or 4 (males)/ 7 (females) mg/kg/day in rats and 0.2, 0.8, or 3 mg/kg/day (including subcutaneous injection of major human metabolites of daprodustat) in mice.

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[12] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.
[13] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Daprodustat was negative for mutagenic or clastogenic potential in the in vitro bacterial reverse mutation assay, the in vitro human lymphocyte chromosomal aberration assay, and the in vivo rat bone marrow micronucleus assay.

In a fertility and early embryonic development study in rats, daprodustat was administered orally at doses of 2, 7, or 100 mg/kg/day in females, resulting in reduced body weight gain and decreased mean uterine weight. Decreased number of corpora lutea, implantations, and live fetuses, and increased post-implantation loss at 41-times the MRHD based on BSA in the presence of maternal toxicity.

Applicant's Review of Literature
Since daprodustat is an NME, no review of the literature was requested from the applicant.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed regarding daprodustat and its effects on fertility and found no relevant articles.

DISCUSSION AND CONCLUSIONS

Pregnancy
Limited human pregnancy outcome data for daprodustat is available from the sponsor's PVDB. No human pregnancy outcome data was found in the published English language literature. Mechanism of action and findings from animal studies suggest potential for fetal harm from exposure to daprodustat. DPMH also recommends including a Clinical Consideration that CKD can both be associated with adverse pregnancy outcomes. DPMH refers to the final NDA action for final labeling.

Pregnancy would be expected to be uncommon in women on dialysis (the indicated population) and a traditional pregnancy registry or a claims database study would likely be unsuccessful due to low enrollment. Therefore, DPMH recommends a postmarketing requirement (PMR) Descriptive Pregnancy Safety Study to follow-up on maternal and infant outcomes of pregnancies that do occur.

Additionally, DPMH recommends that the applicant submit annual reports of daprodustat utilization rates amongst females of reproductive potential (females aged 15 to 50 years) calculated cumulatively from the time of initial approval. If there appears to be substantial use of daprodustat in females of reproductive potential, then this would be considered new safety information that would trigger FDAAA and would result in the Agency issuing a PMR for pregnancy registry study at that time.

Lactation
There are no data on the presence of daprodustat in human milk, its effects on a breastfed infant or on milk production. Pharmacokinetic parameters such as low molecular weight (≈393 Daltons) and the presence of daprodustat in rat milk suggest it is likely that daprodustat will be present in human milk. The high protein binding (99%) suggest that the amount present is likely to be low. However, given the spectrum of serious adverse events

that can be seen with daprodustat in adults, such as thrombotic vascular events, hypertension, hypersensitivity reactions and malignancy, breastfeeding is not recommended during treatment with daprodustat, and for one month after the last dose.

Given the low incidence of pregnancy and live births in the indicated population and the recommendation against use during breastfeeding, a PMR for a lactation study would not be feasible. The alternative of performing a lactation study in healthy volunteers would not be ethically permissible in my opinion because even a single dose of daprodustat could potentially cause thrombosis in a predisposed population of recently pregnant/lactating women.

Females and Males of Reproductive Potential
There were no studies of the adverse effects of daprodustat on fertility. Recommendations for pregnancy testing or recommendations for contraception while taking daprodustat would not be appropriate given that the fetal harm warning is based on adverse effects in a single animal species at multiples greater than 10 times the maximum recommended human dose (MRHD). Therefore, DPMH recommends that subsection 8.3 be omitted from the labeling.

LABELING RECOMMENDATIONS
DPMH revised the Highlights and subsections 8.1, 8.2 and section 17 of daprodustat labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Daprodustat Pregnancy and Lactation Labeling

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JANE E LIEDTKA
12/01/2022 02:35:52 PM

TAMARA N JOHNSON
12/01/2022 02:42:55 PM

LYNNE P YAO
12/06/2022 11:09:57 AM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	216951
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Daprodustat
Indication	Anemia of Chronic Kidney Disease
Applicant	Glaxo Smith Klein (GSK)
Requesting Division	Division of Non-malignant Hematology (DNH)
Primary Reviewer	Ling Lan, MD, PhD Clinical Analyst, DILI Team, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer, Non-clinical	Edwige Chiogo-Vouffo, PhD, PharmD DILI Team, OND/DHN
Reviewer Office of Pharmacoepidemiology	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Frank A. Anania, MD Acting Director, OND/DHN
Assessment Date	Nov 25, 2022

Context: Daprodustat (DAPRO) is an orally delivered, small molecule inhibitor of hypoxia inducible factor prolyl-hydroxylase (HIF-PH) indicated use in anemia associated with chronic kidney disease (CKD). No HIF-PH are approved in the US. The applicant reported four potential Hy's Law cases observed with DAPRO use in five phase 3 trials. The Division of Non-malignant Hematology (DNH) requested advice by providing assessment of potential DILI cases resulting from DAPRO use and to provide advice on hepatic safety.

Executive Summary: NDA data for DAPRO do not identify a significant liver injury risk that would hold up approval. There were no Hy's Law cases. However, there were issues regarding retrieval bias and missing data that may have impaired a more thorough evaluation. (b) (4)

Consultation Sections:

Section 1.0 – Target Disease and Rationale
Section 2.0 - ADME pertinent to DILI
Section 3.0 - Non-clinical data pertinent to DILI.
Section 4.0 - Clinical data
Section 5.0 – Assessment & Recommendations.

Appendix A: Daprodustat drug-drug interaction summary
Appendix B: Study design schematics

Abbreviations:
AP or ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AT: aminotransferase (ALT or AST)
CKD: chronic kidney disease
CPK: creatinine phosphokinase
DAPRO: daprodustat
DARBE: darbepoietin
DB: direct bilirubin
DD: dialysis dependent
DILI: drug-induced liver injury
EPO: erythropoietin
ESA: erythropoiesis-stimulating agent (e.g., darbepoeitin)
GGT: gamma-glutamyl transferase
HIF-PH: hypoxia inducible factor prolyl-hydroxylase
IP: investigational product
LDH: lactate dehydrogenase
MACE: major adverse cardiovascular event
ND or NDD: non-dialysis dependent
rh-EPO: recombinant human erythropoietin
R-value: ALT/ULN ÷ ALP/ULN
TB: total bilirubin
ULN: upper limit of normal

1.0 Target Disease and Rationale

Target disease is anemia associated with chronic kidney disease. (b) (4)

(b) (4)

2.0 ADME data

2.1 Absorption: DAPRO (a parent drug for human administration) showed an oral bioavailability (AUC-po/AUC-IV) of 78-89% in mice, 45% in dog, and 34% in monkey. Evaluation of the systemic exposure of DAPRO and its metabolites showed that ratios of parent to metabolite mean AUC and C_{max} for all quantifiable metabolites

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[1] (DARRTS session must be opened first for link to work)
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806442a5

were <0.0003 suggesting relatively low plasma metabolite concentrations following five-day repeated oral dosing. Hence oral bioavailability of DAPRO was lower in dogs and monkeys compared to mice. Low plasma exposure of the metabolites was observed compared to the parent drug being the primary component in circulation.

2.2 Distribution: In all preclinical species (mouse, rat, rabbit, dog, monkey), in vitro plasma protein binding of DAPRO was high at ≥95%. In vitro, binding was also high for human albumin (>99.3%) suggesting low concentrations in tissues. No evidence of concentration dependent protein binding was observed. Some metabolites showed low plasma protein binding (<34%) in vitro. Most tissue concentrations of DAPRO were lower than observed in blood, including the liver. After a single oral dose of 14C-DAPRO (10 mg/kg) given to Sprague Dawley rats, the ratio of liver to blood radioactivity was 0.32 to 0.36 at 24 hours.[2] However, the applicant did not send maintenance dosing data on liver concentrations of DAPRO. Hence, DAPRO is expected to be highly albumin bound in clinical trials with low volume of distribution. However, the possibility of liver accumulation of DAPRO with maintenance dosing is not clear.

2.3 Metabolism and Elimination: The parent drug DAPRO was the primary radioactive component across species. The applicant conducted a mass-balance study with the following results. In monkeys, unchanged DAPRO accounted for 54% of the sample radioactivity and 39% of the dose. The remaining radioactivity in monkeys was primarily in the form of oxidative metabolites (41% of the sample radioactivity and 30% of the dose)[3]. Studies using human CYP enzymes and pooled human liver microsomes led to the identification of eleven metabolites.

