# Statistical Analysis Plan

**Study ID:** 214066

**Official Title of Study:** An Integrated Pharmacokinetic and Safety Open-label Basket Trial of Daprodustat for the Treatment of Anemia Associated with Chronic Kidney Disease in Male and Female Children and Adolescents Aged 3 Months to Under 18 Years Requiring or Not Requiring Dialysis.

**NCT number:** NCT05682326

**Date of Document:** 14 Jul 2025 (Most recent document date)

# DOCUMENTATION OF STATISTICAL METHODS

Statistical Analysis Plan (Study 214066) dated 23-January-2025

Study Data Analysis Plan (Study 214066)

CCI [redacted]

# Statistical Analysis Plan for Interventional Studies

SAP Text Version Number: Final v1.0
SAP Text Date: 23-Jan-2025

**Sponsor Name:** GlaxoSmithKline Research & Development Limited

**Protocol Number:** 214066
**Protocol Title:** An Integrated Pharmacokinetic and Safety Open-label Basket Trial of Daprodustat for the Treatment of Anemia Associated with Chronic Kidney Disease in Male and Female Children and Adolescents Aged 3 Months to Under 18 Years Requiring or Not Requiring Dialysis.

**Protocol Version and Date:**
Amendment 02 (18-Nov-2022)

CCI [redacted]

**Authors:** PPD

**Notice of Confidential and Proprietary Information:**

## Revision History

| Version # | Date (DD-Mmm-YYYY) | Document Owner | Revision Summary |
|---|---|---|---|
| v1.0 | 23-Jan-2025 | PPD | Final version. |

I confirm that I have reviewed this document and agree with the content.

## Approvals

**CCI Approval**

| | | |
|---|---|---|
| PPD | PPD | 01/28/2025 |
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**GSK Approval**

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## Table of Contents

# 1. Glossary of Abbreviations

| Abbreviation | Description |
|---|---|
| ADPKD | Autosomal Dominant Polycystic Kidney Disease |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine Aminotransferase |
| ALP | Alkaline Phosphatase |
| ARPKD | Autosomal Recessive Polycystic Kidney Disease |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| CAKUT | Congenital Abnormalities of the Kidney and Urinary Tract |
| CERA | Continuous Erythropoietin Receptor Activator |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| $C_{max}$ | Maximum Plasma Concentration |
| CRF | Case Report Form |
| CTMS | Clinical Trial Management System |
| D | Requiring Dialysis |
| DMP | Data Management Plan |
| DMPK | Drug Metabolism and Pharmacokinetics |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| ESA | Erythropoiesis Stimulating Agent |
| ESKD | End Stage Kidney Disease |
| FCS | Full Conditional Specification |

| Abbreviation | Description |
|---|---|
| FDA | Food and Drug Administration |
| FOCBP | Females of Childbearing Potential |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| GSK | GlaxoSmithKline |
| HD | Hemodialysis |
| Hgb | Hemoglobin |
| HOI | Health Outcome of Interest |
| HR | Heart Rate |
| ICE | Intercurrent Event |
| ICF | Informed Consent Form |
| IDMC | Independent Data Monitoring Committee |
| INR | International Normalized Ratio |
| IPKS | Integrated Pharmacokinetic Set |
| IR | Immediate Release |
| IRT | Interactive Response Technology |
| IV | Intravenous |
| LFT | Liver Function Test |
| LLQ | Lower Limit of Quantification |
| MCH | Mean Corpuscular Hemoglobin |
| MCV | Mean Corpuscular Volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| N/A | Not Applicable |
| NA | Not Applicable |
| ND | Not Requiring Dialysis |
| NQ | Non-Quantifiable |
| PBPK | Physiological Based Pharmacokinetics |
| PD | Peritoneal Dialysis |

| Abbreviation | Description |
|---|---|
| PEG | Polyethylene Glycol |
| PK | Pharmacokinetic |
| POPPK | Population Pharmacokinetics |
| PT | Preferred Term |
| PY | Person-Year |
| QD | Once Daily |
| QTc | Corrected QT Interval |
| QTcF | QT Interval Corrected using Fridericia's Formula |
| RBC | Red Blood Cell |
| rhEPO | Recombinant Human Erythropoietin |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SI | International System of Units |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SS | Safety Set |
| TAST | Transferrin Saturation |
| TEAE | Treatment-Emergent Adverse Event |
| TESAE | Treatment-Emergent Serious Adverse Event |
| TFL | Table, Figure and Listing |
| TfOS | Tablets for Oral Suspension |
| ULN | Upper Limit of Normal |
| UNS | Unscheduled Visit |
| WBC | White Blood Cell |
| WHO | World Health Organization |

# 2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

The study protocol includes two independent sub-trials for pediatric patients with chronic kidney disease (CKD) either not yet requiring dialysis (ND) and requiring dialysis (D). This SAP will guide statistical analysis for both sub-trials. Tables, figures and listings (TFLs) will be provided for both sub-trials in a separate document.

## 2.1. Responsibilities

CCI will perform the statistical analyses and is responsible for the production and quality control of all TFLs. GlaxoSmithKline (GSK) Research & Development Limited will perform Pharmacokinetic (PK) analysis; hence, PK methods and TFLs will be described in a separate document.

## 2.2. Timings of Analyses

A primary analysis and a series of Independent Data Monitoring Committee (IDMC) meetings were planned for each sub-trial (D/ND) per study protocol. However, only one final analysis will be performed for both sub-trials (D/ND) combined due to study being terminated early.

Refer to Section 8.1 for general methods for statistical analysis to account for early termination and Section 14 for other changes from analysis planned in protocol due to early termination.

# 3. Study Objectives

Study objectives are listed below. Refer to Section 5 for the corresponding study endpoints to each objective. Refer to Section 14 for the changes from analysis planned in protocol.

## 3.1. Primary Objective (Safety)

Describe the safety of daprodustat, overall (all ages) and in each age group.

## 3.2. Secondary Objectives

### 3.2.1. Secondary Safety Objective

Describe changes in other parameters relevant to safety, overall and in each age group.

### 3.2.2. Secondary Efficacy Objectives

- Describe the effect of daprodustat on Hgb, overall and in each age group (and additionally overall in all ages by Erythropoiesis Stimulating Agent (ESA) use [yes/no] at study enrollment).
- Describe the change in required dose over time, in each age group.

### 3.2.3. Secondary Pharmacokinetic Objectives

Secondary pharmacokinetic objectives are listed here but the analysis methods along with TFLs will be described in a separate document.

- Characterize the PK of daprodustat in each age group.
- Describe the systemic exposure to daprodustat metabolites M2, M3, M4, M5, M6, and M13 in each age group.

## 3.3. Tertiary Objectives

- Evaluate the incidence of health outcomes of interest in a CKD population during the study, overall and in each age group.
- Assess the acceptability and palatability of the immediate release (IR) tablets and tablets for oral suspension (TfOS). Analysis for this objective will not be performed due to study being terminated early.

# 4. Study Details/Design

## 4.1. Brief Description

This is an open-label, basket, single arm, international, multicenter trial, evaluating PK (4 weeks), safety (52 weeks) and Hgb response (52 weeks) to oral daprodustat in children and adolescent participants with anemia associated with CKD incorporating 2 independent sub-trials (D/ND). These 2 sub-trial populations (D/ND) differ in their degree of CKD, and hence the requirement for dialysis, and are cared for by the same teams and centers. The design and conduct of these 2 sub-trials (D/ND) are therefore described in a single master protocol: they will share operational aspects but represent independent populations, recruited, conducted, and analyzed separately.

The purpose of this study is to investigate the PK, safety and efficacy (Hemoglobin [Hgb] response) of daprodustat in pediatric participants aged 3 months to less than 18 years with anemia associated with CKD requiring and not requiring dialysis (who will be studied sequentially in 4 decreasing age groups: 12 to <18 years, 6 to <12 years, 2 to <6 years and 3 months to <2 years).

All participants who are approached for this study will already be participating in the prospective observational Cohort Study 212914, also running at the same trial sites. For all study participants, the study will consist of the following periods:

- Screening period of up to 4 weeks, although the Screening and Day 1 (Baseline) visits can be performed on the same day.
- Treatment Period: All eligible participants are planned to receive daprodustat for fifty-two weeks. PK assessments in the first 4 weeks of dosing (Integrated PK Phase) are required in the initially recruited subset of participants in each age group (a minimum of 4 participants per age group, aiming for approximately 10, 6, 4 and 4 participants for the age groups 12 to <18 years, 6 to <12 years, 2 to <6 years and 3 months to <2 years respectively) for each sub-trial. These participants, who undergo the Integrated PK Phase, continue seamlessly with further dosing, but further recruitment of their age group and the opening up of recruitment in the next sequential younger age group is prohibited until the data (PK, safety and Hgb response) from each Integrated PK Phase are analyzed, and no concerns for continuing the study as planned are detected. Optional PK sampling is offered to non-Integrated PK Phase participants.
- Follow-up period of 4 weeks off treatment after the participants complete the 52-week treatment period.

As this is an open-label single arm trial, where all participants are on active treatment with daprodustat, clinical and laboratory parameters will not be blinded during the study. Investigators may adjust daprodustat dose from the Week 2 visit based on Hgb response using an age specific dose adjustment algorithm (refer to “Dose Adjustment Algorithm” section of the study protocol for details).

Participants in the ND sub-trial reaching the requirement for dialysis will remain in the study and will continue to receive daprodustat, remaining in the ND sub-trial unless they withdraw consent. Participants in either sub-trial who undergo kidney transplantation will be withdrawn from the study.

The end of the study of each sub-trial (D/ND) is defined as the date of the last visit of the last participant in the respective sub-trial (D/ND). A participant is considered to have completed the study if the participant has completed all study visits, including the last Follow-up Visit at Week 56, regardless of whether daprodustat treatment was received during the entire study period. A participant is considered to have completed the study intervention if the participant has not been discontinued prematurely from study intervention and has completed the last required on-treatment visit (Week 52), regardless of whether daprodustat treatment was received during the entire study period.

## 4.2. Participant Selection

All participants who are approached for this study will already be participating in the prospective observational Cohort Study 212914, also running at the same trial sites.

The screening period can be up to 4 weeks, although Screening and Day 1 visits can be performed on the same day. Blood tests for eligibility checked at Screening do not need to be repeated if the Day 1 visit is performed within 7 days of the Screening Visit.

Inclusion and exclusion criteria for study population are listed in the study protocol, please refer to the appropriate sections for details. Participants are eligible to be included in the study if all of the inclusion criteria apply at the Screening and Day 1 visits. Participants are excluded from the study if any of the exclusion criteria apply at the Screening and Day 1 visits, unless otherwise specified.

## 4.3. Determination of Sample Size

Sample size for the Integrated PK Phase was planned based on feasibility. Overall, 24 participants for each sub-trial were planned to provide PK data. A minimum of 4 participants (aiming for at least the following: 10, 6, 4 and 4 participants for the 4 age groups [oldest to youngest respectively]) with PK data from each age group was required to confirm (or adjust if required) the PK predicted dosing strategy for the 4 age groups.

In each sub-trial, a total of approximately 60 participants across all age groups were planned to be enrolled (120 participants in total for the entire study). The study was not formally powered, but the sample size was based on feasibility and also ensures that frequent Adverse Events (AEs) would likely be detected. Since a minimum of 60 participants were to be exposed to daprodustat in each sub-trial, there would be at least a 90% chance of observing at least 1 subject with the AE if the rate of the AE occurs with a frequency greater than 3.76%.

Change in Hgb from baseline would be assessed at every study visit. By way of illustration, at the 12-week time point with 60 participants enrolled and assuming a combined 17% dropout and Intercurrent Event (ICE) rate, 50 participants were expected to have a Hgb measurement. This would allow estimation of mean Hgb change from baseline to Week 12 with a precision of 0.4 g/dL, where precision was defined as the symmetrical 95% confidence interval (CI) half width, assuming a population rate standard deviation (SD) of 1.4 g/dL [KDOQI, 2006]. No sample size re-assessment was planned.

A sufficient number of participants were to be screened to enable 60 participants to be enrolled into each sub-trial. The screen failure rate was estimated to be low given pre-screening in the Cohort Study (212914) from which these participants are recruited.

However, due to study termination early, the numbers of participants in each sub-trial (D/ND) did not reach the planned size. Only enrolled participants will be included in the final analysis.

### 4.4. Treatment Assignment and Blinding

This is an open-label, single arm study. All enrolled subjects will receive the study drug. No treatment assignment or blinding was needed.

### 4.5. Administration of Study Medication

Starting dose selection and dose adjustment algorithm are discussed in the study protocol. Interactive Response Technology (IRT) will ensure the participants receive the correct dose allocation, and in case of a birthday resulting in a change in age group, IRT will ensure the correct age group dose algorithm is applied. To ensure IRT can allocate correct dispensing of study medication, month and year of birth will be collected at enrollment and IRT will check for participants, who with a birthday move into the next age group during the course of the 52-week treatment period, weigh the minimum weight for that new age group (if not, participants will remain in the prior age group).

### 4.6. Study Procedures and Flowchart

Schedule of activities are summarized in Table 1.

