CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216951Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

Note: This is a corrected review that does not change the overall recommendations/conclusions of the original review dated December 20, 2022.

1. Application/Product Information

NDA Number.	216951
Applicant Name	GlaxoSmithKline Intellectual Property (No. 2) Limited England
Drug Product Name	JESDUVROQ (daprodustat)
Dosage Form.	Tablet
Proposed Strength(s)	1 mg, 2 mg, 4mg, 6 mg, and 8 mg
Route of Administration	Oral
Maximum Daily Dose	24 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of anemia due to chronic kidney disease in adult patients on dialysis and not on dialysis.
Drug Product Description	• Daprodustat Tablets, 1 mg, are gray film-coated, round (approximately 7 mm in diameter), biconvex tablets, debossed with “GS KF” on one face. • Daprodustat Tablets, 2 mg, are yellow film-coated, round (approximately 7 mm in diameter), biconvex tablets, debossed with “GS V7” on one face. • Daprodustat Tablets, 4 mg, are white film-coated, round (approximately 7 mm in diameter), biconvex tablets debossed with “GS 13” on one face. • Daprodustat Tablets, 6 mg, are pink film-coated, round (approximately 9 mm in diameter), biconvex tablets debossed with “GS IM” on one face. • Daprodustat Tablets, 8 mg, are orange film-coated, round (approximately 9 mm in diameter), biconvex tablets debossed with “GS 5E” on one face.
Co-packaged product information	Not Applicable
Device information:	Not Applicable

Storage Temperature/ Conditions	Store at 20°C to 30°C (68°F to 86°F).		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Ben Zhang ONDP/DNDAPI/NDB3;	Zhengfu Wang ONDP/DNDAPI/NDB3;
	Drug Product/ Labeling	Akm Khairuzzaman ONDP/DNDPIII/NDPB5	Mohan Sapru ONDP/DNDPIII/NDPB5
	Manufacturing	Liya Tang OPMA/DPMAIII/PMB7; Haitao Li OPMA/DPMAIII/PMB7	Feiyan Jin OPMA/DPMAIII/PMB7; Sharmista Chatterjee OPQ/OPMA/DPMAII
	Biopharmaceutics	Debasis Ghosh ONDP/DB/BB3	Haritha Mandula ONDP/DB/BB3
	Microbiology	Julia Marre OPMA/DMAI/MAB2	Nandini Bhattacharya OPMA/DMAI/MAB2
	Other (specify):	Ileana Barreto-Pettit, Lead Investigator for drug product pre-approval inspection (PAI); Seneca Toms, Lead Investigator for drug substance pre-approval inspection (PAI); Sharmista Chatterjee, ETT Lead	
	RBPM	Grafton Adams OPRO/DRBPMI/RBPMB2	
	ATLs	Theodore Carver ONDP/DNDPIII/NDPB5 Sharmista Chatterjee OPQ/OPMA/DPMAII	
Consults	Not Applicable		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

The drug product expiry dating period is 36 months, when the drug product is stored at 20°C to 30°C (68°F to 86°F).

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background
The Applicant submitted a New Drug Application (NDA) seeking marketing approval for Daprodustat, an hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI), indicated for the treatment for anemia due to chronic kidney disease in adults on dialysis and not on dialysis. Daprodustat tablets are manufactured in five strengths, 1 mg, 2 mg, 4mg, 6 mg, and 8 mg, and are intended to be taken orally once daily and three times weekly. Daprodustat is designated as a new molecular entity (NME). This NDA was accepted into FDA Emerging Technology Program based on the adoption of a continuous manufacturing process for the drug product, and the tablet drug product may be manufactured by either a continuous or a batch process. Aspects of this dual approach are addressed in the drug product, manufacturing process, and biopharmaceutics reviews. Because of this manufacturing strategy adopted by the Applicant, two manufacturing process reviews are included in this Integrated Quality Assessment, for both the continuous and batch manufacturing processes.

2.) Drug Substance:
The daprodustat drug substance is a white to off-white crystalline, non-hygroscopic, powder that is practically insoluble to very slightly soluble in water and aqueous buffers. Daprodustat is a synthetic molecule without any chiral centers and is manufactured (b) (4) (b) (4) The drug substance manufacturer provided adequate data with respect to characterization of the structure of the drug substance, and appropriate risk assessments were performed with respect to ICH M7 for process impurities and related substances. The proposed regulatory starting materials are adequately justified per ICH Q11. The drug substance review concluded that the manufacturing process and controls were adequate. See also the manufacturing review summary, including review of the (b) (4) drug substance manufacturing process. The drug substance

release specification includes appropriate tests and acceptance criteria to support the quality of the drug substance as a part of the overall control strategy. The specification includes tests for polymorphism and particle size, which were appropriately justified, as described in the drug product and biopharmaceutics reviews. The stability data support a (b) (4) re-test period under long-term storage conditions (b) (4)

3.) Drug Product:

The daprodustat drug product is a film-coated, immediate release tablet containing compendial excipients commonly used in oral tablet formulations. The drug product is manufactured using either of two different manufacturing processes designed to product the same drug product: a batch process or a continuous process. Each process includes (b) (4) Daprodustat drug product manufactured using both types of processes were bridged with a bioequivalence study, and no differences were observed in batch and stability data for batches manufactured using either process. The review concluded that critical quality attributes of the drug product were properly identified and appropriately controlled in the specification. Risk assessments for impurities included the risk of potential process-related impurities, related substances, degradants, elemental impurities, and (b) (4) The drug product packaging consists of an HDPE bottle with an induction heat-seal liner and (b) (4) cap.

The review of the stability data for the drug product identified an issue related to two-tiered microbiological testing proposed in the drug product specification. The Applicant proposed, in lieu of microbial limits testing for every batch, to conduct water activity testing followed by microbial limits testing if water activity exceeds a specified limit. This approach was initially found not to be adequately justified but was subsequently deemed acceptable based the Applicant's submission of additional supporting information and a revised stability protocol for the stability testing of annual lots. See also the product quality microbiology review of the drug product specification and test methods. Out-of-specification (OOS) results were obtained for water activity testing after 12 months for several batches, and although all lots have passed microbiological testing, the drug product review concluded based on these results that the acceptable shelf life is limited to the maximum 36 months of real time stability data. A shelf life of 36 months for the drug product is granted based on up to 36 months long-term (30ºC/75%RH) and 6 months accelerated (40ºC/75%RH) stability data.

4.) Manufacturing:

This application was accepted into FDA Emerging Technology Program. Daprodustat tablets are film-coated tablets for immediate release (b) (4) (b) (4) for five dosage strengths (1 mg, 2 mg, 4 mg, 6 mg, 8 mg). The drug product is intended to be commercially manufactured either by a Continuous Process (an emerging technology) or a Batch Process. Tablets produced by Batch Process are manufactured by a contract manufacturer (b) (4) (b) (4)

Tablets produced by the Continuous manufacturing Process are manufactured at Glaxo Wellcome UK using (b) (4) (b) (4)

The drug product content uniformity (CU) is monitored (b) (4) (b) (4) (b) (4) Acceptance criteria applied is based on (b) (4) method to ensure (b) (4)% confidence level with (b) (4)% coverage. The firm also committed, as a lifecycle consideration for (b) (4) testing, to performing (b) (4) testing

(b) (4) for a minimum of two batches per tablet strength if manufactured and for at least one confirmation batch per tablet strength to support any planned lifecycle change. The drug product quality is also ensured (b) (4)

Batch size by the Continuous Process is defined (b) (4) (b) (4) (b) (4) The proposed commercial process is validated at the commercial manufacturing site.

Daprodustat drug substance is manufactured by (b) (4) (b) (4)

Manufacturing Facilities: Pre-approval inspections (PAIs) were held for the drug substance manufacturing site at Jurong, Singapore (FEI 3002807079) and the continuous drug product manufacturing site in Ware, UK (FEI 3003262904). OPMA assessors participated as subject matter experts in both PAIs. The outcome of both PAIs was NAI (no action indicated). All other facilities were approved based on the previous history of each facility or classified as not needing evaluation. The overall recommendation with respect to facilities is Approval.

