PROTOCOL AND PROTOCOL AMENDMENTS

Protocol 214066 Amendment 02 dated 18-November-2022

TITLE PAGE

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 Number: 214066/Amendment 02

Compound Number: GSK1278863

Brief Title: **A**nemia **S**tudies in **C**KD: **E**rythropoiesis via a **N**ovel PHI **D**aprodustat - **P**ediatric (ASCEND-P)

Study Phase: Phase 3a

Acronym: ASCEND-P

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Approval Date: 18 Nov 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 02	18 Nov 2022	TMF-15144431
Amendment 01	22 June 2022	TMF-14729908
Original Protocol	09 December 2021	TMF-13909650

Amendment 02 / 18 Nov 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:
The primary rationale for Amendment 02 is to include heart failure (HF) and esophageal/gastric erosions as adverse events of special interest (AESIs) following recent review of the clinical trial data in the adult daprodustat global development program. The description of the changes to the protocol by adding HF and esophageal/gastric erosions as an AESI are provided in the table below. Additional changes are to provide further clarity. A description and brief rationale for each change is provided in the table below.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 2.3.1. Table 3 Risk Assessment	Addition of HF and esophageal/gastric erosions as potential risk of clinical significance in Table 3, with a summary of the data/rational for risk and mitigation strategy.	To add in HF and esophageal/gastric erosions as AESIs following recent review of the clinical trial data in the adult daprodustat global development program.
Section 8.3.6. Adverse Events of Special Interest	Addition of 2 new AESIs defined for this protocol	To add in HF and esophageal/gastric erosions as AESIs following recent review of the clinical trial data in the adult daprodustat global development program
Section 5.1. Inclusion Criteria	Revision of wording of inclusion criterion 4, from acceptable method of contraception, to a highly effective method of contraception.	To align with the wording in Appendix 10.4, as requested by a Regulatory Agency.
Section 4.6. Hemoglobin Target Range and Frequency of Checks	Revision to Table 11 for participants requiring temporary stop but already on the lowest dose step.	To provide guidance on dose level for restart in these scenarios.

Section 8.4.1. Integrated PK Phase	Addition of new reference.	To refer to updated guidance on blood volume sampling in minors.
Throughout protocol	Minor editorial updates	To correct spelling and formatting.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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.

Brief Title:
Anemia **S**tudies in **C**KD: **E**rythropoiesis via a **N**ovel PHI **D**aprodustat - **P**ediatric (ASCEND-P)

Rationale:
Anemia associated with chronic kidney disease (CKD) affects most children with moderate to advanced CKD, occurring in 58% of patients with CKD stage 2 and increasing to 93% in patients with CKD stage 5. As in adults, anemia results primarily from impaired erythropoietin production by the failing kidneys and can be treated by interventions that restore erythropoietin deficiency.

Daprodustat has been extensively studied in adults for the treatment of anemia associated with CKD, demonstrating dose-dependent increases in hemoglobin (Hgb) in CKD patients who were not receiving erythropoiesis stimulating agent (ESA) therapy for their anemia, or the ability to effectively replace existing ESA therapy in CKD patients on prior stable therapy. Daprodustat has not been investigated in a pediatric population of renal anemia, where, despite available treatments of injectable ESA therapy and standard of care (SoC) iron supplementation, there remains an unmet medical need for alternative treatments.

The purpose of this study is to investigate the pharmacokinetics (PK), safety and efficacy (Hgb response) of daprodustat in children (aged 3 months to 11 years) and adolescents (aged 12 to 17 years) with anemia of CKD in both ESA users and non-users.[*]

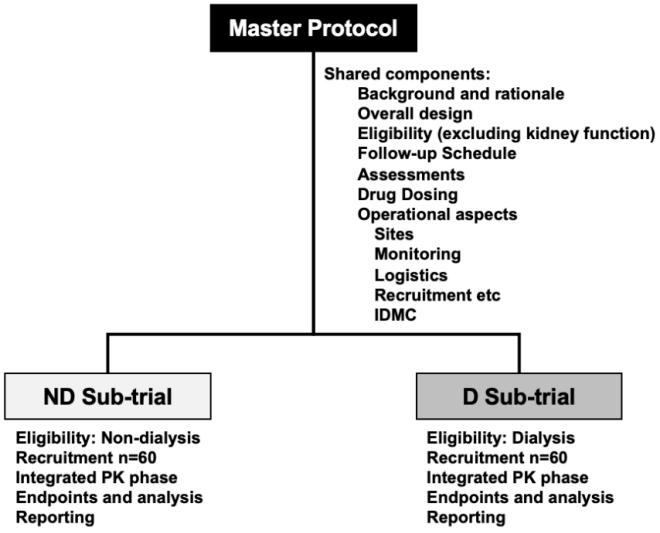
Overall Design:
This protocol describes 2 independent, prospective, interventional, open-label, single arm trials, evaluating PK (4 weeks), safety (52 weeks) and efficacy (Hgb response over 52 weeks) of oral daprodustat in pediatric patients with CKD:

- not yet requiring dialysis (non-dialysis [ND]),
- requiring dialysis (D).

[*] ESA users are defined as patients who received at least 1 dose of ESA in the 3 months (90 days) prior to enrollment for the treatment of anemia associated with CKD. This includes patients on a "dose hold" (zero dose) at the time of enrollment.

Conducting separate trials in these 2 populations is a regulatory commitment. However, given that the 2 trials differ only in the degree of kidney function at entry and their dialysis status, the ND and D trials are presented as sub-trials (hereafter the ND and D sub-trial) in a master protocol. Trial stages, procedures, analyses and reporting will remain separate for the ND and D sub-trials unless otherwise specified. Operational aspects will be unified within the master protocol to promote efficiency, as shown in the figure below.

Two Independent Sub-trials within a Master Protocol



Abbreviations: IDMC = independent data monitoring committee.

Brief Summary:

The purpose of this study is to investigate the PK, safety and efficacy (Hgb response) of daprodustat in pediatric participants aged 3 months to less than 18 years with anemia associated with CKD (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 eligible participants will receive daprodustat for 52 weeks. PK assessments in the first 4 weeks of dosing are required in the initially recruited subset of participants in each age group (Integrated PK Phase) for each sub-trial (ND/D). These participants, who undergo the Integrated PK Phase, continue seamlessly with further dosing in the sub-trial, 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 is analyzed, and no concerns for continuing the study as planned are detected.

Concomitant SoC therapy is permitted (with the exception of erythropoietin and its analogues), including iron supplementation at the discretion of the investigator to ensure iron replete status.

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. Participants will attend a study site visit at Screening and Day 1 (Baseline) before starting daprodustat (study intervention) at the end of Day 1 assessments. To allow flexibility, Screening and Day 1 Visits can be conducted up to 4 weeks apart but may also 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. After commencement of daprodustat, participants will be seen at Week 2 and Week 4 Visits to assess the initial safety and Hgb response to daprodustat. Further visits while participants remain on daprodustat are scheduled at 4-weekly intervals up to Week 28, then every 8 weeks up to Week 52. There is a Follow-up Visit at Week 56, 4 weeks after the last dose of daprodustat. Between Weeks 28 to 52, an extra Hgb check visit should be undertaken if a dose change has been made and the next scheduled visit is not within 4 weeks. An unscheduled (UNS) visit (at any time during the study) may be conducted if, in the opinion of the investigator, the participant would benefit from additional monitoring of Hgb sooner than the next scheduled visit (within 4 weeks) and/or for other parameters or if there is a safety concern.

Number of Participants:
Overall, the study will enroll approximately 120 participants, aged 3 months to <18 years with anemia associated with CKD, divided equally across the 2 sub-trials (ND/D). Each of the 2 sub-trials will include 24 participants in their respective Integrated PK Phase, with a minimum of at least 4 participants required from each of the 4 age groups (12 to <18 years, 6 to <12 years, 2 to <6 years, 3 months to <2 years).

Intervention Groups and Duration:
All participants will receive oral daprodustat for a total of 52 weeks and will be followed for an additional 4 weeks after completing treatment. The lowest dose level defined (0.125 mg once daily [QD]) will be achieved by dosing 0.25 mg three times a week (TIW). All other dose steps involve QD dosing frequency.

The initial starting dose is dependent on the participant's Hgb at baseline, ESA and dialysis status. Dose adjustment, according to an age specific algorithm within the range 0.125 mg to 24 mg QD equivalent, will be performed to achieve and maintain the Hgb within a target range.

Data Monitoring Committee:
An Independent Data Monitoring Committee (IDMC) will be utilized in this study. In this study, the IDMC is responsible for oversight of safety and specifically for:

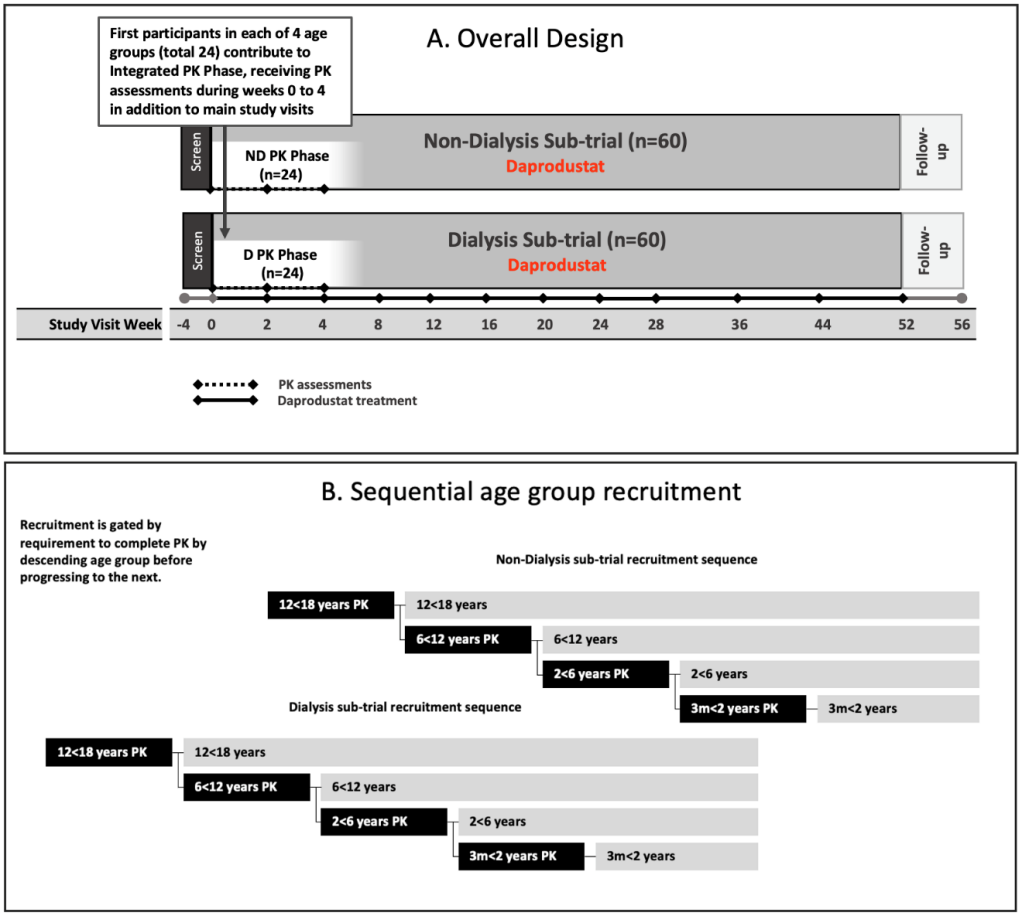
1. confirming the dosing strategy in the younger age groups (based on comparison of the actual PK data generated in the Integrated PK Phase of each sub-trial in each age group versus that predicted by a physiological based pharmacokinetic [PBPK] model, as well as review of available safety and Hgb data within this Phase and the sub-trial at that time),
2. permitting further recruitment in an age group once their Integrated PK Phase is completed, and,
3. allowing sequential recruitment to the younger age groups.

Objectives and Endpoints:

Objectives	Endpoints
Primary (Safety)	
• Describe the safety of daprodustat, overall (all ages) and in each age group.	• Incidence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), and AEs leading to study intervention discontinuation.
Secondary Safety	
• Describe changes in other parameters relevant to safety, overall and in each age group.	• Changes from baseline in laboratory safety parameters, blood pressure (BP), heart rate (HR), height and weight at each time point.
Secondary Efficacy	
• Describe the effect of daprodustat on Hgb, overall and in each age group (and additionally overall in all ages by ESA use [yes/no] at study enrollment).	At each study time point: • Hgb value. • Hgb change from baseline. • Hgb above, below and within the target range (10 to 12 g/dL).
• Describe the change in required dose over time, in each age group.	At each study time point: • Daprodustat dose. • Daprodustat dose change from starting dose. During the course of the study: • Number of dose changes.
Secondary Pharmacokinetic	
• Characterize the PK of daprodustat in each age group.	• PK parameters: maximum plasma concentration (C_{max}) and Area Under the Curve (AUC) at steady state.
• Describe the systemic exposure to daprodustat metabolites M2, M3, M4, M5, M6 and M13 in each age group.	• Plasma concentrations of each daprodustat metabolite at pre-dose (trough) between Week 2 to Week 4, and corresponding C_{max} if data permit.

1.2. Schema

Figure 1 Schema of Study Design



Abbreviations: m = months

Figure 1A). Two parallel sub-trials are conducted, in the ND and D populations respectively. For each sub-trial, 24 participants contribute to an integrated 4-week PK study which overlaps with the first 4 weeks of a 52-week, 60-participant safety study. Thus, 60 participants are recruited overall to each sub-trial, of which 24 contribute to the Integrated PK Phase.

Figure 1B). For each sub-trial, 4 age groups will be studied sequentially in the Integrated PK Phase: 12 to <18 years, 6 to <12 years, 2 to <6 years and 3 months to <2 years. Twenty-four participants (with a minimum of at least 4 participants from each age group) must complete this Integrated PK Phase. Further recruitment to that age group will pause until the IDMC agrees that further participants from that age group can be recruited and participants from the next younger age group can in turn commence enrollment to their Integrated PK Phase. Participants in the Integrated PK Phase continue dosing after Week 4 in the main study without interruption.

1.3. Schedule of Activities

The Schedule of Activities (SoA) is presented 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
Physical exam	X	X				X			X		X		X	X [g]		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)
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]													

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)
STUDY INTERVENTION																	
IRT	X	X	X	X	X	X	X	X	X	X	X	X		X [g]	X	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 participant is confirmed as eligible and is enrolled into the study). PK sampling is required for those participants 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 participant 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 participant 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 participant 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 participant, see Section 8.2.3.

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 participant 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 participant's age and plotted on age and gender appropriate charts as per SoC at the site, see Section 8.2.1.

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 Section 7.1.1 and Section 10.5

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 (maximum 8) hour time intervals after taking the first dose of daprodustat, which should be taken in the clinic on Day 1, once the participant 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..

2. INTRODUCTION

2.1. Study Rationale

Anemia associated with chronic kidney disease (CKD) affects most children with moderate to advanced CKD, occurring in 58% of patients with CKD stage 2 and increasing to 93% in CKD stage 5 [Atkinson, 2010]. Data from the Chronic Kidney Disease in Children (CKiD) consortium indicate that once CKD stage 3b is reached (estimated glomerular filtration rate [eGFR] below 45 mL/min/1.73m^2), hemoglobin (Hgb) declines by 0.3 g/dL for every further 5 mL/min/1.73m^2 decline in glomerular filtration rate (GFR) [Fadrowski, 2008]. As in adults, anemia results primarily from impaired erythropoietin (EPO) production by the failing kidneys [Atkinson, 2018], although other factors associated with the uremic milieu such as iron deficiency and inflammation may be contributing factors. During fetal development, EPO synthesis occurs in both the liver and kidneys. Hepatic synthesis declines during the first trimester and ceases during the first few months of life [Dame, 2000], such that infants and children are dependent on renal EPO synthesis to maintain erythropoiesis. Anemia associated with CKD in children can be successfully treated by interventions that restore EPO deficiency [Fischbach, 2018].

Daprodustat:

Daprodustat, a hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI), holds promise as a novel treatment to correct Hgb in the treatment of anemia associated with CKD. Daprodustat stimulates erythropoiesis through the inhibition of HIF-prolyl-4-hydroxylases, PHD1, PHD2 and PHD3, resulting in nuclear accumulation of HIFα and increased transcription of HIF-responsive genes including EPO.

Daprodustat has been extensively studied in 5338 adults in clinical trials to date for the treatment of anemia associated with CKD, including a comprehensive Phase 3 program and additionally has been licensed (June 2020) and commercially available since August 2020 in Japan for the treatment of anemia in adult patients with CKD, both on dialysis and not on dialysis.

In the adult CKD studies conducted to date, daprodustat has produced either dose-dependent increases in Hgb in patients who were not receiving recombinant human erythropoietin (rhEPO), an erythropoiesis stimulating agent (ESA) therapy for their anemia, or has demonstrated the ability to effectively replace existing ESA in patients who were on prior stable rhEPO therapy. Overall, treatment with daprodustat has been well tolerated. The most frequent (≥10%) adverse events (AEs) reported in completed adult trials with daprodustat were hypertension, urinary tract infection, and peripheral odema in participants not on dialysis; and hypertension, diarrhea and dialysis hypotension in participants on dialysis.

Whilst daprodustat has been extensively evaluated in an adult population with anemia of CKD, both requiring and not requiring dialysis, no studies have been conducted in patients <18 years of age. Therefore, there is a need to generate data in children and adolescents to confirm the safety of daprodustat and determine an appropriate dose

strategy (starting and maintenance dose) based on the results of pediatric pharmacokinetic (PK) data and exposure-response knowledge and modelling from the adult program. In this study a lower age boundary of 3 months will be used.