After oral administration of a single dose of [^{14}C] DAPRO (10 mg/kg) to fasted rats, the primary route of elimination was in feces (86.3 to 87.5 percent). Mean urinary excretion recovered only 10.5 to 8.74% of the parent drug. In dogs, parent drug was eliminated primarily in feces (74% dose) and bile (6% dose). Urinary excretion accounted for just 2% of the administered dose. Monkey studies revealed similar results, except urinary excretion was higher at 13%.

In monkeys, biliary excretion is the primary route of excretion (53% of the dose) with fecal and urinary routes accounted for 24% and 16%, respectively. Parent compound and metabolites were primarily eliminated via hepatobiliary and feces in humans as well, after single 300 mg oral dose.

In summary, DAPRO undergoes oxidative metabolism in the liver, but most excretion is by unchanged parent compound. The primary route of DAPRO and metabolite elimination is via bile and feces.

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[2] NDA216951 (216951 - 0048 - (48) - 2022-07-05 - ORIG-1 /Clinical Pharmacology/Response To Information Request) - Pharmacokinetics Tabulated Summary (#116)
[3] NDA216951 (216951 - 0081 - (81) - 2022-10-19 - ORIG-1 /Biometrics/Response To Information Request) - Report Body (#5)

2.4 Transporter inhibition: In vitro evaluation of DAPRO and its six metabolites did not demonstrate inhibition of OAT1-, OAT3-, OCT2-, and MATE2-K mediated transport. In vitro inhibition by DAPRO for human transporters OATP1B1 and OATP1B3 was observed with IC_{50} values of 6 and 11μM respectively. There was no data on inhibition of either BSEP or MRP2.

3.0 Non-clinical data

3.1 In vitro data: CYPC28 appears to account for 95% of DAPRO oxidative metabolism and is the primary mechanism for DAPRO degradation, and moderate inhibition of CYP2C8 raises the possibility of drug accumulation with CYP3A4 having a minor (5%) contribution.

DAPRO presented minimal potential for concentration-dependent P450 inhibition of CYP1A2, 2C9, 2C19, 2D6, or 3A4, and no potential for metabolism-dependent inhibition was reported. DAPRO demonstrates moderate inhibition of CYP2C8, but it is not clear whether this is a time-dependent inhibition (TDI). DAPRO appears to possess low potential for in vivo drug-drug interactions (DDIs) since it inhibits CYP450, 1A2, 2C9, 2D6, and 3A4 with no metabolism-dependent CYP3A4 inhibition.

Overall, DAPRO could accumulate in the liver, if TDI of CYP2C8 occurs. Also, DAPRO may be subject to victim drug-drug interaction (DDI) for inhibitors of CYP2C8 (e.g., trimethoprim, gemfibrozil) (**Appendix A**).

3.2 Animal data:

3.2.1 *Serum markers*: Several animals studies suggest enzyme elevations with DAPRO. We highlight a few studies.

Following a 13-week PO administration of DAPRO 60 mg/kg/day in male mice, there was an increase in ALT and AST (7.58 and 2.82X control values, respectively). At 3, 30, and 60 mg/kg/day dosing, total bilirubin increased 1.4, 2.9, and 2.8 x control, respectively.[4] The applicant did not provide bilirubin fractionation data. In a 13-week PO administration of DAPRO in rats, there were also increases in transaminases and ALP at doses of DAPRO ≥20 mg/kg/day. In a seven-day oral, 120 mg/kg/da administration to beagle dogs there was an increase in ALP of 2.1 x baseline on average.

Following a 14-day oral administration at 100 mg/kg/day in eight Cynomolgus monkeys, ALT increased by 2.4 x baseline on average with more modest increase in ALP noted (22% increase only). A second monkey study showed increases in both AP and bilirubin following a 39-week, daily dose of 50 mg/kg. AP and TB elevations were dose- and time-on-drug dependent with maximum changes from baseline of

[4] NDA216951 (216951 - 0081 - (81) - 2022-10-19 - ORIG-1 /Biometrics/Response To Information Request) - Report Body (#41)

1.7 x for AP and 2.8 x for bilirubin.[5] The applicant suggested the increase in ALP was due to increase hematopoiesis in trabecular bone because of the lack of liver histopathology findings. Fractionation of TB was not provided.

Overall, several animal studies suggest elevation in liver enzymes and bilirubin may occur, but only one study had significant histopathologic correlation in the liver (see 3.2.2).

3.2.2 *Liver histopathology studies*: Only one study had liver histopathology that correlated with serum liver enzyme elevations. One of 12 mice receiving 60mg/kg/day for 13 weeks had an increase in transaminases that correlated with hepatic necrosis. Rats receiving 26-week gavage had significant liver histologic necrosis but in the setting of other organ damage and thromboses.

3.2.3 Summary of non-clinical data: We found the non-clinical data related to DILI risk mixed and incomplete (**Table 1**), overall, the data suggest a potential for liver injury in clinical trials.

Table 1: Summary non-clinical data pertinent to DILI risk

Item	Finding
In vitro studies	
Major CYPs	CYP2C8
Reactive metabolites (i.e., glutathione trapping)	Unclear data provided
Mitochondrial inhibition	No data found
BSEP or MRP2 inhibition	No data found.
Animal studies	
Elevation in liver analytes (e.g., ALT, ALP, TB)	Increase in transaminases and bilirubin in mouse; Increase in ALT, AST, and ALP in rats and dogs; increase in ALT, ALP, and bilirubin in monkeys.
Liver histology findings (Animal studies)	One in 12 mice in one study suggested liver necrosis; other studies showed minimal to no changes.

Source: DILI team

4.0 Clinical data:

4.1 In class or near class DILI data: (b) (4) [redacted]

4.2 Summary of studies

This consult focuses on five global phase 3 studies (ASCEND) that included 8158 dialysis and non-dialysis subjects (**Table 2**). See **Appendix B** for study schematics

[5] NDA216951 (216951 - 0081 - (81) - 2022-10-19 - ORIG-1 /Biometrics/Response To Information Request) - Report Body (#23)

[6] (DARRTS Session must be opened first for link to work.) https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806442a5

for these five studies. The ASCEND studies used non-inferiority study design for MACE endpoints. Studies 200808, 201410 and 200807 are event driven studies.

In total, the DAPRO clinical program included sixteen phase 1, ten phase 2 and eight phase 3 (three in Japan and five multi-national) studies. The applicant stated that there were no potential DILI events in the 26 phase 1 and 2 studies based on central and non-study site data.

Table 2: Summary of Phase III ASCEND Studies[7]

Study Name	Study Number	Population	Control	Blinding	N	Duration (years)
Non-dialysis						
ASCEND-NHQ	205270	Non-dialysis, not receiving rhEPO	placebo	double blind	614	0.5
ASCEND-ND	200808	Non-dialysis, mixed prior rhEPO[a]	darbepoetin	open label	3872	1.86[b]
Dialysis						
ASCEND-ID	201410	Incident dialysis, limited prior rhEPO[c]	darbepoetin	open label	312	1
ASCEND-D	200807	Dialysis, prior rhEPO	rhEPO[d]	open label	2964	2.48[b]
ASCEND-TD	204837	Hemodialysis, prior rhEPO	epoetin alfa	double blind	407	1

Abbreviations: rhEPO=recombinant human erythropoetin or its analogs.

a. Patients on prior rhEPO and not on prior rhEPO were both recruited into the study.
b. Median years of follow-up for cardiovascular endpoints.
c. Not regularly using routine rhEPO prior to randomization.
d. Hemodialysis patients: epoetin alfa; peritoneal dialysis patients: darbepoetin.

Source: Clinical overview, Page 11

Study design features related to DILI assessment:

Inclusion criteria: Dialysis dependent (D), incident dialysis (ID) studies will include subjects with chronic kidney disease without specification of etiology. Baseline hemoglobin levels must be 8 to 11.5 g/dL. Non-dialysis dependent (ND and NHQ) studies will include subjects with chronic kidney disease, not otherwise specified. Basline hemoglobin levels must be 8-10 g/dL not on ESAs, and 8-11 g/dL on ESAs.

Exclusion criteria: ALT > 2 x ULN; TB > 1.5 x ULN; and any unstable liver or biliary disease per investigator assessment, generally defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

[7] NDA216951 (216951 - 0048 - (48) - 2022-07-05 - ORIG-1 /Clinical Pharmacology/Response To Information Request) - Clinical Overview (#11)

Stopping criteria: included detailed "Liver Safety Required Actions and Follow up Assessments" as Appendix 8. Other phase 3 study protocols also have similar stopping criteria and assessment.