## Table 1: Schedule of Activities

| Procedure | Screening (-4 weeks to Day 1) | Treatment Period | | | | | | | | | | | | Extra Hgb Check Visit | | Early Discontinuation from Study Intervention / Withdrawal Visit | Follow -up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Week 2 (± 3 days) | Week 4 (-7 to +2 days) | Week 8 (-7 to +2 days) | Week 12 (-7 to +2 days) | Week 16 (-7 to +2 days) | Week 20 (-7 to +2 days) | Week 24 (-7 to +2 days) | Week 28 (-7 to +2 days) | Week 36 (-7 to +2 days) | Week 44 (-7 to +2 days) | Week 52 (-7 to +2 days) | UNS at Any Time Day 1 to Week 56 [a] | 4-weekly if needed (Weeks 32, 40 & 48) [b] | | Week 56 (-7 to +2 days) |
| Informed consent | X | | | | | | | | | | | | | | | | |
| **ELIGIBILITY ASSESSMENTS** | | | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | X | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | |
| Medical and treatment history | X | | | | | | | | | | | | | | | | |
| 12-lead ECG [c] | X | | | | | | | | | | | | | | | | |
| **SAFETY ASSESSMENTS** | | | | | | | | | | | | | | | | | |
| AE/SAE assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs (BP, HR) [d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height, weight [e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Procedure | Screening (-4 weeks to Day 1) | Treatment Period | | | | | | | | | | | | Extra Hgb Check Visit | | Early Discontinuation from Study Intervention / Withdrawal Visit | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Week 2 (± 3 days) | Week 4 (-7 to +2 days) | Week 8 (-7 to +2 days) | Week 12 (-7 to +2 days) | Week 16 (-7 to +2 days) | Week 20 (-7 to +2 days) | Week 24 (-7 to +2 days) | Week 28 (-7 to +2 days) | Week 36 (-7 to +2 days) | Week 44 (-7 to +2 days) | Week 52 (-7 to +2 days) | UNS at Any Time Day 1 to Week 56 [a] | 4-weekly if needed (Weeks 32, 40 & 48) [b] | | Week 56 (-7 to +2 days) |
| Physical exam | X | X | | | | X | | | X | | X | | X | X [g] | | X | X |
| Tanner staging | | X | | | | | | | | | | | X | | | X [f] | |
| **LABORATORY ASSESSMENTS** | | | | | | | | | | | | | | | | | |
| Hgb (full blood count) | X | X | X | X | X | X | X | X | X | X | X | X | X | X [g] | X | X | X |
| Iron parameters (TSAT, ferritin) | X | X | | X | X | X | X | X | X | X | X | X | X | X [g] | X [g] | X | X |
| Creatinine, urea/BUN, potassium, sodium, calcium | X | X | | X | X | X | X | X | X | X | X | X | X | X [g] | X [g] | X | X |
| LFTs (+INR [h]) | X | X | | X | X | X | | | X | | X | | X | X [g] | X [g] | X | X |
| Pregnancy test (FOCBP only)[i, l] | X | X | X | X | X | X | X | X | X | X | X | X | X | X [g] | X [g] | X | X |
| PK Sampling (Optional unless in the Integrated PK Phase) | | X [j] | X [k] | X [k] | | | | | | | | | | | | | |
| **STUDY INTERVENTION** | | | | | | | | | | | | | | | | | |

| Procedure | Screening (-4 weeks to Day 1) | Treatment Period | | | | | | | | | | | | Extra Hgb Check Visit | | Early Discontinuation from Study Intervention / Withdrawal Visit | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | Week 2 (± 3 days) | Week 4 (-7 to +2 days) | Week 8 (-7 to +2 days) | Week 12 (-7 to +2 days) | Week 16 (-7 to +2 days) | Week 20 (-7 to +2 days) | Week 24 (-7 to +2 days) | Week 28 (-7 to +2 days) | Week 36 (-7 to +2 days) | Week 44 (-7 to +2 days) | Week 52 (-7 to +2 days) | UNS at Any Time Day 1 to Week 56 [a] | 4-weekly if needed (Weeks 32, 40 & 48) [b] | | Week 56 (-7 to +2 days) |
| IRT | X | X | X | X | X | X | X | X | X | X | X | X | | X [g] | X [g] | X | X |
| Daprodustat dispensing | | X | X | X | X | X | X | X | X | X | X | X | | X [g] | X | | |
| **OTHER** | | | | | | | | | | | | | | | | | |
| Blood transfusion/ iron supplement status | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dialysis modality /transplant status | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Acceptability and Palatability Questionnaire | | | X | | | | | | | | | | | | | | |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Abbreviations:** AE = adverse events; BP = blood pressure; BUN = blood urea nitrogen; eCRF = electronic case report form; ECG = electrocardiogram; FOCBP = females of childbearing potential; Hgb = hemoglobin; HR = heart rate; INR = international normalized ratio; IRT = interactive response technology; LFT(s) = liver function test(s); PK = pharmacokinetics; rhEPO = recombinant human erythropoietin; SAE = serious adverse event; TSAT = transferrin saturation; UNS = Unscheduled Visit.

NOTE:

- All visit timings are relative to Day 1. Daprodustat will be dispensed to cover the visit period (plus permitted time window) at each dispensing visit. An IRT transaction will be required to dispense daprodustat. Additional IRT transactions may occur to dispense additional daprodustat in case replacement is needed.
- Blood tests for eligibility checked at Screening do not need to be repeated if the Day 1 Visit is performed within 7 days of the Screening Visit.
- All Day 1 procedures will be before the first of dose of daprodustat, **except** for post dose PK sampling on Day 1 (which occurs at the end of Day 1 once a subject is confirmed as eligible and is enrolled into the study). PK sampling is required for those subjects in the Integrated PK Phase, otherwise PK sampling is optional.

a. An unscheduled (UNS) /extra check Hgb Visit may be conducted at any time during the study if, in the opinion of the investigator, the subject would benefit from additional monitoring of Hgb and/or other parameters if clinically indicated.

b. From Week 28, an extra Hgb check Visit should be arranged 4 weeks after the last dose visit if:
   - At the last study visit:
     - there was a dose change
     - if dosing was temporarily withheld as Hgb >12.5 g/dL
     - a dose reduction was needed but the subject was on lowest dose already
   - Since the last study visit the following occurred:
     - a moderate CYP2C8 was prescribed
     - a rhEPO or analogue was given in error
     - a Hgb check performed outside of the study indicates a dose change is needed
   - In the opinion of the investigator the subject would benefit from continued 4-weekly Hgb checks:
     - as the Hgb is at the upper end of the target range
     - waiting 8 weeks for the next Hgb check is considered too long.

c. If prolonged QT/QTcF is noted, 2 additional ECG measurements should be obtained and the average QT/QTcF of the triplicate assessment used for eligibility determination. No further ECG monitoring is required, unless as indicated as part of routine care of a subject, see "Electrocardiogram" section of the study protocol.

d. BP and HR will be assessed with using an appropriate size cuff. BP and HR should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions. Three consecutive BP measurements will be obtained, of which the median will be recorded.

e. Height (or supine length in the very young) and weight will be measured as appropriate for the subject's age and plotted on age and gender appropriate charts as per SoC at the site, see "Physical Examinations" section of the study protocol.

f. Tanner Staging is not needed if early discontinuation from study intervention, only if an early study withdrawal visit.

g. If clinically indicated or required (IRT drug dispensing) at the extra UNS Visit (at any time during the study).

h. If liver monitoring is required after Day 1, INR should also be performed, see "Liver Chemistry Stopping Criteria" and "Appendix 5: Liver Safety: Required Actions and Follow-up Assessments" sections of the study protocol.

i. Pregnancy tests will be conducted using urine, unless estimated Glomerular Filtration Rate (eGFR) ≤15 mL/min/1.73m$^2$ when a serum human chorionic gonadotrophin (hCG) is required.

j. A total of 3 samples to be collected at 0.5 to 1.5 hour, >1.5 to 3 hour, and >4 hour (maximum 8) time intervals after taking the first dose of daprodustat, which should be taken in the clinic on Day 1, once the subject is confirmed as enrolled in the study having passed screening.

[k] A total of 4 samples to be collected pre-dose, then at 3 time intervals post administration of the daprodustat dose (which should be taken in the clinic on that day) as follows: 0.5 to 1.5 hour, >1.5 to 3 hour, and ≥4 hour time (maximum 8 hour) intervals. It is recommended that the PK samples are taken at Week 2, but flexibility in collecting these 4 PK samples is allowed over the first 2 to 4 weeks provided each sample is collected at a different specified time interval]). If a participant has PK sampling deferred to Week 4, but is put on a dose hold at Week 2 (as the Hgb>12.5 g/dL), then the PK sampling should be delayed until the visit after daprodustat is restarted.

[l] **For Argentina ONLY**: Pregnancy testing will be performed every 4 weeks for FOCBP as required by local law.

# 5. Endpoints

The protocol indicated that the endpoints would be assessed for each sub-trial (D/ND), overall and by age groups. However, due to early termination of the study, results will be presented by sub-trial (D/ND) but will not be split by age groups.

## 5.1. Primary Safety Endpoint

Incidence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), and AEs leading to study intervention discontinuation for each sub-trial (D/ND).

## 5.2. Secondary Safety Endpoints

Changes from baseline in laboratory safety parameters, blood pressure (BP), heart rate (HR), height and weight at each time point for each sub-trial (D/ND).

## 5.3. Secondary Efficacy Endpoints

At each study timepoint for each sub-trial (D/ND)

- Hgb values and ESA use (yes/no) at study enrollment
- Changes in Hgb values from baseline and ESA use (yes/no) at study enrollment
- Incidence of Hgb above, below and within the target range (10 to 12 g/dL) and ESA use (yes/no) at study enrollment
- Daprodustat dose
- Changes in daprodustat dose from the starting dose

During the course of the study for each sub-trial (D/ND)

- Number of dose changes

## 5.4. Secondary Pharmacokinetic Endpoints

Secondary pharmacokinetic endpoints are listed here but the analysis methods along with TFLs will be described in a separate document.

- PK parameters, including maximum plasma concentration ($C_{max}$) and Area Under the Curve (AUC) at steady state will be determined at the end of the study for each dose level overall then for each sub-trial (D/ND).

- Plasma concentrations of each pre-defined metabolite at pre-dose (trough) between Week 2 to Week 4, and corresponding $C_{max}$ if data permit will be determined at the end of the study for each dose level overall and for each sub-trial (D/ND).

## 5.5. Tertiary Other Health Outcomes of Interest

During the study, the incidence of other health outcomes listed below:

- Related to Hgb and rescue therapy:
    - Use of iron supplements (oral/IV/both)

- Blood transfusion
- Use of recombinant human erythropoietin (rhEPO) and analogues[1]

- Related to changes in kidney function or intervention:
  - Transplantation
  - Switch between dialysis modalities for D participants only
  - End stage kidney disease (ESKD)[2] for ND participants only
- Other:
  - Death
  - All-cause hospitalization
  - Thrombosis (defined as: vascular access thrombosis, deep vein thrombosis or pulmonary embolism)
  - All-cause loss of vascular access patency.

Responses from Palatability and Acceptability Questionnaire include but limited to:

- Palatability rating (good, acceptable, neither good nor bad, bad, very bad).
- Ease of swallowing (very easy, easy, neither easy nor difficult, difficult, very difficult).

[1] Unscheduled use of rhEPO or analogues is captured in the endpoint but should not be used as a rescue therapy.

[2] ESKD is defined as at least one of the following:

- an estimated Glomerular Filtration Rate (eGFR), based on the Schwartz equation of <15mL/min/1.73m$^2$
- new kidney transplantation
- the requirement for maintenance dialysis for ≥30 days

# 6. Analysis Sets

## 6.1. Screened Set

The Screened Set will include all participants who had a valid Informed Consent Form (ICF) and were screened for eligibility. Participants will be included in the age group based on their age at screening.

## 6.2. Enrolled Set

The Enrolled Set will include all participants who have passed the screening and entered the study. Screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility criteria but not needed) are excluded from the Enrolled Set as they did not enter the study.

## 6.3. Safety Set

The Safety Set (SS) will include all participants who were enrolled and took at least one dose of study medication. The SS will be used for all study population summaries, analyses of safety endpoints, efficacy endpoints and other health outcomes of interest.

## 6.4. Integrated Pharmacokinetic Set

The Integrated Pharmacokinetic Set (IPKS) will include all participants in the SS who participated in the Integrated PK Phase of the study and who had at least one non-missing PK assessment and who had at least one non-missing post-dose PK assessment associated with an actual study drug administration (non-quantifiable values will be considered as non-missing values). The IPKS will be used for dose decision making during the trial.

## 6.5. All Pharmacokinetic Set

The All Pharmacokinetic Set will include all participants in the SS who had at least one non-missing PK assessment (non-quantifiable values will be considered as non-missing values) from both Integrated PK Phase and Optional Sampling.

# 7. Primary and Key Secondary Estimands

Primary target estimand and the secondary efficacy target estimand for the study are described in this section. Pharmacokinetic estimand will be described in a separate document.

## 7.1. Primary Estimand

The primary target estimand is the proportion of participants with AEs, SAEs, AESIs, and AEs leading to study intervention discontinuation of daprodustat in children and adolescents with anemia of CKD in each sub-trial (D/ND), regardless of permanent study intervention discontinuation, disruptions or delays in study intervention, intermittent use of rescue therapy or unplanned ESA use.

- Population: Children and adolescent participants with anemia associated with CKD
- Variable: Incidence of AEs, SAEs and AESI from Day 1 to 56 weeks. AEs leading to study intervention discontinuation from Day 1 to 52 weeks of treatment.
- Population-level summary: Proportion of participants with AEs, SAEs, AESI and AEs leading to study intervention discontinuation.
- Intercurrent events:
    - Permanent study intervention discontinuation due to any reason, disruptions and delays in study intervention, intermittent use of rescue therapy and unplanned use of ESA therapy will be addressed using treatment policy strategy, meaning that all safety data will be included regardless of the occurrence of this particular ICE.
    - Kidney transplantation or death will be handled using while-on-treatment strategy, where safety data up to the time of transplantation or death will be used for analysis.
    - For ND participants only, transition to dialysis will be addressed with treatment policy strategy where all safety data will be used regardless of the occurrence of the transition.

## 7.2. Key Secondary Estimand

The secondary efficacy target estimand is the Hgb endpoints at each study time point in children and adolescents with anemia of CKD in each sub-trial (D/ND), regardless of disruptions or delays in study intervention whilst still continuing study intervention (daprodustat) and before any unplanned ESA therapy or rescue therapy.

- Population: Children and adolescent participants with anemia associated with CKD
- Variable: At each study timepoint:
    - Hgb value
    - Change in Hgb value from baseline
    - Hgb above, within and below the target range (10 to 12 g/dL)
- Population-level summary: At each study timepoint:
    - Summary statistics of Hgb value, including number of observed Hgb values, number of missing Hgb values, mean, SD, and median of the observed Hgb values.
    - Mean change in Hgb value from baseline, including number of observed Hgb values, number of missing Hgb values, mean, SD, and median.
    - Number and percentage of participants with Hgb above, below and within the target range (10 to 12 g/dL).
- Intercurrent events:

- Disruptions and delays in study intervention will be addressed using treatment policy strategy, where the treatment effect of interest is determined regardless of the occurrence of the ICE and no imputations will be conducted.
- Permanent study intervention discontinuation due to any reason will be addressed using while-on-treatment strategy, where unobserved Hgb results beyond study intervention discontinuation will not be imputed or included for analysis.
- Unplanned use of ESA therapy within the trial will be addressed using while-on-treatment strategy, where the Hgb values will be excluded for the period of 8 weeks following the occurrence of the intercurrent event from analysis and will not be imputed.
- Intermittent use of rescue therapy within the trial will be addressed with while-on-treatment policy strategy, where the Hgb values from the date of initial use of rescue therapy until 8 weeks after the last dose of rescue therapy will be excluded from analysis and will not be imputed.
- Kidney transplantation or death will be handled using while-on-treatment strategy, where data up the time of transplantation or death will be used for analysis, no missing Hgb values beyond that will be imputed.
- For ND participants only, transition to dialysis will be addressed with treatment policy strategy. All observed data will be used for analysis regardless of the ICE, and missing data will not be imputed.