2.2. Background

The definition of anemia in children is not straightforward. In contrast to adults with CKD, where a fixed cut-off value for Hgb level of <11.0 g/dL has been used to define anemia, the Hgb concentration values that define anemia in children are dependent on age and sex. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines [KDOQI, 2006] for anemia uses World Health Organization (WHO) age specific Hgb values to define anemia in children with CKD. An alternative source for normative Hgb values is the National Health and Nutrition Examination Survey (NHANES) III data [Hollowell, 2005], which reports age and sex specific fifth percentile values; these levels are used by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) to define anemia, see Table 2.

Table 2 KDIGO and NKF-KDOQI Guidelines Age Definition of Renal Anemia

KDIGO guidelines (based on WHO normative values)			NKF-KDOQI guidelines (based on NHANES III normative values – 5th percentile)		
Age (years)	Hgb value (g/dL)		Age (years)	Hgb value (g/dL)	
	Males	Females		Males	Females
0.5 to <5	<11.0	<11.0	1-2	10.7	10.8
5 to <12	<11.5	<11.5	3-5	11.2	11.1
12 to <15	<12.0	<12.0	6-8	11.5	11.5
>15	<13.0	<12.0	9-11	12.0	11.9
			12-14	12.4	11.7
			15-19	13.5	11.5

While KDIGO guidelines for treatment of anemia in children with CKD specifically avoid recommending a target Hgb level at which to initiate an ESA, KDOQI guidelines suggest initiating treatment at a Hgb concentration <11.0 g/dL. This level is also recommended by the European Pediatric Peritoneal Dialysis Working Group (EPPWG) with the rationale of improved quality of life and survival.

Observational studies relate Hgb levels to mortality, where an elevated risk of mortality is present when Hgb levels are <9.9 g/dL compared with levels >9.9 g/dL (adjusted Relative Risk [RR] 1.52; 95% Confidence Interval [CI] 1.03 to 2.26 p<0.05) [Warady, 2003]. Additionally, ESA therapy to maintain Hgb level >10 g/dL was associated with improved cardiac index, reduction in left ventricular hypertrophy and improved exercise tolerance [Morris, 1994]. The EPPWG does not recommend an upper limit for Hgb level, while NKF-KDOQI has most recently suggested that Hgb level should be 11 to 12 g/dL [Keithi-Reddy, 2009].

Current treatment and unmet medical need:

To date, treatment of CKD associated anemia has relied on iron supplementation, blood transfusion and rhEPO, all of which have important limitations in childhood. Iron administration is often necessary to optimize rhEPO therapy [Atkinson, 2011], but oral supplements are associated with gastrointestinal (GI) side effects and intravenous (IV) infusions are time and resource intensive and may result in infusion reactions [Auerbach, 2010]. Blood transfusion increases the risk of transplant sensitization and may limit access to transplantation. Furthermore, rhEPO requires frequent injections that are traumatic to the young [McLenon, 2019] and results in circulating EPO concentrations above the physiological range. Therefore, there is an unmet need for alternative treatments for renal anemia.

Daprodustat may confer advantages over rhEPO or its analogues. It is an oral medication, hence, avoids the need for regular injections that is inherent to rhEPO therapy, and unlike rhEPO, does not require cold-chain storage, which can pose a logistical challenge in some healthcare regions.

2.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK1278863 (daprodustat) can be found in the Investigator's Brochure (IB). Table 3 and the following section outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Risk Assessment

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (Daprodustat)		
Excessive erythropoiesis leading to thrombosis and/or tissue ischemia	In animal studies, excessive erythropoiesis (Hgb/hematocrit > upper limit normal) attributed to daprodustat was associated with vascular congestion, microthrombi, and tissue ischemia in a number of organs. In the Phase 2 proof of concept study, a high incidence of discontinuation due to Hgb stopping criteria (Hgb >13.5 g/dL or Hgb increased >1 g/dL over any 2-week period) was observed. In non-dialysis (ND) participants administered 10 mg, 25 mg, 50 mg or 100 mg of daprodustat daily, a total of 21 of 61 participants (34%) met these criteria. In hemodialysis (HD) dependent participants administered either 10 mg or 25 mg of daprodustat daily, a total of 8 of 31 participants (26%) met these criteria. Phase 2 dose-ranging studies and associated statistical and dose response modelling has informed Phase 3 dose rationale, starting doses, dose steps, and dose adjustment scheme to optimize Hgb management. Integrated AE data including 2 global Phase 3 cardiovascular outcomes studies (200807/ASCEND-D and 200808/ASCEND-ND): Few participants experienced a possible thrombosis-related AE in the setting of excessive erythropoiesis (25/3419 [0.7%] participants on daprodustat vs. 14/3407 [0.4%] on rhEPO; relative risk [RR] 1.78 [0.93,3.42])[a]. Following review of clinical data received to date, erythropoiesis has not been identified as a safety concern for daprodustat when dose is managed appropriately according to target Hgb.	• Specific eligibility criteria related to Hgb requirements for entry are detailed in Section 5. • Hgb will be closely monitored throughout the dosing period as outlined in Section 4.6. • Specific guidance for dose adjustment or temporary discontinuation of daprodustat based on measured Hgb is provided in Section 4.6 and Section 7.1.3 respectively. • Monitoring of emerging safety data by an internal GSK Safety Review Team and an IDMC. The IDMC will be provided with safety data at the IDMC decision time points described in Section 9.4.1.
Worsening hypertension	In a dog cardiovascular study, single oral doses of daprodustat (up to 90 mg/kg) did not produce effects on blood pressure (BP). Marketed rhEPO and its analogues have been associated with risks related to uncontrolled hypertension, including the need for initiation of or increases in antihypertensive therapy when used in patients with anemia of CKD (i.e., 25% Epogen, 27% Mircera, and 40% Aranesp treated patients with renal anemia required	• Specific eligibility criteria related to BP, including exclusion of participants with uncontrolled hypertension, see Section 5.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	initiation or increase in their antihypertensive medications; hypertensive encephalopathy and seizures have been reported. The contribution of rhEPO-associated hypertension to the unfavorable effects on cardiovascular outcomes remains uncertain). Integrated AE data from clinical trials with daprodustat, including 2 global Phase 3 cardiovascular outcomes studies (200807/ASCEND-D and 200808/ASCEND-ND): • The majority (>90%) of participants had baseline history of hypertension. • No meaningful difference was seen between treatment groups in this AESI (637/3419 [18.6%] daprodustat vs. 676/3407 [19.8%]; RR 0.94 [0.85,1.03])[a]. • Although no clinically meaningful changes in BP were observed, a similar proportion of patients treated with daprodustat required an increase in anti-hypertensive medications as compared to rhEPOs in both the D (23% daprodustat vs 21% rhEPO) and the ND (33% daprodustat vs 30% darbepoetin alfa) populations. Following review of clinical data received to date, no increased risk for hypertension relative to rhEPO has been identified for daprodustat.	• BP will be closely monitored throughout the dosing period as outlined in the SoA in Section 1.3. • Monitoring of emerging safety data by an internal GSK Safety Review Team and an IDMC.
Drug-drug interactions	Daprodustat is a substrate of CYP2C8. Co-administration of daprodustat with the strong CYP2C8 inhibitor, gemfibrozil increased the maximum plasma concentration (C_{max}) and area under the curve (AUC) of daprodustat, 4- and 19-fold, respectively, while co-administration of the weak inhibitor, trimethoprim increased the C_{max} and AUC of daprodustat by 1.3- and 1.5-fold, respectively. Population PK analysis from completed Phase 2 studies suggests that co-administration of daprodustat with a moderate CYP2C8 inhibitor (clopidogrel) leads to a ~2-fold increase in AUC, with no clinically significant increase in the measured Hgb response. Although CYP2C8 induction studies were not performed, co-administration of daprodustat with an inducer of CYP2C8 (e.g., rifampin/rifampicin) may decrease the exposure of daprodustat.	• Co-administration of daprodustat with strong CYP2C8 inhibitors, (e.g., gemfibrozil) and inducers, (e.g., rifampin/rifampicin) is not permitted as outlined in Section 5.2 and Section 6.8.1. • Specific guidance on the management of potential drug-drug interactions and concomitant medications is provided in Section 6.8 and Section 7.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Hgb will be closely monitored throughout the dosing period as outlined in the SoA in Section 1.3. • Specific guidance for (permanent or temporary) discontinuation of daprodustat based on achieved Hgb is provided in Section 7.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team and an IDMC.
Death, myocardial infarction (MI), stroke, heart failure (HF), thrombo-embolic events, thrombosis of vascular access at Hgb levels which are within the normal range (i.e., not polycythemic conditions)	Marketed rhEPO/ESAs have been associated with an increased risk for death and serious cardiovascular events when used in patients with anemia of CKD. Clinical studies with marketed rhEPO/analogues have suggested "higher" target Hgb, rate of Hgb rise of greater than 1 g/dL in any 2-week period, and/or higher doses may contribute to these risks. Daprodustat has been shown to be non-inferior to ESAs in terms of first occurrence of major adverse cardiovascular events (MACE) defined as all-cause mortality, non-fatal MI and non-fatal stroke in both D patients (374/1487 [25.2%]) daprodustat vs 394/1477 [26.7%] rhEPO; hazard ratio [HR] 0.93 [0.81, 1.07]) and ND patients (378/1937 [19.5%] daprodustat vs 371/1935 [19.2%] darbepoetin; HR 1.03 [0.89, 1.19])[b]. Analysis of time to first occurrence of fatal or non-fatal thromboembolic events (deep venous thrombosis, pulmonary embolism, vascular access thrombosis) in each of the cardiovascular outcomes studies showed daprodustat did not significantly reduce the risk of fatal or non-fatal thromboembolic events compared with rhEPO in D patients (185/1487 [12.4%] daprodustat vs 215/1477 [14.6%] rhEPO; HR 0.84 [0.69, 1.02]) or ND patients (64/1937 [3.3%] daprodustat vs 51/1935 [2.6%] darbepoetin; HR 1.27 [0.88, 1.84])[b]. Analysis of time to first occurrence of fatal or non-fatal hospitalization for HF in each of the cardiovascular outcomes studies showed daprodustat did not significantly reduce the risk of hospitalization for HF (fatal or non-fatal) compared with rhEPO in D patients (112/1487 [7.5%] daprodustat vs 101/1477 [6.8%] rhEPO;	• Specific eligibility criteria related to cardiovascular risk are outlined in Section 5.2. • Hgb will be closely monitored throughout the dosing period as outlined Section 4.6. • Monitoring of emerging safety data by an internal GSK Safety Review Team and an IDMC.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	HR 1.10 [0.84, 1.45]) or ND patients (140/1937 [7.2%] daprodustat vs 115/1935 [5.9%] darbepoetin; HR 1.22 [0.95, 1.56])[b]. Following review of clinical data received to date, no increased risk for serious cardiovascular events relative to rhEPO has been identified for daprodustat.	
Cancer-related mortality and tumor progression and recurrence	Marketed rhEPOs have been associated with increased risk of cancer related morbidity and mortality when used in patients with cancer. Administration of 60 mg/kg daprodustat to mice caused minimal increases in circulating vascular endothelial growth factor (VEGF) while significant EPO increases were observed. In clinical studies with daprodustat up to 4 weeks duration, a dose-ordered increase in VEGF plasma concentrations, an angiogenic factor that has been implicated in tumor growth, was observed at doses ranging from 10 to 150 mg. In clinical studies up to 24 weeks duration at doses up to 25 mg, changes in VEGF plasma concentrations were variable but similar relative to control. Integrated AE data from clinical trials with daprodustat, including 2 global Phase 3 cardiovascular outcomes studies (200807/ASCEND-D and 200808/ASCEND-ND): No meaningful difference was seen between treatment groups in the occurrence of this AESI (119/3419 [3.5%] daprodustat vs. 121/3407 [3.6%] rhEPO; RR 0.98 [0.76,1.26])[a]. Clinical experience to date is not yet sufficient to substantiate or refute this as a safety concern for daprodustat.	• Specific eligibility criteria related to personal history of malignancy are outlined in Section 5.2. • Stopping criteria for participants with treatment emergent malignancy are outlined in Section 7.1. • Monitoring of emerging safety data by an internal GSK Safety Review Team and an IDMC.
Esophageal and gastric erosions	In animal studies, undesirable GI effects including emesis, abnormal feces and/or decreased food consumption/body weight loss and stomach erosions/ulcers with hemorrhage were observed with daprodustat. In rodents stomach erosions observed with IV and oral administration of daprodustat. Gender-averaged systemic exposure (AUC) at the no observed adverse effect levels (NOAEL) are 3.3-fold (monkeys) and 737-fold (rats) above human exposure (25 mg daprodustat).	• Suspected GI bleeding or significant symptoms consistent with erosion should be investigated clinically and diagnostically as per SoC and as clinically warranted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In clinical trials to date with daprodustat, mild-moderate GI signs and symptoms represent the most frequently reported AE, however causal association has not been established. Integrated AE data from clinical trials with daprodustat, including 2 global Phase 3 cardiovascular outcomes studies (200807/ASCEND-D and 200808/ASCEND-ND): no meaningful difference was seen between treatment groups in reports of this AESI (130/3419 [3.8%] daprodustat vs. 130/3407 [3.8%] rhEPO; RR 1.00 [0.79,1.26]) [a]. However, treatment group differences occurred in opposite directions in the two trials: 200807/ASCEND-D: daprodustat: 60 (4%), rhEPO: 82 (6%) and 200808/ASCEND-ND: daprodustat: 70 (4%), darbepoetin: 48 (2%)[a]. Following review of clinical data received to date, GI erosions have not been identified as a safety concern for daprodustat.	• Monitoring of emerging safety data by an internal GSK Safety Review Team and an IDMC.

a. Dosing frequency adjusted
b. Full intention to treat follow-up
Abbreviations: AE = adverse event; AESI = adverse event of special interest; AUC = area under the curve; BP = blood pressure; CI = confidence interval; CKD = chronic kidney disease; C_{max} = maximum plasma concentration; D = dialysis; ESA = erythropoiesis stimulating agent; GI = gastrointestinal; HD = hemodialysis; Hgb = hemoglobin; HF = heart failure; HR = Hazard Ratio; IDMC = independent data monitoring committee; IV = intravenous; MACE = major adverse cardiovascular events; ND = non-dialysis; NOAEL = no observed adverse effect level; rhEPO = recombinant human erythropoietin; RR = relative risk; SD = standard deviation; SoC = standard of care; VEGF = vascular endothelial growth factor; vs. = versus

2.3.2. Benefit Assessment

Study 214066 is a 52-week, open-label, basket, single arm, international, multicenter study to investigate the PK, safety and efficacy (Hgb response) of oral daprodustat in the treatment of anemia associated with CKD in participants aged 3 months to 17 years.

Benefit has not been established with daprodustat in participants less than 18 years of age. However, in clinical trials of 52 weeks or longer in duration in adult participants with anemia associated with CKD, it has been shown that daprodustat increased Hgb to target range with an acceptable safety profile.

It is planned to use the study results as the basis for regulatory submissions for daprodustat for the treatment of pediatric renal anemia.

2.3.3. Overall Benefit: Risk Conclusion

Data from daprodustat preclinical and clinical development support the ability of daprodustat to stimulate erythropoiesis through inhibition of the HIF-PHI pathway and consequently treat anemia associated with CKD.

There are no known evident safety concerns with daprodustat to date that would preclude investigation in pediatric participants with anemia associated with CKD stage 3 to 5 not yet requiring dialysis (non-dialysis [ND]) and those with CKD stage 5d, undergoing dialysis (D); either peritoneal dialysis (PD) or hemodialysis (HD). Furthermore, this protocol employs precautions to mitigate known and potential risks to study participants. Given these precautions, as well as the potential benefit that daprodustat holds for the treatment of anemia associated with CKD compared to the current standard of care (SoC), the overall benefit-risk balance is considered to be positive.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objectives and endpoints (see Table 4) and estimands (see Section 3.1 and Section 3.2) are identical for the ND and D sub-trials, but will be separately assessed in each sub-trial, overall (all ages) and within each age group (except for PK and dose change, which is within each age group only).

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary (Safety)	
• Describe the safety of daprodustat, overall (all ages) and in each age group.	• Incidence of AEs, Serious Adverse Events (SAEs), AESIs, and AEs leading to study intervention discontinuation.
Secondary Safety	
• Describe changes in other parameters relevant to safety, overall and in each age group.	• Changes from baseline in laboratory safety parameters, blood pressure (BP), heart rate (HR), height and weight at each time point.
Secondary Efficacy	
• Describe the effect of daprodustat on Hgb, overall and in each age group (and additionally overall in all ages by ESA use [yes/no] at study enrollment).	At each study time point: • Hgb value. • Hgb change from baseline. • Hgb above, below and within the target range (10 to 12 g/dL).
• Describe the change in required dose over time, in each age group.	At each study time point: • Daprodustat dose. • Daprodustat dose change from starting dose. During the course of the study: • Number of dose changes.
Secondary Pharmacokinetic	
• Characterize the PK of daprodustat in each age group.	• PK parameters: maximum plasma concentration (C_{max}) and area under the curve (AUC) at steady state.
• Describe the systemic exposure to daprodustat metabolites, M2, M3, M4, M5, M6 and M13 in each age group.	• Plasma concentrations of each daprodustat metabolite at pre-dose (trough) between Week 2 to Week 4, and corresponding C_{max} if data permit.

Objectives	Endpoints
Tertiary	
• Evaluate the incidence of health outcomes of interest in a CKD population, overall and in each age group.	During the study, the incidence of other health outcomes of interest related to the following: • Hgb and rescue therapy: o Use of iron supplements (oral/IV/both). o Blood transfusion. o Use of rhEPO and analogues. • Changes in kidney function/intervention: o Transplantation. o End stage kidney disease (ESKD) *(ND only*).*[a] o Switch between dialysis modalities (*D only*). • Other: o Death. o All-cause hospitalization. o Thrombosis. o All-cause loss of vascular access patency.
• To assess the acceptability and palatability of the immediate release (IR) tablets and tablets for oral suspension (TfOS).	Participant related Palatability and Acceptability Questionnaire to 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).

a. * ESKD in the ND sub-trial population defined as at least one of the following:
- an estimated eGFR, based on the Schwartz equation of < 15mL/min/1.73 m^2
- new kidney transplantation
- the requirement for maintenance dialysis for ≥30 days

3.1. Pharmacokinetic Estimand

The PK target estimand aims to assess the geometric mean of PK parameters C_{max} and AUC at steady state following administration of daprodustat up to 4 weeks in children and adolescents with anemia of CKD in 2 sub-trials (ND/D) while on treatment and regardless of disruptions or delays in treatment.