4.3 Population level screening and DILI analysis on biomedical analytes

4.2.1 *Biochemical Laboratory Data Issues*

1. Missing non-study site data: – Information request (IR) for non-study site liver chemistries resulted in 33 potential Hy's law cases (18 on DAPRO and 15 on comparator) instead of the originally reported six cases (4 DAPRO, 2 comparator).

   We discovered there were missing non-study site lab data from the ADLB dataset. We issued an IR on April 12, 2022, jointly with DNH. See item #1 quoted below for the relevant inconsistencies. The applicant confirmed there were missing non-study site lab results. They conducted a subsequent search in case report forms to locate non-study site data and update the ADLB dataset, as requested. After multiple consequent IRs, on August 5, 2022, the applicant submitted the updated ADLB dataset for each ASCEND study and ISS including central and non-study site lab results.

   a. IR request April 12, 2022:[8]

> For study level information,
> a. Update all study level ADLB dataset for each of the five Phase 3 studies (205270, 200807, 200808, 201410 and 204837) to include all liver enzymes, total bilirubin and direct (or conjugated) bilirubin regardless of whether they were collected during an unscheduled visit or from a non-study-site lab. We found the following inconsistencies between the ADLB and other data submitted:
>   i. Subject (b) (6) had an acute hepatic failure/injury event with elevated liver tests reported in the narrative. However, these abnormal tests were not included in the Study 200808 ADLB dataset submitted on 2/24/2022.
>   ii. Study 205270 CSR reported a placebo subject (ID: (b) (6) is a potential Hy's law case with ALT 237 u/l on Day 51. However, the ADLB dataset did not include liver tests around this unscheduled visit on Day 51.
>
> Such inconsistencies undermine the accuracy of eDISH plotting.

2. Missing ALP values in ADLB datasets: There was no ALP values in nearly all ISS subjects (98.4%). Thus, despite some non-clinical data suggesting possible ALP elevation associated with DAPRO, we were not able to assess this possibility in the clinical trials.
3. Other issues: There are duplicate subject IDs in the latest ADLB ISS dataset that posed challenges for DILI analysis.

4.2.2 *ISS (N=8158, 5 global P3 ASCEND studies)*

[8] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8065759c

The DILI team study level analyses below are based on the latest ADLB dataset for ISS. For all ISS subjects, there were no clear imbalances in incidence of ALT/AST elevations, jaundice, or cases meeting Hy's law liver test criteria between subjects receiving DAPRO versus those in comparator arms **Table 3**.

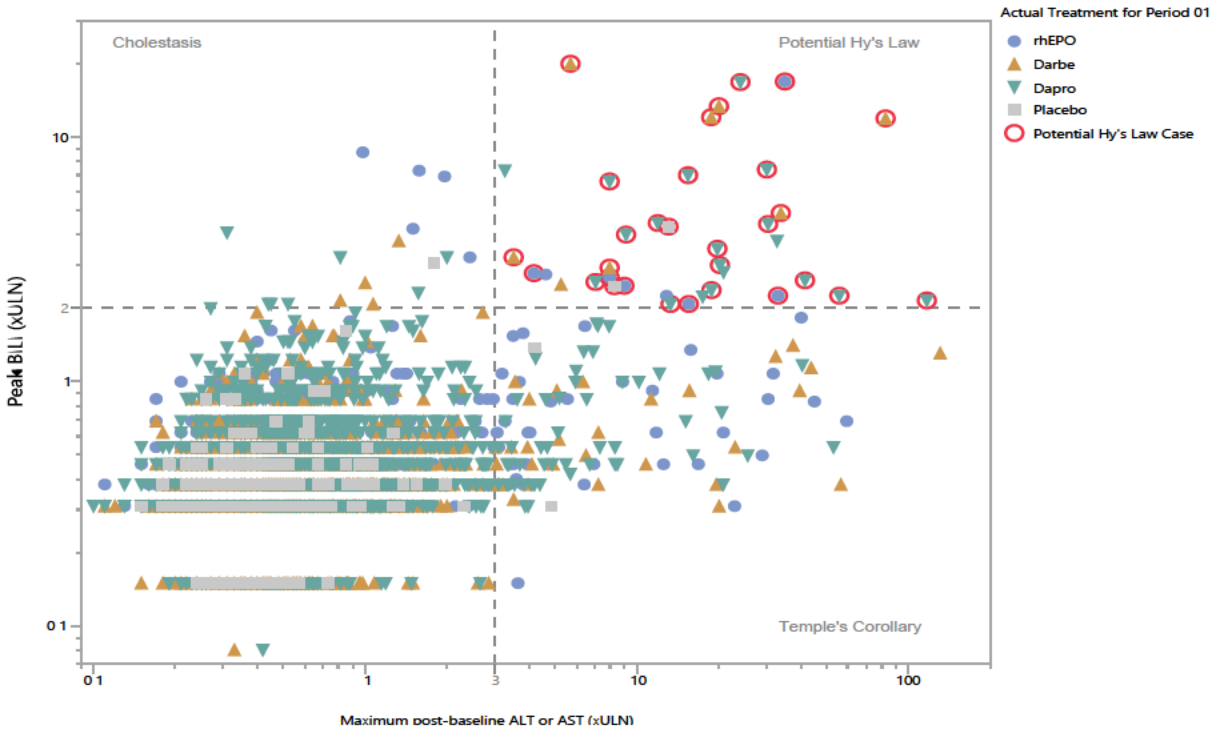
Table 3: Overall Liver Biochemistry by Treatment in ISS

	DAPRO	Placebo	rh-EPO	DARBE
ISS	**N = 4154**	**N = 306**	**N = 1610**	**N = 2088**
Hy's Law quadrant (ALT/AST ≥ 3 x ULN & BILI ≥ 2 x ULN)	18 (0.4%)	2 (0.7%)	6 (0.4%)	7 (0.3%)
ALT/AST ≥ 3 x ULN	71 (1.7%)	4 (1.4%)	49 (3.0%)	40 (1.9%)
ALT/AST ≥ 5 x ULN	47 (1.1%)	2 (0.7%)	25 (1.6%)	26 (1.2%)
ALT/AST ≥ 10 x ULN	26 (0.6%)	1 (0.3%)	18 (1.1%)	16 (0.8%)
Total BILI ≥ 2 x ULN	27 (0.6%)	3 (1.0%)	13 (0.8%)	12 (0.6%)

DAPRO = daprodustat; rh-EPO = recombinant human erythropoietin; DARBE = darbepoietin
Source: DILI team analyses results

eDISH plotting had numerous cases in the Hy's Law quadrant but no imbalance between DAPRO and comparator arms. Those circled in red carried a heightened risk of meeting Hy's Law due to peak transaminase and TB being within 30 days of each other (**Figure 3**).

Figure 3: eDISH Plot for ISS



Source: JMP Clinical 8.0 results
Note that red circles indicate total bilirubin ≥ 2 x ULN within 30 days of aminotransferase ≥ 3 x ULN and ALP < 2xULN; Hy's law quadrant: 33 cases after removing 6 duplicate subject IDs (3 were in Hy's law quadrant) from ADLB dataset.

4.2.3 *Each ASCEND Study*: Overall, the comparison within each study shows similar liver biochemistry profiles between DAPRO and comparators (placebo, rh-EPO and DARBE).

The two largest ASCEND studies (200807 and 200808) present similar liver biochemistry results between the DAPRO arm and the comparator arm (rhEPO or DARBE) on percentage of cases in Hy's law quadrant, ALT/AST elevation and jaundice (**Table 4**). The two double blinded Studies 205270 and 204837 had higher percent of cases with elevated liver biochemical analytes in the comparator arms (placebo or rh-EPO) versus DAPRO arm. Study 210410 had higher percent ALT/AST ≥ 3 x ULN) but less ALT/AST 0 ≥ 10 x ULN in DAPRO arm relative to DARBE arm. The limited sample size makes interpretation of these findings inconclusive.