5.) Biopharmaceutics Aspects of the Drug Product:

The daprodustat drug substance is insoluble in aqueous buffers near physiological pH and is predicted based on an ADMET predictor to have high

permeability, and the Applicant has designated it as a BCS Class II drug substance. Based on stability data, there is no change in [redacted] (b) (4) polymorphic form [redacted] (b) (4) indicating that a change in daprodustat morphology that would affect dissolution is unlikely, although particle size may have an impact on drug release. The Applicant manufactured tablets containing [redacted] (b) (4) drug substance and performed an in vivo bioequivalence (BE) study using 100 mg tablets and used these data to support the acceptance criteria for particle size in the drug substance specification.

The daprodustat drug product is an immediate-release tablet. The Applicant conducted a BE study to establish bioequivalence between the continuous and batch manufacturing processes, and this study met the BE acceptance criteria. In addition, in vivo and in vitro studies support the equivalency of all tablet strengths. No bridging between the Phase 3 and commercial drug products was deemed necessary. The Applicant performed bioavailability and pharmacokinetic studies with product variants with differentiated dissolution profiles to establish a dissolution safe space with respect to critical bioavailability attributes. The adequacy of these studies was confirmed by the clinical pharmacology reviewer, and the review concluded that future batches with dissolution profiles meeting criteria within the dissolution safe space can be considered bioequivalent.

With regards to dissolution test method development, optimization with regards to small changes [redacted] (b) (4) yielded an acceptable dissolution method with adequate data to bridge from Procedure C used for Phase 3 clinical batches to the commercial Procedure E. For the batch manufacturing process, film-coated tablets will be tested. For the continuous manufacturing process, the proposed dissolution method will be performed using tablets collected across six approximately equally spaced intervals in each run, [redacted] (b) (4) which was deemed acceptable based on [redacted] (b) (4) (b) (4) [redacted] (b) (4) and other data. The proposed dissolution acceptance criterion of Q= [redacted] (b) (4) % at 45 min is supported by dissolution data from 30 pivotal clinical batches and BE batches. The biopharmaceutics review concluded that NDA 216951 is adequate with respect to the proposed dissolution test method and supporting biopharmaceutics information.

6.) Microbiological Aspects of the Drug Product:

Although this is a non-aqueous, non-sterile, tablet drug product, a microbiology review was requested to address an issue in the drug product stability testing with respect to assurance of microbiological quality during the drug product review (see the drug product review). Specifically, the Applicant proposed to test for water activity instead of microbial limits testing in the drug product release and stability specifications, but did not justify this approach using appropriate data, including a history of acceptable test results for microbial limits and description of microbiological controls during manufacturing. In response to information requests, the Applicant provided additional information regarding the manufacturing process, microbiological controls, historical batch data, and the history of the manufacturing sites. In addition, the Applicant updated the post-approval stability protocol and stability committment to include microbial limits testing at 12, 24, 36, 48, and 60 months for annual commercial batches placed on stability. This information and change to the stability commitment were deemed adequate to address the microbiological concerns.

7.) Quality Labeling Aspects of the Drug Product:

The review of the product quality labeling concluded that the prescribing information and labels for the container and carton were adequate, provided that the storage condition is revised in each of these to change the storage condition throughout the labeling. This requirement will be communicated to the Applicant.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None.

Comparability Protocols (PACMP): No
Comments: None.

Additional Lifecycle Comments:

Lifecycle considerations for the review team:

Drug substance specification: The drug substance is a BCS class II compound. Any change in drug substance specification, (b) (4) (b) (4) would require a PAS and may require a relative BA study.

Drug product content uniformity testing: The Applicant committed, as needed in the future, to performing (b) (4) testing (b) (4) for a minimum of two drug product batches per tablet strength if manufactured and for at least one confirmation batch per tablet strength, to support any planned lifecycle change.

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	JESDUVROQ (daprodustat) tablets, for oral use
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Tablets: 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Unscored Tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	None
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	None. Its an immediate release tablet.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	Not a parenteral product.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	This is a new molecular entity, there is no USP monograph.
For radioactive products, include radiation dosimetry	N/A	Not a radioactive product.

for the patient and healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	Not applicable.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Tablet
Strength(s) in metric system	Adequate	1 mg, 2 mg, 4 mg, 6 mg, and 8 mg.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	This is a new molecular entity, there is no USP monograph.

Continued on next page.....

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	(b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Unscored tablet.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product.

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	JESDUVROQ (daprodustat) tablets, for oral use
Dosage form(s) and route(s) of administration	Adequate	Solid oral tablet
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	This is a new molecular entity, there is no USP monograph.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Provided in alphabetical order under labeling section 11, page 11 to 12.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not a parenteral injectable dosage form.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	There is no alcohol in the formulation.
Sterility statement (if applicable)	N/A	Not a sterile product.
Pharmacological/Therapeutic class	Adequate	Provided under section 11 as *"inhibitor of hypoxia inducible factor (HIF)-prolyl-4-hydroxylases (PHD)1, PHD2 and PHD3."*
Chemical name, structural formula, molecular weight	Adequate	Provided under section 11, page 11-12.
If radioactive, statement of important nuclear characteristics.	N/A	Not a radioactive compound.

Other important chemical or physical properties (such as pKa or pH)	Adequate	Its solid oral product. Information regarding poorly soluble characteristics of the drug has been provided under section 11.
For oral prescription drug products, include gluten statement (if applicable)	N/A	None
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	N/A	None
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	There is no USP monograph.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Tablet
Strength(s) in metric system	Adequate	1 mg, 2 mg, 4 mg, 6 mg, and 8 mg.
Available units (e.g., bottles of 100 tablets)	Adequate	packaged in bottles of 30 (b) (4)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Adequately provided for each strength under the section 16.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Unscored tablet
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not an injectable product.
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	There is no special instruction.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	The Applicant's recommended storage temperature is (b) (4) (b) (4) (b) (4) Based on the formulation, if the labeling is revised to 20°-30° C (68°-86° F), there is no concern/risk at the suggested lower temperature because this is a solid oral tablet (b) (4) (b) (4) Hence, the PI and container labels are recommended to be edited to read as: "Store at 20°-30° C (68°-86° F)".
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made*	N/A	There is no "latex-free" statement in the labeling.

with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	Adequate	(b) (4) (b) (4) there is no statement under section 16.

1.2.5 Other Sections of Labeling

There is no other sections of labeling that contain product-quality related information such as warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenteral, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol].

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Container labeling has the following information: GlaxoSmithKline (b) (4) Made in Singapore.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): The only quality related aspects that are provided in the medication guide is as follows:

(b) (4)