The primary estimand is described by the following attributes:

Population	Children and adolescent participants with anemia associated with CKD in the ND/D sub-trials.
Treatment	Daprodustat immediate release (IR) tablets or tablets for oral suspension (TfOS).

Intercurrent Events (ICEs)	• Permanent treatment discontinuation due to any reason addressed with while on treatment strategy. Treatment effect is only considered before the ICE occurs. • Disruptions in treatment and treatment delays addressed with treatment policy strategy. • Unplanned use of strong CYP2C8 inhibitors and inducers (which are prohibited during the study) are addressed with treatment policy strategy.
Endpoints	PK parameters: C_{max} and AUC at steady state.
Summary Measure	Geometric mean of C_{max} and AUC at steady state.

Rationale for estimand:
The motivation for the while on treatment strategy to deal with permanent treatment discontinuation is to estimate the PK parameters when participants have actually taken the dose/treatment. However, treatment policy strategy will be used in case of disruptions in treatment, treatment delays and unplanned use of strong CYP2C8 inhibitors and inducers (which are prohibited during the study, see Section 6.8.1). This is because PK data collected under these circumstances is still relevant and the model used to derive the PK parameters of interest (C_{max} and AUC) can account for these ICEs and produce meaningful values of C_{max} and AUC for participants affected by these ICEs.

3.2. Main Study Estimands

Primary and Key Secondary Main Study Estimands:
The primary target estimand for the Main Study is the proportion of participants with AEs, SAEs, AESIs, and AEs leading to treatment discontinuation of daprodustat in children and adolescents with anemia of CKD in the 52-week ND/D sub-trials, regardless of permanent treatment discontinuation, disruptions or delays in treatment, intermittent use of rescue therapy or unplanned ESA use.

The secondary efficacy target estimand for the Main Study is the Hgb endpoints at each study time point in children and adolescents with anemia of CKD in the 52-week ND/D sub-trials, regardless of disruptions or delays in treatment and transition to dialysis (ND sub-population only) whilst still continuing study intervention (daprodustat) and before any unplanned ESA therapy or rescue therapy.

The primary and key secondary estimands are described by the following attributes:

Population	Children and adolescent participants with anemia associated with CKD in the ND/D sub-trials.
Treatment	Daprodustat IR tablets or TfOS.
ICEs	• Permanent treatment discontinuation due to any reason, addressed with treatment policy strategy, i.e., the treatment effect of interest is determined regardless of the occurrence of

	the ICE, except for Hgb endpoints, which are addressed with while-on-treatment strategy. • Disruptions in treatment or treatment delays addressed with treatment policy strategy, i.e., the treatment effect of interest is determined regardless of the occurrence of the ICE. • Unplanned use of ESA therapy addressed with treatment policy strategy, i.e., the treatment effect of interest is determined regardless of the occurrence of the ICE, except for Hgb endpoints which are addressed with while-on-treatment strategy, i.e., the Hgb values are excluded for the period of 8 weeks following the occurrence of the ICE. • Intermittent use of rescue therapy within the trial is addressed with treatment policy strategy, i.e., the treatment effect of interest is determined regardless of the occurrence of the ICE, except for Hgb endpoints, which are addressed with while-on-treatment strategy i.e., the Hgb values are excluded from the date of unplanned ESA use until 8 weeks after the last dose of unplanned ESA. • Transition to dialysis (ND sub-trial only) addressed with a treatment policy strategy. • Kidney transplantation and death addressed with, while-on-treatment strategy.
Primary Safety	
Endpoints	Incidence of AEs, SAEs and AESI from Day 1 to 56 weeks of treatment. AEs leading to study intervention discontinuation from Day 1 to 52 weeks of treatment.
Summary Measure	Proportion of participants with AEs, SAEs, AESI and AEs leading to study intervention discontinuation.

Secondary Efficacy	
Endpoints	At each study time point: • Hgb value. • Change in Hgb from baseline. • Hgb above, below and within the target range (10 to 12 g/dL).
Summary Measure	At each study time point: • Summary statistics of Hgb value (number, mean, SD, median, 25th percentile [P25], 75th percentile [P75], minimum, maximum). • Mean change in Hgb from baseline (number, mean, SD, median, P25, P75, minimum, maximum). • Proportion of participants with Hgb above, below and within the target range (10 to 12 g/dL).

Rationale for estimand:
The primary interest lies in the safety of daprodustat for the treatment of anemia associated with CKD for the entire study duration; therefore, the treatment policy strategy is used regardless of disruptions in treatment, treatment delays, intermittent use of rescue therapy and/or unplanned use of ESA therapy, which reflect clinical practice. All safety data will be included up to the end of the period or up to the end of the follow-up period in the analysis irrespective of the occurrence of this ICE. Transition to dialysis (ND sub-trial only) is also addressed with treatment policy strategy.

The secondary efficacy interest lies in the Hgb response to oral daprodustat for the treatment of anemia associated with CKD for the entire study duration; therefore, the treatment policy strategy is used regardless of disruptions in treatment or treatment delays, which reflect clinical practice. However, while-on-treatment strategy is used for the ICEs of intermittent use of rescue therapy and/or unplanned use of ESA therapy for the period of 8 weeks following the occurrence of the ICE, since these ICE may confound interpretation of Hgb response to daprodustat. Permanent treatment discontinuation for any reason is also addressed with while-on-treatment strategy.

Transition to dialysis (ND sub-trial only) is addressed with treatment policy strategy.

For participants who undergo a kidney transplantation, data will be considered up to the time of transplantation; therefore, this ICE is addressed with, while-on-treatment strategy. Such participants stop study intervention (daprodustat) and discontinue the study (see Section 7.2). Participants who die during the trial will be addressed with, while-on-treatment strategy.

4. STUDY DESIGN

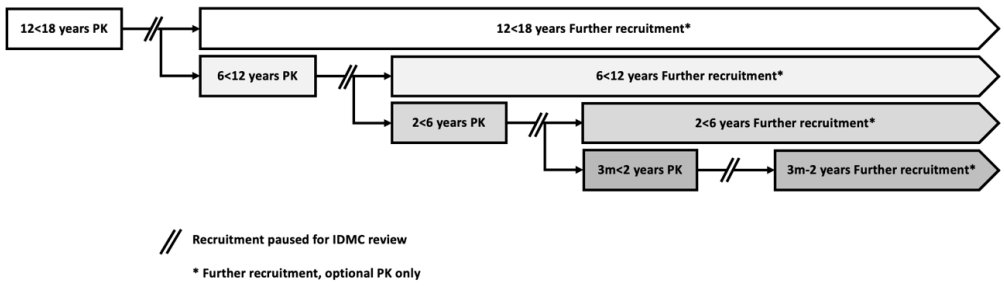
4.1. Overall Design

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 (ND and D).

These 2 sub-trial populations (ND and D) differ only in the degree of CKD, hence the requirement for dialysis, and are cared for by the same teams and centers. The design and conduct of these 2 sub-trials are therefore described in a single master protocol: they will share operational aspects but represent independent populations, recruited, conducted and analyzed separately. A graphical representation of the study design is shown in Figure 1.

The points at which Independent Data Monitoring Committee (IDMC) reviews occur, when trial conduct decisions are required, is shown in Figure 2.

Figure 2 Pauses to Recruitment After Each Integrated PK Phase



For all study participants, the study will consist of the following:

- Screening period of up to 4 weeks, although the Screening and Day 1 (Baseline) 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.
- Fifty-two-week treatment period with daprodustat. For the 24 participants in each sub-trial (ND/D) contributing to the Integrated PK Phase, the first 4 weeks of the 52-week treatment period will include sampling for PK. Optional PK sampling is offered to non-Integrated PK Phase participants.
- Follow-up period of 4 weeks off treatment.

All participants (who meet the eligibility criteria) will receive the first dose of daprodustat at the Day 1 Visit and will continue on treatment for a planned total of 52 weeks.

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 (see Section 4.6) using an age specific dose adjustment algorithm (see Section 4.5).

Participants in the ND sub-trial reaching the requirement for dialysis will remain in the study and will continue to receive daprodustat, remaining in that (ND) sub-trial unless they withdraw consent. Participants who undergo kidney transplantation will be withdrawn from the study (see Section 7.2).

Trial centers are required to also undertake an observational Comprehensive Cohort Study 212914, from which all participants in this study (214066) must be recruited.

4.2. Scientific Rationale for Study Design

Study Population:
The study will enroll male and female participants aged 3 months to 17 years with anemia associated with CKD, in 2 distinct sub-populations differing only by their CKD stage and dialysis requirement (ND: CKD stage 3 to 5 not yet receiving dialysis and D: CKD stage 5d undergoing PD or HD). This study population describes a broad group of participants considered likely to benefit from daprodustat therapy for their renal anemia. In addition, the population replicates that studied in adults, allowing extrapolation of dosing strategy, efficacy and safety to the pediatric population.

Basket Trial:
The operational efficiency is enhanced by running the 2 distinct ND/D populations within one master protocol. The integrity of the sub-trial populations is preserved by its separate recruitment, study conduct, IDMC decision making, analysis and reporting.

Single Arm Design:
Daprodustat has been shown to be efficacious, well tolerated and with a favorable risk-benefit profile in adults with anemia associated with CKD. Therefore, it is appropriate to provide an active treatment to all pediatric participants. Since this is a rare disease population, where clinical trials have historically struggled to recruit, a single arm design rather than a larger active controlled clinical trial is considered a more feasible approach. Comparator data are possible to derive from the literature or retrospectively and prospectively from the Cohort Study 212914, which acts as a feeder pool for this interventional study. The single arm design adequately allows for PK, safety and Hgb response to daprodustat to be evaluated.

Study Intervention Duration:
The total study intervention duration is 52 weeks. To achieve the study objective, which is to evaluate the safety (primary) and Hgb response (secondary) in the study population, a 52-week treatment period with daprodustat is deemed appropriate. The initial 4-week dosing period enables PK data at steady state to be collected for within trial decision making (Integrated PK Phase in the initially recruited [minimum 4] participants per age group) and to be used for the Population PK modelling undertaken at the end of the trial

(using all PK data: from the Integrated PK Phase plus optional PK sampling from non-Integrated PK Phase participants).

Staggered Recruitment with IDMC Decision Making:
The trial design includes steps to ensure the safety of participants throughout the study, independent for each sub-trial. These include the following:

- Within sub-trial PK analysis from each Integrated PK Phase, allowing the physiological based pharmacokinetic (PBPK) model predictions for adult to pediatric dose scaling to be confirmed (actual PK data in line with PBPK model predictions), or the PBPK model to be adjusted if deemed necessary. Hgb and safety data available from the sub-trial will also be reviewed as part of the decision making.
- Staggered recruitment sequential by decreasing age group, so a younger age group cannot be opened until the Integrated PK Phase from the next older age group has been completed and analyzed and their dosing strategy confirmed.
- Limited recruitment per age group, until their Integrated PK Phase is completed and analyzed.
- IDMC oversight of each sub-trial in general and additionally responsible for all decision making steps within each sub-trial, including permission to recruit in age groups (see Table 15).
- Hgb will be closely monitored and the dose adjustment algorithm allows dosing to be tailored to the individual participant's needs (Section 4.6).

Nested Interventional Trial within the Cohort Study 212914:
Nesting this interventional study within the Cohort Study 212914 is considered advantageous for the following main reasons:

- Pediatric CKD patients are rare and consent rates to interventional studies are historically lower compared to observational studies, so nesting of this daprodustat interventional study within an observational cohort (participants pre-screened, pre-consented for 214066 approach within the 212914 Cohort Study), is likely to both accelerate enrollment and facilitate retention in a highly competitive environment.
- The time delay for recruitment of the younger age groups (until the Integrated PK Phase is complete and analyzed in the next older age group) means for the younger participants in the Cohort, there is a lead time. This will provide time for younger participants and their caregivers to become familiar with research prior to approach for enrollment in an interventional trial.
- Because the schedule of assessments in the prospective Cohort Study 212914 is similar with respect to outcomes of interest in this 214066 study, offering Study 214066 participation from within the Cohort allows use of the 'control' Comprehensive Cohort data as a comparator for the single arm 214066 study should this be required for regulatory purposes.

4.2.1. Participant Input into Design

Patient and caregiver consultation process was undertaken in collaboration with the United States (US) National Kidney Foundation (NKF) and concluded in July 2021. Patients and caregivers feedback have informed aspects of the study design.

4.3. Justification for Dose

In vitro studies have shown that isolated erythroid colony forming units from infants and adults have a similar quantitative response after stimulation by EPO [Rhondeau, 1988]. Similarly, the approved starting doses of rhEPO used to treat anemia associated with CKD are the same in adult and pediatric patients [Aranesp USPI, 2019; Epogen USPI, 2017]. It has been noted that during maintenance treatment of anemia, pediatric patients tend to require higher per kg doses than adult patients [KDIGO, 2012; KDOQI, 2006; Port, 2009], and this is reflected in data collected in the North American Pediatric Renal Transplant Cooperative Study [NAPRTCS, 2011], where the mean weight-normalized dose of rhEPO decreased over increasing age cohorts. Collectively, these data suggest the PK/pharmacodynamic relationship in children with CKD is not expected to be appreciably different to adult patients.

Due to the time-varying ontogeny in the drug metabolism of daprodustat as well as time-varying changes in body weight across age groups, a PBPK approach was utilized to estimate the potential starting doses for the different age groups using a validated PBPK model for daprodustat in healthy adults [GSK Document number 2019N396674_00]. The PBPK model was derived using the Simcyp Pediatric Absorption Distribution Metabolism Excretion (ADME) Simulator which has 3 components to interrogate the known physiological and biochemical changes in a model to predict PK changes with age in healthy individuals [Abduljalil, 2014]. Therefore, doses for each age group are predicted by matching the pediatric systemic exposure (AUC) of daprodustat to that in adult.

The summary of estimated apparent clearance (dose/AUC) of daprodustat using PBPK in each age group is shown in Table 5, which also shows the predicted ratio of the pediatric to adult dose. Dose proportionality and time-independent PK is assumed when determining the doses in the pediatric population. It should be noted that although these predictions are for healthy individuals, daprodustat PK is generally similar between healthy individuals and renal impairment patients.

Table 5 Apparent Oral Clearance of Daprodustat by Age Group and Predicted Dose Equivalent to a 2 mg Adult Dose

Age Group	PBPK Model Weight Range Assumptions (kg)	CLpo (L/h) Geometric Mean	Dose (mg)	Ratio Pediatric to Adult Dose
Adults (≥18 years)	42.0 to 123.6	31.7	2	Not applicable
12 to <18 years	25.3 to 123.5	25.3	2	1/1
6 to <12 years	14.6 to 59.0	13.5	1	1/2
2 to <6 years	9.8 to 30.0	7.0[a]	0.5	1/4
3 months to <2 years	4.2 to 19.5	2.3[a]	0.25	1/8

Abbreviations: CLpo = Apparent oral clearance

a. The lowest clearance (worst case scenario) from the predictions in the respective age groups using different assumptions of CYP2C8 ontogeny in children. Source: Table 12 GSK Document number 2019N396674_00

4.4. Starting Dose

4.4.1. Starting Dose in the 12 to <18 years Age Group:

For the oldest age group (12 to <18 years), the starting dose of daprodustat administered once daily (QD) is already pre-defined (based on the PBPK model predictions) to be the same as in adults and is determined, as appropriate, by the following:

- Baseline Hgb values in participants not on an ESA (Table 6), or
- Prior ESA dosage requirement in participants not on dialysis (Table 7), or
- Prior ESA dosage requirement in participants undergoing dialysis (Table 8).

4.4.2. Starting Dose in the Younger Age Groups:

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 these tables (Table 6, Table 7 and Table 8), based on the predicted scaling (ratio of adult to pediatric dose) in Table 5.