Table 4: Liver Biochemistry by Study

	DAPRO	Placebo	Rh-EPO	DARBE
Study 200807 (ASCEND-D)	**N=1482**		**N=1474**	
Hy's Law quadrant (ALT/AST ≥ 3 x ULN & BILI ≥ 2 x ULN)	9 (0.5%)		6 (0.4%)	
ALT/AST ≥ 3 x ULN	29 (2.0%)		45 (3.0%)	
ALT/AST ≥ 5 x ULN	22 (1.5%)		23 (1.6%)	
ALT/AST ≥ 10 x ULN	12 (0.8%)		16 (1.1%)	
Total BILI ≥ 2 x ULN	12 (0.8%)		13 (0.9%)	
Study 200808 (ASCEND-ND)	**N=1937**			**N=1933**
Hy's Law quadrant	8 (0.4%)			7 (0.4%)
ALT/AST ≥ 3 x ULN	34 (1.8%)			38 (2.0%)
ALT/AST ≥ 5 x ULN	23 (1.2%)			24 (1.2%)
ALT/AST ≥ 10 x ULN	13 (0.7%)			14 (0.7%)
Total BILI ≥ 2 x ULN	10 (0.5%)			12 (0.6%)
Study 201410 (ASCEND-ID)	**N = 157**			**N=155**
Hy's Law quadrant	1 (0.6%)			0
ALT/AST ≥ 3 x ULN	4 (2.5%)			2 (1.3%)
ALT/AST ≥ 5 x ULN	2 (1.3%)			2 (1.3%)
ALT/AST ≥ 10 x ULN	1 (0.6%)			2 (1.3%)
Total BILI ≥ 2 x ULN	1 (0.6%)			0
Study 205270 (ASCEND-NHQ)	**N=308**	**N=306**		
Hy's Law quadrant	0	2 (0.7%)		
ALT/AST ≥ 3 x ULN	1 (0.3%)	4 (1.4%)		
Study 204837 (ASCEND-TD)	**N =270**		**N =136**	
ALT/AST ≥ 3 x ULN	3 (1.1%)		4 (2.9%)	
ALT/AST ≥ 5 x ULN	0		2 (1.5%)	
Total BILI ≥ 2 x ULN	1 (0.4%)		0	

DAPRO = daprodustat; rh-EPO = recombinant human erythropoietin; DARBE = darbepoietin

Source: DILI team based on ISS ADLB dataset

4.1 Case level analysis

4.1.1 *Summary of cases*: We assessed 25 subjects exposed to DAPRO and falling in Hy's Law quadrant. None were considered probable DILI due to DAPRO. Only one was considered possible with alcohol as a competing cause. Alternate causes for liver injury as listed in the **Table 5**.

Table 5: Causality assessments of 25 subjects on DAPRO in Hy's Law quadrant across the ISS.[9]

#	ID	Study	Causality Score^	Alternate diagnosis	Age (yr)	Sex	Race
1	(b) (6)	200808	4	Alcohol (?)	65	M	White
2		205270	5	Autoimmune hepatitis	65	M	Black AA
3		200807	5	Biliary disease, cholecystitis	60	M	Asian
4		200807	5	Biliary disease, gallstone disease	80	F	White
5		200808	5	Biliary disease, gallstone disease	67	F	White
6		200808	5	Biliary disease, gallstone disease	72	F	Asian
7		200807	5	Biliary disease, gallstone disease	65	F	White
8		200807	5	Biliary disease, gallstone disease	88	F	White
9		200807	5	Biliary disease, gallstone disease	75	M	White
10		200808	5	Biliary disease; hemobilia	78	F	White
11		200807	5	COVID-19 pneumonia	60	M	Black AA
12		200808	5	DILI: Allopurinol	60	F	Asian
13		200808	5	DILI: Herbal dietary supplement	39	F	Asian
14		200808	5	HCC RFA treatment	75	M	Asian
15		200807	5	HCC TACE Rx	67	M	Asian
16		200807	5	Heart failure	72	M	White
17		200808	5	Heart failure, congestive hepatopathy	61	M	White
18		200807	5	Hepatitis B	55	M	White
19		200807	5	Hepatitis B	57	M	White
20		200808	5	Hepatitis B	66	M	White
21		201410	5	Shock liver	75	M	White
22		200807	5	Shock liver/pneumonia associated	81	F	White
23		200807	5	Shock liver/sepsis	48	F	Black AA
24		200807	5	Unknown	24	F	White
25		200808	5	Unknown	59	F	White

8 Biliary disease
3 Hepatitis B
3 Shock liver
2 Heart failure
2 HCC (liver cancer) therapy
2 DILI: non-daprodustat
1 Alcohol
1 Autoimmune hepatitis
1 COVID-19
2 Unknown

^1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

4.1.2: *Case of interest*: Only one case was considered weakly possible versus unlikely DILI due to DAPRO and this subject had a reasonable alternative explanation of alcohol liver damage though alcohol intake history was contradictory and unclear.

Case (b) (6) (Study 200808): Weak possible to unlikely DILI due to DAPRO

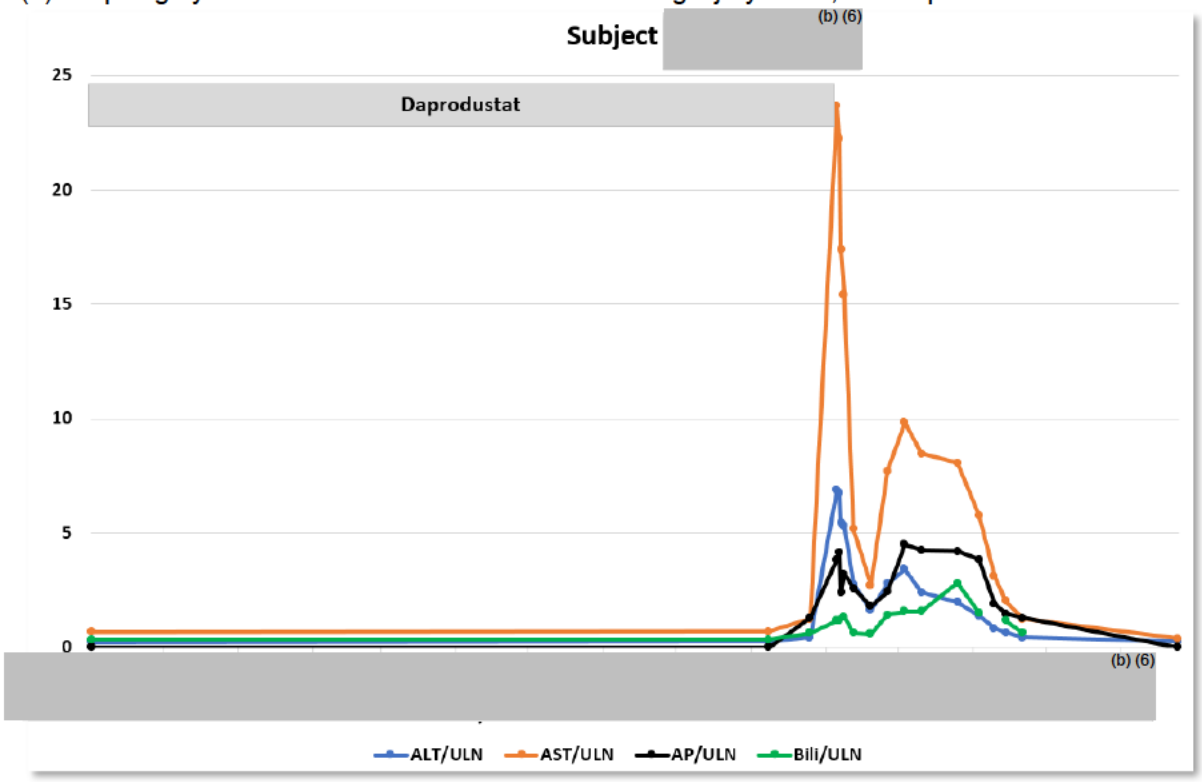
Summary: This is a 65-year-old-white man enrolled in Belgium.

[9] DILI Team Access database and Excel spreadsheet.