# 8. General Aspects for Statistical Analysis

## 8.1. General Methods

- All analyses and outputs will be produced using SAS® version 9.4 or later.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), and median. Categorical variables will be summarized using number of observations (n), frequency and percentages of participants.
- All relevant participant data will be included in listings. All participants entered into the database will be included in participant data listings. The listings will be generally sorted by age group and participant ID for each sub-trial (D/ND), unless otherwise specified. Data collected at unscheduled visits will not be included in summary tables but will be included in data listings.
- Due to study being terminated early, all participants enrolled are from the 12 to <18 years group. Unless otherwise specified, all results will be displayed by sub-trial (D/ND) for the 12 to <18 years group only. For PK analysis, results will be displayed overall and by sub-trials (D/ND).

## 8.2. Key Definitions

- Baseline value for any laboratory parameter or vital sign is defined as the last non-missing value prior to the start date and time of the study drug.
- Study day is calculated as the date of event/assessment/specimen collection – the first dose of the study drug. One day will be added if resulting study day ≥ 0.
- Duration of any event is defined as end date of the event – start date of the event + 1.
- Duration of any event in weeks is defined as (end date of the event – start date of the event + 1) / 7, rounded to one decimal place.
- Duration of any event relevant to PK analysis is defined as end date and time of the event – start date and time of the event displayed in the format of HHMMSS.
- Change from baseline = post-baseline value – baseline value
- Percent change from baseline = (post-baseline value – baseline value) / baseline value * 100
- Pre-treatment phase is defined as any time point prior to the first dose of the study drug, i.e., date < date of the first dose.
- On-treatment phase is defined as any time point on or after the first dose of the study drug and on or prior to the last dose of the study drug + 1 day, i.e., date of the first dose ≤ date ≤ date of the last dose + 1 day.
- Integrated PK Phase is defined as the first 4 weeks of dosing in the initially recruited subset of participants in each age group (a minimum of 4 participants per age group; aiming for

approximately 10, 6, 4 and 4 participants for the age groups 12 to <18 years, 6 to <12 years, 2 to <6 years and 3 months to <2 years respectively), during which PK assessments are required.

- Post-treatment follow-up phase is defined as any time point within 4 weeks off treatment, i.e., date of the last dose + 1 day < date ≤ date of the last dose + 28 days.

## 8.3. Missing Data

For the purposes of assessing treatment emergence (defined as the events with a start date on or after the commencement of daprodustat, i.e., Day 1) for AEs or classifying medications into prior/concomitant, the following algorithms will be used for partially missing dates. However, the assessment dates (start date, stop date) without imputation will be presented in the listings.

For start dates of the events:

- Only the year is reported: if the participant received the first dose of study intervention in the reported year, date of first dose of study intervention will be used as the start date; otherwise '1 January' will be used as the start date.
- Only the month and year are reported: if the participant received the first dose of study intervention in the reported month and year, the date of first dose of study intervention will be used as the start date; otherwise, the first day of the reported month and year will be used as the start date.

For stop dates of the events:

- Only the year is reported: if the last visit (including any planned or unscheduled visits) is in the reported year, the date of last visit will be used as the stop date; otherwise, '31 December' will be used as the stop date.
- Only the month and year are reported: if the last visit is in the reported month and year, the date of last visit will be used as the stop date; otherwise, the last day of the reported month and year will be used as the stop date.

If an AE has the start date completely missing, this AE will be considered as treatment-emergent, unless the stop date is before first dose of the study intervention.

If a medication has the stop date completely missing, this medication will be considered as ongoing and concomitant.

## 8.4. Age Imputation

Imputation rule for age as full date of birth is not collected in eCRF:

- Month and year of birth is available from eCRF/IRT data.
- Since the day of the birthdate is not collected then a '01' will be used for the day.

### 8.5. Visit Windows

The visits recorded in study database will be used for all analyses. There is no plan to reassign visits based on actual visit dates where the visit designations documented in EDC will be used for analysis.

### 8.6. Pooling of Centers

This study was planned to be conducted at approximately 60 sites in 15 countries. All data will be combined for summaries and analyses.

# 9. Demographic, Other Baseline Characteristics and Medication

## 9.1. Participant Disposition and Withdrawals

The numbers of participants screened, the numbers and percentages of screen failures, and enrolled will be summarized for each sub-trial (D/ND). The denominators for the percentages are the total number of participants screened. For all screen failed participants, reasons for screen failures will be displayed in a listing. In the event of multiple screening attempts, the final screening screen status and reasons for screen failures, if applicable, will be used for summary.

The numbers and percentages of participants who discontinue study treatment, who are withdrawn from the study early and who complete the study will be summarized for each sub-trial (D/ND). Primary reasons for study treatment discontinuation and early study withdrawals will be summarized. The denominators for the above percentages are the numbers of participants enrolled within each sub-trial (D/ND). All relevant data will be displayed in listings.

Enrolled participants with any inclusion and exclusion criteria deviations will be displayed in a listing for each sub-trial.

## 9.2. Protocol Deviations

Protocol deviation management at CCI is detailed in Protocol Deviation and Non-compliance Management CCI. For details on the process for defining analysis datasets refer to Data Review and Definition of Analysis Sets, see SOP CCI. All participant data will be reviewed for the occurrence of protocol deviations. Identified protocol deviations will be recorded in the Clinical Trial Management System (CTMS). All deviations will be categorized as important or not important. All protocol deviations (both important and not important) will be displayed in a listing for each sub-trial (D/ND). Because most analyses will be based on the Safety Set, no participants will be excluded from reporting due to protocol deviations.

### 9.3. Demographic and Baseline Characteristics

Demographic and other baseline characteristics will be summarized in a table and displayed in a listing for the Safety Set for each sub-trial (D/ND), including the following variables:

- Age at enrollment (years)
- Sex (male, female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- High level race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown)
- Race detail (American Indian or Alaska Native, Asian – Central/South Asian Heritage, Asian – East Asian Heritage, Asian – Japanese Heritage, Asian – South East Asian Heritage, Black or African American, Native Hawaiian or Other Pacific Islander, White – Arabic/North African Heritage, White – White/Caucasian/European Heritage, Unknown)
- Height at screening (in cm)
- Weight at screening (in kg)
- Body Mass Index (BMI) (in $kg/m^2$) calculated as Weight (kg) / [Height $(m)^2$]

### 9.4. Baseline Disease Characteristics

The following baseline disease characteristics will be displayed in a listing for the Safety Set for each sub-trial (D/ND):

- Type of dialysis (hemodialysis, peritoneal dialysis) for D participants only
- Use of iron supplements (Yes, No)
- ESA usage at enrollment (ESA user, ESA non-user)
  - ESA type for ESA users, including epoetin or an analogue, darbepoetin alfa, methoxy polyethylene glycol (PEG)-epoetin beta / continuous erythropoietin receptor activator [CERA] / epoetin beta pegol
- Standardized ESA dosage in epoetin IV U/week for ESA users, where the conversion formulas between different drugs are given below:
  - Standard ESA intravenous (IV) dose (U/week) = 161/113 × (epoetin subcutaneous dose (units)) / frequency
  - Epoetin IV: darbepoetin alfa = 250U : 1µg
  - Darbepoetin alfa: methoxy Polyethylene Glycol-epoetin beta = 1 : 1.2µg
  - Epoetin IV: methoxy PEG-epoetin beta = 208 U : 1µg
- eGFR at screening ($mL/min/1.73m^2$)
- Hgb at screening (g/dL)
- Hgb category at screening (<10g/dL, 10-12g/dL, >12g/dL)
- Primary CKD Etiology (congenital abnormalities of the kidney and urinary tract [CAKUT], inflammatory, other)
  - CAKUT: congenital renal disease, congenital obstructive uropathy, congenital reflux nephropathy, other
  - Inflammatory: glomerulonephritis, interstitial nephritis, pyelonephritis, secondary to auto-immune disease, acute kidney injury (e.g., drug related, sepsis, pre-renal), inflammatory cause of failed kidney transplant, other.

  - Other medical condition: nephrotic syndrome, diabetic renal disease, cystic kidney disease (autosomal dominant polycystic kidney disease [ADPKD], autosomal recessive polycystic kidney disease [ARPKD], nephronophthisis, other), traumatic loss of kidney, non-inflammatory cause of failed kidney transplant, other.
- Hospitalization within 3 months prior to enrollment (Yes, No)
- Vascular access (Yes, No) and type (central venous catheter, central venous catheter non-tunneled, arteriovenous fistula, arteriovenous graft)
- Duration of dialysis at screening in days, calculated as (Screening Date - Dialysis Start Date) + 1.
- CKD Stage (Stage 3, Stage 4, Stage 5)

### 9.5. Medical History

Medical histories are collected based on the pre-specified list of medical history terms provided in the electronic case report form (eCRF), where the sites have the option to enter any medical histories that are not covered in the pre-specified list, and these will be summarized under the category "Other". All medical histories will be categorized as past medical histories and current medical conditions based on the responses to the question "Ongoing at Screening", where past medical histories are those not ongoing at screening and current medical conditions are ongoing at screening. Medical history will not be summarized in any outputs.

### 9.6. Concomitant Medication and Therapy

Concomitant medication or therapy is defined as any medication or therapy that the participant is receiving at the time of enrollment or receives during the study, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements. All concomitant medications and therapies will be coded using WHO Drug Global B3 Sep 2024 or later (refer to Data Management Plan [DMP] for schedule of up-versioning). All concomitant medications and therapies will be displayed in a listing for all enrolled participants for each sub-trial (D/ND), including all general medications, ESA therapies, blood products, and iron supplements.

### 9.7. Extent of Exposure

Only enrolled participants may receive the study drug, in the form of either film-coated IR tablets or TfOS. Since the film-coated IR tablet and TfOS have similar formulations and tablet compositions, and the IR tablets and an oral solution had similar PK in previous studies, no dose adjustment between preparations is required. To support the correct dispensing of study drug for each study participant throughout the study, the IRT will be programmed with the starting dose based on their baseline status (age group, Hgb, ESA usage, and dialysis status) and any dose adjustment required based on their Hgb response to daprodustat.

The duration of the study drug will be calculated as (date of last dose – date of first dose + 1) / 7. Dose strength and dosing frequency will be documented in the databases, based on which the total amount of drug administered per treatment period (defined as the period between two scheduled study visits) can be calculated via the formula $\sum_{t=1}^{T} Dose_t \times Freq_t$ where T is the total number of different dose strength and frequency combinations during the treatment period of interest. All relevant data will be displayed in a listing for each sub-trial (D/ND).

### 9.8. Treatment Compliance

Overall treatment compliance is defined as [number of tablets dispensed – (number of tablets returned + number of tablets lost)] / number of tablets per day / (dose stop date – date start date + 1) × 100%. If there are dose changes during the course of the study, number of tablets per day used in the calculation will be the weighted average of the numbers of tablets per day with the weights being duration of each dose level, i.e., stop date at that dose level – start date at that dose level + 1. Similar method will be used to calculate treatment compliance per treatment period (defined as the period between two scheduled study visits). All relevant data used in calculating treatment compliance will be displayed in a listing for each sub-trial (D/ND).

# 10. Safety

The population used for safety analyses will be the Safety Set. Safety will be assessed based on AEs, clinical laboratory safety data, liver monitoring/stopping event, ECG parameters, height and weight, and vital signs. Planned time points for all safety assessments are listed in the Table 1 – Schedule of Activities. Additional time points for safety tests (such as vital signs, physical examinations and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

## 10.1. Adverse Events / Adverse Drug Reactions

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of the study intervention, whether or not considered related to the study intervention. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 or later (refer to the DMP for schedule of dictionary up-versioning) and will be summarized by system organ class (SOC) and preferred term (PT), or by SOC, PT and maximum intensity, or by PT alone as appropriate.

Per Section 7.1, all AEs will be handled using either treatment policy strategy or while-on-treatment strategy. Only death and kidney transplantation will be handled via while-on-treatment strategy where all AEs up to the occurrence of ICE will be included for analysis, whereas all other ICEs will be handled via treatment policy strategy where all AEs regardless of the occurrence of ICEs will be included for analysis.

### 10.1.1. Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those AEs with a start date on or after the commencement of daprodustat (Day 1) regardless of end dates. TEAEs will be summarized separately by SOC and PT. All AEs will be displayed in listings for each sub-trial (D/ND).

### 10.1.2. Adverse Events of Special Interest

The investigator or site staff will be responsible for detecting, documenting, and reporting any events that may represent the AESIs listed below:

- Death, myocardial infarction (MI), stroke, heart failure, thromboembolic events, thrombosis of vascular access.
  - Death
  - MI
  - Stroke
  - Heart failure
  - Thromboembolic event
  - Thrombosis of vascular access
- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis.
- New diagnosis of hypertension or worsening of existing hypertension
  - New diagnosis of hypertension
  - Worsening of existing hypertension
    - New resistant hypertension: hypertension despite treatment with at least 3 (maximal or maximally tolerated doses of) antihypertensive medications.
    - Hypertensive emergency: severely elevated BP associated with acute end-organ damage.

    - Hypertensive urgency: severely elevated BP without the presence of acute end-organ damage.
- Cancer related mortality and tumor progression and recurrence.
- Esophageal and gastric erosions

Potential AESIs will be identified through a pre-defined terms of interest process in which pre-defined lists of AE preferred terms corresponding with each AESI will be used to identify events considered to be potential AESIs. AESI definitions will be added once finalized. Sites will be prompted via query to complete any necessary additional information for these AESIs in the eCRF.

Thrombosis and tissue ischemia events will be considered to be secondary to excessive erythropoiesis if during the window of [AE start date – 30 days, AE start date +15 days] any one of the following 3 events occurs:

• Any Hgb value ≥ 13 g/dL (measured pre-dialysis)

• Hgb increase > 2 g/dL over 2 weeks (+1 week)

o Note: for programming purposes, a +1 week window is applied, corresponding to the allowable visit window, to look for increases > 2 g/dL over 3 weeks

• Hgb increase > 4 g/dL over 4 weeks (+1 week)

o Note: for programming purposes, a +1 week window is applied, corresponding to the allowable visit window, to look for increases > 4 g/dL over 5 weeks

To identify Hgb increases that meet the increase criterion above, all Hgb values taken within [AE start date – 58 days, AE start date + 15 days] will be identified. This corresponds to identifying Hgb values that occurred 4 weeks before the [AE start date – 30 days, AE start date +15 days] window of interest.