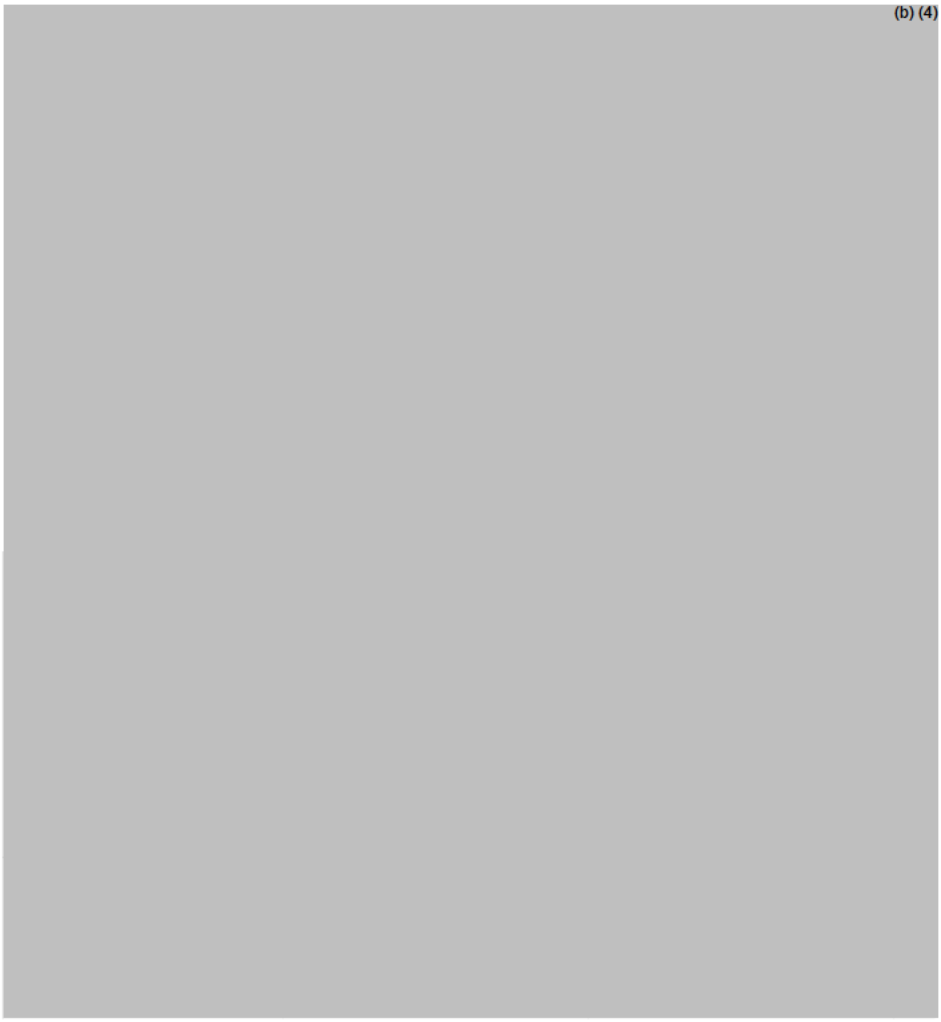
Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Medication Guide (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	JESDUVROQ (daprodustat) tablets, for oral use
Special preparation instructions (if applicable)	N/A	None
Storage and handling information (if applicable)	Adequate	The medication guide does not repeat the storage condition. However, the package insert, and bottle labeling has instruction.
Active ingredient(s) (if applicable)	Adequate	Yes
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Yes

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(b) (4)



Similar labeling has been provided for the other strengths.

3.2 Carton Labeling

There is no carton

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	(b) (4)
Strength(s) in metric system	Adequate	1 mg, 2 mg, 4 mg, 6 mg, and 8 mg.
Route(s) of administration	Adequate	For oral use
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Not a salt.
Net contents (e.g., tablet count, volume of liquid)	Adequate	Provided (30 (b) (4) tablets)
"Rx only" displayed on the principal display	Adequate	Provided
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Applicant proposed (b) (4) (b) (4) CMC Team edited the PI to read as "Store at 20°-30° C (68°-86° F)". Applicant will be instructed to change the container labelling accordingly.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	The product container does not contain a desiccant.
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	Not a parenteral product
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not a parenteral product

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	
Name of manufacturer/distributor /packer	Adequate	GlaxoSmithKline (b) (4) Made in Singapore.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *{Adequate}*

Storage condition recommendation has been changed in the PI by the CMC review team. Applicant should be informed to change their container labeling accordingly.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Akm Khairuzzaman, Ph.D. 9/6/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Mohan Sapru, Ph.D., 9/6/2022

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Akm Khairuzzaman

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Mohan Sapru

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	JESDUVROQ[1] (Daprodustat) Tablet for the treatment of anemia of Chronic Kidney Disease (CKD) in patients on dialysis and not-on-dialysis.
NDA Number	216951
Assessment Cycle Number	1
Drug Product Name/ Strength	Daprodustat Tablet/ 1mg, 2 mg, 4 mg, 6 mg, 8 mg (b) (4) (b) (4)
Route of Administration	Oral
Applicant Name	GSK
Therapeutic Classification/ OND Division	Oncology/Division of Non-Malignant Hematology
RLD/RS Number	NA
Proposed Indication	For the treatment of anemia due to Chronic Kidney Disease in patients on dialysis and not-on-dialysis

Assessment Recommendation: **Adequate**

Assessment Summary:

On February 1, 2022, the Applicant submitted a New Drug Application (NDA) seeking approval to commercialize Daprodustat Tablets as a treatment for anemia due to chronic kidney disease in adult patients on dialysis and not on dialysis. Daprodustat is a hypoxia-inducible prolyl hydroxylase inhibitor. Daprodustat Tablets 1 mg, 2 mg, 4 mg, and 8 mg are intended to be used orally once daily and three times weekly with a maximum recommended daily dose of 24 mg. All strengths were used in pivotal Phase III clinical and BE studies. No biowaiver for any of the strengths is requested.

Drug substance, daprodustat, is a white to off-white crystalline, non-hygroscopic, powder. It has two pKa values: 3.24 (carboxylate) and 6.18 (enolate). Based on ADMET predictor, daprodustat exhibits high permeability. It is insoluble in array of physiological pH. Based on its solubility and permeability, the Applicant designated it as BCS Class II drug substance.

Polymorphic screening study data indicated the existence of (b) (4) which is thermodynamically stable and consistently manufactured using the proposed drug substance manufacturing process. Based on stability data, there is no form change on storage of drug substance or drug product which ensures no effect on dissolution due to change of morphology of drug substance.

Like any low solubility drug substance, particle size of daprodustat is expected to influence the dissolution. During the development Phase, the Applicant manufactured tablets using

[1] Request for proprietary name review (SN 002)

(b) (4) drug substance (Phase I and Phase II clinical study products). To determine the effect of particle size of drug substance on the pharmacokinetics (PK) of daprodustat, the Applicant performed an in vivo BE study (PHI114703) with 100 mg strength tablets manufactured with (b) (4) drug substance. Based on this study, Daprodustat Tablets with particle sizes of (b) (4) µm meet BE criteria and are deemed bioequivalent. While BE study was conducted with 100 mg strength which is about 10-100 times more than the to-be-marketed strength, the relevancy of the product performance using 100 mg strength is unclear. Following an information request by drug product reviewer (April 13, 2022), the Applicant provided justification for the use of 100 mg strength for particle size BE study and also, as recommended by the Agency, proposed a specification for drug substance particle size. The proposed particle size specification ((b) (4) µm) is supported by in vivo BE data and Pivotal Phase III clinical batches ((b) (4) µm to (b) (4) µm). From a biopharmaceutics standpoint, it is acceptable. Drug product reviewer also confirmed the adequacy of the proposed drug substance particle size specification.[2]

Drug product is an immediate release tablet. Tablets are formulated as round, bi-convex, film-coated, debossed on one side, and color-coded for strength. Tablets are not scored. (b) (4) (b) (4) While 10 mg strength tablet was used in pivotal Phase III Clinical Study, it is not intended to be marketed at this time. (b) (4) (b) (4) (b) (4) (b) (4) The Tablets will be packaged in (b) (4) (b) (4) closure. Tablets are manufactured using (b) (4) by either continuous process or batch process. The Applicant indicated both manufacturing processes will be used for to-be-marketed drug products.

For Phase I clinical studies, 2 mg, 5 mg, 25 mg, and 100 mg tablets were manufactured using (b) (4) batch process (b) (4) For Phase II clinical studies, 0.5 mg, 1 mg, 2 mg, 5 mg, 25 mg, and 100 mg tablets were manufactured using (b) (4) batch process (b) (4) Between Phase I and Phase II products, there is no change of composition (b) (4) (b) (4) (b) (4) Since there is no significant change of relevant doses, no bridging between Phase I and Phase II is necessary.