Table 6 Starting Dose of Daprodustat for ESA Non-Users

Baseline Hgb (g/dL)	Daprodustat starting dose per age group (mg, QD)			
	Adults and 12 to <18 years	6 to <12 years	2 to <6 years	3 months to <2 years
<9	4	2	1	0.5
≥9	2	1	0.5	0.25

Table 7 Starting Dose of Daprodustat in ESA Users, Not on Dialysis

Prior ESA dose at Baseline			Daprodustat starting dose per age group (mg, QD)			
Epoetins (incl biosimilars) (convert SC to IV U/week)[a]	**Darbepoetin alfa** (µg/4wk SC/IV)[b]	**Methoxy PEG-epoetin beta** (µg/month SC/IV)[c,d]	**Adults and 12 to <18 years**	**6 to <12 years**	**2 to <6 years**	**3 months to <2 years**
≤2000[e]	≤30	≤40	1	0.5	0.25	0.125
>2000 to <20,000	>30 to 300	>40 to 360	2	1	0.5	0.25
≥20,000	>300	>360	4	2	1	0.5

Abbreviations: PEG = polyethylene glycol. SC = subcutaneous, IV = intravenous, U = units

a. Standard rhEPO IV dose (U/week) = 161/113 x (epoetin SC dose (units))/(frequency) [Besarab, 2002].
b. Conversion of 250U:1µg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008].
c. Conversion of 1:1.2 µg (darbepoetin alfa:methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [Choi, 2013].
d. Conversion of 208 U:1 µg (epoetin IV:methoxy PEG-epoetin beta)
e. This includes ESA users on a zero dose / dose-hold at the time of enrolment

Table 8 Starting Dose of Daprodustat in ESA Users, Undergoing Dialysis

Prior ESA dose at Baseline			Daprodustat starting dose per age group (mg, QD)			
Epoetins (incl biosimilars) (convert SC to IV U/week)[a]	**Darbepoetin alfa** (µg/4wk SC/IV)[b]	**Methoxy PEG-epoetin beta** (µg/month SC/IV)[c,d]	**Adults and 12 to <18 years**	**6 to <12 years**	**2 to <6 years**	**3 months to <2 years**
≤2000[e]	≤30	≤40	4	2	1	0.5
>2000 to <10,000	>30 to 150	>40 to 180	6	3	1.5	0.75
≥10,000 to <20,000	>150 to 300	>180 to 360	8	4	2	1
≥20,000	>300	>360	12	6	3	1.5

Abbreviations: PEG = polyethylene glycol. SC = subcutaneous, IV = intravenous, U = units, ug = micrograms

a. Standard rhEPO IV dose (U/week) = 161/113 x (epoetin SC dose (units))/(frequency) [Besarab, 2002].
b. Conversion of 250U:1µg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008].
c. Conversion of 1:1.2 µg (darbepoetin alfa:methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [Choi, 2013].
d. Conversion of 208 U:1 µg (epoetin IV:methoxy PEG-epoetin beta)
e. This includes ESA users on a zero dose / dose-hold at the time of enrollment

If the actual PK data from each sub-trial age group Integrated PK Phase are in line with the PBPK model predictions, then the starting dose will be as outlined above. However, as described in Section 9.3.1, if more than 50% of the data lie outside the 95% Prediction Intervals (PIs) of the PK simulations, the PBPK model will be updated and a new scaling (pediatric to adult ratio) proposed for use in the next younger age group (i.e., Table 6, Table 7 and Table 8) will be updated for the 3 younger age groups). Note: the new

starting doses may be rounded to the nearest available tablet strength if new scaling is required.

See Section 4.7 for the role of the IDMC in communicating the starting dose for the 3 younger age groups.

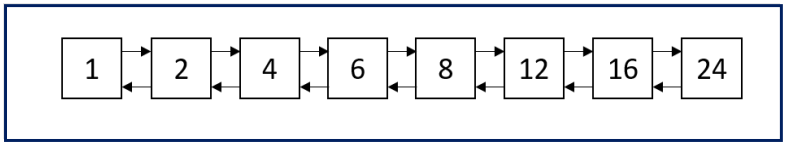
4.5. Dose Adjustment Algorithm

Between Weeks 2 to 52, the dose of daprodustat should be adjusted if required (see Section 4.6), one dose step at a time, to achieve/maintain a Hgb within the target range of 10 to 12 g/dL.

4.5.1. Dose Adjustment Algorithm in the 12 to <18 Years Age Group

As exposure in the oldest age group (12 to <18 years) is predicted to be the same as adults, the dose adjustment algorithm will be similar to adults, see Figure 3. The dose in this study (for both the ND/D sub-trials), as in the adult Phase 3 program, cannot exceed 24 mg QD.

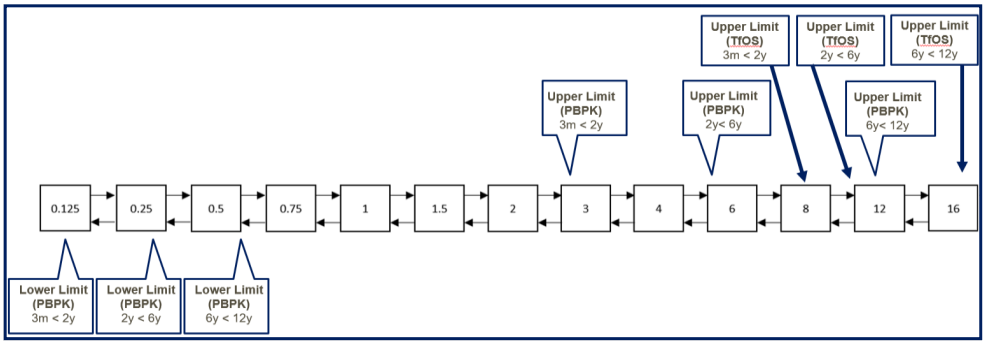
Figure 3 Dose Adjustment Algorithm in the 12 to <18 Years Age Group



4.5.2. Dose Adjustment Algorithm in the Younger Age Groups

A common dose adjustment algorithm will be utilized for the 3 younger age groups, see Figure 4.

Figure 4 Dose Adjustment Algorithm in the Younger Age Groups (<12 years)



Abbreviations: m = months; PBPK = physiological based pharmacokinetics; TfOS = tablets for oral suspension; y = years.

These dose steps (shown in Figure 4) for the 3 younger age groups are derived by applying the adult to pediatric ratio from the PBPK model to the dosing steps for adults (see Table 9) and then lining up the doses in ascending order. This is a conservative approach, and in some cases may mean a slightly smaller dose increment than the predicted to match adult exposure, e.g., a 6 to <12 year old moves between 0.5 to 0.75 to 1 mg in a common dose algorithm rather than between 0.5 to 1 mg (see Table 9). No age group has a larger step than adult equivalent titration.

Table 9 Dose Adjustment Algorithm Predicted by the PBPK Model

Age Group	Ratio pediatric to adult dose	Dose steps predicted by the PBPK model (mg QD)							
12 <18 years	1/1	1	2	4	6	8	12	16	24
6 <12 years	1/2	0.5	1	2	3	4	6	8	12
2 <6 years	1/4	0.25	0.5	1	1.5	2	3	4	6
3 months <2 years	1/8	0.125	0.25	0.5	0.75	1	1.5	2	3

Dosing Limits of the Common Dose Adjustment Algorithm for the 3 Younger Age Groups:

The upper limit of dosing in each of the 3 younger age groups can be considered based upon the following:

- PBPK predicted equivalent exposure to adult dose of 24 mg in each age group (see Table 9 or scaling adjusted as a consequence of an Integrated PK Phase), and
- maximum dose based on the limit on the number of tablets with a TfOS formulation (see Table 10 and also Section 6.1 for the TfOS limits per age group).

If ongoing data suggests that a pediatric population needs a higher dose than that predicted by the PBPK model in the younger age groups to match the top dose (24 mg) in adults, the IDMC **may** allow the dosing algorithm upper limit for the 3 younger age groups to include extra (higher) dose steps than the top dose predicted by the PBPK model. However, the maximum dose in each age of the younger age groups cannot exceed the limit on the number of tablets with a TfOS formulation (see Table 10).

Table 10 Extra Dose Steps for the Younger Age Groups based on TfOS Excipient Limits

Age Group	Top dose predicted by the PBPK Model from Table 9 (mg QD)	Maximum dose permitted with TfOS see Section 6.1 (mg QD)	Extra dose steps that may be included in the dosing algorithm above the PBPK model top dose prediction if the IDMC allow (mg QD)
6 <12 years	12	16	16
2 <6 years	6	12	8, 12
3 months <2 years	3	8	4, 6, 8

As described in Section 4.4.2 for the starting dose, if a new scaling (pediatric to adult ratio) is required based on the results of an Integrated PK Phase, the new ratio will be applied to adjust the upper/lower dose limits of the common dose algorithm for the next younger age group (the dose steps within the algorithm will remain unchanged). Note: the new dose limits may be rounded to the nearest available tablet strength if new scaling is required.

It will be the responsibility of the IDMC to confirm the dosing strategy (starting dose and dose adjustment algorithm upper/lower limits) in each of the 3 younger age groups (see also Section 4.7), based on the following:

- pediatric to adult dose scaling predicted by the PBPK model (confirmed or as adjusted by the actual PK data collected), and also
- taking into account the ongoing knowledge of the:
  - Hgb response and safety from the 4 week Integrated PK Phases from each age group in each sub-trial (ND/D).
  - Overall Hgb and safety data from each sub-trial to date.

Note: Participants, who with a birthday move into the next age group during the course of the 52-week treatment period, will be allowed to be dosed (if required based on Hgb response, see Table 11) to the dosing limits defined for their current age, provided they weigh the minimum weight for that new age group, as specified in Table 12. For example:

- A participant aged 5 years 9 months at study enrollment cannot be dosed higher/lower than the limits set by the IDMC for a 2 to <6 year old. However, after their 6th birthday, their upper/lower limits of the dosing algorithm will move to their new age category of 6 to <12 years) provided they weigh at least 15.3 kg.
- A participant aged 11 years 9 months at study enrollment cannot be dosed higher/lower than the limits set by the IDMC for a 6 to <12 year old. However, after their 12th birthday, they will then follow the dosing algorithm of the 12 to <18 years old provided they weigh at least 25.3 kg and are able to swallow IR tablets, otherwise they must remain in the 6 to <12 years age group algorithm taking the TfOS.

Interactive Response Technology (IRT) will ensure the participant receives the correct dose allocation in case of an age group change. As age is required to allow correct dispensing of study medication, month and year of birth will be collected at enrollment.

4.6. Hemoglobin Target Range and Frequency of Checks

In adults, the dose of daprodustat is adjusted if required, one step at a time in the range of 1 to 24 mg, to ensure the patient's Hgb is within a target range.

In this study, the target range for Hgb is 10 to 12 g/dL, the same for all ages and regardless of dialysis status (ND or D) or within the D sub-trial population, their dialysis modality (PD or HD).

For pediatric patients, nephrologists dose adjust ESA therapy in accordance with both Hgb and clinical response. At Study Weeks 2, 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52, the Hgb will be checked.

At Week 2:
Hgb will be measured to ensure there is no rapid rise following commencement of daprodustat.

- If a rapid rise is observed (>1 g in 2 weeks), the dose should be adjusted to the next lower dose step.
- If the Hgb value at Week 2 is >12.5 g/dL, daprodustat will be stopped and reintroduced at the next lower dose at a subsequent visit when the Hgb is ≤12.0 g/dL.
- Otherwise, no change in dose is made at Study Week 2.

From Week 4 until Week 52 (end of daprodustat dosing):
The dose may increase, decrease, be temporarily interrupted or stay the same based on Hgb response as shown in Table 11.

Table 11 Dose Adjustment Based on Hgb from Week 4 Onwards

Dose adjustment	Hgb status
To the next higher dose	• Hgb <10.0 g/dL and is not increasing (<0.5 g/dL) compared to previous visit. OR • Hgb is within the target range 10.0 to 12.0 g/dL but in the opinion of the investigator the patient is still symptomatic due to their anemia. *Note: if the participant is already on the highest dose step and requires a dose increase, maintain their age-defined maximum dose and re-check Hgb in 4 weeks.*

Dose adjustment	Hgb status
To the next lower dose	• If the Hgb is >12.0 but ≤12.5 g/dL. OR • the Hgb increased by >2.0 g/dL in 4 weeks. OR • the Hgb increased by >1.0 g/dL in 2 weeks. *Note: if the participant is already on the lowest dose step and requires a dose reduction, withhold dosing and re-check Hgb in 4 weeks, dosing should restart at the lowest dose step when the Hgb is* ≤12.0 g/dL.
To temporarily stop	• If the Hgb is >12.5 g/dL, temporarily withhold dosing and check Hgb at the next study visit in 4 weeks. Restart at the next lower dose when the Hgb is ≤12.0 g/dL. *Note: From Week 28 if the next study visit is more than 4 weeks from date of test, schedule an extra Hgb check Visit in 4 weeks.* *Note: if the participant is already on the lowest dose step at the time of the temporary stop, dosing should restart at the lowest dose step at the next study visit when the Hgb is* ≤12.0 g/dL.
No change	• Otherwise maintain at the same dose.

The SoA (see Section 1.3) up to Week 28 requires visits every 4 weeks, where Hgb is checked. From Week 28 until Week 52 (when daprodustat treatment ceases), an extra Hgb Visit (at Week 32, 40 or 48) should be conducted 4 weeks after the previous study visit, if any of the following apply:

- At the previous study visit:
  - A dose change was required (see Table 11).
  - Dosing was temporarily withheld as follows:
    - Hgb >12.5 g/dL (see Table 11), or
    - the participant was already on the lowest dose in the dose adjustment algorithm and a dose reduction was required (see Table 11 and Section 4.5).

- The following occurs and the next study visit is not due within 4 weeks and a:
  - Moderate CYP2C8 inhibitor has been prescribed (see Section 6.8).
  - rhEPO or analogue has been administered in error (see Section 6.8.3).
  - Hgb check performed outside of the study (routine SoC or emergency) indicates that a dose change is needed (see Table 11).

- In the opinion of the investigator, the:
  - Participant would benefit from continued 4-weekly Hgb checks.
  - Hgb is at the upper end of the target range and waiting 8 weeks for the next Hgb check is considered too long.

In addition to the above, an unscheduled (UNS) Visit at any time during the study may be conducted if, in the opinion of the investigator, the participant would benefit from

additional monitoring of Hgb sooner than the next scheduled visit (within 4 weeks) and/or for other parameters or if there is a safety concern. If an UNS Visit is performed, then the UNS electronic case report form (eCRF) pages should be completed. If a dose change is required, then the investigator should urgently contact the medical monitor, who can authorize a manual override of the IRT system to amend the allocated dose.

4.7. Role of the IDMC in Confirming the Dosing Strategy

The dosing strategy is expected to be the same in either sub-trial (ND/D) and although their Integrated PK Phases will be analyzed and considered independently, the same review and decision making by the IDMC will be required, see also Section 9.4.1.

The IDMC will be responsible for confirming the decision to open up recruitment for each sequential age group (6 to <12 years, 2 to <6 years and 3 months to <2 years) in turn within each sub-trial, and for confirming the following:

- Starting dose in the next younger age group (Section 4.4.2).
- Upper and lower limits of the common dose adjustment algorithm in these age groups (Section 4.5.2).

The IDMC decision will be based (separately for each sub-trial) on the following:

- PBPK model predictions for adult to pediatric dose scaling, confirmed or updated by the actual PK data analyzed after completion in each age group Integrated PK Phase.
- 4-week Hgb and safety data from each age group's Integrated PK Phase.
- Ongoing Hgb and safety data from all participants in each sub-trial.

For the oldest age group (12 to <18 years), the starting dose and dose adjustment algorithm is already pre-defined as the same as in adults. After the 12 to <18 year PK data in the Integrated PK Phase is available, the appropriate pediatric dose ratio to achieve a matching adult exposure to daprodustat is proposed by the GSK study team and provided to the IDMC (i.e., PBPK model predictions are confirmed or the model updated in light of the actual PK data collected). Assuming no concerns from the review of the Hgb response and safety listings during the Integrated PK Phase of the 12 to <18 years, the IDMC will allow:

- Further recruitment into the Main Study of the 12 to <18 years age group.
- Limited recruitment into the study with the Integrated PK Phase of the 6 to <12 years age group, also confirming the dosing strategy (starting dose and dose adjustment algorithm limits) in this age group.

In turn, once the 6 to <12 year Integrated PK Phase data are available and provided no concerns (from Hgb and safety data from their Integrated PK Phase and from the 12 to <18 years age group also in the trial and available to date), the IDMC will permit recruitment into the Integrated PK Phase for the 2 to <6 years age group and also confirm their dosing strategy (starting dose and limits of the dose adjustment algorithm). Finally,

in similar fashion, the youngest age group, the 3 month to <2 years, will be opened to recruitment and their dosing strategy confirmed.

Requirement for a Protocol Amendment with respect to dosing:
A protocol amendment for dosing will **not** be produced and the IDMC communication, for both the starting dose and dose adjustment algorithm limits, will serve as the basis for the dosing strategy for the 3 younger age groups provided:

- there are no safety concerns
  and
- the 12 to <18 year age group dosing is confirmed to be the same as for adults, as specified in this protocol for starting dose (see Section 4.4.1) and dose adjustment (see Section 4.5.1),
  and
- for the younger age groups, all doses proposed remain within the limits specified in Figure 4, even if the PBPK model needs updating (revised scaling for the younger age groups).

However, **a substantial protocol amendment for approval will be written,** and no further recruitment into the study will be permitted until all required approvals for the revised protocol are in place, if the IDMC consider:

- after review of the Integrated PK Phase data that the dosing strategy for the 12 to <18 years needs to be adjusted (i.e., is not the same as adults as specified in this protocol)[†],
  and/or
- after review of the Integrated PK Phase data, that the dosing limits for the 3 younger age groups deviates from that outlined in Figure 4,
  and/or
- safety concerns are detected.

The IDMC composition, role and format for dosing communications for the 3 younger age groups will be fully described in an IDMC Charter.

4.8. End of Study Definition

The end of the study (EOS) Overall is defined as the date of the last visit of the last participant in the study of the last sub-trial (ND or D) to finish. As these sub-trial populations (ND/D) are handled separately within the master basket trial protocol, their last participant visit will differ, particularly if recruitment rate varies between the 2 sub-trial populations. Therefore, an EOS ND and an EOS D is also defined. However, for the purposes of clinical trial disclosure and EOS notification to the Health Authorities

[†] Should the dosing strategy for the 12 to <18 years age group need to be adjusted, the protocol amendment will include a requirement for PK collection in a subset of newly recruited participants in that age group who will start with the revised dosing.

and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) the EOS Overall will be used.

With each sub-trial, a participant is considered to have completed:

- the study ("study completer"), if he/she has completed all study visits within their sub-trial (ND or D), including the last Follow-up Visit at Week 56, regardless of whether daprodustat treatment was received during the entire study period.

- study intervention ("treatment completer"), if he/she has not been discontinued prematurely from study intervention (see Section 7.1) and has completed the last required on-treatment visit (Week 52) within their sub-trial, regardless of whether daprodustat treatment was received during the entire study period.

5. STUDY POPULATION

This study will enroll patients aged 3 months to <18 years with anemia associated with CKD, within 2 separate sub-trial populations (ND and D). Participants may or may not be receiving treatment with ESAs prior to study entry. Overall, the entire study population describes a group of CKD patients likely to benefit from treatment with daprodustat.