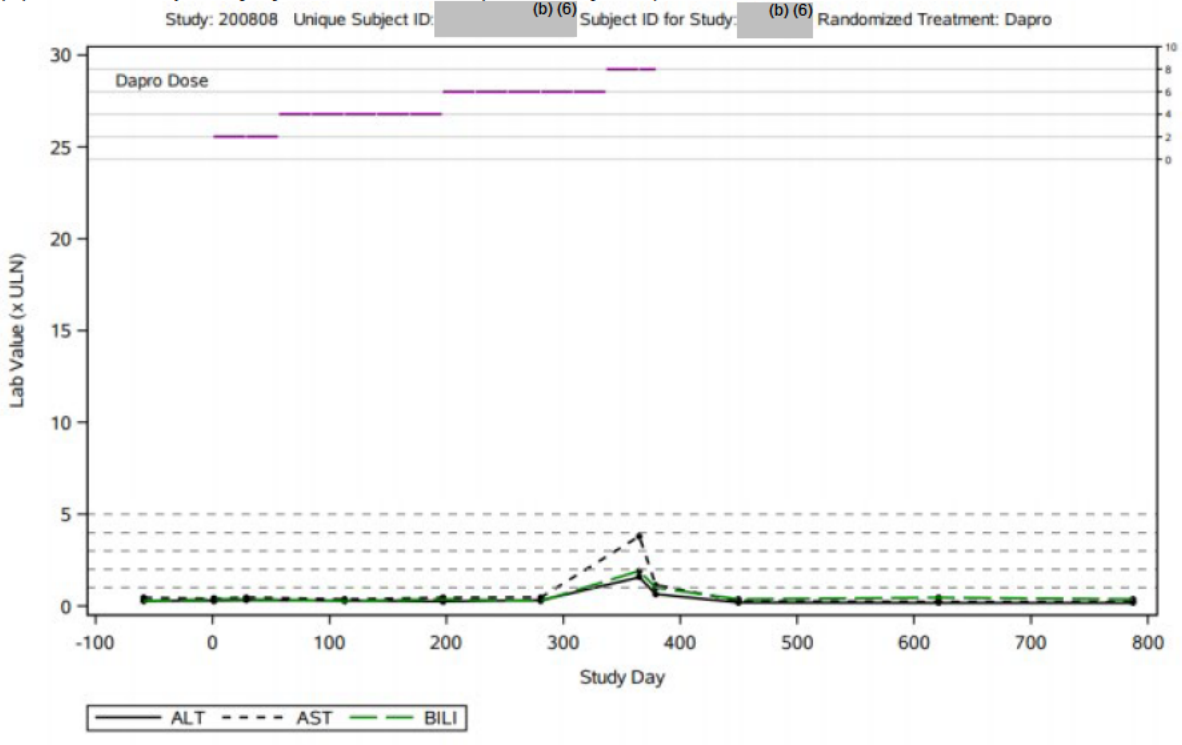
At baseline, the subject had hepatic steatosis, morbid obesity, sleep apnea, hyperuricemia, hyperlipidemia, left ventricular diastolic dysfunction, hypertension, past history of Epstein-Barr virus infection (no further details given) and erysipelas of the lower legs. No history of alcohol use given at enrollment and there was no mention of drug abuse either. He took no concomitant medications pertinent to liver injury risk. ALT was 14 U/L, AST 22 U/L, and TB 0.4 mg/dL. No AP values were available. [Hereafter, ALT and AST values are in U/L and bilirubin is in mg/dL.]

The subject started DAPRO on (b) (6) (Day 0). Liver tests remained normal through (b) (6) (Day 281). On (b) (6) (Day 309), his ALT was 421, AST 876, AP 449, TB 1.39. DAPRO was stopped. No symptoms reported. Despite no alcohol history at enrollment, alcohol use was now listed as 5 units/week at the time of enzyme elevation. Later chart review by the investigator suggested up to 5-6 beers per day through (b) (6), followed by 2-3 per day, thereafter. He was hospitalized and had "mild" transient hypotension the next day (98/62). CPK was elevated up to max of 420 U/L but then fell and did not rise again with the second bump in enzymes (**Figure 4**). TB that was predominantly direct peaked on a second rise to 3.4 mg/dL. Evaluation testing was negative except no HCV RNA was reported, and a (+) EBV IgM was found. The "micro department" considered the EBV IgM as "irrelevant" and due to past exposure. The applicant's virologists agreed. Imaging showed fatty liver but no biliary disease or other acute changes. Liver was "small volume" on CT. No splenomegaly. He was discharged after two days. Thereafter his enzymes fell but then rose again before falling to baseline some weeks later. INR rose to 1.24 without encephalopathy.

Figure 4: Line graph of liver chemistries over time, Subject (b) (6)
(a) Graphing by DILI team with outside lab results during injury event, but no prior lab results[10]



(b) Lab values pre-injury without outside (non-study site) lab values[11]



[10] Graph by DILI Team based on Table 4, Narrative FDA IR 10.
[11] Figure 1, Narrative FDA IR 10

Figure Legend: (a) Graph created by DILI Team based on outside lab values but without pre-injury values. (b) Graph provided by applicant documented normal ALT and AST through study day 281, but no elevations over 4x ULN due to missing outside lab values.

Assessment: This subject had possible to unlikely DILI due to DAPRO. The latency is long, and alcohol competes because of the unclear alcohol history and AST to ALT ration being over two. However, the AST peak is atypically high for alcoholic hepatitis. Independent single expert assessment suggested this case as possible DILI. An independent HAC deemed it unlikely with shock liver as the alternative, though shock would not explain the second rise in enzymes and bilirubin. The DILI Team considered surreptitious alcohol use as the best competing diagnosis.

5.0 Assessment & Recommendations

5.1 Assessment: DAPRO is an oral, small molecule inhibitor of HIF-PH being developed for anemia associated with chronic renal insufficiency.

Non-clinical data for DILI risk was mixed but overall suggest some potential for liver injury. Animal models provide evidence for enzyme elevations, but only one study had significant histopathological correlation. DAPRO appears to inhibit the CYP used for its own metabolism so potential for intra-hepatic drug accumulation may exist. Also, metabolite reactivity (e.g., glutathione trapping) and mitochondrial inhibition data were not clearly presented and therefore difficult for the DILI team to interpret.

The initial ADLB dataset for the clinical trials identified six subjects (three on DAPRO) that met transaminase and TB criteria for Hy's Law. However, upon information request for the inclusion of non-study site laboratory results, the number rose to at least 25 subjects on DAPRO segregating to the Hy's Law quadrant. Because the addition of these values to the ADLB dataset was dependent on post-hoc identification of potential safety issues, it is unclear whether the capture of outside values was complete because it retrospectively and not per protocol. In addition, AP values were conspicuously absent in 98.4% of subjects. AP assessment is fundamental to DILI risk assessment on study and case level analyses. Indeed, the level of AP rise in relation to transaminase elevation is part of the definition of Hy's Law. Lastly, there were instances of multiple subject identification numbers for the same subject.

With these caveats in mind, we did not find imbalances in transaminase or TB elevations between active and comparator arms. Case level analyses of the subjects on DAPRO and meeting transaminase and TB criteria for Hy's Law did not reveal any probable DILI cases. Thus, in the final analysis, we did not identify any subjects meeting Hy's Law in the ISS. However, given the lack of applicant data for AP levels, we are unable to comment on the risk of cholestatic injury.

Overall, we do not see a liver injury risk that would prevent approval, but there were limitations in our analyses. If the need and efficacy for this drug are substantial, we

can support approval with appropriate labeling. Post approval pharmacovigilance may be appropriate given the limitations of the data the applicant provided.

5.2 Recommendations:

1. Labeling should suggest monitoring liver enzymes and bilirubin at baseline and as clinically indicated.
2. Consider including liver injury as part of post-market research with pharmacovigilance.

