Daprodustat for Treatment of Anemia of CKD in Pediatric Patients: Protocol for the ASCEND-P Trial Within a Cohort

Abstract Number: WCN23-0672

Thomas F Hiemstra[1], Jennifer G Vick[2], Juliet C Roberts[1]

[1]GSK, Stevenage, Hertfordshire, UK; [2]GSK, Durham, North Carolina, USA

Aims

The Anemia Studies in Chronic Kidney Disease (CKD): Erythropoiesis via a Novel prolyl hydroxylase inhibitor (PHI) Daprodustat - Pediatric (ASCEND-P) study aims to investigate the pharmacokinetics (PK), safety, and efficacy (hemoglobin [Hgb] response) of the novel hypoxia-inducible factor-PHI daprodustat in children and adolescents with anemia of CKD.

Background

Anemia associated with CKD occurs in 58% of pediatric patients with CKD stage 2, increasing to 93% in pediatric patients with CKD stage 5.[1] Anemia associated with CKD in children can have a significant impact on quality of life, developmental milestones, and physical activity.

Anemia of CKD can be successfully treated using interventions that restore erythropoietin deficiency.[2] However, regular erythropoietin injection can be particularly challenging in children,[3] and oral alternatives are urgently needed.

The novel, oral therapy, daprodustat has demonstrated non-inferiority for both efficacy and safety in adult patients with anemia of CKD, in both dialysis and non-dialysis populations.[4,5]

ASCEND-P has been designed as a basket trial of two independent, prospective, interventional, open-label, single arm sub-trials, evaluating PK, safety, and efficacy (Hgb response) of oral daprodustat in pediatric and adolescent patients with CKD, in populations not-yet requiring dialysis (non-dialysis [ND]) and requiring dialysis (D).

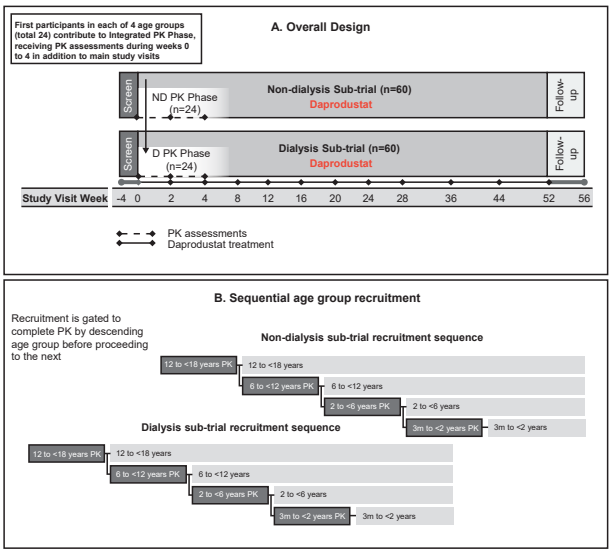
Methods

ASCEND-P (NCT05682326): an open-label, basket, single-arm, international, multicenter trial, to evaluate PK (4 weeks), safety (52 weeks) and Hgb response (52 weeks) to oral daprodustat in children and adolescent patients with anemia of CKD incorporating 2 independent sub-trials (ND and D).

Pediatric patients 17 years and younger with CKD stage 3 or worse requiring treatment for renal anemia will be enrolled in a global, prospective, observational cohort, basket study with 2 independent populations (ND and D).

Participants will receive standard-of-care treatment for renal anemia, with erythropoietins as appropriate. Eligible cohort study participants will be approached for enrollment into ASCEND-P when their age group is open for recruitment (see **Figure 1**). Patients will undergo monthly study visits for the first 6 months, at least 4-weekly visits up to Week 28 and 8-weekly visits thereafter up to Week 52. The study design is shown in **Figure 1**.

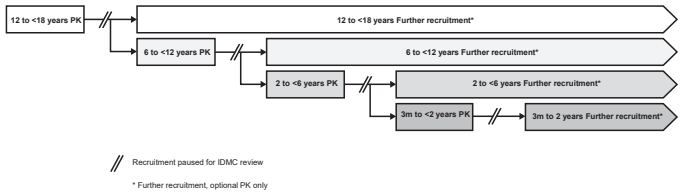
Figure 1. Study Design



A. Two parallel sub-trials, 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. B. 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 ≥4 participants from each age group) must complete this Integrated PK Phase. Further recruitment to that age group will pause until the Independent Data Monitoring Committee (IDMC) agrees that further participants from that age group can be recruited and participants from the next younger age group can in turn commence enrolment to their Integrated PK Phase. Participants in the Integrated PK Phase continue dosing after Week 4 in the main study without interruption.