Regardless of their dialysis status, the present study will allow patients not on an ESA with a Hgb level 7.0 to 11.0 g/dL and those receiving treatment with ESA if they have a Hgb concentration of 9.5 to 12.0 g/dL to enroll in the study. The same eligibility criteria apply to both the sub-trials (ND/D) in this study, apart from the requirement for dialysis. Recruitment will close to each sub-trial, and if required within a specific age group, when the requisite number of participants have been enrolled.

The prospective approval of protocol deviations to recruitment and eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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.

To be eligible for this study, participants must be offered approach (as determined in Study 212914) and fulfill all of the following criteria at the Screening and Day 1 Visits:

Age:

1. Participant must be 3 months to <18 years of age.
   Note: Infants born prematurely (under 32 weeks of gestation) should have a chronological age of at least 6 months.

Type of Participant and Disease Characteristics:

2. Participants who have anemia associated with CKD as follows:

ND sub-trial	D sub-trial
CKD stage 3, 4, 5 (not on dialysis) based on eGFR using the bedside Schwartz equation <60 mL/min/1.73m^2 [Schwartz, 2009]	Prevalent dialysis patients (Stage 5d CKD) defined as those in receipt of maintenance dialysis of ≥30 days duration
AND • If not using ESAs, Hgb 7.0 to 11.0 g/dL OR • If using ESAs, Hgb 9.5 to 12.0 g/dL	

Weight:

3. Weight restrictions apply to participants for each age group. This takes into account:

- In the 3 younger age groups (<12 years), the number of TfOS they may receive in the trial to ensure dosing is well below excipient limits. The weight used for excipient limit calculation in each age group is based on WHO median weights in girls (lighter than boys) minus 2 SD for the youngest child in each age group (i.e., 6 years, 2 years and 3 months).

- The minimum weight used in the PBPK model assumptions, see Section 4.3.

- Relevant for the youngest patients (3 months), the minimum weight also takes into account the amount of blood required for study time points relative to percentage of blood volume in order to comply with guidance for clinical trials in children [Paediatric Population: Recommendations, 2008], see Section 8.4.1.

Participants must weigh or exceed the minimum weight required for study entry tabulated for their age group, as indicated in the second column of Table 12:

Table 12 Minimum Weight Per Age Group

Age Group	Minimum Weight Required for Study Entry (kg)	Minimum Weight for TfOS Excipient Limit (based on WHO Weight for Girls, median-2SD) (kg)	Lowest Weight Used in the PBPK Model (kg)
12 to <18 years	25.3	Not applicable[b]	25.3
6 to <12 years	15.3	15.3	14.6
2 to <6 years	9.8	9.0	9.8
3 months to <2 years	5.0[a]	4.5	4.2

Abbreviation: SD = standard deviation

a. The minimum weight of 4.5kg (WHO median weight – 2SD) for the youngest age group is revised upwards to 5.0 kg to take into account the blood draw limit, see Section 8.4.1

b. The 12 to <18 years age group are not dosed with TfOS, therefore the minimum weight limit in this age group is based on the PBPK model assumptions

Sex and Contraceptive/Barrier Requirements:

4. A female participant is eligible to participate if she is either:

   - premenarcheal, or
   - not pregnant as confirmed by a negative human chorionic gonadotrophin (hCG) test if of reproductive potential. Testing requires serum hCG if eGFR≤15 mL/min/1.73m^2. Otherwise, a urine hCG test is acceptable.

   Females of childbearing potential (FOCBP) must commit to consistent and correct use of a highly effective method of contraception (see Section 10.4) until at least 30 days after the last dose of daprodustat. A pregnancy test is required for FOCBP. This test will be performed at the initial Screening and at each scheduled visit whilst in the study including the follow-up visit (see Section 8.2.5).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Note: If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.

Informed Consent and Assent:

5. The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian (as defined in Section 10.1.3) and the participant's assent, when applicable, before any study-specific activity is performed (unless a waiver of informed consent has been granted by an IRB/IEC). All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand.

6. The participant capable of providing signed and dated written assent, signs and dates a written assent form (age-appropriate) and the parent/guardian signs and dates a written informed consent form (ICF) for study participation prior to the initiation of any study-related activities. The informed consent is described in Section 10.1.3.

Other:

7. A legal guardian or primary caregiver must be available to help the study site personnel ensure follow-up; support the participant to attended assessment days according to the SoA in Section 1.3 (e.g., able to comply with scheduled visits, study procedures, and accurately dispense study intervention as directed).

5.2. Exclusion Criteria

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.

Participants are excluded from the study if any of the following criteria apply at the Screening and Day 1 Visits (unless otherwise stated):

CKD Related Criteria:

1. Kidney transplant recipient with a functioning allograft.
2. Scheduled for elective kidney transplantation within 3 months.

Anemia Related Criteria:

3. Iron deficiency, defined as:
   - Transferrin saturation (TSAT) < 20%, or
   - Ferritin <25 ng/mL.
4. Aplasias: History of bone marrow aplasia or pure red cell aplasia.
5. Active hemolysis.
6. Other causes of anemia: e.g., untreated vitamin B12 deficiency, untreated folate deficiency, thalassemia major, sickle cell disease or myelodysplastic syndrome.
   Note: Sickle cell trait is acceptable if the participant otherwise meets entry criteria.
7. GI bleeding: Evidence of actively bleeding gastric, duodenal or esophageal ulcer disease or clinically significant GI bleeding within the last 4 weeks.

Other Disease Related Criteria:

8. History of malignancy within the last 2 years or currently receiving treatment for cancer, or renal lesions, for which, in the opinion of the investigator, malignancy cannot be excluded.
   Note: In the case of localized squamous cell or basal cell carcinoma of the skin that has been definitively treated, the exclusion timeline is within the last 4 weeks.
9. Unresolved acute or active chronic infection requiring antimicrobial therapy.
10. History of significant thrombotic or thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, stroke, myocardial infarction [MI]) within the last 8 weeks.
11. Heart failure (HF): Chronic Class IV HF, as defined by the New York Heart Association (NYHA) functional classification system.
12. Current uncontrolled hypertension as determined by the investigator.
13. 12-lead electrocardiogram (ECG) finding (at Screening):
    - An abnormal ECG finding from the 12-lead ECG conducted at Screening if considered to be clinically significant and would impact the participant's participation during the study based on the evaluation of the investigator and a pediatric cardiologist.
    - QT interval corrected using Fridericia's formula (QTcF) > 480 msec, or
    - QT interval corrected for heart rate (QTc) >500 msec in participants with bundle branch block.
14. Liver abnormality/disease:
    - Alanine aminotransferase (ALT) >2× upper limit of normal (ULN).
    - Bilirubin >1.5× ULN (isolated bilirubin >1.5× ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
    - Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice.

Note: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones and chronic hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.

Prior/Concomitant Therapy:

15. Participants who have previously received treatment with any HIF-PHI, including daprodustat within the last 30 days.
16. Participants who have previously failed to respond to treatment with daprodustat or any other HIF-PHI.
17. Participants, who have received within the last 7 days, or anticipate receiving during the study, strong inhibitors of CYP2C8 (e.g., gemfibrozil) or strong inducers of CYP2C8 (e.g., rifampin/rifampicin).

Other Investigational Product/Clinical Study:

18. Other investigational product/clinical study: Participants who have received treatment with an investigational agent (biologic or non-biologic) within the past 30 days or 5 drug half-lives whichever is longer, with the exception of treatments or vaccines for SARS-CoV-2 with provisional or emergency approval. The term “investigational” applies to any drug not approved for sale in the country in which it is being used or investigational formulations of marketed products.
19. Participants who are currently participating in any other clinical study of an investigational medicinal product (IMP).

Other Exclusions:

20. Females ONLY: Participant is pregnant, breastfeeding or is of reproductive potential and does not agree to one of the contraceptive options listed in the List of Highly Effective Methods for Avoiding Pregnancy in Section 10.4.
21. Participants with any history of hypersensitivity to daprodustat or its excipients, or to any other HIF-PHI.
22. Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the participant at unacceptable risk, which may affect study compliance or prevent understanding of the aims or investigational procedures or possible consequences of the study.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, previous trial participation, eligibility criteria, any protocol deviations and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened within 6 weeks under the original informed consent if, in the opinion of investigator, the participant fails on a reversible parameter at Screening which has been addressed (e.g., iron status). Note: a new consent maybe required in this 6 week period if a birthday occurs in that time which changes the legal requirement for consent in their country, e.g., assent to consent requirement from the participant). Participants who are rescreened after 6 weeks need to be re-consented prior to undergoing any Screening procedures. There are no limits on the number of rescreens, provided the eligibility parameter(s) that the participant did not meet can be addressed.

Rescreened participants will be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment /Administration of Study Intervention

There is no reason for administration of study intervention (daprodustat) on Day 1 to be delayed when inclusion/exclusion criteria are met at the Screening and Day 1 Visits. Whilst the screening period can last up to 4 weeks, the 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 Screening.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The study intervention in this trial is daprodustat.

6.1. Study Intervention Administered

Daprodustat (GSK1278863) is a HIF-PHI that has been investigated as a treatment in adults for anemia associated with CKD in both ND and D patients. Daprodustat will be provided to all pediatric participant age groups as shown in Table 13.

Table 13 Study Intervention Formulations for Participant Groups

Film-coated IR tablets	Dosage levels 1 to 24 mg in: • Age group 12 to <18 years. • Age group 6 to <12 years who can swallow IR tablets.
TfOS	Dosage levels 0.125 mg to 16 mg in: • Age group 6 to <12 years who can swallow the IR tablets but need a dosage of 1.5 mg or less than 1 mg. • Age group 6 to <12 years who cannot swallow IR tablets. • Age groups 2 to <6 years and 3 months to <2 years.

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. All dose levels are administered QD, except the lowest dose step possible, 0.125 mg QD, which is administered as 0.25 mg three times weekly (TIW). The 0.125 mg QD dose and 0.25 mg TIW dose are expected to achieve similar Hgb response as was observed when 2× QD doses, administered as TIW doses, resulted in similar Hgb responses [Bailey, 2019]. The study intervention is described in Table 14 and Figure 5.

Table 14 Study Intervention Administered

Intervention Label	Daprodustat
Type	IR tablets TfOS
Dose Formulation	**IR tablets: round, bi-convex, film coated tablets.** • Tablet strengths of 1 mg (gray), 2 mg (yellow) and 4 mg (white) are 7 mm in diameter. • Tablet strengths of 6 mg (pink) and 8 mg (orange) are 9 mm in diameter.

	TfOS: bi-convex, film coated tablets. • The 0.25 mg strength tablets are green, round, bi-convex and 6 mm in diameter. • The 1.5 mg strength tablets are purple 8.5 x 4.5 mm oval and bi-convex. • The 2 mg strength tablets are white 8.5 x 4.5 mm oval and bi-convex. There are no score lines for any of the current tablet formulations.
Unit Dose Strength(s)	**IR tablet strengths:** • 1 mg, 2 mg, 4 mg, 6 mg and 8 mg **TfOS:** • 0.25 mg, 1.5 mg and 2.0 mg
Dosage Level(s)	**QD dosing dose steps with IR tablets:** • 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, 24 mg **QD dosing dose steps with TfOS:** (except *) • 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg (* The 0.125 mg QD dose step is achieved as a 0.25 mg dosed three time weekly [TIW])
Route of Administration	Oral
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by the Sponsor
Packaging and Labelling	Daprodustat tablets are packed in white, opaque high-density polyethylene (HDPE) bottles with child-resistant closures.

The contents of the label will be in accordance with all applicable regulatory requirements.

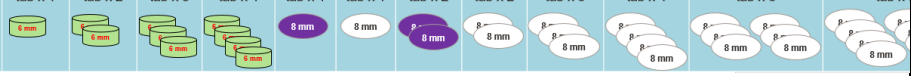
Figure 5 IR and TfOS Dosage Steps

IR QD dosing

GSK1278863 dose (mg)	1 mg	2 mg	3 mg	4 mg	6 mg	8 mg	12 mg	16 mg	24
Daprodustat (Tablet , QD)	1 mg tab x 1	2 mg tab x 1	1 mg tab x 3	4 mg tab x 1	6 mg tab x 1	8 mg tab x 1	6 mg tab x 2	8 mg tab x 2	8 mg x

TfOS QD dosing

GSK1278863 dose (mg)	0.25 mg	0.5 mg	0.75 mg	1 mg	1.5 mg	2 mg	3mg	4 mg	6 mg	8 mg	12 mg	16 mg
Daprodustat (Tablet , QD)	0.25 mg tab x 1	0.25 mg tab x 2	0.25 mg tab x 3	0.25 mg tab x 4	1.5 mg tab x 1	2 mg tab x 1	1.5 mg tab x 2	2 mg tab x 2	2 mg tab x 3	2 mg tab x 4	2 mg tab x 6	2 mg tab x



Up to 4 TfOS can be suspended in a 5 mL volume and up to 8 tablets require a total volume of 10 mL.

TfOS TIW dosing

The 0.125 mg QD dose step is achieved by oral administration of 0.25 mg TfOS TIW

GSK1278863 dose (mg)	0.125 mg
Daprodustat (Tablet, TIW)	0.25 mg tab x 1 TIW

The excipients used in the IR and TfOS are safe for administration in the pediatric population participating in the study. To ensure dosing is well within excipients limits with TfOS, the maximum number of tablets able to be taken per age group has been defined as follows:

- 8 TfOS in the 6 to <12 years age group (equating to a top dose of 16 mg)
- 6 TfOS in the 2 to <6 years age group (equating to a top dose of 12 mg)
- 4 TfOS in the 3 months to <2 years age group (equating to a top dose of 8 mg)

To support the correct dispensing of study medication for each study participant throughout the study, the IRT will be programmed with the starting dose based on their baseline status (Hgb, ESA usage and dialysis status, see Section 4.4) and any dose adjustment required based on their Hgb response to daprodustat (see Section 4.5).

6.2. Preparation, Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions (see Pharmacy Manual) have been maintained during transit for all daprodustat received and any discrepancies are reported and resolved before use of daprodustat.

Only participants enrolled in the study may receive study intervention (daprodustat) and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention are provided in the Pharmacy Manual.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single arm study. All screened participants will be identified by a unique participant number that will remain consistent for the duration of the study. Upon completion of all the required screening assessments, eligible participants will be registered into the study by the investigator or authorized site staff.

6.4. Study Intervention Compliance

Participants who administer daprodustat at home will be instructed to return all unused medication at each clinic visit. A record of the number of daprodustat tablets, dispensed to and taken by, each participant will be maintained and reconciled with study intervention and compliance records. Deviation(s) from the prescribed dosage regimen should be recorded.

Daprodustat start and stop dates, including dates for study intervention delays and/or dose reductions will also be recorded in the eCRF. At Week 2 and for any UNS (at any time) or extra Hgb (after Week 28) Visits, compliance checking will only be performed if the dose of daprodustat is changed.

6.5. Dose Modification

The dose of daprodustat should be adjusted according to Hgb response (see Section 4.6) using the age-specific dosing algorithm (see Section 4.5). The maximum dose in this study is 24 mg QD (12 to <18 years age group only) and the dosing in the younger age groups (<12 years of age) should not exceed that specified in Table 10 in Section 4.5.2.

6.6. Continued Access to Study Intervention after the End of the Study

There is no existing or planned Expanded Access Program for daprodustat. If continuing therapy for anemia associated with CKD is needed after the completion of this study, licensed ESAs should be used as per SoC. However in line with GSK's policy on compassionate use/expanded access, GSK recognizes that there may be instances when it is appropriate for healthcare professionals to seek an unapproved medicine for treatment use for a patient where no satisfactory alternative exists. Unsolicited requests for continued access to daprodustat for participants of this trial will be considered where licensed ESAs are not suitable.

6.7. Treatment of Overdose

There is no specific antidote for overdose with daprodustat. The expected manifestations of daprodustat overdosage include signs and symptoms associated with an excessive and/or rapid increase in Hgb concentration. Daprodustat is highly protein bound; thus, clearance of daprodustat by HD or PD is very low and these are not effective methods to enhance the elimination of daprodustat. Daprodustat metabolites are, in part, cleared via HD. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care be instituted, as dictated by the participant's clinical status.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until daprodustat can no longer be detected systemically (at least 5 days).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Unless specified as a prohibited medication in Section 6.8.1, all concomitant medications should be considered permitted provided they are not contraindicated for the individual participant concerned.

Co-administration of daprodustat with moderate CYP2C8 inhibitors (e.g., clopidogrel, teriflunomide, deferasirox) should be performed with caution. If one of these medications is started, stopped or the dose is changed, the Hgb should be checked at the next study visit or, between Weeks 28 to 52, an extra Hgb check Visit should be performed if the next study visit is not due within 4 weeks, see Section 4.6.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded, along with:

- reason for use,
- dates of administration including start and end dates, and
- dosage information including dose and frequency.

The study medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Prohibited Medications

Use of any of the following prescription drugs, from Screening until 7 days after the last dose of daprodustat, is prohibited and will constitute a protocol violation:

- Strong inhibitors of CYP2C8 (e.g., gemfibrozil)
- Strong inducers of CYP2C8 (e.g., rifampin/rifampicin)
- ESA agents (rhEPO and its analogues[‡] and other HIF-PHIs if approved for pediatric use during the conduct of this study).
- No other investigational agents (including other HIF-PHIs) or devices are permitted from study entry through completion of the study.

[‡] For participants receiving ESA treatment prior to study entry, the investigator should schedule the Day 1 Visit (and Screening Visit, if intending Screening and Day Visits are the same day) to coincide, as closely as possible, with the date of the next scheduled ESA administration. Examples are provided in the table below:

ESA Schedule	Last ESA Dose	Day 1 (Baseline)
TIW	Monday Tuesday Wednesday	Wednesday Thursday Friday
Weekly	Wednesday	Following Wednesday
Every two weeks	2 weeks before Day 1	2 weeks after last ESA dose
Every four weeks	4 weeks before Day 1	4 weeks after last ESA dose

In general, GSK study participants can be vaccinated against COVID-19 using vaccines authorized via limited regulatory mechanisms (e.g., Emergency Use Authorization) or approved via accelerated or full approval mechanisms. Use of other candidate COVID-19 vaccines that have not received limited, accelerated, or full authorization/approval, and are only in use as part of a clinical trial, are not allowed.