_____

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, Division of Hepatology and Nutrition
CDER/OND

_____

Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

_____

Frank A Anania, MD
Acting Director, Division of Hepatology and Nutrition
CDER/OND

Appendix A: Daprodustat Drug-drug Interaction Summary[12]

Enzyme/Transporter	Result/Recommendation
Strong CYP2C8 inhibitors, such as gemfibrozil	3.92-fold increase in Cmax and 18.6-fold increase in AUC: **Contraindicated**
Moderate CYP2C8 inhibitors, such as clopidogrel	POPPK: 1.17-fold increase in Cmax and 1.59-fold increase in AUC: **No dosing adjustment recommended**
Weak CYP2C8 inhibitors, such as trimethoprim	1.28-fold increase in Cmax and 1.48-fold increase in AUC: **No dosing adjustment recommended**
Sensitive CYP2C8 substrate, such as pioglitazone	No effect on pioglitazone Cmax or AUC: **No dosing adjustment recommended**
Strong CYP2C8 inducers, such as rifampin, rifampicin	Potential for decreased exposure: **Increased monitoring Hgb is required** when initiating or stopping therapy with CYP2C8 inducers
Sensitive OATP1B1/OATP1B3 substrate, such as rosuvastatin	No effect on rosuvastatin Cmax or AUC: **No dosing adjustment recommended**
Inhibitors of BCRP	Disposition and biotransformation profiles do not support clinically relevant DDI: **No dosing adjustment recommended**
Phosphate Binders	POPPK: 0.843-fold change in Cmax and 0.918-fold change in AUC: **No dosing adjustment recommended**
Acid Reducing Agents	POPPK: 1.06-fold increase in Cmax and 0.996-fold change in AUC: **No dosing adjustment recommended**
Oral Iron	POPPK: 1.14-fold increase in Cmax and 1.02-fold increase in AUC: **No dosing adjustment recommended**

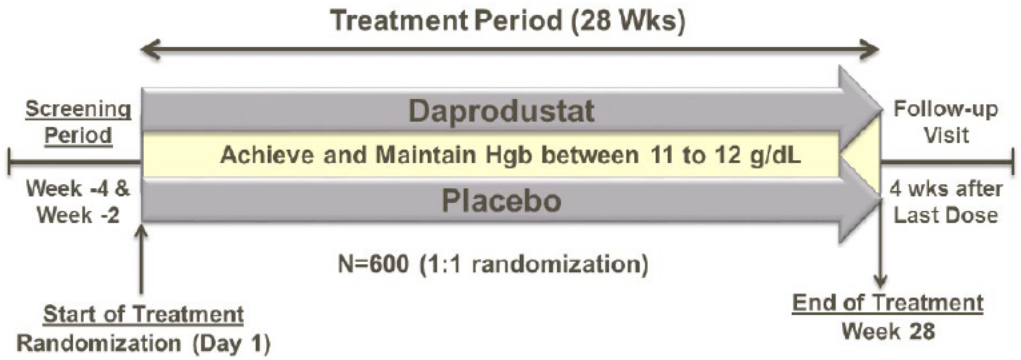
Source: m2.7.2 Section 3.1.4
Abbreviations: AUC=area under the concentration-time curve, BCRP=breast cancer resistance peptide, Cmax=maximum concentration, CYP=cytochrome P450, DDI=drug-drug interactions, OAT=organic anion-transporting polypeptide, POPPK=pharmacokinetics population.

[12] NDA216951 (216951 - 0048 - (48) - 2022-07-05 - ORIG-1 /Clinical Pharmacology/Response To Information Request) - Clinical Overview (#18)

Appendix B: Schematics for ASCEND studies

ASCEND-NHQ:

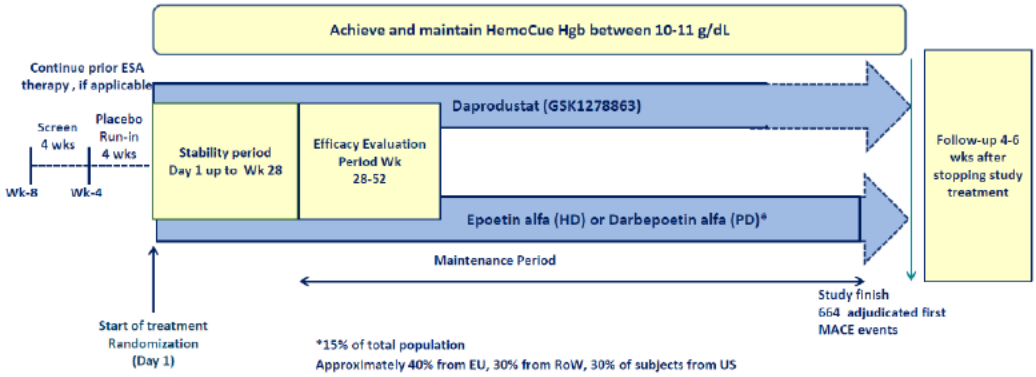
Figure 1 **Study Schematic**



Source: Study 205270 (ASCEND-NHQ) CSR page 29

ASCEND-D

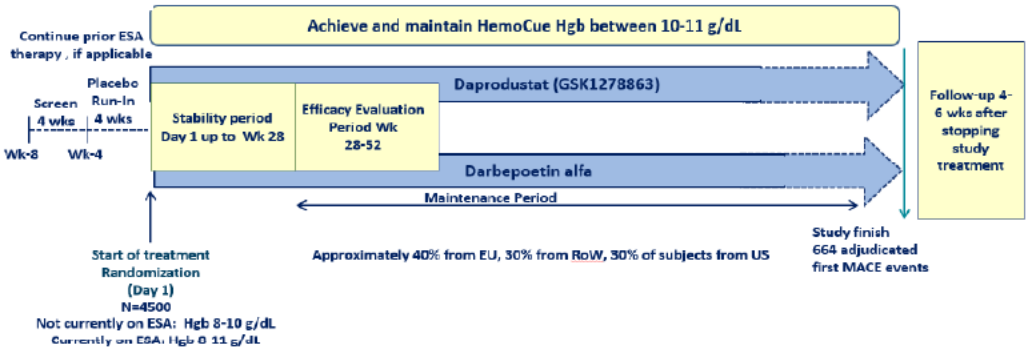
Figure 2 **Study 200807/ASCEND-D Schematic**



Source: Study 200807 CSR Page 49

ASCEND-ND

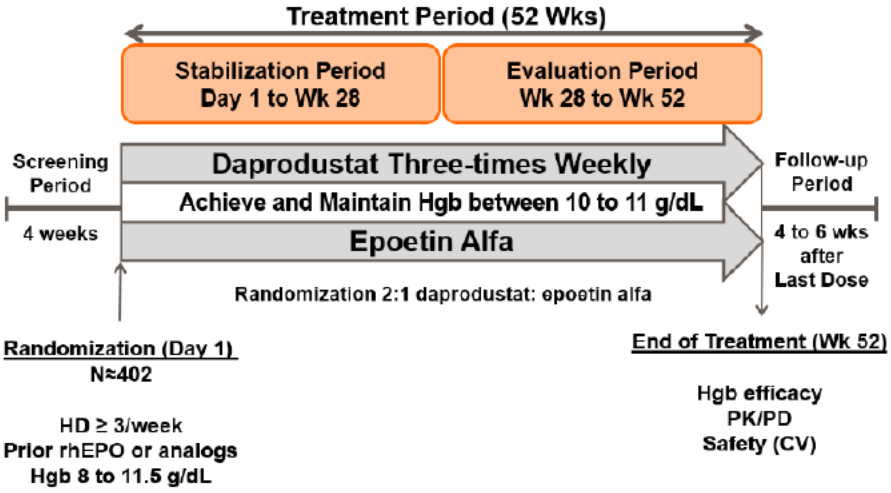
Figure 3 **Study 200808/ASCEND-ND Schematic**



Source: Study 200808 CSR, page 52.

ASCEND-TD

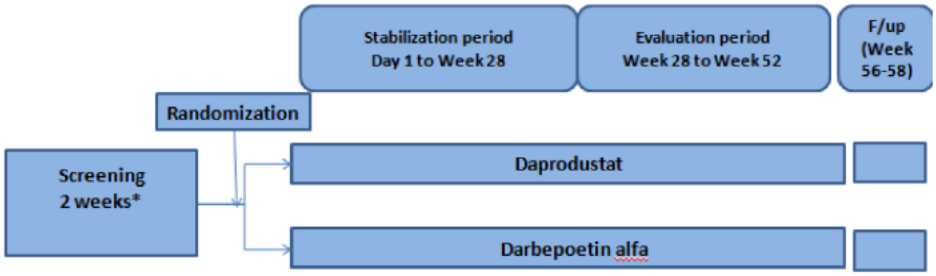
Figure 4 **Study Schematic**



Source: Study 204837 (ASCEND-TD) CSR, page 39

ASCEND-ID

Figure 5 **Study Schematic**



* Screening period may be extended by an additional 4 weeks for ultrasound examination, IV iron supplementation and/or vitamin B12 treatment as needed.