Formulation used in Phase III pivotal clinical studies, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, and 10 mg tablets were manufactured using continuous process (b) (4). Noted, Phase III products (continuous process) and to-be-marketed products contain about (b) (4) Although, not used for pivotal Phase III clinical study, to-be-marketed product manufactured by batch process also contains (b) (4) As discussed earlier, the Applicant conducted

[2] Drug product Review

an in vivo BE study (PHI114703) to determine the effect of drug substance particle size and concluded that [redacted] drug substance are bioequivalent. Therefore, a bridging for [redacted] drug substance is established. To establish BE between daprodustat tablets made by two different manufacturing process (Continuous process or Batch process), the Applicant conducted BE Study #213002 Part A with all strengths. The study met the BE acceptance criteria. Therefore, a bridge between Batch process and Continuous process is established.

The Applicant indicated that "*for commercial formulations, the* [redacted] *tablet formulations are identical unit dose composition*." The only difference is color of the coatings for commercial product compared to Phase III product (white) to achieve visual differentiation across the tablet strengths. Based on our assessment, no bridging between Phase III product and commercial product is necessary.

The Applicant also conducted BE study (#207727 Part 1) to demonstrate BE between 2 mg strength and 4 mg strength. In addition, comparative dissolution data in multimedia using all strengths are provided. The in vivo and in vitro studies were performed to establish equivalency between tablet strengths. The in vivo and in vitro data support the equivalency of all strengths.

The Applicant developed a dissolution safe space. The method involves biopharmaceutics risk assessment, identification of potential critical bioavailability attributes (CBAs), manufacturing of product variants with differentiated dissolution profiles using the proposed commercial dissolution method, and finally clinical PK study with target and variant batches to determine whether dissolution profiles changes affect the in vivo PK performance. The Applicant identified [redacted] for continuous process and [redacted] for batch process as critical process parameters. Relative BA study (213002 Part A) with target batch and variant batches comply with BE criteria.[3] Based on the result of this study, a safe space is established. So, future batches with in vitro dissolution profiles within in vitro dissolution safe space would be considered bioequivalent. It is noted that dissolution safe space [redacted] also validates the proposed design space for [redacted] continuous process and batch process.

The Applicant provided report on the evolution of the dissolution method during the development phase. While there are some differences in those methods (Procedure A to Procedure E), the dissolution apparatus (USP II) and dissolution medium (potassium phosphate buffer pH 6.8) are the same for all methods. The [redacted] was used for Procedure A only but [redacted] was used in Procedure B-E. Both methods (Procedure A and B) were developed for tablet formulation across 0.5 mg to 100 mg tablet strengths. Later further optimization of Procedure B led to Procedure C [redacted]

[3] Adequacy of BE studies were confirmed by the reviewer of the Office of Clinical Pharmacology (email communication xx/xx/

This method (Procedure C) was used for analysis of pivotal Phase III clinical batches. Procedure D was developed as an optimized better discriminating method (b) (4) (b) (4) (b) (4) (b) (4) However, Procedure D was never used for the release and only used for development batches. Finally, (b) (4) (b) (4) the proposed commercial method, Procedure E, was developed. The Applicant reasoned (b) (4) (b) (4) The Applicant provided dissolution method development report including selection of the dissolution apparatus, dissolution medium, surfactant and discriminating ability of the method to detect changes in critical bioavailability attributes. A method validation study including robustness of the proposed dissolution method is also provided. Since Procedure C was used for pivotal Phase III clinical study, a bridging with the proposed commercial method, Procedure E, is required. To establish bridging, the Applicant provided dissolution data for batches using both methods. From biopharmaceutics standpoint, the bridging with Procedure C is established and Procedure E is acceptable as the proposed commercial dissolution method.

(b) (4) The proposed commercial dissolution method is sensitive enough to detect any changes to product quality during the manufacturing run time. The safe space developed by using samples with differential dissolution, which also ensures product quality. The dissolution data from process validation batches for all strengths exhibited similarity (f2>50). Therefore, considering totality of the information (e.g., safe space, design space (b) (4) and real time data from process validation batches for all strengths) the collection of samples (b) (4) is adequate.

The proposed dissolution acceptance criterion of Q= (b) (4)% at 45 min is supported by dissolution data from 30 pivotal clinical batches and BE batches. It is adequate.

Table 1: Proposed and Approved Dissolution Method (Procedure E)

Source	Apparatus	Paddle Speed	Medium	Volume	Temp	Acceptance Criterion
In House	USP II	50 rpm	30 mM Phosphate Buffer pH 6.8	500 ml (1 mg Tablet) 900 mL (2-8 mg Tablets)	37°C	Q= (b) (4)% in 45 min

Table 2. Summary of BE studies (relevant to Biopharmaceutics)(summarized by this reviewer)

Study Identifier	Study Objective	Treatment Details	Batches Used
PHI114703	To determine the effect of particle size on the pharmacokinetics of single oral 100mg doses	100 mg daprodustat ((b) (4) µm (b) (4) percentile particle size); oral, single Dose	Lot 101248873 & 101275802
207727 Part 1	To evaluate the bioequivalence of daprodustat tablets (2 mg tablet vs. 4 mg tablet) (Part 1)	Part 1 (fasted state): 2 mg, 4 mg daprodustat; oral	2 mg: Lot 162395412; 4 mg: 162395413
213022 Part A	To characterize single-dose pharmacokinetic (PK) profile of 4 mg daprodustat tablets with two different dissolution profiles made by Process 2 relative to the reference 4 mg daprodustat tablet made by Process 1.	Part A: 4 mg daprodustat: Process 1, Dissolution profile #1 Process 2 and Dissolution profile #2 Process 2	UX3G/202418607; (Process 1) 424521/202420296 and 4245422/202420297 (Process 2) (all film-coated tablets)
213022 Part B	To establish bioequivalence (BE) between daprodustat tablets made by two different manufacturing processes, Process 1 and Process 2, for the following dose strengths administered as a single-dose: 1, 2, 4, 6, and 8 mg	Part B: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg daprodustat: Process 1 and Process 2	1 mg: AEAS/202419689; 2 mg: MJ4B/202418489; 4 mg: UX3G/202418607; 6 mg: RY7L/202418492; 8 mg: 252F/202420665 (all Process 1) 1 mg: 4230522/202420289; 2 mg: 424502/202420290; 4 mg: 4245417/202420294; 6 mg: 424508/202420299; 8 mg: 4324885/2024212278 (all Process 2) (all film-coated tablets)

CQAs	Initial Risk Ranking*	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
API Particle size	High	(b) (4)	Low	(b) (4)
Polymorphic form	Medium		Low	
(b) (4)	High		Low	
Hardness of Tablet (b) (4)	Medium		Low	
(b) (4)	Medium		Low	
	Medium		Low	

*from Biopharmaceutics perspective

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
• Original Submission (SN 001) • Response to FDA Request/Comment: CMC(SN 009) • Response to FDA Request/Comment: CMC(SN 012) • Response to FDA Request/Comment: CMC(SN 017) • Response to FDA Request/Comment: CMC (SN 042) • Response to FDA Request/comment: CMC (SN 080)	02/01/2022 03/31/2022 04/14/2022 04/28/2022 06/22/2022 10/07/2022

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: None

B.1 BCS DESIGNATION
Assessment: NA

Solubility:
Daprodustat is practically insoluble in an array of physiological pH.

Table 3. Solubility of Daprodustat at 25°C

pH	Solubility at 25°C (µg/mL) after 24 hours
1.2	<0.05
2.0	<0.05
3.0	<0.05
4.0	<0.05
5.0	1
6.0	7
7.0	54
8.0	596

Solvent	Solubility (mg/mL)	Description
Simulated Gastric Fluid (SGF), pH 1.6	<0.001	Practically Insoluble
Fasted State Simulated Intestinal Fluid (FaSSiF), pH 6.5	0.049	Practically Insoluble
Fed State Simulated Intestinal Fluid (FeSSiF), pH 6.5	0.585	Very Slightly Soluble
Phosphate buffered saline (pH = 7.4)	0.208	Very Slightly Soluble
Water	0.074	Practically Insoluble

Permeability:
The Applicant stated that human permeability of daprodustat is 2.5 x 10^{-4} cm/sec (predicted using ADMET predictor). So, the permeability is considered high.