A summary table of AESIs by category, sub-categories, and PTs will be provided.

#### 10.1.3. Handling of Missing Data

Adverse events with missing start or end dates (for AEs that are not recovering/resolving) will be imputed according to the method described in Section 8.3. The original dates will be shown in listings.

#### 10.1.4. Summary Tables

The following AE summary tables will be provided for each sub-trial (D/ND), where the numbers and percentages of participants, and numbers of events are included.

- TEAEs by SOC and PT
- TEAEs leading to study intervention discontinuation by SOC and PT
- TESAEs by SOC and PT
- TESAEs by SOC and PT (number of participants and occurrences)
- TE AESIs by category, subcategory, and PT

### 10.2. Laboratory Evaluations

Blood samples for hematology and clinical chemistry, and urine samples for pregnancy test will be collected according to the Schedule of Activities in Table 1.

Hematology and clinical chemistry parameters will be summarized based on SI units or conventional units as appropriate, see Tables 2 and 3 for the lists of laboratory parameters along with the corresponding SI units and conversion factors to SI units from other units. Descriptive statistics for actual values and change from baseline will be provided for all safety laboratory parameters with continuous results. In addition, corresponding frequency tables will also be provided to summarize the number and percentages of participants with normal or abnormal laboratory results, where abnormal laboratory results will be further broken down into low or high compared with normal ranges. Post-baseline laboratory results at each planned visit and the worst-case post-baseline results overall relative to baseline will be summarized using frequencies tables, where numbers and percentages shifted to low, to normal or no change, and to high will be calculated. Given that these laboratory evaluations will be performed by local laboratories, normal ranges might differ from one site to another. The determination of abnormality will be dependent upon the normal ranges entered by sites in the database.

Table 2 – Laboratory Parameters, SI Units and Conversion Factors for Clinical Chemistry

| Laboratory Parameter | Units | SI Unit | Conversion Factor |
|---|---|---|---|
| Sodium<br>Potassium | MEQ/L | MMOL/L | 1 |
| | MMOL/L | MMOL/L | 1 |
| | MEQ/DL | MMOL/L | 10 |
| Calcium | MMOL/L | MMOL/L | 1 |
| | MG/L | MMOL/L | 0.02495 |
| | MVAL/L | MMOL/L | 0.499 |
| | MG% | MMOL/L | 0.2495 |
| | MG/DL | MMOL/L | 0.2495 |
| | MEQ/L | MMOL/L | 0.499 |
| Creatinine | MCMOL/L | UMOL/L | 1 |
| | MG% | UMOL/L | 88.4 |
| | UMOL/L | UMOL/L | 1 |
| | MG/DL | UMOL/L | 88.4 |
| | MG/L | UMOL/L | 8.84 |
| | MMOL/L | UMOL/L | 1000 |
| Ferritin | UG/L | UG/L | 1 |
| Transferrin Saturation | % | % | 1 |
| | Ratio | % | 100 |
| eGFR | ML/MIN/1.73M2 | ML/MIN/1.73M2 | 1 |
| BUN | MG/DL | MG/DL | 1 |
| Urea | MMOL/L | MMOL/L | 1 |
| | MG/DL | MMOL/L | 0.357 |
| | MG% | MMOL/L | 0.357 |
| | G/L | MMOL/L | 35.7 |

Abbreviations: SI = International System of Units; eGFR = Estimated Glomerular Filtration Rate; BUN = Blood Urea Nitrogen

Table 3 – Laboratory Parameters, SI Units and Conversion Factors for Hematology

| Laboratory Parameters | Units | SI Unit | Conversion Factor |
|---|---|---|---|
| Hematocrit | Fraction of 1 | 1 | 1 |
| | Ratio | 1 | 1 |
| | % | 1 | 0.01 |
| | L/L | 1 | 1 |
| | ML/DL | 1 | 0.01 |
| Hemoglobin | G/L | G/L | 1 |
| | G/DL | G/L | 10 |
| | MMOL/L (FE) | G/L | 16.1134 |
| | MMOL/L | G/L | 16.1134 |
| | G% | G/L | 10 |
| Platelet Count<br>WBC - Total<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils<br>Neutrophils<br>Erythrocytes - RBCs | 1000/UL | GI/L | 1 |
| | 10^3/UL | GI/L | 1 |
| | /MM3 | GI/L | 0.001 |
| | K/CUMM | GI/L | 1 |
| | THOU/CUMM | GI/L | 1 |
| | 10^9/L | GI/L | 1 |
| | GI/L | GI/L | 1 |
| | CELLS/MM$^3$ | GI/L | 0.001 |
| | THOU/MCL | GI/L | 1 |
| | PER CUMM | GI/L | 0.001 |
| | 10^5/CUMM | GI/L | 100 |
| | K/UL | GI/L | 1 |
| | /MCL | GI/L | 0.001 |
| | /NL | GI/L | 1 |
| | 10^3/CUMM | GI/L | 1 |
| | KCELLS/UL | GI/L | 1 |
| | 10^3/MM3 | GI/L | 1 |
| | CELLS/UL | GI/L | 0.001 |
| | 10^4/UL | GI/L | 10 |
| | 10^6/L | GI/L | 0.001 |
| | B/L | GI/L | 1 |
| | CELLS/NL | GI/L | 1 |
| | THOU/UL | GI/L | 1 |
| MCV | FL | FL | 1 |
| MCH | PG | PG | 1 |
| Reticulocytes | 10^12/L | TI/L | 1 |
| | 10^6/UL | TI/L | 1 |
| | 10^4/UL | TI/L | 0.01 |

| Laboratory Parameters | Units | SI Unit | Conversion Factor |
|---|---|---|---|
| | CELLS/MM3 | TI/L | 0.0000001 |
| | 10^6/CUMM | TI/L | 1 |
| | MIL/MM3 | TI/L | 1 |
| | MILL/MCL | TI/L | 1 |
| | CELLS/UL | TI/L | 0.0000001 |
| | CELLS/PL | TI/L | 1 |
| | MILL/UL | TI/L | 1 |
| | CELLS/NL | TI/L | 0.001 |
| | 10^3/UL | TI/L | 0.001 |
| | K/UL | TI/L | 0.001 |
| | CELLS/MCL | TI/L | 0.0000001 |
| | TI/L | TI/L | 1 |
| | 10^3/CUMM | TI/L | 0.001 |
| | GI/L | TI/L | 0.001 |
| | THOU/CUMM | TI/L | 0.001 |
| | 10^9/L | TI/L | 0.001 |
| | THOU/UL | TI/L | 0.001 |
| | 10^6/MM3 | TI/L | 1 |
| | /MM3 | TI/L | 0.0000001 |
| Lymphocytes %<br>Monocytes %<br>Eosinophils %<br>Basophils %<br>Neutrophils % | % | % | 1 |
| | Ratio | % | 100 |

Abbreviations: SI = International System of Units; WBC = White Blood Cell; RBC = Red Blood Cell; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin

In the event that a site will only be able to provide WBC count with differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils) results in either % or absolute value, the formulas below will be used to convert between results in % and absolute value. Actual values and changes from baseline in both % and absolute value will be summarized by visit. However, the summary of numbers and percentages of participants with normal or abnormal WBC count with differential results and the listing of subjects with any abnormal hematology results will be only based on the original parameter, results of which are reported by sites.

Neutrophils/Lymphocytes/Monocytes/Eosinophils/Basophils % = (Absolute Value of Neutrophils/Lymphocytes/Monocytes/Eosinophils/Basophils / Absolute Value of WBC Total) × 100

Absolute Value of Neutrophils/Lymphocytes/Monocytes/Eosinophils/Basophils = Neutrophils/Lymphocytes/Monocytes/Eosinophils/Basophils % × Absolute Value of WBC Total / 100

Participants with any abnormal hematology and clinical chemistry results will be displayed in a listing.

### 10.3. Liver Chemistry

Liver events are assessed and monitored via LFTs (+INR), for which blood samples are collected according to the Schedule of Activities in Table 1. All laboratory parameters will be summarized based on SI units, see Table 4 for the list of laboratory parameters along with the corresponding SI units and conversion factors to SI units from other units, Table 5 for the PCIs for selective parameters. Descriptive statistics for actual values and change from baseline will be summarized for each parameter by planned study visits for each sub-trial (D/ND). A listing will be provided for participants with any hepatobiliary laboratory abnormalities, where abnormality criteria include Alanine Aminotransferase (ALT) ≥3×Upper Limit of Normal (ULN) and total bilirubin ≥2×ULN (>35% direct bilirubin with bilirubin value is on or up to 28 days after ALT value), ALT ≥3×ULN and INR >1.5 (with INR value is on or up to 28 days after ALT value), hepatocellular injury[3], hepatocellular injury and total bilirubin ≥2×ULN, ALT ≥3×ULN, ALT ≥5×ULN, ALT ≥8×ULN, ALT ≥10×ULN and ALT ≥20×ULN.

Two figures will be generated, including a scatter plot of the maximum ALT (/ULN) measurements among all study visits versus the baseline results (/ULN) for each sub-trial (D/ND) and a scatter plot of the maximum bilirubin (/ULN) among all study visits versus the maximum ALT (/ULN) among all study visits for all participants for each sub-trial (D/ND).

Participant with any abnormal LFT (+INR) results will be displayed in a listing. For participants experiencing any liver stopping events, a liver stopping event profile will be provided.

Table 4 - Laboratory Parameters, SI Units and Conversion Factors for Liver Chemistry

| Laboratory Parameters | Units | SI Unit | Conversion Factor |
|---|---|---|---|
| Bilirubin<br>Direct Bilirubin | UMOL/L | UMOL/L | 1 |
| | MG/DL | UMOL/L | 17.1 |
| | MCMOL/L | UMOL/L | 1 |
| | MG% | UMOL/L | 17.1 |
| | MG/L | UMOL/L | 1.71 |
| ALT | IU/L | IU/L | 1 |
| | MMOL/H/L | IU/L | 16.663 |
| | MCKAT/L | IU/L | 58.824 |
| | MCMOL/SL | IU/L | 58.824 |
| | MCMOL/HML | IU/L | 16.663 |
| | UKAT/L | IU/L | 58.824 |
| ALP | IU/L | IU/L | 1 |
| | UKAT/L | IU/L | 59.988 |
| | MCKAT/L | IU/L | 59.988 |
| AST | IU/L | IU/L | 1 |

[3] Hepatocellular injury is defined as [ALT/ALT ULN) / (ALP/ALP ULN)] > 5 and ALT >3×ULN where ALT and ALP values must occur on the same day.

| Laboratory Parameters | Units | SI Unit | Conversion Factor |
|---|---|---|---|
| | MCKAT/L | IU/L | 59.988 |
| | UKAT/L | IU/L | 59.988 |
| Total Protein | G/L | G/L | 1 |
| | G/DL | G/L | 10 |
| | MG% | G/L | 0.01 |
| | G% | G/L | 10 |
| | MG/DL | G/L | 0.01 |
| INR | Fraction of 1 | 1 | 1 |
| | % | 1 | 0.01 |
| | Ratio | 1 | 1 |

Abbreviations: SI = International System of Units; ALT = Alanine Aminotransferase; ALP = Alkaline Phosphatase; AST = Aspartate Aminotransferase; INR = International Normalized Ratio

Table 5 – PCIs for Laboratory Parameters of Liver Chemistry

| Laboratory Parameters | PCI | |
|---|---|---|
| | Lower | Upper |
| ALT | NA | ≥3×ULN |
| Bilirubin | NA | ≥2×ULN |
| INR | NA | >1.5 |

PCIs for the parameters not included in Table 5 are identical to the lower and upper normal ranges provided by local sites.

### 10.4. Vital Signs

Vital signs will include systolic and diastolic BP and HR, which will be taken during all scheduled visits according to the Schedule of Activities in Table 1. BP and HR will be assessed using an appropriate size cuff, the assessment of which should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones). Three consecutive BP measurements will be obtained, of which the median will be recorded and be used for summary purposes. Descriptive statistics will be provided for the actual values of systolic BP, diastolic BP and HR at each study visit as well as change from baseline for each sub-trial (D/ND). All vital signs will be displayed in a listing for each sub-trial (D/ND).

### 10.5. ECG

A 12-lead ECG will be administered only during screening visit with participants in supine position. HR, PR interval, QRS duration and QR (uncorrected) interval will be measured. QTcF will be calculated (machine read or manually). If prolonged QT/QTcF is noted, two additional ECG measurements should be obtained, the mean results of which will be used for determining whether eligibility criteria are met for inclusion. There is no QT stopping criteria and no further ECG monitoring is required during subsequent study visits unless indicated as part of routine care of the participants. ECG results will not be displayed in any outputs.

### 10.6. Physical Examination

Height (in cm) and weight (in kg) will be measured at each study visit according to the Schedule of Activities specified in Table 1. Descriptive statistics will be provided for the actual values of height and weight at each study visit as well as change from baseline by age group. Any unexpected persistent change in trajectory of height/weight should be recorded as an AE. All height and weight assessments will be displayed in a listing.

A complete physical examination will be performed during study visits specified in Table 1, including, at a minimum, assessments of the ears, nose and throat, skin, cardiovascular, respiratory, GI and neurological systems. Physical examination findings will not be displayed in any outputs.

# 11. Efficacy

Efficacy analyses are part of the secondary objective of the study and will be on the assessments of Hgb and daprodustat dose over time. The Safety Set will be used for efficacy analyses.

## 11.1. Effect of Daprodustat on Hgb

The dose response of participants to daprodustat will be assessed by measurement of Hgb, where planned timepoints for all Hgb assessments are provided in the Schedule of Activities in Table 1. Hgb also serves to determine where a dose change is needed, see study protocol for details.

### 11.1.1. Analysis Methods

Similar to safety laboratory results, Hgb results will be obtained from local laboratories and entered into database by sites. Descriptive statistics (including number of observed Hgb values, number of missing Hgb values, mean, SD, and median of observed Hgb values) will be provided for the actual Hgb value at each study visit and change in Hgb from baseline at each subsequent study visits for all study participants for each sub-trial (D/ND). Additionally, the proportions of participants with Hgb above, within and below the target range (10 to 12 g/dL) will be summarized for each sub-trial (D/ND). No inferential testing will be performed.

Individual Hgb values will be plotted over time for each participant along with the corresponding daprodustat dose at each study visit.

All Hgb results will be displayed in a listing for each sub-trial (D/ND).

### 11.1.2. Handling of Unobserved Data

According Section 7.2, the following ICEs will be handled via while-on-treatment strategy.