6.8.2. Standard of Care, including Iron Management

During the study (from Screening until the participant's final visit), investigators are expected to monitor the participant's overall clinical status to ensure standards of care are met to enable consistency of practice with KDIGO guidelines or local equivalent.

Iron status is checked regularly as per the SoA (Section 1.3). If iron deplete, the investigator should choose the route of administration and dose of iron based on the participant's iron status and local clinical practice. Investigators should be guided by local/regional guidelines; however it is strongly recommended that:

- Ferritin is maintained >100 ng/mL.
- TSAT is maintained >20%.
- Iron (excluding multivitamins) is not administered in the following situations:
  - Ferritin >800 ng/mL and TSAT >20%, or
  - TSAT >40%.

6.8.3. Rescue Therapy

The use of rescue therapy is at the discretion of the investigator.

For Anemia:
Rescue therapy may be needed if Hgb fails to respond adequately despite dose adjustment or the participant is unable to tolerate daprodustat.

If a participant has a low Hgb as a result of an acute or subacute event with an identifiable cause (e.g., GI bleed, blood loss due to surgery, vascular access or trauma), the treatment should be directed to the specific cause. Daprodustat should be continued at the current dose unless Hgb is >12.0 g/dL as a consequence of a blood transfusion, in which case according to Section 4.6, the daprodustat dose should be decreased (Hgb >12.0 to ≤12.5 g/dL) or withheld (Hgb >12.5 g/dL) and Hgb checked again at the next scheduled study visit or at an extra study visit within the next 4 weeks if a study visit is not due in that time frame.

Blood transfusions
Blood transfusions should only be given if, in the opinion of the investigator, the benefit of transfusion outweighs the risks. Any blood transfusion (whole blood/packed red blood cells and number of units) should be recorded in the eCRF. Daprodustat can be continued at the current dose unless Hgb is >12.0 g/dL as a consequence of a blood transfusion, in which case according to Section 4.6, the daprodustat dose should be decreased (Hgb >12.0 to ≤12.5 g/dL) or withheld (Hgb >12.5 g/dL) and Hgb checked again at the

next scheduled study visit or at an extra study visit within the next 4 weeks if a study visit is not due in that time frame.

Need for other ESA treatment

The use of rhEPOs and their analogues should be avoided during the study (Section 6.8.1). If a rhEPO is given in error, the participant can continue in the study and on study intervention (daprodustat) ensuring that Hgb is assessed within 4 weeks of the administration of the rhEPO either at the next study visit (or from Study Week 28 at an extra Hgb check Visit if the next study visit is not within that time frame). The dose of daprodustat should be adjusted if required (Section 4.5) according to the Hgb response (Section 4.6).

If in the opinion of the investigator the participant needs an alternative to study intervention (daprodustat) then the participant should permanently discontinue daprodustat but otherwise should remain in the study as planned, unless they withdraw their consent (Section 7.1). The use of rhEPO or its analogues, and if applicable the reason for study intervention cessation, should be recorded in the eCRF.

For Kidney Function:

Rescue intervention may be needed during the study if a participant's kidney function continues to deteriorate.

Kidney Transplantation

Participants should be screen failed if they are scheduled for an elective living donor kidney transplant within 3 months of study entry (Section 5.2). However, participants may still enroll in the study if they are being evaluated for (or confirmed as requiring) a kidney transplant but surgery is not yet booked. In case a suitable donor is found during the course of the study, and transplantation is performed, the participant should be withdrawn from the study (Section 7.2).

Participants in the ND Sub-trial Transitioning to Dialysis

Participants in the ND sub-trial who need to start dialysis should not be withdrawn from the study and should continue on study intervention (daprodustat), aiming to keep their Hgb within the target range of 10 to 12 g/dL (Section 4.6) as per the dose adjustment algorithm (Section 4.5).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The definition of EOS, "study completers" and "treatment completers" is provided in Section 4.8. Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. Participants must be permanently discontinued from treatment with daprodustat for any of the following reasons:

- Pregnancy: Any female participant who becomes pregnant.
- Receives a diagnosis of cancer (with the exception of localized squamous cell or basal cell carcinoma).
- Need for, or use of, prohibited medications (Section 6.8.1) including use of strong inhibitors of CYP2C8 (e.g., gemfibrozil) or strong inducers of CYP2C8 (e.g., rifampin/rifampicin) for ≥14 days.
- Receives a kidney transplant (Section 6.8.3 and Section 7.2).
- Need for rhEPO or its analogues (Section 6.8.3).
- Meets the liver chemistry stopping criteria (Section 7.1.1).

Participants who discontinue study treatment prematurely for any reason should, where possible, continue in the study per protocol until the final Visit at Week 56 (except for kidney transplant participants who should be withdrawn from the study, see Section 7.2).

Reasons for premature discontinuation of study treatment must be captured in the eCRF, e.g., AE, lack of efficacy, protocol deviation, pregnancy, investigator discretion, consent withdrawal, lost to follow-up, study termination.

If a participant experiences an organ-threatening or life-threatening event, the investigator should discuss continuation of daprodustat with the GSK medical monitor.

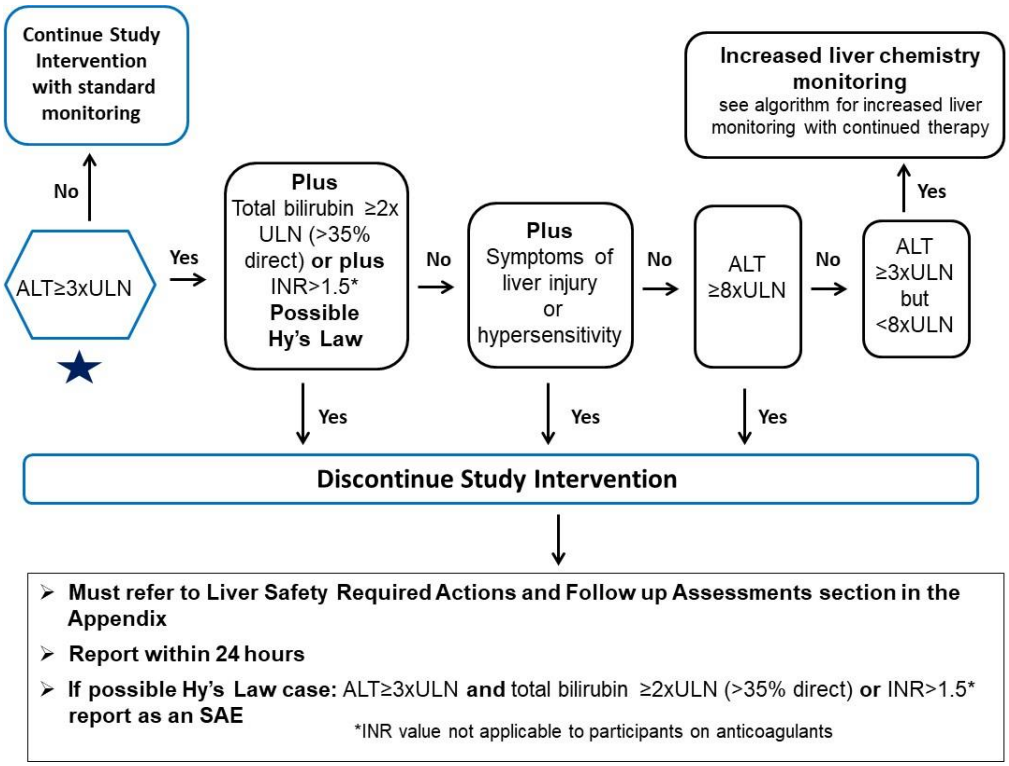
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention (daprodustat) for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the Liver Stopping and Monitoring Event Algorithm (Figure 6), or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

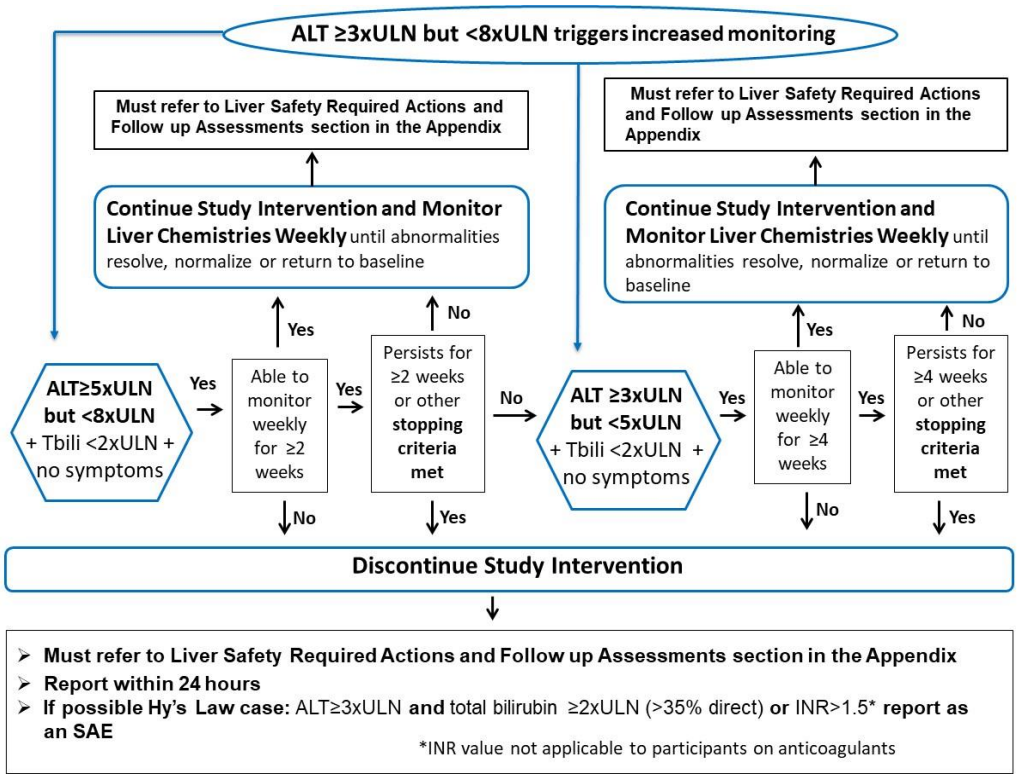
Figure 6 Liver Stopping and Monitoring Event Algorithm



Abbreviations: ALT = alanine aminotransferase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

If the ALT is ≥3×ULN but <8×ULN and according to Figure 6 study intervention (daprodustat) can be continued with increased liver chemistry monitoring, the increased liver chemistry monitoring should be performed as shown in Figure 7.

Figure 7 Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3×ULN but <8×ULN



Abbreviations: ALT = alanine aminotransferase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

Refer to Appendix 5 for required Liver Safety Actions and Follow-up Assessments.

7.1.2. QTc Stopping Criteria

There is no QTc stopping criterion, as per the adult Phase 3 studies, in view of the reassuring Thorough QT study and no concerns identified to date.

7.1.3. Temporary Discontinuation

As described in Table 11 in Section 4.6, if the Hgb is >12.5 g/dL, daprodustat should be temporarily withheld and checked in 4 weeks at the next study visit (or from Study Week 28 an extra Hgb check Visit should be performed 4 weeks later if the next scheduled visit is not within that timeframe). Restart is permitted at the next lower dose when the Hgb is ≤12.0 g/dL.

7.1.4. Rechallenge

7.1.4.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2. Participant Discontinuation/Withdrawal from the Study

The legal guardian and the pediatric participant have the right to withdraw permission (consent or assent, respectively) at any time during the study. If the study staff identify any reluctance in the legal guardian or pediatric participant (e.g., signs of verbal or physical dissent) about continued participation in the study, the pediatric participant's continuation in the study should be re-evaluated. The same principles that govern permission/assent/consent also govern its withdrawal.

A participant will be withdrawn from the study for the following reason:

- Withdrawal of consent or assent if applicable (a pediatric participant's dissent should be respected).
- Undergoes a kidney transplant.

At the time of discontinuation from the study, if possible, an early discontinuation visit should be conducted. See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention (if applicable) and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant and/or caregiver (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at home or alternative approved locations other than the clinical trial site to perform study assessments (at the discretion of the investigator). The site may work with GSK to use a centrally appointed home nursing vendor for conduct of study assessments.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the SoA (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study does not exceed recommendations for blood sampling in a pediatric population by age or weight (see Table 12).

Race and ethnicity will be collected for all participants in order to satisfy regulatory requirements for some jurisdictions and to allow appraisal of the extent to which disadvantaged and minority groups are represented in the trial population.

8.1. Efficacy Assessments

The dose response of participants to daprodustat will be assessed by measurement of Hgb. Hgb also serves to determine where a dose change is needed, see Section 4.6.

Planned timepoints for all Hgb assessments are provided in the SoA. Hgb should be checked and the dose adjusted if required, as defined in the protocol in Section 4.6 and Section 4.5 respectively.

8.2. Safety Assessments

Planned time points for all safety assessments are listed in the SoA (Section 1.3). 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.

8.2.1. Physical Examinations

Children and adolescents with CKD, particularly those with ESKD, are frequently growth impaired, so at a given age, they can often be expected to have the weight of a smaller/younger child/adolescent.

Height (or supine length in the very young) and weight will be measured at each study visit as appropriate for the participant's age and plotted on age and gender appropriate charts as per SoC at that site, for example using height z scores for chronological age and body mass index (BMI) z scores for height age (the age corresponding to the 50th percentile of the participant's measured height) as a means of monitoring percentile-parallel growth and weight gain. Any unexpected persistent change in trajectory, should be recorded as an AE.

The investigator should contact the medical monitor if any participant's weight falls below that specified as the minimum weight for their age group (see Table 12).

A complete physical examination will include, at a minimum, assessments of the ears, nose and throat, skin, cardiovascular, respiratory, GI and neurological systems.

8.2.2. Vital Signs

Vital signs will include systolic and diastolic BP and HR.

BP and HR will be assessed using an appropriate size cuff. BP and HR 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.

8.2.3. Electrocardiogram

A 12-lead ECG for screening exclusion criterion (see Section 5.2) will be obtained in the supine position. HR, PR interval, QRS duration and QT (uncorrected) interval will be measured. QTcF will be calculated (machine-read or manually). If prolonged QT/QTcF is noted, 2 additional ECGs measurements should be obtained. Determination of whether eligibility criteria are met will be based on the average of the triplicate assessment.

There is no QT stopping criteria Section 7.1.2 and no further ECG monitoring is required unless indicated as part of routine care of the participant.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the local laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be available as source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or study medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory tests (as defined in Section 10.2) and the PK sampling (see Section 8.4.1), must be conducted in accordance with the SoA (Section 1.3) and the laboratory manual (for PK sampling).

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5. Pregnancy Testing

Refer to Section 5.1 for pregnancy testing inclusion criteria.

Pregnancy testing in FOCBP should be conducted at each study visit, including the 56-week follow-up visit. Pregnancy testing may consist of a:

- serum hCG test, or
- urine hCG test if the eGFR is higher than 15mL/min/1.73m^2.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AEs or SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7.1).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of informed consent until the follow-up visit (Week 56) at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

Clinical Presentation of Adverse Events:
Study site staff should instruct the legal guardians and caregivers, on how to report signs and symptoms (e.g., crying and pain) in the individual pediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhea, sleepiness, variation in the intensity and pattern of crying, etc.). These non-specific symptoms may be the only manifestations of some adverse reaction observed in young children. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

Care will be taken not to introduce bias when detecting an AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire

about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3.6), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reaction (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 30 days after the last dose of study intervention.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant's pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study participants he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention (Section 7.1).

8.3.6. 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 (using preferred terms):

- Death, MI, stroke, HF, thromboembolic events, thrombosis of vascular access.
- Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis.
- New diagnosis of hypertension or worsening of existing hypertension.[§]
- Cancer related mortality and tumor progression and recurrence.
- Esophageal and gastric erosions.

The results of any investigation should be recorded on the AE page and the relevant AESI page of the participant's eCRF.

8.3.7. Tertiary Endpoints

8.3.7.1. Other Health Outcomes of Interest

The incidence of the protocol-defined health outcomes of interest listed in Section 9.3.2.4 are of particular importance in a pediatric population with anemia associated with CKD. At each visit, the investigator should indicate in the eCRF if one of these outcomes has occurred in the interval since the last study visit, ensuring that the details of any such outcomes are reported in the AE and/or concomitant medication eCRF pages as appropriate.

[§] Worsening of existing hypertension defined as occurrence of one or more of the following:
- 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.

8.3.7.2. Acceptability and Palatability Assessment

The acceptability and palatability of the 2 formulations used in this study (IR and TfOS) will be assessed by a participant questionnaire at Week 2.

8.4. Pharmacokinetics

8.4.1. Integrated PK Phase

Blood samples for determination of daprodustat and its major metabolites plasma concentration will be collected post dosing on Day 1, and, prior and post dosing at Week 2. If the PK samples are not convenient to perform at the Week 2 Study Visit, then these can be deferred to Week 4, as indicated in the SoA (Section 1.3). The 4 PK samples at Week 2 may also be split between Weeks 2 and 4 provided the dose of daprodustat is taken in clinic (to be sure of the exact time of dosing) and the 4 samples taken across the 2 Study Visits at Weeks 2 and 4 cover all 4 time intervals required (pre-dose, 0.5 to 1.5 hour [h], >1.5 to 3 h and ≥4 to 8 h).