Reviewer's Comment: Based on solubility and permeability data, the Applicant designated daprodustat as BCS Class II. The assessment of BCS category is beyond the scope of this review. Note, no biowaiver request is submitted based on BCS classification.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

Dissolution Method

Daprodustat Tablets are an immediate release tablet (1 mg, 2 mg, 4 mg, 6 mg, 8 mg) intended for once daily dosing. An overview of the development of dissolution methods is provided in Table 4. The Applicant stated that Procedure A and B have been previously developed for tablet formulation across 0.5 mg to 100 mg tablet strength range in early clinical studies. Following the narrowing of the tablet strength, a dissolution method (Procedure C) was developed as an optimized dissolution method for testing of Daprodustat tablets during Phase III clinical trial. Later, Procedure D was developed as a supposedly better discriminatory method. However, Procedure D was used for development purposes only. The proposed commercial method, Procedure E, is an optimization of Procedure D. (b) (4)

(b) (4)

(b) (4) The Applicant provided a DOE study to demonstrate the implication of each of the above parameters. Equivalency of Procedure C and Procedure E was evaluated. The Applicant also proposed (b) (4) dissolution method (b) (4) The method development report including discriminating ability of the method to detect changes to critical bioavailability attributes and validation of the method including robustness of the method during minor changes to dissolution parameters were also provided.

Table 4. Overview of Development of Dissolution Method

(b) (4)

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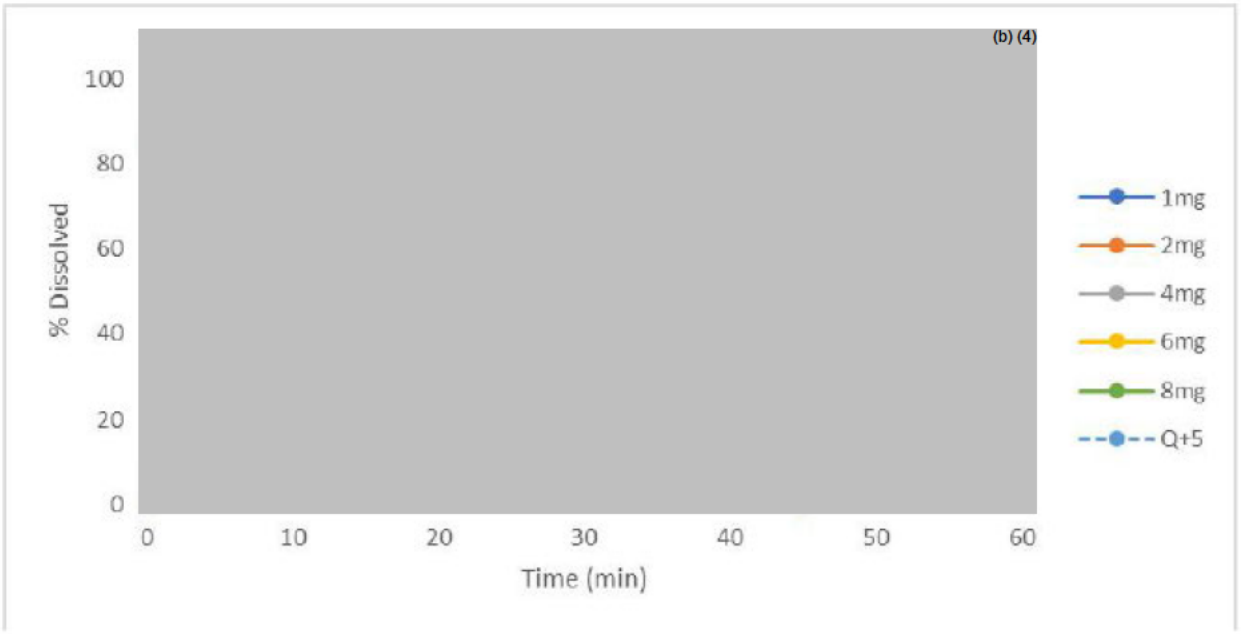
Dissolution Acceptance Criterion

The Applicant proposed a single point dissolution acceptance criterion based on ICHQ6A for immediate release dosage forms. The proposed dissolution acceptance criterion for Daprodustat Tablets is Q= (b) (4)% at 45 minutes. The Applicant stated that the dissolution acceptance criterion is set based on observed dissolution profiles from clinical batches and the primary stability batches as well as impact of the dissolution on biopharmaceutics, in vivo/in vitro bioequivalence data, relative bioavailability study and f2 statistical analysis.

Figure 3. Dissolution Profiles of Daprodustat Tablets (all strengths) (primary stability and pivotal Clinical batches)(reproduced from 3.2.P.5.6)



Based on Phase I First-in-human study (PHX11427) in healthy volunteers, the Applicant concluded that no saturable pharmacokinetics (Cmax, AUC0-t) was observed up to 300 mg dose which indicates that dissolution is not rate limiting to absorption. Based on BE study 207727 (2 mg vs 4 mg) and in vitro dissolution data, strength equivalency is demonstrated across all strengths. The (b) (4) 4 mg strength and this strength is considered to set specification for all strengths.

Relative bioavailability study 213022 Part A included two batches of Daprodustat Tablets, 4 mg, made by the Batch Process that had been manufactured to give differentiated dissolution profiles in relation to the target dissolution profile of the reference batch of Daprodustat Tablets, 4 mg made by the Continuous Process. Profile 1 is manufactured at (b) (4) the design space. Profile 2 is manufactured (b) (4) the design space and is designed to not meet a Q of (b) (4)% at 45 minutes at Stage 1 testing.

Figure 4. Mean Dissolution Data* and Dissolution Profiles (Procedure E) of Batches (4 mg) used in Study 213022 Part A

Batch#	5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min
4245421		58.8%	72.7%	80.6%	85.8%	89.7%	95.7%	98.7%
4245422		43.1%	56.3%	65.4%	72.1%	77.4%	86.9%	92.6%
UX3G	49.9%	75.6%	84.4%	88.8%	91.4%	93.2%	96.0%	97.4%

*compiled by this reviewer from individual dissolution data submitted in SN 012.

Table 7. Outcome of Relative Bioavailability Study with Differentiated Dissolution

Parameter	Treatment	N	Adjusted Geometric Mean	Ratio (Process 2 Dissolution /Process 1)	90% CI
AUC(0-t) (h*ng/mL)	(b) (4)	35	155.5	-	-
		35	159.9	**1.028**	(0.9699, 1.090)
		34	158.5	**1.019**	(0.9602, 1.081)
Cmax (ng/mL)		35	68.22	-	-
		35	71.06	**1.042**	(0.9308, 1.166)
		34	71.51	**1.048**	(0.9349, 1.175)

The results from the BE study indicated that all three batches are equivalent. So, 45 min time point does not reject the biorelevant batch although it was manufactured (b) (4) (b) (4) design space. It is noted that, 30 min time point would have rejected the biorelevant batch.

Reviewer's Comment:
Based on ICHQ6A, "*single-point measurements are normally considered suitable for immediate release dosage forms*." So, the proposed single point dissolution is acceptable. On March 29, 2022, we requested individual dissolution data from pivotal Phase III clinical and registration batches. The Applicant provided a response on April 14, 2022 (SN 012). The Applicant stated that individual dissolution data for 94 batches (BE batch, registration, and stability batches) are provided in 3.2.R.3 original submission. Individual dissolution data for another 30 batches used in pivotal clinical studies and 32 registration/stability batches (15 batch process and 16 continuous process) are provided in SN 012 (see Table 8 and 9). Based on new information, dissolution data from 30 pivotal clinical batches and BE batches were assessed to understand the clinically relevant dissolution profiles. The proposed acceptance criterion of Q= (b) (4)% in 45 min is also supported by BE batches. It is acceptable.