- Permanent study intervention discontinuation due to any reason: any unobserved Hgb results after study intervention discontinuation will not be considered missing and will not be imputed; any observed Hgb results, if collected, will not be included for analysis.
- Unplanned use of ESA therapy: Hgb values within 8 weeks following the unplanned use of ESA therapy will be collected but will not be included in the analysis due to ESA's potential confounding effect on the interpretation of Hgb response; no imputation will be performed either.
- Intermittent use of rescue therapy (including use of iron supplements [oral/IV/both], blood transfusions and use of ESA and analogues): Hgb values from the date of initial use of rescue therapy until 8 weeks after the last dose of rescue therapy will be collected but will not be included in the analysis or imputed.
- Kidney transplantation or death: unobserved Hgb results after the event will not be considered missing and will not be imputed; any observed Hgb results, if collected, after kidney transplantation will not be included for analysis.

Disruption in study intervention, delays in study intervention, and transition to dialysis (for ND participants only) will be handled via treatment policy strategy where all observed Hgb results will be included for analysis, but no imputations will be performed for any missing Hgb results.

### 11.2. Dose Change Over Time

The other secondary efficacy analysis will be based on the required daprodustat dose over time, where descriptive statistics (mean, SD, and median) for daprodustat dose at each study visit will be summarized for each sub-trial (D/ND).

Individual daprodustat dose over time for each participant will be plotted along with the corresponding Hgb results at each study visit.

# 12. Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of daprodustat and its metabolites (GSK2391220 [M2], GSK2531403 [M3], GSK2487818 [M4], GSK2506102 [M5], GSK2531398 [M6], and GSK2531401 [M13]) will be collected at the time points indicated in Table 1 – Schedule of Activities. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring. Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

Plasma analysis will be performed under the control of Bioanalysis, Immunogenicity, and Biomarkers - In Vitro/In Vivo Translation Platform/Scinovo, GlaxoSmithKline, the details of which will not be covered in current document but will be included in the SRM. Concentrations of daprodustat and its metabolites (GSK2391220 [M2], GSK2531403 [M3], GSK2487818 [M4], GSK2506102 [M5], GSK2531398 [M6], and GSK2531401 [M13]) will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

A PK dataset will be delivered to GSK for PK analysis and will comprise substituting NQ values as follows:

- If one or more non-quantifiable (NQ) values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration.
- If NQ values occurs between measurable concentrations or after the last measurable concentration in a profile, the NQ values will be set to ½ LLQ

## 12.1. Sub-group Pharmacokinetic Analyses

Plasma daprodustat concentrations from each age group will be compared to predicted concentration-time profiles prior to enrolling the next younger age group into the study. If more than 50% of the daprodustat PK data does not lie within the pre-specified 95% prediction intervals of the PK simulations for the current age group, the PK data will be applied to update the physiologically-based pharmacokinetic (PBPK) SimCYP® model and undertake further simulations for time course of drug concentrations. GSK Clinical Pharmacology Modeling & Simulation (CPMS) and GSK Drug Metabolism & Pharmacokinetics (DMPK) will be responsible for the sub-group PK assessment.

## 12.2. Population Pharmacokinetics (POPPK) Analyses

At the end of the study, when all PK data are available, a POPPK analysis may be performed. This will be the responsibility of GSK CPMS and details will be included in a separate POPPK analysis plan. The results of the POPPK analysis will be reported separately.

## 12.3. Pharmacokinetic / Pharmacodynamic Analyses

Expanding the current adult Dose-Hgb model to incorporate pediatric Hgb data from this study may be explored and will be the responsibility of GSK CPMS; details they will be included in a separate Dose-Hgb model analysis plan and will be reported separately.

# 13. Other Health Outcomes of Interest

Analysis of other health outcomes of interest will be based on the Safety Set, including the endpoints described in Section 5.5 which can be divided into four categories: outcomes related to Hgb and rescue therapy, outcomes related to changes in kidney or intervention, other outcomes, and palatability and acceptability questionnaire.

## 13.1. Outcomes Related to Hgb and Rescue Therapy

Information related to Hgb and rescue therapy is documented on the eCRF page "Health Outcome of Interest: Status (HOI)" at each study visit and "Health Outcome of Interest: Status (Day 1)" at baseline, where the incidence of each outcome of interest will be linked to the corresponding concomitant medications log, including

- Use of iron supplements (oral/IV/both)
- Blood transfusion
- Use of ESA and analogues

All incidences of the use of iron supplements, blood transfusion, and ESA and analogues along with relevant information will be displayed in a listing for each sub-trial (D/ND).

## 13.2. Outcomes Related to Changes in Kidney Function or Intervention

The following outcomes are included in this category, each of which is assessed at each study visit.

- Transplantation
- Switch between dialysis modalities for D participants only
- ESKD for ND participants only

No outputs will be provided for these outcomes related to changes in kidney function or intervention.

## 13.3. Other Outcomes

The additional health outcomes of interest include below,

- Death documented on eCRF pages "Adverse Event", "Death" and "Study Conclusion"
- All-cause hospitalization
- Thrombosis (defined as: vascular access thrombosis, deep vein thrombosis or pulmonary embolism)
- All-cause loss of vascular access patency

Information related to all-cause hospitalization, thrombosis and all-cause loss of vascular access patency are all documented on eCRF pages "Health Outcome of Interest: Status (HOI)", "Thromboembolic Event/Thrombosis of Vascular Access" and "Thrombosis/Tissue Ischemia".

A listing will be provided to display all-cause hospitalizations for each sub-trial (D/ND). A listing of death will be provided for each sub-trial (D/ND) if there are any deaths during the study. No outputs will be provided for thrombosis or all-cause loss of vascular access patency.

### 13.4. Palatability and Acceptability Questionnaire

A palatability and acceptability questionnaire will be administered at Week 2, but results will not be summarized in any outputs.

## 14. Changes from Analysis Planned in Protocol

Due to study being terminated early, all results will be displayed for each sub-trial (D/ND) unless otherwise specified and will not be split by age group, since all participants enrolled are from the 12 to <18 years group.

The originally planned analyses for the tertiary endpoints below will not be implemented due to limited data availability.

- During the study, the incidence of other health outcomes of interest related to
  - Change in kidney function/intervention:
    - Transplantation
    - ESKD for ND participants
    - Switch between dialysis modalities for D participants
  - Other:
    - Death
    - Thrombosis
    - All-cause loss of vascular access patency
  - Participant related Palatability and Acceptability Questionnaire:
    - Palatability rating (good, acceptable, neither good nor bad, bad, very bad).
    - Ease of swallowing (very easy, easy, neither easy nor difficult, difficult, very difficult).

## 15. Reference List

1. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anaemia in Chronic Kidney Disease. Am J Kidney Dis. 2006;47(5 Suppl 3):S11-145

2. North American Paediatric Renal Trials and Collaborative Studies NAPRTCS 2011 Annual Dialysis Report https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf

3. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4(11):1832-1843

# 16. Programming Considerations

## 16.1. General Considerations

- One separate SAS program will be created for each output.
- One output file can contain several outputs. Or each output will be stored in a separate file.
- Output files will be delivered in both rich text format (rtf) and portable document format (pdf).
- Numbering of TFLs will follow GSK TFL numbering guidelines, where study population tables will start from 1.1 and end with 1.n, efficacy tables will start from 2.1 and end with 2.n, safety tables will start from 3.1 and end with 3.n, pharmacokinetics tables will start 4.1 and end with 4.n and listings will start with 16.1 and end with 16.x. All numberings within each section are continuous with an increment of 1.

## 16.2. Table, Figure, and Listing Format

### 16.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 10.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 10.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

### 16.2.2. Headers

- All output will have the following header at the top left of each page:
- Protocol: GSK214066

- Population: Screened | Enrolled | Safety
- All output will have Page n of N at the top right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table).
- The data cut date will appear on the top right corner of each page, right below page numbers, in the format for "Data as of DDMMYYYY".

16.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 1.1). A decimal system with a single decimal point is used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table 1.1
First Line of Title
Second Line of Title if Needed

16.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include 'unit' in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of participants in the analysis set.
- The order of study groups in the tables and listings will be in the order of Dialysis and Non-Dialysis when applicable.

16.2.5. Body of the Data Display

**16.2.5.1.** *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;

- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

**16.2.5.2.** *Table Conventions*

- Units will be included where available.
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

| Severity Rating | N |
|---|---|
| severe | 0 |
| moderate | 8 |
| mild | 3 |

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more participants.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

| | |
|---|---|
| N | XX |
| Mean | XXX.X |
| SD | X.XX |
| Median | XXX.X |

- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Percentages that are <0.1% are displayed as "<0.1%". Unless otherwise noted, for all percentages, the number of participants in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.
- Tabular display of adverse event data will be presented by SOC with the highest occurrence overall in decreasing order, assuming all terms are coded. Within each SOC, adverse events (by preferred term) will be displayed in decreasing order of occurrence. If incidence for more than 1 term is identical, they will then be sorted alphabetically.

- The percentage of participants will normally be calculated as a proportion of the number of participants assessed in the relevant treatment group (or overall) for the analysis set presented. Details regarding the selection of denominators will be described in footnotes, as necessary.
- For categorical summaries (number and percentage of participants) where a participant can be included in more than one category, a footnote or programming note will be added describing whether the participant is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

**16.2.5.3.** *Listing Conventions*

- Listings will be sorted for presentation in order of unique subject ID, subject ID, visit/collection day, and visit/collection time for each sub-trial (D/ND).
- Dates will be displayed in the format of yyyy-mm-dd. Missing portions of dates will be left blank. Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified.
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

**16.2.5.4.** *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible.
- Participant specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the listing source (i.e., Data source: Listing 16.xxx').

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
  Example
  Data source: Listing 16.1, Listing 16.2, Listing 16.3

## 17. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in CCI Developing Statistical Programs SOP CCI .

CCI Developing Statistical Programs SOP CCI , Conducting the Transfer of Biostatistical Deliverables SOP CCI and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

# 18. Index of Tables

## 18.1. Study Populations

| Number | Table Name | Analysis Population |
|---|---|---|
| 1.1 | Summary of Subject Status and Subject Disposition at Study Conclusion | (Screened Set) |
| 1.2 | Summary of Subject Treatment Status and Reasons for Discontinuation of Study Treatment | (Safety Set) |
| 1.3 | Summary of Demographic Characteristics | (Safety Set) |

## 18.2. Efficacy

| Number | Table Name | Analysis Population |
|---|---|---|
| 2.1 | Summary of Hgb Values (in g/dL) by Visit | (Safety Set) |
| 2.2 | Summary of Changes in Hgb Values (in g/dL) from Baseline by Visit | (Safety Set) |
| 2.3 | Summary of Proportion of Subjects with Hgb Values (in g/dL) Above, Within and Below the Target Range by Visit | (Safety Set) |
| 2.4 | Summary of Daprodustat Dose (mg) by Visit | (Safety Set) |

## 18.3. Safety

| Number | Table Name | Analysis Population |
|---|---|---|
| 3.1 | Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term | (Safety Set) |
| 3.2 | Summary of Treatment-Emergent Adverse Events Leading to Study Intervention Discontinuation by System Organ Class and Preferred Term | (Safety Set) |
| 3.3 | Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term | (Safety Set) |
| 3.4 | Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) | (Safety Set) |
| 3.5 | Summary of Treatment-Emergent Adverse Events of Special Interest by Category, Subcategory and Preferred Term | (Safety Set) |
| 3.6 | Summary of Hematology Results by Visit and Changes from Baseline | (Safety Set) |
| 3.7 | Summary of Hematology Results Relative to Normal Range, Post-Baseline Relative to Baseline by Visit | (Safety Set) |
| 3.8 | Summary of Clinical Chemistry Results by Visit and Changes from Baseline | (Safety Set) |
| 3.9 | Summary of Clinical Chemistry Results Relative to Normal Range, Post-Baseline Relative to Baseline by Visit | (Safety Set) |
| 3.10 | Summary of LFTs (+INR) Results by Visit and Changes from Baseline | (Safety Set) |

| Number | Table Name | Analysis Population |
|---|---|---|
| 3.11 | Summary of Vital Signs by Visit and Change from Baseline | (Safety Set) |

# 19. Index of Figures

## 19.1. Efficacy

| Number | Figure Name | Analysis Population |
|---|---|---|
| 2.1 | Plots of Individual Hgb Values (in g/dL) and Daprodustat Dose (mg) over Time by Subject | (Safety Set) |

## 19.2. Safety

| Number | Figure Name | Analysis Population |
|---|---|---|
| 3.1 | Scatter Plot of Maximum vs. Baseline for ALT | (Safety Set) |
| 3.2 | Scatter Plot of Maximum Bilirubin vs. Maximum ALT - eDISH | (Safety Set) |

## 20. Index of Listings

| Number | Listing Name | Analysis Population |
|---|---|---|
| 16.1 | Listing of Subjects Screened/Rescreened | (Screened Set) |
| 16.2 | Listing of Reasons for Study Treatment Discontinuation | (Enrolled Set) |
| 16.3 | Listing of Reasons for Study Withdrawal | (Enrolled Set) |
| 16.4 | Listing of Protocol Deviations | (Enrolled Set) |
| 16.5 | Listing of Subjects with Inclusion/Exclusion Criteria Deviations | (Enrolled Set) |
| 16.6 | Listing of Demographics Characteristics | (Enrolled Set) |
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| 16.9 | Listing of All Adverse Events | (Enrolled Set) |
| 16.10 | Listing of Reasons for Considering as a Treatment-Emergent Serious Adverse Event | (Enrolled Set) |
| 16.11 | Listing of Laboratory Tests and Associated Reference Ranges | (Enrolled Set) |
| 16.12 | Listing of Subjects with Any Abnormal Hematology Results | (Enrolled Set) |
| 16.13 | Listing of Subjects with Any Abnormal Chemistry Results | (Enrolled Set) |
| 16.14 | Listing of Subjects with Any Abnormal LFTs (+INR) Results | (Enrolled Set) |
| 16.15 | Listing of Concomitant Medication/Therapy | (Enrolled Set) |
| 16.16 | Listing of Study Treatment Accountability | (Enrolled Set) |
| 16.17 | Listing of All Hgb Values (in g/dL) | (Enrolled Set) |
| 16.18 | Listing of Hospitalizations | (Enrolled Set) |
| 16.19 | Listing of Liver Monitoring/Stopping Event Reporting | (Enrolled Set) |
| 16.20 | Liver Stopping Event Profile | (Enrolled Set) |
| 16.21 | Listing of All Vital Signs | (Enrolled Set) |
| 16.22 | Listing of Plasma Concentration (ng/mL) – Time (h) Data | (All PK) |
| 16.23 | Listing of Hepatobiliary Laboratory Abnormalities | (Enrolled Set) |
| 16.24 | Listing of Deaths | (Enrolled Set) |

## 21. Shells

The Table, Figure and Listing mock shells are provided in a separate document.