At Day 1 and at Week 2 (or if needed at Week 4), the daily dose of daprodustat should be taken in the clinic and not at home. This information is summarized below:

At Day 1:

- Take the first dose whilst still in the clinic.
- Then take **3 samples:** 0.5 to 1.5 h, >1.5 to 3 h and ≥4 h time (maximum 8 h) intervals after taking the first dose of daprodustat. These limited time point samples are needed to compare with repeat dose data.

At Week 2 Visit (and/or at Week 4 if not fully performed at Week 2):

- Take the pre-dose sample.
- Then take the morning dose (as previously dispensed) whilst still in the clinic (the participant should not have taken the dose at home before the visit).
- Then take **3 further samples:** 0.5 to 1.5 h, >1.5 to 3 h and ≥4 h time (maximum 8 h) intervals post dose.

Note:

- If a participant is allocated to start on 0.125 mg QD (achieved by administration of 0.25 mg TIW), dose as normal but if a 0.25 mg tablet is due to be taken on the Week 2 (or Week 4) Visit day, the tablet should not be given at home that morning but administered in the clinic after the pre-dose blood sample is taken.
- If at Week 2, a participant has already taken their daprodustat dose prior to arrival in clinic, then reschedule the PK sampling to Week 4, reminding the participant not to take their dose at home on the day of the Week 4 visit.
- If the PK sampling is to be done at Week 4 (having been deferred from Week 2) and the participant has already taken their daprodustat at home the morning of the Week 4 Visit, omit the pre-dose sample and take those post dose samples that are

possible to collect for the time intervals 0.5 to 1.5 h, >1.5 to 3 h and ≥4 h time (maximum 8 h), noting the time of PK sampling in the eCRF and the participants as accurate as possible estimation of the time of home administration of daprodustat.

- If PK sampling is deferred to Week 4, but the participant has been put on dose hold at Week 2 (as the Hgb is >12.5 g/dL), then PK sampling should be delayed until the visit after daprodustat is restarted.
- PK samples can be taken before, during or after dialysis.

The date and timing (24-hour clock time) of PK sampling, daprodustat dosing and any concomitant medications taken needs to be recorded for each participant. At Week 2 (and/or Week 4), the participant needs to provide the time of last dose before the day of PK assessments (for the pre-dose trough estimation). A PK reminder card will be given to all participants undergoing PK assessments so they may record this time. This card will also serve as a reminder not to take their daprodustat dose at home on the day of the PK assessments.

Approximately 1.0 mL of blood (0.5 mL of plasma) is required for the assay. Therefore, the total blood volume for PK sampling on any occasion, and over the 2 (or 4) week sampling period in the PK Phase, will not exceed ~7 mL, ~1.09% of blood volume of a 1 year old child (assuming 80 mL/kg and 8 kg body weight). Together with the other blood draws required in the first 4 weeks, given that the minimum body weight required at study entry is 5 kg (see Table 12), the total volume of blood required will not exceed the recommended 1% blood volume draw limit per day or 3% blood volume draw limit over 4 weeks [Paediatric Population: Recommendations, 2008, Minors: Recommendations, 2017].

Processing, storage, and shipping procedures are provided in the laboratory manual.

8.4.2. Optional PK Sampling

For participants who cannot participate in the Integrated PK Phase as this is now closed in their age group, there will also be an opportunity to contribute to the PK dataset between Day 1 and Week 4. The sampling will replicate the requirements and schedule as described in the Integrated PK Phase (Section 8.4.1), but this is entirely optional.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Not applicable.

8.8. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. A separate analysis plan will include details of the population PK modelling. This section is a summary of the planned statistical analyses of the study endpoints. The 2 sub-trials (ND/D), as per their recruitment and conduct, will be analyzed and reported separately (overall and within each age group, except for PK and dose change which is within each age group only).

9.1. Statistical Hypotheses

There are no formal hypotheses pre-specified.

This study is designed to provide information on the PK profile within the trial (to confirm the appropriate starting dose and dose adjustment algorithm, as predicted by a PBPK model to achieve similar drug exposures in the pediatric population to adults) and at the end of the trial used for a Population PK model to derive the PK parameters C_{max} and AUC in a pediatric population, as well as inform the safety and Hgb response of daprodustat over a total treatment period of 52 weeks, when used in children and adolescent participants aged 3 months to <18 years with anemia associated with CKD in ND and D populations.

9.2. Analysis Sets

For purposes of analysis, the following participant analyses sets are defined:

Participant Analyses Sets	Definition/Criteria
Screened	All participants who had a valid ICF and were screened for eligibility.
Enrolled	All participants who entered the study (who received study intervention or underwent a post screening study procedure). Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.
Safety	All participants in the Enrolled analysis set who take at least 1 dose of study intervention (daprodustat). The Safety analysis set will be used for Main Study summaries including: study population, safety, efficacy (Hgb) and other health outcomes of interest.
Integrated PK	All participants in the Safety analysis set who participated in the Integrated PK Phase of the study and who had at least 1 non-missing PK assessment (non-quantifiable values will be

Participant Analyses Sets	Definition/Criteria
	considered as non-missing values). The Integrated PK analysis set will be used for dose decision making during the trial (comparison of the obtained plasma concentration values to those predicted by the PBPK model).
All PK (Integrated PK Phase and Optional Sampling)	All participants in the Safety analysis who had at least 1 non-missing PK assessment (non-quantifiable values will be considered as non-missing values). The All PK analysis set will be used for the Population PK model to derive the C_{max} and AUC.

9.3. Statistical Analyses

9.3.1. PK Analyses

During the study (Integrated PK Phase participants only):

In each sub-trial, the PK data (all available plasma concentration data) from each age group will be compared with the pre-specified PK simulations using the pediatric PBPK model. If more than 50% of the data lie outside the 95% PIs of the PK simulations, the PBPK model will be updated and simulations undertaken to determine the dosing (adult to pediatric ratio) to be used in the next younger age group.

A plot of the individual plasma PK concentration data overlaid with the PBPK model predictions will be provided.

At the end of the study (All PK data collected):

Population PK modelling approach will be undertaken using the All PK analysis set in both sub-trials, to derive C_{max} and AUC of daprodustat at steady state, using the estimand approach as described in Section 3.1.

Plasma concentration of daprodustat will be provided and where appropriate dose normalized plasma concentration of daprodustat will be summarized by nominal assessment time window in each age group in each sub-trial. Scatter plot of plasma concentration of daprodustat (dose normalized) by actual time will be plotted, separated where appropriate by age group and/or sub-trial.

In addition, if sufficient data available, similar descriptive analysis and plotting as above will be conducted for plasma concentration data for each metabolite.

If data permit, population PK modelling may be undertaken using all the plasma concentration data collected in this study, adjusting for age, weight and other covariates where needed, for daprodustat and/or each metabolite.

The final population PK model for daprodustat or its metabolites in adults will be used as the basis when conducting the modelling in the pediatric population.

Full details of the population PK analyses will be provided in the analysis plan, and results will be reported separately.

9.3.2. Main Study Analyses

All analyses will be performed on the Safety Population using the estimand approach as described in Section 3.2.

9.3.2.1. Primary Safety Analyses

The primary endpoint for this study is the incidence of AEs, SAEs, AESIs and AEs leading to study intervention discontinuation. The number and percentage of participants with each event of interest will be produced separately in each sub-trial (ND/D), overall and by each age group.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary and summarized by preferred term and System Organ Class. All AEs, SAEs, AESI, and AEs leading to study intervention discontinuation will be summarized as described in Section 3.2. Any AEs and SAEs prior to Day 1 and commencement of daprodustat will be summarized separately. Separate summaries will be provided for all AEs, drug-related AEs, severe AEs, SAEs, fatal SAEs, AESIs and for AEs leading to study intervention discontinuation.

9.3.2.2. Secondary Safety Analyses

All secondary safety endpoints will be summarized descriptively separately in each sub-trial (ND/D) overall and where appropriate within each age group.

Change from baseline in vital signs (BP and HR), height, weight and laboratory safety data (urea/BUN, creatinine, electrolytes, liver function tests [LFTs], calcium and full blood count with differential) will be summarized descriptively.

9.3.2.3. Secondary Efficacy Analyses

The mean Hgb value, mean change in Hgb from baseline and the proportion of participants with Hgb above, below and within the target range endpoints will be assessed at each study time point in each of the sub-trials, overall (all ages) and in each age group and additionally overall (all ages) by ESA use at study enrollment. The effect of daprodustat on maintenance of Hgb and need for change in required daprodustat dose over time will also be summarized.

Descriptive statistics will be presented in tabular and graphical format for mean Hgb value and mean change from baseline. No inferential testing will be performed. Line

plots of mean Hgb value over time will be produced. In addition, individual plots will be presented for Hgb values. The number and the percentage of participants with Hgb above, below or within the target range will be produced at each study visit.

The other secondary efficacy endpoints that describe the change in the required dose over time will be summarized and presented in each age group. The assigned dose by visit will be summarized using mean, SD, minimum, P25, median, P75, and maximum. In addition, the assigned dose by visit will also be summarized by using the number and percentage of participants assigned to each dose level. Stacked bar graphs displaying assigned dose at all scheduled visits starting with Day 1 will be provided. During the course of the study, the number and percentage of participants with 0, 1, 2…, 10, or >10 dose adjustments will be summarized in each age group. In addition, the number of dose adjustments per participant will be presented using summary statistics.

The Hgb data collected from each study population over the total 52 weeks may be utilized (after the study) to develop a population PK/pharmacodynamic (dose-Hgb) model. This modelling work will be based on the dose-Hgb model that will be developed from the adult global Phase 3 studies.

9.3.2.4. Tertiary Endpoints

Other Health Outcomes of Interest

During the study, the incidence of other health outcomes of interest listed below, will be presented using summary statistics (i.e., the number and percentage of participants) in each sub-trial (ND/D) overall and where appropriate within each age group.

- Related to Hgb and rescue therapy:
  - Use of iron supplements (oral/IV/both)
  - Blood transfusion
  - Use of rhEPO and analogues
- Related to changes in kidney function or intervention:
  - Transplantation
  - ESKD *(ND only)*
  - Switch between dialysis modalities *(D 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.

Acceptability and Palatability Assessment

The acceptability and palatability of the 2 formulations used in this study (IR and TfOS), as assessed by a participant questionnaire at Week 2, will be summarized descriptively by formulation.

9.4. Interim Analysis

9.4.1. Integrated PK Phase

There will be no formal interim analysis in the Integrated PK Phase. However, as described in Section 4.7, there are pre-defined time points when a decision is required in each sub-trial based on the Integrated PK Phase data.

Twenty-four participants across all age groups in each sub-trial population (ND/D) are required to provide PK data in the Integrated PK Phase, with a minimum of 4 participants in each age group. As recruitment will be harder as the age groups get younger, it is envisioned to recruit to the Integrated PK Phase in each sub-trial (ND/D) approximately the following: 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.

After the required number of participants have completed the 4 week Integrated PK Phase and the PK data has been analyzed, meetings with the GSK Study Team will be held to review the following from that age group's 4-week Integrated PK Phase:

- Actual PK data, in comparison to the PBPK model predictions.
- Hgb response up to Week 4 and any excursions outside the target range.
- Listing of safety events: AEs, SAEs, AESIs and AEs leading to study intervention discontinuation occurring during the 4-week PK Phase observation period.

In addition, Hgb and safety data available from all ages in each sub-trial to date will also be provided.

The GSK Study Team will then make a proposal for the ratio of the pediatric to adult dose ratio for the next younger age group. This proposal along with the above raw data, will be shared with the IDMC, who are required to confirm:

- If further recruitment from the same age group can proceed with optional PK assessment.
- If limited recruitment (requiring the Integrated PK Phase) to the next (younger) age group can be allowed.
- The dosing strategy (starting dose and dose adjustment algorithm limits) in the next younger age group.

Figure 2 (in Section 4.1) illustrates the IDMC decision points in the trial and Table 15 illustrates the total of the 10 IDMC decisions required at the 4 distinct time points (which is repeated independently for each sub-trial [ND/D] population).

Table 15 Decisions Required After Each Integrated PK Phase

Decision point	PK data available	Decision required
1	12 to <18 years	1. Allow further recruitment for the current age group of 12 to <18 years (with optional PK) 2. Permit limited recruitment (n≥4) to the study with Integrated PK Phase in the next younger age group (6 to <12 years) 3. Confirm dosing strategy for the next younger age group (6 to <12 years)
2	6 to <12 years	4. Allow further recruitment for the current age group of 6 to <12 years (with optional PK) 5. Permit limited recruitment (n≥4) to the study with Integrated PK Phase in the next younger age group (2 to <6 years) 6. Confirm dosing strategy for the next younger age group (2 to <6 years)
3	2 to <6 years	7. Allow further recruitment for the current age group of 2 to <6 years (with optional PK) 8. Permit limited recruitment (n≥4) to the study with Integrated PK Phase in the youngest age group (3 months to <2 years) 9. Confirm dosing strategy for the youngest age group (3 months to <2 years)
4	3 months to <2 years	10. Allow further recruitment for this youngest age group of 3 months to <2 years (with optional PK)

9.4.2. Main Study

No interim analyses is planned to be performed in the main study, but can be provided if requested by the IDMC or Regulatory Authorities

9.5. Sample Size Determination

9.5.1. Integrated PK Phase

Sample size for the Integrated PK Phase is based on feasibility, since it will be increasingly difficult as the age groups get younger to collect such data. Overall, 24 participants for each sub-trial (ND/D) will 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 is required to confirm (or adjust if required) the PK predicted dosing strategy for the 3 younger age groups.

9.5.2. Main Study

In each sub-trial (ND/D), a total of approximately 60 participants across all age groups will be enrolled.

The sub-trials are not formally powered, but the sample size is based on feasibility and also ensures that frequent AEs would likely be detected. Since a minimum of 60 participants will be exposed to daprodustat in each sub-trial, there is at least a 90% chance of observing at least 1 participant with the AE if the rate of the AE occurs with a frequency greater than 3.76%.

Change in Hgb from baseline will 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 ICE rate, 50 participants are expected to have a Hgb measurement. This will allow estimation of mean Hgb change from baseline to Week 12 with a precision of 0.4 g/dL, where precision is defined as the symmetrical 95% CI half width, assuming a population rate SD of 1.4 g/dL [KDOQI, 2006]. No sample size re-assessment is planned.

Sufficient number of patients will be screened to enable 60 participants to be enrolled. The screen failure rate is estimated to be low given pre-screening in the Cohort Study (212914) from which these participants are recruited.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- Reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., American Academy of Pediatrics [AAP], European Union Academy of Paediatrics) or Health Department guidelines.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent and Assent Process

Legal Guardian Consent and Pediatric Participant Assent Processes:

- The investigator, or a person designated by the investigator, will provide the legal guardian with the written ICF and the participant with the assent if applicable. They must be informed that participation is voluntary. The legal guardian will be required to sign written consent, and the participant if applicable will be required to sign written assent, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center after the nature of the study has been fully explained and before performance of any study-related activity.
- Assent requirements for pediatric participants may vary across regions and countries; local regulations should be followed as appropriate.
- The medical record must include a statement that written informed consent from the legal guardian and assent from the pediatric participant (if deemed appropriate by local ethics review or local regulations) were obtained before the participant was enrolled in the study and the date the written consent and assent were obtained. The medical record should describe how the clinical investigator determined that the person signing the ICF was the participant's legal guardian. The authorized person obtaining the informed consent must also sign the ICF and assent form attesting that the pediatric participant did not show signs of dissent particularly in those studies including toddlers and small children; it should be written in language appropriate to the child's developmental and functional status.
- Participants and their legal guardian must be re-consented and re-assented to the most current version of the ICF(s) during their participation in the study.
- Minor participants who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their legal guardian still wants them to participate.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the informed consent and assent forms must be provided to the participant and the participant's legal guardian.
- As appropriate, participants may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for

confidential reasons, which, at their request, would not be shared with their legal guardian, unless required by local law.
- Stored samples will be coded throughout the sample storage and analysis process and will not be labelled with personal identifiers. Participants may withdraw their consent/assent for their samples to be stored for research.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant and legal guardian must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant and legal guardian must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Independent Data Monitoring Committee

An IDMC with external experts experienced in treating pediatric patients with CKD will be utilized to ensure external objective review of the safety data at regular intervals throughout the study and to provide the decision making as outlined in Section 4.7 and Section 9.4.1.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants' received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.

- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on a printed case report form (CRF) or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report (CSR).
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan or equivalent Contract Research Organizations (CRO) document.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment:
The First Center Initiated will counted as the study start date.

Study/Site Termination:
GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 16 will be performed by the local laboratory of the trial site. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

Table 16 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet count Red blood cell count Hgb Hematocrit International Normalized Ratio (INR)[1]	Red blood cell indices: - Mean cell volume - mean corpuscular hemoglobin - %Reticulocytes	White Blood Cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Sodium	Potassium	Aspartate aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Urea/Blood Urea Nitrogen (BUN)	Creatinine	Alanine aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total protein
	Iron indices: - Ferritin - Transferrin saturation (TSAT)	Calcium	Alkaline phosphatase[2]	
Pregnancy testing	• Highly sensitive human chorionic gonadotropin (hCG) pregnancy test (as needed for FOCBP)[3]			

NOTES:
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.5 All events of ALT ≥3 ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.
3. Local urine testing will be standard for the protocol unless the eGFR is less than or equal to 15 mL/min/1.73m^2 or participants are dialysis dependent, in which case serum testing is required.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfil any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT ≥3×ULN AND total bilirubin ≥2×ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Moderate: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. • Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Medical Monitor by telephone. • Contacts for SAE reporting can be found in Study Reference Manual.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in Study Reference Manual.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Females are considered FOCBP (fertile) following menarche. For individuals with permanent infertility due to a medical cause, investigator discretion should be applied.