Table 8. Summary of Dissolution Data from 30 pivotal Clinical Batches (all strengths) (range%, USP <711> Stage 1, n=6) (Procedure C) (summarized by this reviewer)

Strength	Batch#	5'	10'	15'	20'	30'	45'	60'
1 mg	R757741	(b) (4)						
	R820913							
	R849789							
2 mg	R757600							
	R802930							
	R849792							
4 mg	R757601							
	R802931							

Strength	Batch#	5'	10'	15'	20'	30'	45'	60'
	R848384							(b) (4)
	R867222							
6 mg	R757604							
	R782893							
	R792716							
	R792717							
	R792718							
	R793209							
	R793211							
	R849793							
	R856476							
	R856481							
8 mg	R757942							
	R782895							
	R783379							
	R794807							
	R794808							
	R794809							
	R848520							
	R848522							
	R856479							
	R856484							
All Strengths	Combined							

Table 9. Summary of Dissolution Data for Daprodustat Tablets used in BE studies (Highlighted method: Procedure C; For 213002 and others using Procedure E)

Study No.	Batch No.	Daprodustat Tablet Strength / Formula Code	Conditions: USP Apparatus 2 (Media, Volume, Paddle Speed)	No. of Dosage Units	Mean % Dissolved (range)							
					15 min	30 min	45 min	60 min	75 min	-	-	-
PHI113634	101248873	(b) (4)	(b) (4) mM potassium phosphate buffer, pH 6.8 + (b) (4) 900 mL (b) (4) rpm	6	97	99	99	99	99 (b) (4)	-	-	-
PHI114703	101275802			6	99	103	104	105	105 (b) (4)	-	-	-
	101275804			6	99	102	103	104	104 (b) (4)	-	-	-
					5 min	10 min	15 min	20 min	30 min	45 min	60 min	-
200232	162395414	6 mg (CT)	(b) (4) mM potassium phosphate buffer, pH 6.8 + (b) (4) 900 mL (b) (4) rpm	6	58	80	88	92	96	99	100 (b) (4)	-
207727	162395412	2 mg (CE)		6	65	85	92	96	99	100	100 (b) (4)	-
	162395413	4 mg (CS)		6	54	75	84	89	94	97	99 (b) (4)	-
					5 min	10 min	15 min	20 min	25 min	30 min	45 min	60 min
213022	202419689	1 mg (FE)	30 mM potassium phosphate buffer, pH 6.8 + (b) (4) 900 mL (2-8mg) (b) (4) rpm	6	64	88	94	97	98	99	100	100 (b) (4)
	202420289	1 mg (FK)		6	-	87	92	93	94	95	97	97 (b) (4)
	202418489	2 mg (FF)		6	66	87	93	96	97	98	100	101 (b) (4)
	202420290	2 mg (FL)		6	-	82	93	96	97	98	98	98 (b) (4)
	202418607	4 mg (FG)		6	56	78	86	90	92	94	97	98

Study No.	Batch No.	Daprodustat Tablet Strength / Formula Code	Conditions: USP Apparatus 2 (Media, Volume, Paddle Speed)	No. of Dosage Units	Mean % Dissolved (range)							
												(b) (4)
	202420294	4 mg (FM)		6	-	75	87	92	94	96	98	98 (b) (4)
	202420296	4 mg (FN)		6	-	55	69	77	82	87	94	98 (b) (4)
	202420297	4 mg (FT)		12	-	41	54	63	70	75	85	92 (b) (4)
	202418492	6 mg (FH)		6	57	80	88	92	94	95	98	99 (b) (4)
	202420299	6 mg (FP)		6	-	79	90	93	95	96	98	97 (b) (4)
					10 min	20 min	25 min	30 min	35 min	40 min	45 min	60 min
	202420665	8 mg (FJ)		6	74	87	90	92	93	94	95	97 (b) (4)
					10 min	15 min	25 min	30 min	35 min	45 min	60 min	-
	202421278	8 mg (FS)		6	78	87	94	96	97	99	100 (b) (4)	-

Batch#	Strength/units	10'	15'	20'	25'	30'	45'	60'
202420296 (424521)	4 mg (n=6)	55% (b) (4)	69% (b) (4)	77% (b) (4)	82% (b) (4)	87% (b) (4)	94% (b) (4)	98% (b) (4)
202420297 (4245422)	4 mg (n=12)	41% (b) (4)	54% (b) (4)	63% (b) (4)	70% (b) (4)	75% (b) (4)	85% (b) (4)	92% (b) (4)

Dissolution Sampling Plan

Sampling & Testing Plan:

Following sampling plan for dissolution samples are provided in 3.2.P.5.1 (SN001:

(b) (4)

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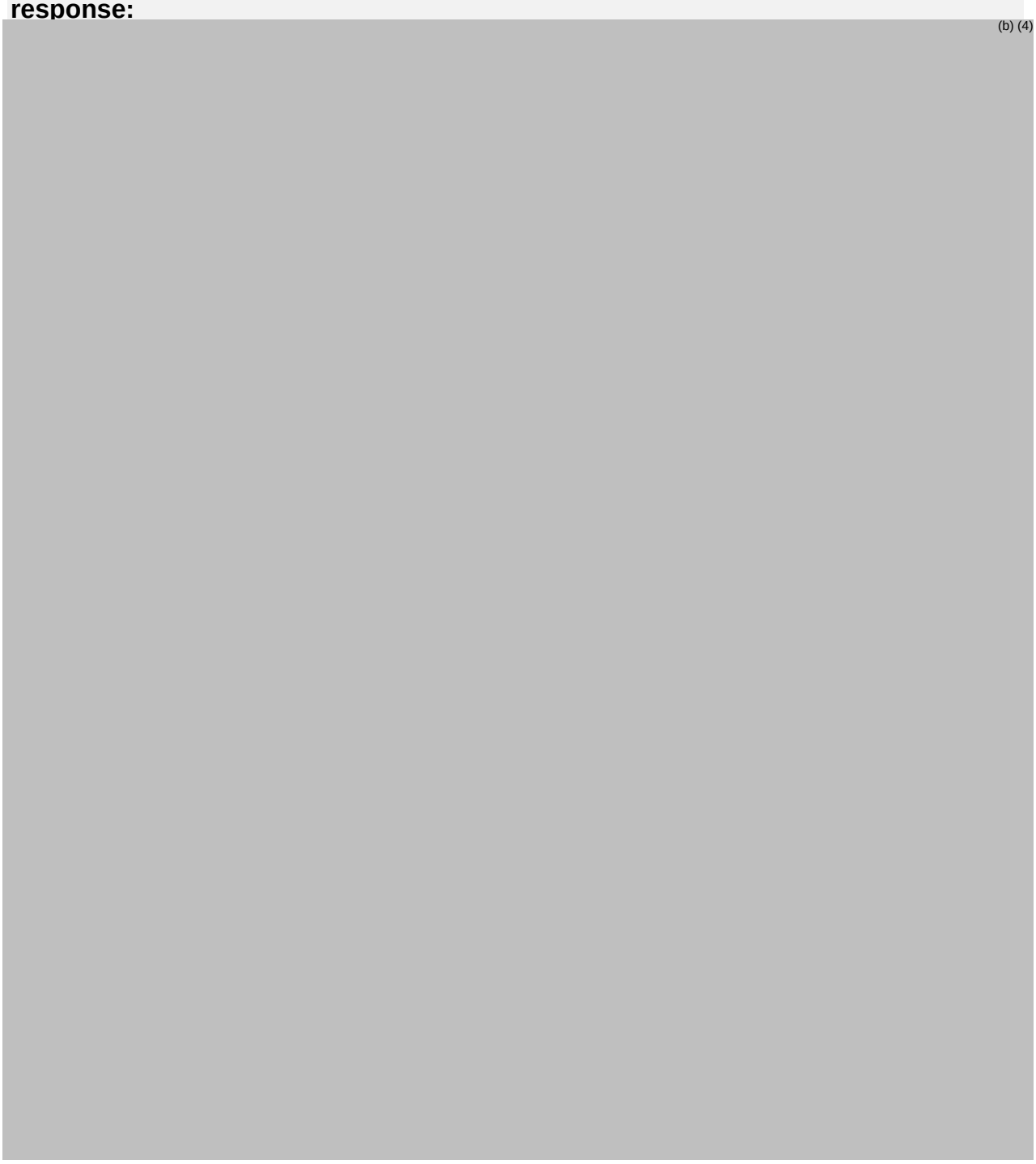
The Applicant provided a response on Oct 7, 2022. Following is a summary of response:

(b) (4)



Evaluation of Response:

The Applicant indicated that proper control strategy is in place to ensure product quality during the continuous run. The proposed commercial dissolution method is sensitive enough to detect any changes to product quality during the manufacturing run time. The safe space developed by using samples with differential dissolution, also provide assurance on product quality. The dissolution data from process validation batches for

all strengths exhibited similarity (f2). Therefore, considering totality of the information (e.g., safe space, design space (b) (4) and real time data from process validation batches for all strengths) the collection of samples (b) (4) is supported.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*
Assessment: *Adequate*

Dissolution Safe Space Development

The Applicant followed following approach for safe space development for daprodustat tablets:

(b) (4)

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(b) (4)

Reviewer's Comment:
The data/information provided in support of the safe space development is adequate. The BE study used to establish the safe space is acceptable based on communication with Clinical Pharmacology review team.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD
Assessment: ***NA***

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*
Assessment: Not Applicable. The proposed product is an immediate release tablet.

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY
Assessment: Not Applicable

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS
Assessment: Not Applicable

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS
Assessment: Not applicable. The proposed product is intended for oral administration.

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS
Assessment: Not applicable. The proposed product is not an abuse-deterrent product.

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: Not Applicable. The proposed product is not intended for pulmonary administration.

B.11 EXTENDED-RELEASE DOSAGE FORMS –*Extended-Release Claim*

Assessment: Not applicable. The proposed product is not an extended-release product.

B.12 BRIDGING OF FORMULATIONS

Assessment: ***Adequate***

The Applicant stated that Daprodustat Tablets 2 mg, 5 mg, 25 mg, and 100 mg were used in Phase I study. Drug substance is (b) (4) Daprodustat Tablets 0.5 mg, 1 mg, 2 mg, 5 mg, 25 mg, and 100 mg were developed for Phase II studies with (b) (4) drug substance. It is noted that the formulation of (b) (4) tablets were (b) (4) . Also, (b) (4) mg are manufactured (b) (4) (b) (4) (b) (4) .

Table 12. Formulations used in Phase I study

(b) (4)

Table 13. Formulations used in Phase II studies, BE Study #PHI114703 for the Assessment of drug substance particle size on PK

Daprodustat Tablet 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, and 10 mg were developed and used in Phase III studies. Of which 1 mg, 2 mg and 4 mg tablets are of the same size and 6 mg, 8 mg and 10 mg tablets are 2x size. Since comparable PK data was noted for product containing (b) (4) drug substance was used for Phase III product. About (b) (4) % (b) (4) was added to Phase III products compared to Phase II products.

Table 14. Formulations used in Pivotal Phase III Clinical Studies

Component	Quantity (mg/tablet)					
Tablet Strength	1 mg	2 mg	4 mg	6 mg	8 mg	10 mg
Formulation Product Code	CD	CE	CS	CT	CU	CG
						(b) (4)
Daprodustat[1]	1.00	2.00	4.00	6.00	8.00	10.00
Mannitol						(b) (4)
Microcrystalline Cellulose						
Hypromellose (b) (4)						
Croscarmellose Sodium						
Colloidal Silicon Dioxide						
(b) (4						
Magnesium Stearate[3]						
(b) (4						
Film-coated tablet weight						

Notes:

(b) (4)

Daprodustat Tablets 1 mg, 2 mg, 4 mg, and 6 mg are intended to be commercialized. For each tablet strength, the compositions of the tablets made by continuous, or batch processes are the same. (b) (4)

(b) (4)

(b) (4) In addition, only difference between Pivotal Phase products and intended commercial products is the coloring agents for the identification of different strengths.

Table 15. Intended Commercial Formulations for Daprodustat Tablets (continuous and batch process)

Component	Quantity (mg/tablet)										Function	Reference to Standard
	1 mg		2 mg		4 mg		6 mg		8 mg			
	Continuous	Batch	Continuous	Batch	Continuous	Batch	Continuous	Batch	Continuous	Batch		
										(b) (4)		
Daprodustat [1]	1.00		2.00		4.00		6.00		8.00		Active	GlaxoSmithKline
Mannitol										(b) (4)	(b) (4)	USP/NF and Ph.Eur.
Microcrystalline Cellulose												USP/NF and Ph.Eur.
Hypromellose (b) (4)												USP/NF and Ph.Eur.
Croscarmellose Sodium												USP/NF and Ph.Eur.
Colloidal Silicon Dioxide												USP/NF and Ph.Eur.
										(b) (4)		USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
Magnesium Stearate [3]	1.50		1.50		1.50		3.00		3.00			USP/NF and Ph.Eur.
										(b) (4)		-

To confirm the bioequivalence of Daprodustat Tablets manufactured by the continuous process and the Batch Process, a pivotal BE study #213002 Part B was performed. For this study, three consecutive production scale batches were made for each tablet strength for both reference product (tablets made by Continuous process) and Test product (Tablets made by Batch process). Among three batches, the batch with the intermediate dissolution profile using the proposed commercial dissolution method (Procedure E) was selected from each process for each tablet strength for BE study. In addition, comparative dissolution profile using Procedure E for each tablet strength is provided.

Table 16. Summary of Bioequivalence data from Study 213002 Part B for Daprodustat Tablet manufactured by Continuous Process (Process 1) and Batch Process (Process 2)

Tablet Dose Strength	Pharmacokinetic Parameter (units)	Treatment	N	Ratio of Process 2/ Process 1	90% CI of the Ratio	%CVw
1 mg	AUC(0-t) (h•ng/mL)	Process 1 Process 2	39 40	1.029	(0.9770, 1.083)	31.7
	Cmax (ng/mL)	Process 1 Process 2	39 40	0.9716	(0.8936, 1.056)	34.6
2 mg	AUC(0-t) (h•ng/mL)	Process 1 Process 2	42 41	0.9496	(0.8914, 1.012)	30.6
	Cmax (ng/mL)	Process 1 Process 2	42 41	0.9006	(0.8107, 1.000)	24.7
4 mg	AUC(0-t) (h•ng/mL)	Process 1 Process 2	42 40	1.010	(0.9533, 1.070)	28.0
	Cmax (ng/mL)	Process 1 Process 2	42 40	0.9703	(0.8665, 1.087)	26.1
6 mg	AUC(0-t) (h•ng/mL)	Process 1 Process 2	42 41	0.9679	(0.9115, 1.028)	35.6
	Cmax (ng/mL)	Process 1 Process 2	42 41	0.9675	(0.8778, 1.066)	33.9
8 mg	AUC(0-t) (h•ng/mL)	Process 1 Process 2	40 40	0.9511	(0.8948, 1.011)	34.9
	Cmax (ng/mL)	Process 1 Process 2	40 40	0.8606	(0.7770, 0.9532)	38.9

NOTE: Cmax of 8 mg did not meet the BE criteria. See discussion in Reviewer's Comment.

Based on comparative dissolution data, 1 mg, 2 mg, and 6 mg showed > (b) (4)% dissolution in (b) (4) minutes, and no f2 calculations are necessary to establish similarity. The similarity value (f2) for 4 mg and 8 mg strengths are 71 and 66, respectively (f2>50 for similarity). So, all strengths demonstrated similarity of dissolution profiles.

In addition, the Applicant conducted tablet strength equivalent assessment across the intended commercial tablet strengths for Daprodustat tablets (1 mg, 2 mg, 4 mg, 6 mg, and 8 mg). The tablets tested were manufactured using continuous process, but the result is applicable to batch process also. An in vivo BE Study#207727 was conducted to assess the equivalence between the 2 mg and 4 mg tablet strengths.