## 22. Appendices

None.

# GSK_214066_Statistical-Analysis-Plan_v1.0_23Jan2025_CLEAN

Final Audit Report 2025-02-03

| | |
|---|---|
| Created: | 2025-01-28 |
| By: | PPD |
| Status: | Signed |
| Transaction ID: | PPD |

## "GSK_214066_Statistical-Analysis-Plan_v1.0_23Jan2025_CLEAN" History

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Challenge: The user completed the signing ceremony.
2025-01-28 - 4:31:34 PM GMT

CCI

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Signing reason: I am the approver

Signature Date: 2025-01-28 - 4:31:35 PM GMT - Time Source: server- IP address: PPD

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PPD authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2025-02-03 - 2:37:08 PM GMT

PPD authenticated with Adobe Acrobat Sign.

Challenge: The user completed the signing ceremony.

2025-02-03 - 2:37:53 PM GMT

Document e-signed by PPD

Signing reason: I am the approver

Signature Date: 2025-02-03 - 2:37:54 PM GMT - Time Source: server- IP address: PPD

Agreement completed.

2025-02-03 - 2:37:54 PM GMT

CCI

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Adobe
Acrobat Sign

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| **Information Type:** | Study Data Analysis Plan (SDAP) |
|---|---|

# TITLE PAGE

| | |
|---|---|
| **Title:** | Modelling Plan for the Population Pharmacokinetic Analysis of Daprodustat (GSK1278863) in Pediatric Participants with Chronic Kidney Disease |
| **Compound Number(s):** | Daprodustat (GSK1278863) |
| **Clinical Study Identifier(s):** | ***Pediatric Studies:*** GSK214066 (Non-Dialysis), GSK214066 (Dialysis) |

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## VERSION HISTORY

| Version | PDAP Date | Change | Rationale |
|---|---|---|---|
| 1 | | Not Applicable | Original version |
| | | | |

**Author(s) and Functional Area:**

| Author Name(s) | Functional Area | Date |
|---|---|---|
| PPD | PPD | |
| | | |

**Approved by:**

| Approver Name(s) | Functional Area | Date |
|---|---|---|
| PPD | PPD | |
| | | |

**CONFIDENTIAL**

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## LIST OF FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADaM | Analysis Data Model |
| ANOVA | Analysis of variance |
| AUC | Area under the concentration-time curve |
| BLQ | Below the limit of quantitation |
| $C_{avg}$ | Average concentration |
| CI | Confidence interval(s) |
| CKD | Chronic kidney disease |
| CL | Clearance |
| CL | Apparent clearance (CL/F) |
| $C_{max}$ | Maximum concentration |
| $C_{min}$ | Minimum concentration |
| CWRES | Conditional weighted residuals |
| CYP | Cytochrome P450 |
| EMA | European Medicines Agency |
| EPO | Erythropoietin |
| ESRD | End-stage renal disease |
| ETA | Interindividual random effect |
| F1 | Relative bioavailability |
| FDA | Food and Drug Administration |
| FOCE-I | First order conditional estimation with interaction |
| GFR | Glomerular filtration rate |
| GOF | Goodness-of-fit |
| HD | Haemodialysis |
| Hgb | Haemoglobin |
| HI | Hepatic impairment |
| HIF | Hypoxia-inducible factor |
| IIV | Interindividual variability |
| IMP | Importance sampling |
| IOV | Inter-occasion variability |
| IPRED | Individual predicted values |
| IWRES | Individual weighted residuals |
| ka | Absorption rate constant |
| KM | Dose amount at half-maximal absorption |
| ND | No dialysis |
| NONMEM | Nonlinear mixed-effects modelling |
| NPC | Numerical predictive check |
| NPDE | Normalized prediction distribution errors |
| OFV | Objective function value |
| pcVPC | Prediction-corrected visual predictive check |
| PD | Peritoneal Dialysis |
| PHI | Prolyl hydroxylase inhibitor |

| | |
|---|---|
| PI | Prediction interval(s) |
| PK | Pharmacokinetic(s) |
| PRED | Population predicted values |
| PsN | Perl-speaks-NONMEM |
| QC | Quality control |
| QD | Once daily |
| Qx | Apparent inter-compartmental clearance (Qx/F) |
| RSE | Relative standard errors |
| RUV | Residual unidentified variability |
| SAEM | Stochastic approximation expectation maximization |
| SAS | Statistical Analysis System |
| SDTM | Study Data Tabulation Model |
| SE | Standard error(s) |
| SIR | Sampling importance resampling |
| TIW | Three times a week |
| Tr | Transit compartment |
| US | United States |
| Vmax | Maximal absorption rate |
| VPC | Visual predictive check |
| Vx | Apparent volume of distribution (central or peripheral: Vx/F) |

## Trademark Information

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| SIMCYP |

# 1. INTRODUCTION

## 1.1. Background

Daprodustat (GSK1278863) is an orally administered small molecule, developed for the treatment of anaemia in CKD patients [1]. Daprodustat is a HIF-prolyl hydroxylase inhibitor (PHI) that has demonstrated the ability to stimulate erythropoiesis and thus increase haemoglobin following oral administration. Several clinical studies have evaluated its pharmacokinetics (PK), safety, and pharmacodynamics in adult healthy participants and CKD patients. The drug has been licensed and commercially available in Japan since August 2020 for the treatment of anaemia in patients with CKD, both on dialysis (D) and not on dialysis (ND) [2].

Currently, there are limited data on the clinical effects of daprodustat in participants <18 years of age. The doses selected for a study in paediatric patients (Study 214066) were based on simulations obtained using a previously developed physiology-based PK model [3], described in Section 1.1.1. In addition, three population PK models in adult patients and healthy participants have also been made available for regulatory submission [4-6] (Section 1.1.2). The population PK models have been revisited in order to analyse collectively the data from the three previously available separate reports, to provide a more comprehensive description of the pharmacokinetic properties of daprodustat (see Section 1.1.3). This model will form the basis for the analysis of pharmacokinetic data in the paediatric patients enrolled into study 214066.

The pediatric study 214066 is an integrated pharmacokinetic and safety open-label basket trial with the aim of assessing the response to treatment of anemia associated with CKD in pediatric participants down to an age of 3 months. Participants might or might not have required dialysis. The enrollment into the study was designed to be staggered by age groups. Initially, adolescent participants (12- <18 years) will be recruited and receive a dose regimen equivalent to that recommended in adult participants (starting dose of 2 mg QD and up-titration based on hemoglobin levels). The study started August 23, 2023. The Sponsor paused recruitment into this clinical study on 16 May 2024 while conducting a review of products and pipeline, whilst only 4 adolescents participants were enrolled into the study. The recruitment pause was not related to any safety concerns. During the recruitment pause, all participants continued the clinical study as per protocol. On 04 September 2024, the Sponsor confirmed that study recruitment would not be re-initiated, and all participants currently enrolled continued the study until the protocol-defined study end. During the study conduct it was foreseen that the outcome of an interim analysis (IA) - based on matching PK and acceptable tolerability of daprodustat – would have provided the elements to: i) continue enrolling adolescents participants to be treated at the same dose levels, and ii) open the enrollment of participant of the subsequent age cohort (6-<12 years), at the corresponding dose foreseen in the protocol (starting dose 1 mg QD). The study should have proceeded opening lower pediatric age cohorts after similar IAs checking the appropriateness of the proposed dosing regimens.

The analyses described in this study data analysis plan (SDAP) will therefore be based on the outcome obtained in these 4 adolescent participant date and has the aim to i) confirm or refine the dosing regimen to be used in the adolescent participants and ii) describe the pharmacokinetics of daprodustat in adolescent participants based on post-hoc estimates of the previously developed population PK model.

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### 1.1.1. Previous Population PBPK Model

A physiologically-based pharmacokinetic (PBPK) model (using the SimCyp® v20.0) of daprodustat (GSK1278863) was developed [3] that successfully predicted pharmacokinetic profiles and parameters across multiple clinical studies in healthy participants. Of note, daprodustat PK in healthy participants and participants with CKD did not show important differences based on the covariate analyses of the population PK models (see Section 1.1.2).

Daprodustat is primarily metabolized by cytochrome P450 (CYP) 2C8 with a minor contribution by CYP3A4. In addition to phase 1 studies in healthy participants, clinical drug-drug interaction (DDI) studies with gemfibrozil (potent CYP2C8 inhibitor) and trimethoprim (weak CYP2C8 inhibitor) were used to identify the relative importance of CYP2C8 pathways in the PBPK model and set relevant pharmacokinetic parameters in the PBPK model. The PBPK model was qualified and verified and demonstrated to be robust and accurate to extrapolate dosing regimens to be adopted in paediatric participants. In particular, PBPK simulations were performed (Simcyp® default), to assess the doses to be used in pediatric participants of different age ranges necessary to match the systemic exposures to daprodustat of adults receiving 2 mg oral single dose. The ratios to adult doses to be adopted in pediatric participants, expected to match the PK doses are reported in Table 1.

**Table 1. PBPK-Defined Doses in Participants of Different Age Ranges Necessary to Match the Systemic Exposures to Daprodustat of Adults receiving 2 mg Oral Single Dose**

| Age Group[a] | Dose (mg) | Ratio to Adult Dose |
|---|---|---|
| >18 years | 2.0 | N/A |
| 12 to <18 years | 2.0 | 1 |
| 6 to <12 years | 1.0 | ½ |
| 2 to <6 years | 0.50 | ¼ |
| 3 months to <2 years | 0.25 | ⅛ |

a. PBPK Simulations conducted with 50 Trials of 10 participants consisting of Pediatric participants falling into the specified age buckets (50% females).

### 1.1.2. Previous Population PK Models

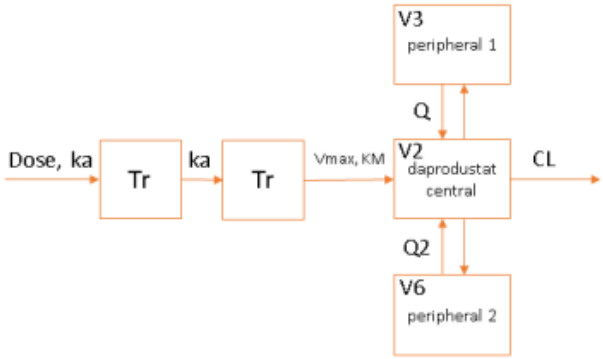
Initially, a population PK model for daprodustat was developed using data obtained from Phase 1 studies in healthy participants. The analysis population was later expanded to include CKD patients enrolled in Phase 2 studies, incorporating PK measurements obtained during dialysis and considering the effects of co-medications [4].

A 3-compartment distribution model with first order elimination described the disposition of daprodustat (Figure 1). The complex and delayed absorption kinetics following tablet administration was characterized using 2 serial transit compartments, with saturable release from the second into the central compartment when daprodustat was administered in fasted conditions. A 4-compartment transit model with saturable release from the fourth into the central compartment was used to describe the PK data under fed conditions.

Allometry was applied to all clearance and volume terms using standard exponents (fixed to 0.75 and 1.00, respectively) to account for the effect of body weight on daprodustat PK. Other covariate effects included reduced clearance (CL) in the HD population and with co-

administration of the cytochrome P450 (CYP) 2C8-inhibitor gemfibrozil, increased relative bioavailability (F1) with gemfibrozil, and a decreased saturable rate of absorption with food intake (Study PHI113634) [4]. Additionally, differences in the absorption model and in peripheral parameters were identified with mild and moderate hepatic impairment (HI) [4]. The PK of metabolites were fitted *a posteriori* via a stepwise approach, using the final Phase 1 daprodustat PK model as parent input [4].

**Figure 1 Structure of the Phase 1 Daprodustat PK Model (Fast Condition)**




Abbreviations: CL = apparent clearance (CL/F); ka = absorption rate constant; KM = dose amount at half-maximal absorption; Qx = apparent inter-compartmental clearance (Qx/F); Tr = transit compartment; Vmax = maximal absorption rate; Vx = apparent volume of distribution (central or peripheral: Vx/F). From [4].

External validation using the above Phase 1 model appropriately described the Phase 2 data but underpredicted variability. An exploratory evaluation of potential covariate effects was therefore considered more informative than a formal model-based approach. In Phase 2 participants, co-administered clopidogrel or phosphate binder, African-American race, and sex were detected as statistically significant covariates [4].

The Phase 1 daprodustat model was then applied to the prediction of PK data from Japanese CKD patients in Phase 3 clinical studies [5]. In this analysis, the structural model remained the same as that for the Phase 1 analysis, assuming fed conditions (N=7 transit compartments). All parameters were fixed to that in the Phase 1 model, except for ka, KM, F1, and residual error to achieve an acceptable fit in Phase 3 participants. In addition, the effect of HD was not required and was removed from the model.

Lastly, an independent model was developed to describe the PK of daprodustat using data from Phase 2/3 studies in CKD patients receiving HD, PD, or no dialysis (ND) [6]. The structural base model was consistent with that for Phase 1 and comprised a 3-compartment disposition and transit compartment (N=5) absorption. In contrast to previous models, the data did not support estimation of food effects or saturable release (maximum dose 48 mg vs. 300 mg in Phase 1) on absorption parameters. Covariate effects included a reduction in CL with clopidogrel use, and higher ka in non-dialysis dependent participants.

A comparison of parameter estimates from daprodustat population PK models is provided in Table 1 (Appendix).

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### 1.1.3. Comprehensive Population PK Model

The above models independently described the PK characteristics of daprodustat across specific sub-populations using approaches that included the estimation of all parameters, or sequential modelling to quantify covariate effects. However, a population PK model that fits all currently available data in adults was lacking, which might lead to queries in future interactions with regulatory agencies. In addition, the availability of such a model, in which the effects of intrinsic and extrinsic factors are characterised in an integrated manner, will provide the basis for further use of the model to support additional studies, including that in paediatric patients.