10.4.2. Contraception Guidance

CONTRACEPTIVES[1] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[2] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.* • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[2] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)[2] • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Highly Effective Methods[3] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.* • Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[3] o Oral o Intravaginal o Transdermal o Injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[3] o Oral o Injectable o Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated

with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
1. Contraceptive use by males or females should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. 2. 2Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. 3. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase 3-4 Liver Chemistry Stopping and Increased Monitoring Criteria are designed to ensure participant safety and evaluate liver event etiology. Liver chemistry stopping criteria are shown in Table 17 and increased liver chemistry monitoring criteria are shown in Table 18.

Table 17 Liver Chemistry Stopping Criteria and Required Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT absolute	ALT ≥8 × ULN
ALT increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3 × ULN **and** total bilirubin ≥2 × ULN (>35% direct bilirubin)
INR[2]	ALT ≥3 × ULN **and** INR>1.5
Cannot monitor	ALT ≥5xULN but <8xULN **and** cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	**Both** ALT ≥3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study intervention. Report the event to GSK **within 24 hours** • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow-up assessments as described in the Follow-up Assessments column • Monitor the participant until liver chemistry levels resolve, stabilize, or return to within baseline (see **MONITORING**) **MONITORING:** **If ALT ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 hours**	• Viral hepatitis serology[4] • Obtain INR and re-check with each liver chemistry assessment until the aminotransferases values show a downward trend • Blood sample for PK analysis, obtained within 1 week after last dose[5] • Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin if total bilirubin ≥2 × ULN • Obtain complete blood count with differential to assess eosinophilia

• Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria (total bilirubin <2 × ULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline **RESTART/RECHALLENGE** **Do not restart/rechallenge participant with study intervention since not allowed per protocol; continue participant in the study for any protocol-specified follow-up assessments.**	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications • Record alcohol use on the liver event alcohol intake form **If ALT ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5** obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct assay should be conducted (if available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected druginduced liver injury (DILI) progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • If liver biopsy conducted complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and hepatitis B core antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Table 18 Liver Chemistry Increased Monitoring Criteria with Continued Therapy (Daprodustat)

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR ≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR ≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilize or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

10.6. Appendix 6: Country-specific Requirements

10.6.1. Country-Specific Requirements for Japan

Purpose and Justification:

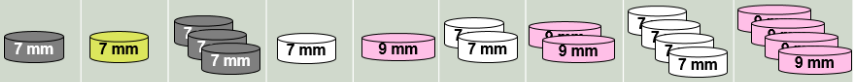
Daprodustat IR has been commercially available as a treatment for renal anemia in adults (≥15 years of age) since August 2020. However, the 8 mg IR tablet is not commercially available and not planned to be developed in Japan. In consultation with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), it has been agreed that the 8 mg IR tablet will not be used for Japanese participants. Therefore, multiples of the 4 mg or 6 mg IR tablets will be used to achieve IR dose steps of 8, 16 and 24 mg. The IRT set up for Japan will be amended as such. The IR and TfOS Dosage Steps shown in Section 6.1 are therefore revised for Japan as shown below.

In order to provide sufficient PK data from participants recruited in Japan, all participants recruited in Japan will be required to undertake PK sampling. Section 8.4.2 is therefore amended for Japan as detailed below.

IR and TfOS Dosage Steps (Japan only)

IR QD dosing

GSK1278863 dose (mg)	1 mg	2 mg	3 mg	4 mg	6 mg	8 mg	12 mg	16 mg	24 mg
Daprodustat (Tablet , QD)	1 mg tab x 1	2 mg tab x 1	1 mg tab x 3	4 mg tab x 1	6 mg tab x 1	4 mg tab x 2	6 mg tab x 2	4 mg tab x 4	6 mg tab x 4



TfOS QD dosing

GSK1278863 dose (mg)	0.25 mg	0.5 mg	0.75 mg	1 mg	1.5 mg	2 mg	3mg	4 mg	6 mg	8 mg	12 mg	16 mg
Daprodustat (Tablet , QD)	0.25 mg tab x 1	0.25 mg tab x 2	0.25 mg tab x 3	0.25 mg tab x 4	1.5 mg tab x 1	2 mg tab x 1	1.5 mg tab x 2	2 mg tab x 2	2 mg tab x 3	2 mg tab x 4	2 mg tab x 6	2 mg tab x 8

Up to 4 TfOS can be suspended in a 5 mL volume and up to 8 tablets require a total volume of 10 mL.

TfOS TIW dosing

The 0.125 mg QD dose step is achieved by oral administration of 0.25 mg TfOS TIW

GSK1278863 dose (mg)	0.125 mg
Daprodustat (Tablet, TIW)	0.25 mg tab x 1 TIW

PK Sampling

Participants in Japan who cannot participate in the Integrated PK Phase, as this is now closed in their age group, will still be required to contribute to the PK dataset between Day 1 and Week 4. The sampling will replicate the requirements and schedule as described in the Integrated PK Phase (Section 8.4.1) and for these participants will not be optional.

10.7. Appendix 7: Protocol amendment history

Amendment 01 / 22 June 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: The primary rationale for Amendment 01 is to add the requirement for a temporary dose hold if the hemoglobin (Hgb) at Week 2 is greater than 12.5 g/dL. Additional changes are to provide further clarity of study requirements and to address regulatory feedback. A description and brief rationale for each change are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis - Brief Summary 4.1. Overall Design 5.1. Inclusion Criteria 5.2. Exclusion Criteria 5.5 Criteria for Temporarily Delaying Enrollment / Administration of Study Intervention	The qualifying time period (between Day 1 and Screening Visits) for not repeating blood tests for eligibility was changed from 5 to 7 days.	To better align with a washout for Erythropoiesis Stimulating Agents (ESA).
1.1 Synopsis – Objectives and Endpoints 3. Objectives, Endpoints and Estimands	Pharmacokinetic Objectives and Endpoints were clarified as being 'Secondary'.	Clarification needed for the purpose of trial disclosure.
1.3. Schedule of Activities – Table 1	For the 'Extra Hgb Check Visit' column, specific timepoints were added in brackets (Weeks 32, 40 and 48).	To specify additional qualifying timepoints for a Hgb check after Week 28 and before Week 52.
	The procedure 'Daprodustat dispensing' was moved to occur in its own row.	For clarity and differentiation from the Interactive Response Technology (IRT) procedure.
	The footer 'g' related to IRT and daprodustat dispensing (if needed) for the additional 4-weekly visits for a Hgb check was removed.	Extra 4-weekly Hgb Check Visits (if required) will be a dispensing visit, so footnote 'g' is not applicable.
1.3. Schedule of Activities – Table 1	For IRT, 'Xs' were added to the early discontinuation/withdrawal visit and follow-up.	An IRT transaction is required to update the participant status.
	For 'Laboratory Assessments', blood urea nitrogen (BUN)	In some regions, BUN is measured instead of urea.

Section # and Name	Description of Change	Brief Rationale
	added as an alternate measurement to urea.	
	For 'Other' procedures, Acceptability and Palatability Questionnaire was added.	Requested by the European Medicines Agency (EMA) Paediatric Investigation Plan (PIP; M04)
	Under the 'Notes': a new first bullet was added indicating visit timings are relative to Day 1; the next bullet was updated and 5 days changed to 7 days.	To clarify visit timings and daprodustat dispensing visits and to better align with an ESA washout.
	For footer 'j', the time intervals were updated: maximum timepoint of 8 h included and the 4-h interval corrected to ≥4 h.	To align with Section 8.4.1.
	For footer 'k', an additional statement was added regarding the delay of PK sampling if a participant undergoes a dose hold.	To align with Section 8.4.1.
	Footer 'l' was added to state that 4-weekly pregnancy tests for females of child-bearing potential to be conducted in Argentina.	Required by local law.
2.1. Study Rationale	Date of commercial availability in Japan corrected to August 2020.	To correctly reflect the date of commercial availability in Japan.
3. Objectives, Endpoints and Estimands	A tertiary endpoint was added related to acceptability and palatability of the tablets.	Requested by the EMA (PIP M04).
3.2 Main Study Estimands	In the 2nd paragraph, wording related to the secondary efficacy target estimands (Hgb endpoints at each timepoint) was updated.	To correctly reflect the estimand strategy for Hgb values.
3.2 Main Study Estimands	In the table describing 'attributes for primary and key secondary estimands': regarding ICEs, 'hypothetical strategy' was replaced with 'while-on-treatment strategy'; regarding Secondary Efficacy Summary Measure, the summary measures for mean change in	To correctly reflect the estimand strategy for Hgb values and to clarify Hgb summary measures.

Section # and Name	Description of Change	Brief Rationale
	Hgb from baseline were specified.	
3.2 Main Study Estimands	In the 'Rationale for estimand' section: in the 2nd paragraph, regarding ICEs, 'hypothetical strategy' was replaced with 'while-on-treatment strategy'; in the last paragraph, for participants who undergo a kidney transplantation, the wording was updated to state they discontinue the study.	To correctly reflect the estimand strategy for Hgb values and to make a correction that participants who undergo a kidney transplantation discontinue the study.
4.2. Scientific Rationale for Study Design	Below 'Nested Interventional Trial within the Cohort Study 212914', wording was updated in the 3rd bullet and the term 'random selection' removed.	Participation in Study 214066 will be offered to all participants of Study 212914 when eligible, rather than by random selection.
4.5.2. Dose Adjustment Algorithm in the Younger Age Groups	In the last paragraph, a statement was removed regarding how a change in age year is counted.	IRT will confirm correct age with the Investigator in the birthday month.
4.6. Hemoglobin Target Range and Frequency of Checks	Below the 'At Week 2' paragraph, a second bullet was added regarding a dose stop if Hgb value is >12.5 g/dL.	To add an applicable dose stop.
	In the 1st paragraph below Table 11, the additional qualifying Hgb visits were specified in brackets (Week 32, 40, 48).	To clarify the additional qualifying Hgb visits.
	In the last paragraph, 'extra check Hgb' was removed.	To focus the paragraph on unscheduled visits.
4.7. Role of the IDMC in Confirming the Dosing Strategy	Related to the paragraph on potential substantial amendments, a footer (†) was added to the 1st bullet to include the requirement for PK collection in a subset of newly recruited participants (12 to <18 years of age) who start with the revised dosing.	To incorporate feedback from the US Food and Drug Administration (FDA) to include additional PK collection if the oldest age group requires revised dosing.
5. Study Population	In the 2nd paragraph, the acceptable range of Hgb for patients not on an ESA was corrected to 7.0 to 11.0 g/dL.	To align with the Hgb range presented in the inclusion criteria.
5.1. Inclusion Criteria	The 2nd paragraph was updated to indicate that participants in	To reiterate that participants must have met eligibility

Section # and Name	Description of Change	Brief Rationale
	Study 212914 must have met eligibility criteria to be approached for this study.	criteria stated in Study 212914 and have been offered approach for enrolment into this study from Study 212914.
5.1. Inclusion Criteria 8.3.5. Pregnancy	In inclusion criterion #4, for females of child-bearing potential, the commitment for using an acceptable method of contraception was changed to 'until at least 30 days after the last dose of daprodustat', and 16 weeks was removed.	To align with adult daprodustat studies wherein contraception is only required post the last dose of daprodustat for 5 times the terminal half-life (approximately 2.4-4 hours) plus 1 menstrual cycle.
	Section 8.3.5 was aligned with inclusion criterion #4 to state that details of all pregnancies in female participants will be collected after the start of study intervention and until 30 days (not 16 weeks) after the last dose of study intervention.	
5.2. Exclusion Criteria	Regarding 'Other Disease Related Criteria', the 'note' below criterion #8 related to history of malignancy was updated and exclusion criterion #9 was added (related to unresolved acute or active chronic infection requiring antimicrobial therapy).	For improved clarity and for safety reasons, respectively.
	Regarding 'Prior/Concomitant Therapy': the wording in criterion #15 was updated to include daprodustat treatment (in the last 30 days) alongside other HIF-PHIs; additionally, the wording in criterion #16 was improved.	To take into account the approved uses of daprodustat and other hypoxia-inducible factor (HIF)-prolyl hydroxylase inhibitor (PHI) in Japan (15 years of age and older) and improve the clarity of the wording related to previous failed response to HIF-PHIs including daprodustat.
5.4 Screen Failures	A statement was added to the 2nd paragraph to state there are no limits on the number of rescreens provided the eligibility parameter(s) can be addressed.	To clarify there is no rescreen limit.

Section # and Name	Description of Change	Brief Rationale
6.1. Study Intervention Administered	In the paragraph below Table 13, explanatory text was added regarding the expected similar responses on Hgb levels with 0.125 mg once daily and 0.25 mg three times weekly dosing.	To provide additional context regarding the administration of the lowest dose (0.125 mg once daily) as 0.25 mg three times weekly.
	In Figure 5 (IR and TfOS Dosage Steps), for the TfOS QD and TIW dosing, 'GSK863' was changed to 'GSK1278863'.	To apply a consistent GSK number to the study intervention.
6.8.1. Prohibited Medications	Regarding ESA agents and participants receiving ESA prior to study entry, a footer was added (‡) to explain the scheduling of the Day 1 visit.	To provide additional guidance in the protocol on daprodustat initiation if switching from an ESA.
8. Study Assessments and Procedures	A new paragraph was added regarding race and ethnicity.	To confirm that race and ethnicity will be collected for all participants.
8.2.4. Clinical Safety Laboratory Tests	In the 5th paragraph, wording was updated to associate the laboratory manual to just PK sampling.	The laboratory manual only relates to PK sampling and not also to other protocol-required laboratory tests.
8.3.7. Other Health Outcomes of Interest (previous heading) renamed to 'Tertiary Endpoints'	Section 8.3.7. was renamed to 'Tertiary Endpoints' and a subsection was added related to 'Acceptability and Palatability Assessment'.	Acceptability and palatability assessments of the formulations was requested by the EMA (PIP M04).
8.4.1. Integrated PK Phase	For the 'At Week 2 Visit': in the 2nd bullet, 'as previously dispensed' was added to the instruction of taking the morning dose; below the 'note', a bullet was added regarding the delay of PK sampling if participant is put on a dose hold at Week 2.	To clarify how PK sampling should be handled if participant is put on a dose hold at Week 2.
9.3.2.2. Secondary Safety Analyses	BUN included as an alternate measurement to urea.	In some regions, BUN is measured instead of urea.
9.3.2.4. Tertiary Other Health Outcomes of Interest (previous heading) renamed to 'Tertiary Endpoints'	Section 9.3.2.4. was renamed to 'Tertiary Endpoints' and an additional endpoint was added related to 'Acceptability and Palatability Assessment'.	Acceptability and palatability assessments of the formulations were requested by the EMA (PIP M04).
9.5.2. Main Study	Wording was updated to state there is 'at least' a 90% chance of observing a participant with	To make the wording more specific.

Section # and Name	Description of Change	Brief Rationale
	an AE; and the SD of 1.4 g/dL for Hgb change from baseline to Week 12 was updated to state it is a 'population rate' SD.	
10.2 Appendix 2: Clinical Laboratory Tests	Table 16 was updated to include BUN as an alternate measurement to urea.	In some regions, BUN is measured instead of urea.
	The 1st 'note' below Table 16 was updated to include the quantitative cut-off for total bilirubin (i.e., ≥2 x ULN).	The number 2 was missing in error.
10.6. Appendix 6: Country-specific Requirements	The purpose and justification statement was updated to indicate the 8 mg IR tablet is not commercially available in Japan and will not be used for Japanese participants. An updated Japan-specific figure on IR and TfOS Dosage Steps was included. The PK Sampling section was updated to clarify the PK sampling will be required for all Japanese participants.	Requested by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).
11. References	An additional reference was added (Bailey, 2019) and electronic links to 2 other references were updated.	To support the updates in Section 6.1. and to ensure active links are cited.
Throughout protocol	Minor editorial updates.	To correct spelling and formatting.

10.8. Appendix 8: Abbreviations and Trademarks

AAP	American Academy of Pediatrics
ADME	Absorption Distribution Metabolism Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic Kidney Disease
CkiD	Chronic Kidney Disease in children
CLpo	Apparent Oral Clearance
C_{max}	Maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
D	Dialysis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

eGFR	Estimated Glomerular Filtration Rate
EPO	Erythropoietin
EPPWG	European Pediatric Peritoneal Dialysis Working Group
EOS	End of Study
ESA	Erythropoiesis Stimulating Agent
ESKD	End Stage Kidney Disease
FOCBP	Females of Childbearing Potential
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
g/dL	Grams per decilter
h	Hour
hCG	Human Chorionic Gonadotrophin
HD	Hemodialysis
HDPE	High-Density Polyethylene
HF	Heart Failure
Hgb	Hemoglobin
HIF	Hypoxia-Inducible Factor
HR	Heart Rate
IB	Investigator's Brochure
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IU	International Units
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	Kilogram
LFTs	Liver Function Tests
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MI	Myocardial Infarction
mL	Milliliter
msecs	Milliseconds
MSDS	Material Safety Data Sheet
NAPRTCS	North American Pediatric Renal Trials and Clinical Studies
ND	Non-Dialysis
NHANES	National Health and Nutrition Examination Survey
NKF	National Kidney Foundation
NKF-KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative

NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
P25	25th Percentile
P75	75th Percentile
PBPK	Physiological Based Pharmacokinetics
PD	Peritoneal Dialysis
PEG	Polyethylene Glycol
PHI	Prolyl hydroxylase inhibitor
PI	Prediction interval
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Device Agency
QD	Once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's formula
QTLs	Quality tolerance limits
rhEPO	Recombinant Human Erythropoietin
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	Schedule of Activities
SoC	Standard of Care

SUSAR	Suspected Unexpected Serious Adverse Reaction
TfOS	Tablets for Oral Suspension
TIW	Three times weekly
TSAT	Transferrin Saturation
U	Units
ug	Micrograms
ULN	Upper Limit of Normal
UNS	Unscheduled
US	United States
USPI	United States Prescribing Information
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

Trademark Information

Trademarks of the GSK group of companies
NONE

Trademarks not owned by the GSK group of companies
Aranesp
Epogen
Mircera
Simcyp Pediatric ADME Simulator

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