F/up=follow up

Source: Study 201410 (ASCEND-ID) CSR, page 35

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/s/

PAUL H HAYASHI
11/29/2022 04:48:29 PM

CLINICAL INSPECTION SUMMARY

Date	July 22, 2022
From	Anthony Orencia M.D., Ph.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Patricia A. Oneal, M.D., Medical Officer Justin Penzenstadler, Clinical Analyst Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Division Director Caden Brennen, M.Sc., Regulatory Health Project Manager Division of Non-malignant Hematology (DNH) Office of Cardiology, Hematology and Nephrology Drugs (OCHEN)
NDA	NDA 216951
Applicant	GlaxoSmithKline
Drug	Daprodustat
NME	Yes
Division Classification	Hypoxia-inducible factor prolyl hydroxylase inhibitor
Proposed Indication	Treatment of anemia of chronic kidney disease in patients on dialysi (b) (4)
Review Type	Standard
Consultation Request Date	March 11, 2022
Summary Goal Date	August 1, 2022
PDUFA Date	February 1, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies 200807/ASCEND-D and 200808/ASCEND-ND were submitted to the Agency in support of a New Drug Application (NDA) for daprodustat, proposed for the treatment of anemia of chronic kidney disease in adult patients on dialysis (b) (4) Four clinical investigator sites (Drs. Barton Cox Brezina, Anjay Rastogi, Chao Sun and Kendra Hendon) were inspected for Studies 200807/ASCEND-D and 200808/ASCEND-ND.

Based on clinical inspections, the study data derived from the above clinical investigator sites appear reliable. The study data submitted to the Agency for assessment are acceptable in support of the proposed indication.

II. BACKGROUND

Daprodustat [GSK1278863] is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). Daprodustat stimulates erythropoiesis through the inhibition of hypoxia-inducible factor prolyl-4-hydroxylases resulting in increased transcription of hypoxia-inducible factor responsive genes including erythropoietin. The proposed indication is for the treatment of anemia of chronic kidney disease (CKD) in patients on dialysis (b) (4)

There are two Phase 3 studies (200807/ASCEND-D and 200808/ASCEND-ND) providing data on the safety profile regarding cardiovascular outcomes and efficacy of daprodustat compared to recombinant erythropoietin (rhEPO). Clinical inspections for these two studies were requested by the review division due to safety concerns related to this study product. This application is scheduled for a public advisory committee meeting.

Study 200807/ASCEND-D

Study 200807/ASCEND-D was a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center, event-driven study in dialysis participants with anemia associated with chronic kidney disease currently treated with erythropoiesis-stimulating agents (ESAs).

The study randomized 2964 participants, aged from 18 years up to 99 years with anemia of CKD who were treated with an ESA for at least six weeks prior to randomization, on dialysis greater than 90 days prior to screening and with a baseline hemoglobin level of 8-11 g/dL while on ESAs. Following the four-week screening period, participants entered a four-week placebo run-in period before entering the treatment period where study treatment was dose-titrated to achieve/maintain the target hemoglobin range (Day 1-Week 28). Prior ESA therapy was continued during the screening and run-in periods. Hemoglobin efficacy was assessed during Weeks 28-52. Study 200807 comprised four study periods: a 4-week screening period, a 4-week placebo run-in period, a treatment period and a follow-up period.

The co-primary study objectives were to compare daprodustat to recombinant human erythropoietin for cardiovascular safety (non-inferiority) and to compare daprodustat to rhEPO for hemoglobin efficacy (non-inferiority).

The co-primary study endpoints were (1) time to first occurrence of adjudicated major adverse cardiovascular events) [MACE, a composite of all-cause mortality, non-fatal myocardial infarction and non-fatal stroke] and (2) mean change in hemoglobin between baseline and evaluation period (mean over Weeks 28 to 52).

The study was conducted at 431 centers in 35 countries that enrolled participants. The study was conducted from September 28, 2016, to November 9, 2020.

Study 200808/ASCEND-ND

Study 200808/ASCEND-ND was a randomized, open-label (sponsor blind), active-controlled, parallel-group, multi-center, event-driven study in non-dialysis participants with anemia associated with chronic kidney disease.

This study randomized 3872 participants, aged from 18 years up to 99 years with anemia associated with CKD not on dialysis, who were either not using ESAs or were current ESA users and with baseline hemoglobin levels of 8-10 g/dL (non-ESAs users) or 8-11 g/dL (ESA users). Following the four-week screening period, participants entered a four-week placebo run-in period before entering the treatment period where study treatment was dose-titrated to achieve/maintain the target hemoglobin range (Day 1-Week 28). Prior ESA therapy was continued during the screening and run-in periods. Hemoglobin efficacy was assessed during Weeks 28-52. This study comprised four study periods: a 4-week screening period, a 4-week placebo run-in period, a treatment period and a follow-up period.

The co-primary study objectives were to compare daprodustat to darbepoetin alfa for cardiovascular safety (non-inferiority), and to compare daprodustat to darbepoetin alfa for hemoglobin efficacy (non-inferiority).

The co-primary efficacy endpoints were (1) time to first occurrence of adjudicated major adverse cardiac events [i.e., consists of all-cause mortality, non-fatal MI (myocardial infarction) and non-fatal stroke] and (2) mean change in hemoglobin between baseline and evaluation period (mean over Weeks 28 to 52).

Study 200808 was conducted at 506 centers in 39 countries. This clinical trial investigation was conducted from September 27, 2016, to April 19, 2021.

III. RESULTS (by site)

1. Barton Cox Brezina, M.D.
Southeastern Clinical Research Institute, LLC.
1521 Anthony Road
Augusta, Georgia 30904

Inspection dates: May 9-19, 2022

This site was inspected for Studies 200807 and 200808.

For Study 200807 (Site 228862), 24 study subjects were screened, five subjects enrolled, and none completed the treatment phase. There were five subjects' records inspected, with emphasis on safety reporting data.

For Study 200808 (Site 228846), 136 study subjects were screened, 45 subjects were enrolled and 28 subjects completed the treatment period. For the 17 subjects who did not complete the study, there were 7 deaths that occurred and 10 early discontinuations. There were 30 patient records inspected, focusing on adverse and patient safety data.

Study administrative files were reviewed and evaluated including FDA 1572 (Statement of Investigator) completion, financial disclosure forms, IRB approvals, clinical site training documentation and monitoring reports.

Investigational product records including shipment, accountability, investigational product storage and temperature handling documents were reviewed.

The site audit involved review of the paper and electronic medical record printouts (KDS electronic medical records). Medidata was utilized as the electronic data capture system for Studies 200807 and 200808. Source records for the enrolled study patients were examined. Subject enrollment per inclusion and exclusion criteria, treatment assignment, adverse events reporting, concomitant medications, vital signs and study visits/procedures were assessed.

Adverse events and serious adverse events were assessed for reporting adequacy. No deaths occurred in Study 200807. Seven deaths occurred at the site in Study 200808; the recorded deaths were not considered to be related to the investigational product. Verifications of adverse events for all five subjects in Study 200807 and 30 subjects in Study 200808 were conducted. The inspection did not identify any underreporting of adverse events.

The primary efficacy data were verified against the data line listings. Selected primary efficacy endpoint raw data were also reviewed in this audit. No discrepancies were noted.

At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

2. Anjay Rastogi, M.D., Ph.D.

University of California Los Angeles
Division of Nephrology
10833 Le Conte Ave, Factor Bldg. 7-155
Los Angeles, CA 90025

Inspection dates: April 25 to May 3, 2022

This site was inspected for Studies 200807 and 200808.

For Study 200807 (Site 223592), 60 study subjects were screened, and 36 subjects enrolled. Nineteen subjects completed the study. Discontinuations for the 17 subjects were for the following reason: efficacy-related reason (1 subject), discontinuation due to geographic relocation (3 subjects), discontinuation due to treatment-rescue reasons (2 subjects); discontinuation due to kidney transplantation (2 subjects); discontinuation due to cancer (1 subject); discontinuation due to patient preference (1 subject); discontinuation due to study burden on patient (1 subject) and discontinuation due to unspecified reasons (6 subjects). The study records for all 36 enrolled subjects were evaluated during the inspection.

For Study 200808 (Site 223520), four study subjects were screened and two patients were enrolled. One subject completed the study and the other patient discontinued (due to kidney transplantation). All enrolled subject records were audited.

Site training records, study regulatory binders, correspondence between the clinical study site and the institutional review board, monitoring, and other sponsor-related documentations were assessed. The following records were evaluated: patient informed consent forms, eligibility documentation, laboratory reports, progress notes, concomitant medications, medical records, protocol deviations, adverse event reporting, study drug accountability, drug storage, drug dispensing and site training records.