Fig 7. Dissolution Equivalence Testing Scheme for Daprodustat Tablets (continuous process)

(b) (4)

Table 17. Dissolution Testing Conditions

(b) (4)

Table 18. Dissolution Equivalence Assessment Summary Across Tablet Strengths

Formulation		pH (b) (4) media 50 rpm[1]	pH (b) (4) media 50 rpm[2]	pH 6.8 media 50 rpm[1]	Proposed commercial method 50 rpm[1]
Strengths	1 mg vs 2 mg	Equivalent	Equivalent	Equivalent	Equivalent
	2 mg vs 4 mg	Equivalent	Equivalent	Equivalent	Equivalent
	2 mg vs 6 mg	Equivalent	Equivalent	Equivalent	Equivalent
	4 mg vs 6 mg	Equivalent	Equivalent	Equivalent	Equivalent
	4 mg vs 8 mg	Equivalent	Equivalent	Equivalent	Equivalent

Notes:
1. Single tablets were used for comparison between strengths.
2. Single tablets and multiple tablets were both assessed.

Table 19. BE Study 207727 data to demonstrate BE between 2 mg and 4 mg tablets

PK Parameter	Treatment Formulation	Number of Subjects	Adjusted Geometric Mean	Ratio (2 mg x 2 / 4 mg x 1)	90% CI
C_{max} (ng/mL)	2 mg x 2	51	88.93	1.04	(0.97, 1.12)
	4 mg x 1	52	85.14		
AUC (0-t) (h.ng/mL)	2 mg x 2	51	182.62	1.02	(0.97, 1.07)
	4 mg x 1	52	179.69		
AUC (0-inf) (h.ng/mL)	2 mg x 2	51	182.80	1.02	(0.97, 1.07)
	4 mg x 1	52	179.87		

Reviewer's Comments:

Based on formulation composition, Phase I and Phase II products are similar. No significant change of formulation is noted. So, no bridging between Phase I and Phase II products is required. The difference between Phase II product and Phase III products are presence of (b) (4) drug substance for Phase III. The Applicant performed a BE study with Tablet manufactured with (b) (4) drug substance (Phase I and Phase II), and tablet manufactured with (b) (4) drug substance (Phase III). Both products met the BE criteria and found to be bioequivalent. So, (b) (4) the Phase II and Phase III products are comparable. Based on dissolution data, there is no significant change of dissolution (b) (4)

To demonstrate bridging of batch vs continuous process, the Applicant conducted BE Study 213002 Part B with all strengths. The study met the BE criteria, in addition, comparative dissolution profiles in QC media exhibited similarity (f2>50 or > (b) (4)% dissolution in (b) (4) minutes) of dissolution profiles for all strengths. It is noted that, Cmax of 8 mg did not meet BE criteria. The Applicant stated that based on clinical experience, clinical efficacy for daprodustat is driven by total exposure (AUC) rather than rate of absorption (Cmax). In addition, the variability was high for 8 mg strength. Based on a communication received from Office of Clinical Pharmacology reviewer, there are no specific concerns. The reviewer indicated that "*the efficacy of daprodustat seems driven by AUC. Although, the sponsor has used dose-response models instead of exposure-response models to guide dose selections because the model with PK exposure (AUC) did not provide a better predictor of response than dose alone*."

The Applicant provided tablet strength similarity using in vivo BE study (#207727) as well as comparative multimedia dissolution study. Based on in vivo and in vitro data, the tablet strengths are equivalent.

Following is a summary of bridging of formulation

(b) (4)

B. 13 BIOWAIVER REQUEST

Assessment: Not applicable. All strengths were used in pivotal Phase III clinical and BE studies

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: Not applicable, none submitted.

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Primary Biopharmaceutics Assessor's Name and Date:

Debasis Ghosh
11/30/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Haritha Mandula
11/30/2022

Debasis Ghosh

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CHAPTER VII: MICROBIOLOGY

Product Information	This is a non-sterile, non-aqueous, film-coated tablet drug product for oral administration that is indicated in the treatment of anemia due to chronic kidney disease in adult patients on dialysis and not on dialysis. The drug product tablets are packaged in HDPE bottles.
NDA Number	216-951
Assessment Cycle Number	001
Drug Product Name/ Strength	Daprodustat Tablets, GSK1278863 (proprietary name: JESDUVROQ) / 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg film-coated tablets
Route of Administration	oral
Applicant Name	GlaxoSmithKline Intellectual Property (No. 2) Limited England
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DNH
Manufacturing Site	Manufacturing – Continuous Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations) Priory Street Ware Hertfordshire, SG12 0DJ, UK Manufacturing – Batch (b) (4)
Method of Sterilization	non-sterile, non-aqueous tablet

Assessment Recommendation: Adequate

Assessment Summary: This is a non-sterile, non-aqueous, film-coated tablet drug product for oral administration.

Submissions being assessed:

Document(s) Assessed	Date Received
Seq-0001 (SDN 1)	01 February 2022
Seq-0017 (SDN 16)	28 April 2022
Seq-0047 (SDN 47)	01 July 2022
Seq-0054 (SDN 54)	21 July 2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: A review of this application was requested by the ATL/Drug product reviewer because a microbiology issue was identified in the stability data.

Information requests were sent to the applicant on 21 June 2022 and on 06 July 2022. The applicant responded in Seq-0047, FDA received date 01 July 2022 and in Seq-0054, FDA received date 21 July 2022. This information is reviewed here.

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

Product Quality Microbiology Assessment

S DRUG SUBSTANCE: The drug substance is not sterile and the applicant is not requesting reduced release/stability bioburden testing for the final drug product. Therefore, the drug substance is not reviewed here.

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

The drug product is a non-aqueous, non-sterile, film-coated tablet. Five presentations of the drug product tablets are proposed (1 mg, 2 mg, 4 mg, 6 mg, and 8 mg). The compositions of the drug product presentations are described in the table below (copied from Description and Composition of the Drug Product).

Table 1 Unit Dose Composition of Daprodustat Tablet Formulations (Continuous and Batch Processes)

Component	Quantity (mg/tablet)										Function	Reference to Standard
	1 mg		2 mg		4 mg		6 mg		8 mg			
	Continuous	Batch	Continuous	Batch	Continuous	Batch	Continuous	Batch	Continuous	Batch		
												(b) (4)
Daprodustat [1]	1.00		2.00		4.00		6.00		8.00		Active	GlaxoSmithKline
Mannitol											(b) (4)	USP/NF and Ph.Eur.
Microcrystalline Cellulose												USP/NF and Ph.Eur.
Hypromellose (b) (4												USP/NF and Ph.Eur.
Croscarmellose Sodium												USP/NF and Ph.Eur.
Colloidal Silicon Dioxide												USP/NF and Ph.Eur.
(b) (4)												USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
												USP/NF and Ph.Eur.
Magnesium Stearate [3]												USP/NF and Ph.Eur.
											(b) (4)	-

Component	Quantity (mg/tablet)										Function	Reference to Standard
	1 mg		2 mg		4 mg		6 mg		8 mg			
	Continuous	Batch	Continuous	Batch	Continuous	Batch	Continuous	Batch	Continuous	Batch		
Film-coating [4]												
(b) (4)											Film-coat	Supplier
											Film-coat	Supplier
											Film-coat	Supplier
											Film-coat	Supplier
											Film-coat	Supplier
											Film-coat Vehicle	USP/NF and Ph.Eur.
Total tablet weight										(b) (4)	-	-

Notes:

(b) (4)

The finished tablets are packaged in HDPE bottles. The number of tablets packaged per HDPE bottle are described in the table below (copied from Container Closure System):

Use	Fill Count	HDPE Bottle	Closure[1]
Sample Pack	7 (b) (4) ((b) (4) 2 mg, 4 mg (b) (4) tablets)	60 cc round, white	33 mm (b) (4) cap with foil induction seal liner
Patient Pack	30 (b) (4) (all strengths)		

Note:

1. We verify in this submission that the following package meets CPSC's standards under 16 CFR 1700.

Assessment: *Adequate*

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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