The points at which IDMC reviews occur, when trial conduct decisions are required, are shown in **Figure 2**.

Figure 2. Pauses to Recruitment After Each Integrated PK Phase



The primary outcome for the ASCEND-P basket trial will be the safety of daprodustat in a pediatric population as determined by the incidence of adverse events (AEs), serious AEs, AEs of special interest and AEs leading to daprodustat discontinuation; study endpoints are listed in **Table 1**.

Table 1. Objectives and Endpoints

Objectives	Endpoints
Primary (Safety) Describe the safety of daprodustat, overall (all ages) and in each age group.	Incidence of AEs, SAEs, AESIs, and AEs leading to daprodustat discontinuation.
Secondary Safety Describe changes in parameters relevant to safety, overall and in each age group.	Changes from baseline in laboratory safety parameters, BP, HR, height, and weight at each time point.
Secondary Efficacy Describe the effect of daprodustat on Hgb, overall and in each age group.	At each study time point: Hgb value, Hgb change from baseline and Hgb above, below and within the target range (10 to 12g/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 PK Characterize the PK of daprodustat in each age group.	PK parameters: C_{max} and 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.
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 (use of iron supplements [oral/IV/both], blood transfusion, use of rhEPO and analogues), changes in kidney function/intervention (transplantation, ESKD [ND only]* or switch between dialysis modalities [D only]), and other (death, all-cause hospitalization, thrombosis, all-cause loss of vascular access patency).
To assess the acceptability and palatability of the immediate release tablets and tablets for oral suspension.	Participant-related Palatability and Acceptability Questionnaire to include but not limited to: palatability rating (good; acceptable; neither good nor bad; bad; very bad) and ease of swallowing (very easy; easy; neither easy nor difficult; difficult; very difficult).

*ESKD in the ND sub-trial population defined as ≥1 of: an eGFR, based on the bedside Schwartz equation of <15mL/min/1.73 m^2, new kidney transplantation or the requirement for maintenance dialysis for ≥30 days.
AESI, AE of special interest; AUC, Area Under the Curve; BP, blood pressure; C_{max}, maximum plasma concentration; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, heart rate; IV, intravenous; rhEPO, recombinant human erythropoietin; SAE, serious AE.

Conclusions

ASCEND-P has been designed as a basket trial of two independent, prospective, interventional, open-label, single arm sub-trials to evaluate the safety and efficacy of daprodustat for the treatment of renal anemia in pediatric patients with anemia of CKD, in both dialysis dependent and pre-dialysis patients (ND and D).

The design of the ASCEND-P study as a trial within a basket cohort study provides an efficient and patient-centered means of evaluating the use of daprodustat as an oral agent for the treatment of anemia of CKD in pediatric populations.

Disclosures

This study was funded by GSK (study code 214066; clinicaltrials.gov ID NCT05682326).

JESDUVROQ (daprodustat) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) now approved in the USA by the Food and Drug Administration (FDA) and indicated for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months. Daprodustat is not currently authorized or approved for use by the European Commission or any other regulatory authorities with the exception of Japan. Daprodustat should not be used off-label.

TFH, JGV, and JCR are employees of, and shareholders in, GSK.

Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors' comments, grammatical editing, and referencing) was provided by Jenni Lawton, PhD, of Ashfield MedComms, UK, an Inizio company, and was funded by GSK.

References

1. Atkinson MA, et al. *Pediatr Nephrol* 2010;25:1699.
2. Fischbach M, et al. *Clin J Am Soc Nephrol* 2018;13:81.
3. McLenon J, Rogers MAM. *J Adv Nurs* 2019;75:30.
4. Singh AK, et al. *N Engl J Med* 2021;385:2325.
5. Singh AK, et al. *N Engl J Med* 2021;385:2313.

Presented at the World Congress of Nephrology | Bangkok, Thailand | March 30 – April 2, 2023