Therefore, the datasets used for developing the models described in Section 1.1.2 are being collectively reanalysed, with the intention to revisit some of the model elements described below:

- Absorption, base model:
    - The number of transit compartment to be used for describing absorption in different conditions (Japanese participants, fed and fast conditions) and the need for the nonlinear absorption terms are being assessed.
- Disposition, base model
    - Effect of body size (body weight, e.g., via estimation of allometric coefficients) is being reassessed.
- Covariates model
    - In addition to body weight, which will be examined also in the light of the emerging pediatric study, relevant covariates highlighted in the previous analyses are being maintained in the model and their effects are being re-assessed (food effect on Vmax, dialysis type on ka and CL, gemfibrozil on F1 and CL, clopidogrel on F1 and CL, CYP2C8 inhibitors on CL,HI on peripheral parameters, African-American race on CL) based on the collective data. Other covariates of clinical interest (age, sex, race, region, CKD status, glomerular filtration rate, CYP2C8 inducers, active dialysis) are being explored.

## 1.2. Analysis Rationale

The analysis described in the present Study Analysis Plan (SDAP) aims to:

i) assess the daprodustat PK data emerging from the pediatric study, with the intention to describe the pharmacokinetics of daprodustat in adolescent participants who have evaluable PK data.

ii) Considering that the study was stopped after enrolment of the first 4 adolescent participants, who were the only participants concluding the study, the analyses also aim to confirm the dosing regimen to be used in cohorts of subjects of adolescents. For this aim, the available daprodustat plasma concentrations (dose-normalized as required) will be projected in a plot together with the reference

plasma concentrations observed in adult participants, defined *via* the PBPK simulation exercise (95%PI) [3]. If ≤50% of observations are outside the prespecified reference levels, the dose algorithm proposed for adolescents will be considered adequate. If instead >50% of observations are outside the prespecified reference levels, model-based simulations based on the population PK model and/or PBPK model may be performed to propose alternative starting dosing regimens, able to more appropriately match the exposures observed in adult participants. The adoption of the starting alternative dosing regimen should be sufficiently flexible considering i) the available dosing strengths, and that ii) daprodustat doses will be anyway modulated using the emerging Hemoglobin data.

This modelling exercise will concern the parent drug, daprodustat. As far as metabolites are concerned, a minimal contribution to daprodustat pharmacology cannot be excluded, but the available information indicate that metabolite contribution to clinical effects is minimal. Indeed, in a cocktail study in mice, the key metabolites of daprodustat showed negligible effect on haemoglobin, haematocrit, and red blood cell count compared to unchanged daprodustat. The PK of metabolites is thus considered out-of-scope in the modelling of paediatric data. Metabolite concentration data will be collected in the paediatric study, but they will simply be described using descriptive statistics.

## 2. ANALYSIS OBJECTIVES

The overall objectives of these analyses are to:

1. Describe the pharmacokinetics of daprodustat in adolescent participants with CKD.

2. Provide support to the dosing regimen to be used in adolescent participants. Considering that the study enrolled only 4 participants in the adolescent age range, this assessment will be based on all participants (both D and ND subtrial/subpopulation)

## 3. STUDY DETAILS

The available data from the GSK214066 study will be included in this population PK analysis. Whilst the study was designed to have a staggered enrollment of the pediatric participants of different age groups (adolescents, i.e., 12-<18 years, followed by participants with 6-<12 years, 2-<6 years, and 3 months-<2 years) (see Section 1.1), eventually the study enrolled only 4 adolescent participants before being stopped.

A summary of the clinical study as it was originally designed is provided in Table 2.

**Table 2 Summary of the GSK214066 Study**

<table>
<tr><th>Study, Phase</th><th>Description</th><th>Population</th><th>Dose Regimen</th><th>No. of Participants</th><th>Sampling</th></tr>
<tr>
<td>214066, Phase 3a</td>
<td>An Integrated Pharmacokinetic and Safety Open-label Basket Trial of Daprodustat for the Treatment of Anemia Associated with Chronic Kidney Disease in Male and Female Children and Adolescents Aged 3 Months to Under 18 Years Requiring</td>
<td>Pediatric CKD patients with anemia requiring (D) or not requiring (ND) dialysis. D substudy/ subpopulation will enroll in both Japan and US; ND substudy/ subpopulation will enroll in Japan only</td>
<td>Assuming the PBPK model predictions are appropriate and unchanged by the PK data collected and analyzed during the study in the Integrated PK Phase, the starting dosing in the younger age groups is also provided in the following tables based on the predicted scaling (ratio of adult to pediatric dose) reported below.<br>Apparent Oral Clearance of Daprodustat by Age Group and Predicted Dose Equivalent to a 2 mg Adult Dose
<table>
<tr><th>Age Group</th><th>PBPK Model Weight Range Assumptions (kg)</th><th>CLpo (L/h) Geometric Mean</th><th>Dose (mg)</th><th>Ratio Pediatric to Adult Dose</th></tr>
<tr><td>Adults (≥18 years)</td><td>42.0 to 123.6</td><td>31.7</td><td>2</td><td>Not applicable</td></tr>
<tr><td>12 to <18 years</td><td>25.3 to 123.5</td><td>25.3</td><td>2</td><td>1/1</td></tr>
<tr><td>6 to <12 years</td><td>14.6 to 59.0</td><td>13.5</td><td>1</td><td>1/2</td></tr>
<tr><td>2 to <6 years</td><td>9.8 to 30.0</td><td>7.0[a]</td><td>0.5</td><td>1/4</td></tr>
<tr><td>3 months to <2 years</td><td>4.2 to 19.5</td><td>2.3[a]</td><td>0.25</td><td>1/8</td></tr>
</table>
Abbreviations: CLpo = Apparent oral clearance<br>Starting Dose of Daprodustat for ESA Non-Users
<table>
<tr><th rowspan="2">Baseline Hgb (g/dL)</th><th colspan="4">Daprodustat starting dose per age group (mg, QD)</th></tr>
<tr><th>Adults and 12 to <18 years</th><th>6 to <12 years</th><th>2 to <6 years</th><th>3 months to <2 years</th></tr>
<tr><td><9</td><td>4</td><td>2</td><td>1</td><td>0.5</td></tr>
<tr><td>≥9</td><td>2</td><td>1</td><td>0.5</td><td>0.25</td></tr>
</table>
Starting Dose of Daprodustat in ESA Users, Not on Dialysis
<table>
<tr><th colspan="3">Prior ESA dose at Baseline</th><th colspan="4">Daprodustat starting dose per age group (mg, QD)</th></tr>
<tr><th>Epoetins (incl biosimilars) (convert SC to IV U/week)[a]</th><th>Darbepoetin alfa (µg/4wk SC/IV)[b]</th><th>Methoxy PEG-epoetin beta (µg/month SC/IV)[c,d]</th><th>Adults and 12 to <18 years</th><th>6 to <12 years</th><th>2 to <6 years</th><th>3 months to <2 years</th></tr>
<tr><td>≤2000[e]</td><td>≤30</td><td>≤40</td><td>1</td><td>0.5</td><td>0.25</td><td>0.125</td></tr>
<tr><td>>2000 to <20,000</td><td>>30 to 300</td><td>>40 to 360</td><td>2</td><td>1</td><td>0.5</td><td>0.25</td></tr>
<tr><td>≥20,000</td><td>>300</td><td>>360</td><td>4</td><td>2</td><td>1</td><td>0.5</td></tr>
</table>
Abbreviations: PEG = polyethylene glycol. SC = subcutaneous, IV = intravenous, U = units<br>a. Standard rhEPO IV dose (U/week) = 161/113 x (epoetin SC dose (units))/(frequency) [Besarab, 2002].<br>b. Conversion of 250U:1µg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008].<br>c. Conversion of 1:1.2 µg (darbepoetin alfa:methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [Choi, 2013].<br>d. Conversion of 208 U:1 µg (epoetin IV:methoxy PEG-epoetin beta)<br>e. This includes ESA users on a zero dose / dose-hold at the time of enrolment</td>
<td>60 D participants; at least 4 D participants with PK for each pediatric age range; eventually at least 24 participants overall<br>Approximately 15 ND participants, at least 1 ND participants with PK for each pediatric age range; eventually at least 3 participants overall (in case of enrolment difficulties participants form the 3 months-1 year of age may be waived).</td>
<td>Week 2: samples collected at 0.5 - 1.5 hour, >1.5 to 3 hour, ≥4 (≤8) hours post-dose. Week 4: samples collected at pre-dose 0.5 -1.5 hour, >1.5 to 3 hour, ≥4 (≤8) hours post-dose. Samples recommended at Week 2 and 4, but flexibility allowed. In case of dose hold, PK sampling should be delayed until the visit after daprodustat is restarted.</td>
</tr>
</table>

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<table>
<tr><th>Study, Phase</th><th>Description</th><th>Population</th><th>Dose Regimen</th><th>No. of Participants</th><th>Sampling</th></tr>
<tr><td></td><td></td><td></td><td>Starting Dose of Daprodustat in ESA Users, Undergoing Dialysis
<table>
<tr><th colspan="3">Prior ESA dose at Baseline</th><th colspan="4">Daprodustat starting dose per age group (mg, QD)</th></tr>
<tr><th>Epoetins (incl biosimilars) (convert SC to IV U/week)[a]</th><th>Darbepoetin alfa (µg/4wk SC/IV)[b]</th><th>Methoxy PEG-epoetin beta (µg/month SC/IV)[c,d]</th><th>Adults and 12 to <18 years</th><th>6 to <12 years</th><th>2 to <6 years</th><th>3 months to <2 years</th></tr>
<tr><td>≤2000[e]</td><td>≤30</td><td>≤40</td><td>4</td><td>2</td><td>1</td><td>0.5</td></tr>
<tr><td>>2000 to <10,000</td><td>>30 to 150</td><td>>40 to 180</td><td>6</td><td>3</td><td>1.5</td><td>0.75</td></tr>
<tr><td>≥10,000 to <20,000</td><td>>150 to 300</td><td>>180 to 360</td><td>8</td><td>4</td><td>2</td><td>1</td></tr>
<tr><td>≥20,000</td><td>>300</td><td>>360</td><td>12</td><td>6</td><td>3</td><td>1.5</td></tr>
</table>
Abbreviations: PEG = polyethylene glycol. SC = subcutaneous, IV = intravenous, U = units, ug = micrograms<br>
a. Standard rhEPO IV dose (U/week) = 161/113 x (epoetin SC dose (units))/(frequency) [Besarab, 2002].<br>
b. Conversion of 250U:1µg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008].<br>
c. Conversion of 1:1.2 µg (darbepoetin alfa:methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [Choi, 2013].<br>
d. Conversion of 208 U:1 µg (epoetin IV:methoxy PEG-epoetin beta)<br>
e. This includes ESA users on a zero dose / dose-hold at the time of enrollment</td><td></td><td></td></tr>
</table>

Abbreviations: CKD = chronic kidney disease; D=dialysis ESA = Erythropoiesis-stimulating agents; ND = no dialysis; PBPK=physiology-based pharmacokinetic model; PK = pharmacokinetics; QD = once daily.

# 4. DATA

## 4.1. Dataset Preparation

The analysis dataset for the final population PK analysis (see Section 5) will be based on source data from SDTM or Analysis Data Model (ADaM) domains. It will be assumed that comprehensive checks have been performed and that source file contents accurately reflect collected clinical study data. Physiologically relevant covariates will be included in the dataset, with particular reference to those identified as clinically relevant based on the latest version of the population PK model (see Section 1.1.3).

The datasets will be assembled as analysis-ready files (*.csv) using Statistical Analysis System (SAS®, Version 9.4) or R (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, URL https://www.R-project.org/), according to appropriate data specifications. If datasets are modified over the course of the analysis, the file name of each version will be unique. This will allow for verification of the different datasets used in each population PK analysis file. For each unique participant, the dataset will include drug dosing history, concentrations with associated sampling times, demographic variables, relevant covariates and any other relevant information.

Quality control (QC) checks will be performed to ensure that all datasets are accurate and reflect the analysis population specified in this analysis plan. All QC processes will be conducted by an independent reviewer to confirm that there are no inconsistencies either in source databases or in scripts used to generate analysis-ready files.

## 4.2. Evaluable Participants

A participant will be included in the analysis if the following criteria are satisfied:

- The participant has at least one measurable observation (daprodustat concentration) with an associated sampling time.
- The participant has relevant dosing data prior to each measurable concentration.
- The participant is not associated with a protocol violation that could confound interpretation of the analysis.

## 4.3. Data Handling

Data records may be considered for exclusion based on the following reasons:

- The value is inconsistent with that for other individuals or with the chronological sequence of study procedures and cannot be resolved through a query resolution process.
- The value does not have adequate supporting information to allow for reasonable and unique assignment as a participant observation.
- The value is associated with documented errors in drug administration, specimen collection, sample handling, or bioanalytical procedures, and may reasonable be expected to produce spurious results.

- The value has been carefully considered and identified as an outlier (see Section 4.3.5).

A listing of all missing and excluded data, together with a reason for their exclusion will be provided as an appendix to the population PK analysis report(s).

### 4.3.1. Missing Dose Information

Records with missing dosing times will be excluded from the analysis. Where appropriate and justifiable, missing dose amount may be imputed using nominal values. However, care will be taken to ensure that "missing" doses are not due to non-compliance or other clinical decisions such as modification due to treatment-emergent adverse events. Dosing data that cannot be imputed will be flagged and excluded from all analyses.

### 4.3.2. Missing Observations

Concentration and/or time data identified as missing will be handled as follows:

- Missing observations and/or sampling times will be excluded from the analysis.
- Observations immediately prior to the first dose (pre-dose) will be retained in the dataset and flagged for exclusion.
- Concentrations associated with missing dosing data will be flagged and excluded.

### 4.3.3. Missing Covariates

Intrinsic or extrinsic covariate data that are missing will be handled as follows:

- Missing continuous covariates at baseline may be imputed using the median value of the full analysis population or appropriate sub-category.
- If appropriate, time-varying continuous covariates identified as missing will be imputed using a last-observation carried forward rule.
- Missing categorical covariates will either be assigned to an independent "missing" category or combined with a relevant subgroup.
- Unlikely covariate values, such as those well outside of an expected range, will be considered on a case-by-case basis.

If the percentage of missing data exceeds 10%, that covariate will be excluded from the analysis, and only assessed for data exploration purposes.

### 4.3.4. Data Below the Limit of Quantitation

Concentrations reported as below the limit of quantitation (BLQ) will be retained in the analysis dataset and flagged using an independent column. If greater than 15% of post dose concentrations are BLQ, these samples maybe treated as censored, and a likelihood-based approach maybe be used to handle these data [7,8]. The approach to handling of BLQ data will be described and justified in the report.

#### 4.3.5. Handling of Outlier Data

Prior to population PK analysis, graphical inspection will be conducted of individual or pooled concentration-time profiles to identify outlier or anomalous data. Additionally, the PK data may be plotted relative to each analysis participant's actual dosing history to detect any anomalies. Following preliminary model runs, concentrations for which the absolute value of conditional weighted residuals (CWRES) are greater than 6 (|CWRES > 6|) will be flagged as questionable. These data may be excluded from the population PK analysis with reasons for their exclusion documented in the modelling report.