Source documents at the clinical study site were compared against patient data listings. The primary efficacy data were verified against the data line listings. All adverse events, serious adverse events and deaths were reviewed for all subjects enrolled in Studies 200807 and 200808. In general, no significant discrepancies were encountered. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

3. Chao Sun, M.D.

3660 Park Sierra Drive, Suite 209
Riverside, CA 92505

Inspection dates: April 18-22, 2022

This site was inspected for Study 200808 (Site 224182). A total of 36 subjects were screened and 13 subjects enrolled. Of the 13 patients who received treatment, the following patients discontinued from study due the following: patient refusal to further participate in the study (1 patient), death (5 subjects) and patient withdrawal due to efficacy concerns (1 subject). All enrolled subject records were reviewed for this site audit.

This inspection covered the following areas: IRB submissions and approvals, correspondence and reporting, sponsor correspondence, informed consent forms, source documents, delegation logs, case report forms, financial disclosure forms, training program documents, investigator agreements, investigational product accountability, monitoring procedures, monitoring logs and protocol adherence.

Source records for the enrolled study patients were examined. Subject inclusion and exclusion criteria, treatment assignment, primary efficacy endpoint, adverse event reporting and concomitant medications were assessed.

The primary efficacy data were verified against the data line listings. Adverse events and serious adverse events were evaluated for reporting adequacy in all enrolled study patients. No discrepancies were noted. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

4. Kendra Hendon, M.D.
320 Park 40 North Boulevard
Knoxville, TN 37923

Inspection dates: April 4-8, 2022

This site was inspected for Study 200808 (Site 223588). A total of 44 subjects were screened and 13 subjects enrolled. Of patients who received treatment, seven subjects who received treatment completed the study, and six subjects discontinued due to the following reasons: patient withdrawal due to poor drug product compliance (1 subject), patient withdrawal due to lack of efficacy response to drug (1 subject), lost to follow-up (1 subject), patient withdrawal of consent (1 subject) and death (2 subjects). Thirteen subject records were reviewed in this audit.

The following regulatory documents, in part, were examined: Investigator's brochures, sponsor correspondence, IRB correspondence, monitor correspondence, training records, study protocols, safety reports, and investigational product accountability and shipping records.

The primary efficacy data were verified against the data line listings. Adverse events and serious adverse events were assessed for reporting adequacy. No discrepancies were noted. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

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MIN LU
07/25/2022 09:54:25 AM

JENN W SELLERS
07/25/2022 11:18:52 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/7/2022

TO: Division of Non-Malignant Hematology (DNH)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216951

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Clinical site: The Office of Regulatory Affairs (ORA) conducted a Remote Regulatory Assessment (RRA) for the site in February 2022, which falls within the surveillance interval. (b) (4) .

The following items were discussed with the site during the RRR close out meeting:

- Failure to report adverse events and concomitant medications for multiple subjects.
- Sporadic data transcription errors and concerns regarding legibility of progress notes.
- Subject (b) (6) was enrolled and dosed prior to the completion of all screening assessments.

OSIS concluded that the data from the audited studies were reliable. However, OSIS recommended that the review division evaluate the impact of the unreported adverse event in one subject on subject safety, the inclusion of data from one ineligible subject on PK and immunogenicity assessments, and the use of concomitant medications by three subjects on the reliability of study data (Final OSIS Review - February 2022).

Analytical site: OSIS inspected the site in (b) (4) The inspection was conducted under the following submission: (b) (4)

The final classification for the inspections was No Action Indicated (NAI). OSIS notes that the current study was initiated within (b) (4) of the pervious inspection and the previously inspected study utilized a similar method of analyses (b) (4)

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Anaheim Clinical Trials, LLC.	2441 West La Palma Avenue, Suite 140, Anaheim, CA
Analytical		(b) (4)

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/s/

FOLAREMI ADEYEMO
07/07/2022 03:01:11 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 14, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Caden F Brennen
DRO-CHEN/DNH

Subject: QT Consult to NDA 216951 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 2/3/2022 regarding the sponsor's QT/QTc assessments. We reviewed the following materials:

- Clinical study report for study PHI113635 (NDA216951 / SDN 0001; link);
- Previous IRT review(s) for IND101291 dated 04/08/2016 in DARRTS (link); and
- Proposed JESDUVROQ (daprodustat) label (NDA216951 / SDN 0001; link).

1 Responses for the review division

Question from the review division: We have received a new NME NDA 216951 submission and are submitting an consult request to review QT/QTc evaluation and its associated data

IRT's response: We previously reviewed the results from a thorough QT study (PHI113635) for daprodustat and concluded absence of QT prolongation at the supratherapeutic dose (500 mg). The supratherapeutic dose covers the high clinical exposure scenario (CYP2C8 inhibition) and provides approximately 10 times the maximum approved dose. Below are proposed edits to the label submitted to SDN 0001 (link) from the CSS-IRT. *Our changes are highlighted (addition, ~~deletion~~).*

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

dose 10 times the maximum recommended dose, daprodustat does not prolong the QTc interval to any clinically relevant extent.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

2 BACKGROUND

Daprodustat is a prolyl hydroxylase inhibitor that is proposed for the indication of treatment of anemia due to chronic kidney disease (CKD) in adults. The maximum daily dose is 24 (b) (4) mg QD (b) (4)

Daprodustat has oral bioavailability of 65% and T_{max} ranging from 1–4 hours. Its volume of distribution is 14.3 L, with blood to plasma ratio of 1.23. Its terminal elimination half-life ($t_{1/2}$) ranges from 1 – 4 hours and is primarily metabolized by CYP2C8 with minor contribution of CYP3A4. Daprodustat has negligible systemic accumulation, consistent with its $t_{1/2}$ and ≥ 24 hr dosing interval. The main circulating moieties are daprodustat (which accounts for 40%) and three metabolites that each account for >10% of the circulating moieties. The predominant metabolites do not exhibit systemic accumulation due to their short $t_{1/2}$ ranging from 1.66 - 4.12 hours. Age and renal impairment have no influence of daprodustat PK, but patients with stage 3-5 CKD had higher systemic exposure (up to 6.9-fold higher in HDD subjects on non-dialysis days) of daprodustat metabolites compared to normal subjects. Hepatic impairment results in up to 2-fold increase in both C_{max} and $AUC_{0-\infty}$. Co-administration of gemfibrozil (a strong CYP2C8 inhibitor) could result to up to 18.6-folds and 3.92-folds higher $AUC_{0-\infty}$ and C_{max}, respectively, compared to daprodustat alone. Based on this pharmacokinetic information, the anticipated high clinical exposure scenario is when daprodustat is co-administered with a strong CYP2C8 inhibitor.

The sponsor assessed the potential for QTc prolongation for daprodustat in a two-part study that aimed to evaluate the pharmacokinetics, safety, and tolerability of a high, single oral dose (500 mg) of daprodustat (Part A), and to assess the effect of single, oral dose of daprodustat on cardiac repolarization (Part B) in healthy volunteers. The results from the sponsor's assessment were reviewed previously. In brief, no significant QTc prolongation effect for daprodustat (doses of 75 mg and 500 mg) was detected in the TQT study. Table 1 shows the results from the by-time point analysis of data from the study. Based on the assessments of the previous IRT review, the supratherapeutic dose (500 mg) produces mean C_m values of (b) (4)-fold the mean C_{max} of 75 mg. This implies that it produces mean C_{max} that is > (b) (4)-fold higher than mean C_{max} of the recommended maximum daily dose of (b) (4). The concentrations observed with the 500 mg dose therefore covers the anticipated high clinical exposure scenario (4-fold increase after co-administration of therapeutic dose with strong CYP2C8 inhibitor) and is approximately (b) (4)-fold the maximum approved dose ((b) (4). The 500 mg dose also provided C_{max} values for the metabolites that are higher than those expected after administration of 75 mg in subjects with CKD.

Table 1. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for daprodustat (75 mg and 500 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis: Part B)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
GSK1278863 75 mg	4	2.2	(0.2, 4.1)
GSK1278863 500 mg	5	0.9	(-1.2, 3.0)
Moxifloxacin 400 mg*	4	11.5	(9.5, 13.5)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.8 ms.

Source Previous IRT for IND101291 dated 04/08/2016 in DARRTS (Link)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

ELIFORD N KITABI
03/14/2022 08:06:25 AM

LARS JOHANNESEN
03/14/2022 08:08:32 AM

CHRISTINE E GARNETT
03/14/2022 08:09:54 AM