The final model may be re-run as a sensitivity analysis with and without the inclusion of these outlying data. Parameter estimates from these two models will then be compared to justify outlier exclusion and may be included as an appendix item in the population PK analysis report(s) where appropriate. The proportion of outliers should be low and can be excluded from the analysis given their potential to negatively impact convergence and/or parameter values.

# 5. ANALYSIS METHODS

## 5.1. Population PK Assessment

A previously developed population PK model will be used to characterise the pharmacokinetics of daprodustat in adolescent patients.

The most recent version of the population PK model of daprodustat, with all the meaningful covariates that were identified, will be used as an initial step to fit the PK data from the paediatric study (e.g., using MAXEVAL=0 option in NONMEM), re-estimation of allometric coefficients, and other parameters may be considered as data permit. All covariate effects identified previously, and retained in the comprehensive population PK model (Section 1.1.3) will be kept in the model. Covariates may be challenged to justify their retention in the model.

### 5.1.1. Model Qualification

The final population PK model will be considered appropriate based on a combination of acceptance criteria and standard diagnostic GOF plots [9]. Acceptability of the model will preferably include stability, convergence, a successful covariance step, and/or low condition number (e.g., <1000). If the condition number ranges between 1000 and 10000, the model will be considered on a case-by-case basis. Other model suitability criteria may include parameter plausibility, and low relative standard errors (RSE, e.g., <30% for fixed effect parameters and <50% for random effect parameters).

Several standard GOF plots will be used to visualize agreement between observed versus model-predicted values and lack of bias. These may include the following:

- Observed versus individual predicted (IPRED) concentrations.
- Observed versus population predicted (PRED) concentrations.
- CWRES versus PRED and time since first dose and/or last dose.
- IPRED versus absolute individual weighted residuals (IWRES).

- ETA-ETA correlations and distribution of inter-individual random effects.
- CWRES and normalized prediction distribution error (NPDE) distributions.

In addition to the above GOF diagnostic plots, the performance of the final population PK model will be evaluated using a visual predictive check (VPC).

## 5.2. Confirmation of Dosing Regimen in Adolescent Participants

The criterion used for exploring the consistency between simulated data in adults and plasma concentration data in the available adolescents participants will be that >50% of the observed concentrations in the specified age group of pediatric participants is included in the 95% prediction intervals of the simulated data in adults at 2 mg.

The 95% prediction intervals of the simulated data in adults are shown in Figure 2 (together with simulated observations in a panel of 4 participants); 95% prediction intervals of adult daprodustat plasma concentrations following repeated dose of 2 mg are also reported in Table in the Appendix.

If the consistency between predicted and observed concentration data will be ensured (see Figure 2, where only 4 out of 16, i.e., 25% of the observed plasma concentrations are outside the predefined prediction intervals), the outcome of the previously defined pediatric simulations can be considered adequate. Therefore, it can be concluded that the dosing regimen proposed in adolescents (equivalent to that applied to adult participants) is reasonable. Based on this information, it might also be inferred that the starting dose foreseen by the protocol for participants 6-<12 years old (starting dose of 1 mg QD subsequently titrated based on hemoglobin levels) is reasonable.

If the consistency between observations and predictions will not be ensured, then the popPK model (see Section 5.1) may be used (after suitable modifications, as required) to propose a different dose to be used in adolescents and/or in participants in the lower pediatric age ranges.

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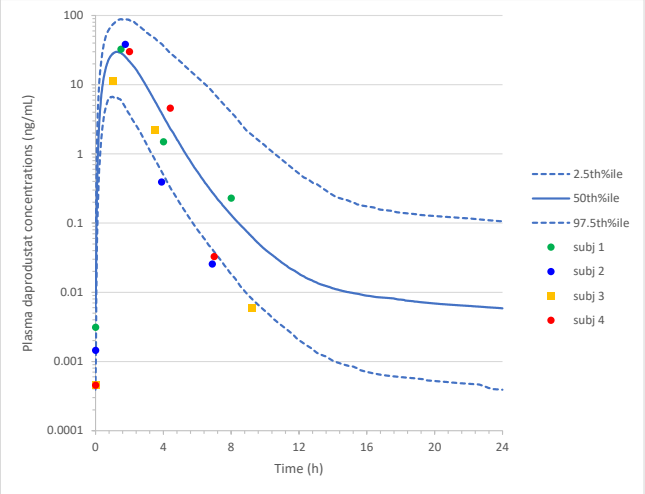
**Figure 2. Overlay of Simulated Daprodustat Plasma Concentrations in Virtual Pediatric Participants after Repeated Dosing of Daprodustat (Normalized to a Dose of 2 mg QD) on the 95% Prediction Interval of Daprodustat Plasma Concentrations in Adults [3].**




# 6. REPORTING

A regulatory compliant standalone population PK report will be developed that details the aims, methods, results, conclusions, and any other supporting information [10]. Key modelling decisions, final NONMEM output (.lst) files, and other relevant code will be included as Appendices. The final report(s) will undergo QC by an independent reviewer that will assess scientific accuracy and appropriate document formatting.

# 7. REFERENCES

1. Investigator's Brochure. Daprodustat (GSK1278863). Version 13 (August 2022).
2. Dhillon S. Daprodustat: First approval. Drugs 2020;80:1491-1497
3. Evaluation of Daprodustat (GSK1278863) Drug-Drug Interaction with Clopidogrel and Application in Pediatric Dose Selection using Physiologically based pharmacokinetic (PBPK) modelling.
4. Population Pharmacokinetic Modeling, including Covariate Analysis, of Daprodustat (GSK1278863) and its Metabolites in Healthy Volunteers and Chronic Kidney Disease patients from Phase 1 and Phase 2 data (07 May 2019).
5. Application of a Population Pharmacokinetic Model of Daprodustat to Data from Japanese CKD Patients in Phase 3 studies PHI204716, PHI201754 and PHI201753 (17 April 2019).
6. Application of a Population Pharmacokinetic Model of Daprodustat in Phase 2/3 Studies 205665, 204837, 201410, 200807 and 200808 (3 Dec 2021).
7. Bergstrand M and Karlsson M. Handling data below the limit of quantification in mixed effect models. AAPS J 2009; 11 (2): 371-380.
8. Beal S. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 2001; 28 (5): 481-504.
9. Food and Drug Administration (FDA). Guidance for Industry on Population Pharmacokinetics. (February 2022). Federal Register.
10. European Medicines Agency (EMA). Guidelines on Reporting the Results of Population Pharmacokinetic Analyses. (June 2007).

# APPENDIX

**Table 1 Parameter Estimates from Daprodustat Population PK Models**

| Parameter | Phase 1 [4] | | | Phase 2 [4] | Phase 2/3 [6] | Phase 3 [5] |
|---|---|---|---|---|---|---|
| | Healthy | Food | HI | | | |
| CL (L/h) | 24.6 | 24.6 | 25.1 | 24.6* | 24.6* | 24.6* |
| V2 (L) | 26.9 | 26.2 | 27.1 | 26.9* | 26.2* | 26.2* |
| Q (L/h) | 0.973 | 0.917 | 1.03 | 0.973* | 0.917* | 0.917* |
| V3 (L) | 3.25 | 3.26 | 3.37 | 3.25* | 3.26* | 3.26* |
| Q2 (L/h) | 0.402 | 0.359 | 0.402 | 0.402* | 0.359* | 0.359* |
| V6 (L) | 24.0 | 27.1 | 24.0 | 24.0* | 27.1* | 27.1* |
| ka (1/h) | 5.02 | 4.96 | 4.82 | 5.02* | 4.96* | 4.96* |
| Vmax (mg/h) | 275 | 299 | 264 | 275* | -- | 299* |
| KM (mg) | 162 | 182 | 145 | 162* | -- | 182* |
| F1 (fixed) | 1.00 | 1.00 | 1.00 | 1.00* | 1.00* | 1.00* |
| Weight on CL (fixed) | 0.75 | 0.75 | 0.75 | 0.75* | 0.75* | 0.75* |
| Weight on V (fixed) | 1.00 | 1.00 | 1.00 | 1.00* | 1.00* | 1.00* |
| Gemfibrozil on CL | -0.893 | -0.896 | -0.893 | -0.893* | -- | -- |
| Gemfibrozil on F | 0.971 | 0.898 | 0.983 | 0.971* | -- | -- |
| Food on Vmax (Study 634) | -0.626 | -0.617 | -0.631 | -0.662 | -- | -- |
| HD on CL | -0.224 | -0.220 | -0.227 | -0.167 | -- | -- |
| ND on CL | -- | -- | -- | -- | 0.456 | -- |
| HI on Q | -- | -- | 0.487 | -- | -- | -- |
| HI on V3 | -- | -- | 0.812 | -- | -- | -- |
| HI on Q2 | -- | -- | -0.639 | -- | -- | -- |
| HI on V6 | -- | -- | -0.727 | -- | -- | -- |
| HI on F | -- | -- | 0.484 | -- | -- | -- |
| Clopidogrel on CL | -- | -- | -- | -0.481 | -0.424 | -- |
| Clopidogrel on F | -- | -- | -- | 0.377 | -- | -- |
| African-American on CL | -- | -- | -- | -0.301 | -- | -- |
| Phosphate binder on KM | -- | -- | -- | 1.59 | -- | -- |
| Female on KM | -- | -- | -- | 0.852 | -- | -- |
| Phase 3 on ka (log-scale) | -- | -- | -- | -- | -0.330 | -- |
| Phase 3 on V2/V3 (log-scale) | -- | -- | -- | -- | 0.432 | -- |
| Phase 3 on Q2 (log-scale) | -- | -- | -- | -- | -1.42 | -- |
| Phase 2B on Q2 (log-scale) | -- | -- | -- | -- | 2.44 | -- |
| Phase 2B on F1 (log-scale) | -- | -- | -- | -- | -0.956 | -- |
| Phase 2B on ka (log-scale) | -- | -- | -- | -- | 0.623 | -- |

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| Parameter | Phase 1 [4] | | | Phase 2 [4] | Phase 2/3 [6] | Phase 3 [5] |
|---|---|---|---|---|---|---|
| | Healthy | Food | HI | | | |
| Phase 3 on F1 | -- | -- | -- | -- | -- | 0.878 |
| Phase 3 on ka | -- | -- | -- | -- | -- | 2.34 |
| Phase 3 on KM | -- | -- | -- | -- | -- | 1.79 |
| Phase 3 HD on ka | -- | -- | -- | -- | -- | 0.524 |
| Phase 3 PD on F1 | -- | -- | -- | -- | -- | 0.689 |
| **Inter-individual variability** | | | | | | |
| IIV CL (%CV) | 16.8 | 15.9 | 20.5 | 16.8* | 75.0 | 15.9 |
| IIV ka (%CV) | 92.0 | 76.7 | 84.3 | 92.0* | 96.4 | 76.7 |
| IIV F1 (%CV) | 27.9 | 26.3 | 30.9 | 27.9* | -- | 26.3 |
| IIV KM (%CV) | 69.0 | 61.0 | 69.5 | 69.0* | -- | 61.0 |
| **Residual error** | | | | | | |
| Proportional (SD) | 0.470 | 0.471 | 0.469 | -- | -- | 0.635 |
| Proportional Fed (SD) | -- | 0.556 | -- | -- | -- | -- |
| Proportional HI (SD) | -- | -- | 0.418 | -- | -- | -- |
| Proportional Phase 2 (SD) | -- | -- | -- | 0.702 | -- | -- |
| Log-additive (except Phase 2b) | -- | -- | -- | -- | 0.979 | -- |
| Log-additive (Phase 2b) | -- | -- | -- | -- | 1.63 | -- |

* Grey text represents fixed parameters.

Abbreviations: CL = apparent clearance (CL/F); CV = coefficient of variation; HD = haemodialysis; HI = hepatic impairment; ka = absorption rate constant; KM = dose amount at half-maximal absorption; ND = no dialysis; PD = peritoneal dialysis; Qx = apparent inter-compartmental clearance (Qx/F); Tr = transit compartment; Vmax = maximal absorption rate; Vx = apparent volume of distribution (central or peripheral: Vx/F).

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**Table 2 Daprodustat Plasma Concentrations after Repeated 2 mg QD in Adults, Simulated by PBPK**

| Time (h) | Percentiles | | |
|---|---|---|---|
| | 2.5th | 50th | 97.5th |
| 0 | 0.000391 | 0.005865 | 0.10584 |
| 0.25 | 0.78103 | 3.661475 | 13.28695 |
| 0.5 | 3.473855 | 13.19735 | 39.28452 |
| 0.75 | 6.108987 | 22.33292 | 60.27049 |
| 1 | 6.712179 | 27.77886 | 73.10667 |
| 1.5 | 6.033509 | 28.84642 | 88.58097 |
| 2 | 3.770527 | 21.71046 | 86.0139 |
| 2.5 | 2.36174 | 15.25755 | 72.75431 |
| 3 | 1.382509 | 9.456743 | 57.22533 |
| 4 | 0.497801 | 3.47939 | 36.25722 |
| 5 | 0.18857 | 1.346953 | 21.57169 |
| 6 | 0.081095 | 0.558439 | 12.86794 |
| 8 | 0.018403 | 0.131487 | 4.004667 |
| 12 | 0.002041 | 0.018547 | 0.519355 |
| 16 | 0.000707 | 0.008919 | 0.174495 |
| 20 | 0.000522 | 0.006892 | 0.126551 |
| 24 | 0.000391 | 0.005865 | 0.10584 |

# Workflow History Report: Start Approval - 11 Jul 2025

14 Jul 2025 07:14 BST

Detailed report on a multi-document workflow

Exported by: PPD

Workflow with Document

Pages: 2

Returned 1 records

| Workflow Name | Workflow Status | Document Name | Document Status | Task Name | Task Owner | Task Verdict | Task Verdict Comment | Task Status | Task Due Date | Task Completion Date |
|---|---|---|---|---|---|---|---|---|---|---|
| Document Name: Statistical Analysis Plan CPMS Modelling Plan for Daprodustat in Pediatric Participants 11 Jul 2025 (1) | | | | | | | | | | |
| Start Approval | Complete | Statistical Analysis Plan CPMS Modelling Plan for Daprodustat in Pediatric Participants 11 Jul 2025 (v1.0) | Approved | Approver Verdict(s) | PPD | Approved | | Completed | 11 Jul 2025 | 11 Jul 2025 16:12 BST |