Daprodustat Tablets

Application Number: NDA 216951

Treatment of Anemia in Patients with Chronic Kidney Disease

Cardiovascular and Renal Drugs Advisory Committee Meeting

Meeting Date: 26 October 2022

Document version: 21 September 2022

Applicant: GSK

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

ACM	all-cause mortality
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AE	adverse event
AESI(s)	adverse event(s) of special interest
AKI	acute kidney injury
AUC	area under the concentration-time curve
CEC	Clinical Events Classification group
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CV	cardiovascular
DF	dosing frequency
DILI	drug-induced liver injury
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EP	evaluation period
EPO	erythropoietin
EPPV	Post-Marketing Phase Vigilance
ESA	erythropoiesis stimulating agent
ESKD	end-stage kidney disease
FDA	Food and Drug Administration
GI	gastrointestinal
Hct	hematocrit
HD	hemodialysis
HDL	high-density lipoprotein
Hgb	hemoglobin
HLT	high level term
HF	heart failure
HIF	hypoxia inducible factor
HR	hazard ratio
IC50	half-maximal inhibitory concentration
ID	incident dialysis
IDMC	Independent Data Monitoring Committee

ITT	intention-to-treat
IV	intravenous
LVEF	left ventricular ejection fraction
M	metabolite
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MCID	minimum clinically important difference
MI	myocardial infarction
mITT	modified intention to treat
MRHD	maximum recommended human dose
NDA	New Drug Application
NI	non-inferiority
SF-36	36-Item Short Form Survey
PE	pulmonary embolism
PHD	prolyl-4-hydroxylase
PHI	prolyl hydroxylase inhibitor
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	post-marketing surveillance
PROs	patient-reported outcomes
PSUR	Periodic Update Safety Report
PT	preferred term
PY	person years
QoL	quality of life
RBC	red blood cell
RR	relative risk
SAE	serious adverse event
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
TEE	thromboembolic events
TIA	transient ischemic attack
TIW	three times weekly
TSAT	transferrin saturation
ULN	upper limit of normal
VAT	vascular access thrombosis
VEGF	vascular endothelial growth factor

Trademark Information

Trademarks of the GSK group of companies
None

Trademarks not owned by the GSK group of companies
HemoCue

1 EXECUTIVE SUMMARY

1.1. Introduction

GSK is seeking approval of daprodustat for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis and not on dialysis, in those not on erythropoietin stimulating agents (ESAs) and in those who are deemed suitable to switch from ESAs. This includes treatment for patients newly starting dialysis (incident dialysis, ID) and those receiving either hemodialysis (HD) or peritoneal dialysis. Daprodustat demonstrates a favorable benefit-risk ratio, with the evidence supporting its use as an oral treatment option for anemia of CKD.

Daprodustat is a member of a new class of drugs which inhibits prolyl-4-hydroxylase (PHD) enzymes, leading to a stabilization of hypoxia-inducible factor (HIF)-alpha and a consequent increase in endogenous erythropoietin (EPO) production and erythropoiesis. Daprodustat is intended to be available as a new oral agent for patients who are not receiving any treatment for their anemia of CKD, or as an alternative therapy to transfusions, ESAs, and iron therapy, when these are considered as treatment options.

Anemia occurs in CKD when there is insufficient iron to support heme production and/or when EPO production is insufficient. Chronic disease can lead to the amount of available iron being reduced by inflammatory mechanisms which impair iron's absorption from the gut and its mobilization from stores. CKD affects a substantial proportion of the US adult general population (15% in 2015-2018) [CDC, 2021] and is progressive: the prevalence of anemia increases with more advanced disease stages: 18.2% in stage 3 to 72.8% in stage 5 and 87% in chronic dialysis patients in the US [Wittbrodt, 2022]. Anemia of CKD is associated with increased risk of death, cardiovascular (CV) events, hospitalizations, increased fatigue, shortness of breath, cognitive impairment, as well as reductions in broader aspects of quality of life (QoL).

This briefing document summarizes key efficacy, safety, and patient-reported outcomes (PRO) data for daprodustat in support of the indications proposed.

1.2. Unmet Need

Anemia is a significant public health challenge that across multiple studies has been shown to be associated with increased risks of mortality, hospitalizations, CV disease, CKD progression, and reduced QoL. When compared with other chronic conditions such as heart failure (HF) and chronic obstructive pulmonary disease (COPD), patients with anemia of CKD have similar QoL, which is notably impaired compared with a healthy population norm. Despite this, it has proven methodologically challenging to demonstrate improvement in QoL on treating CKD patients who have both uremic and anemic symptoms.

Prior to the development of ESAs, red blood cell transfusions (RBCs) were commonly used to treat anemia of CKD. However, blood transfusions carry significant short and long-term risks for patients. Immediate risks post-transfusion that are heightened by CKD, include volume overload and hyperkalemia. Additionally, the biggest concern relates to allosensitization, the risk of which is high even from a single transfusion, and

which decreases a given candidate's possible donor pool, thereby prolonging the time to transplantation. Patients who receive a transfusion while on the transplant wait list in the first 5 years have a nearly 5-fold higher risk of mortality [Obrador, 2013].

ESAs have been approved for the treatment of anemia of CKD since 1989, to decrease RBC transfusions in both non-dialysis and dialysis patients and have been successful in reducing the use of transfusions since their introduction in treated patients. However, recent evidence suggests that, particularly in non-dialysis patients, a substantial proportion do not receive ESA or iron treatment for their anemia. Additionally, despite the risks of transfusion, recent clinical practice indicates that more non-dialysis patients have been receiving a transfusion than those who have been receiving an ESA.

Despite the currently available therapies, treatment of anemia of CKD is suboptimal for many patients. The reasons for suboptimal treatment are multifactorial, including logistical challenges for required in-clinic administration of injectable therapies. This has a particular impact on patients undergoing peritoneal dialysis, those not on dialysis and those living at distance from major treatment centers. As a result of this sub-optimal care, patients are undertreated leading to poor outcomes, including avoidable use of transfusions, detrimental effects on QoL and increased potential for other adverse outcomes. Thus, there remains an unmet need for novel, accessible treatment options.

1.3. Clinical Program

The global Phase 3 program described in this briefing document comprised 5 studies, which enrolled over 8000 participants, with all studies achieving their pre-specified primary objectives. The studies consisted of 2 large open-label CV outcome studies, ASCEND-ND in patients not on dialysis, and ASCEND-D in patients receiving dialysis. Two additional studies evaluated specific patient needs: one in patients starting on dialysis (ASCEND-ID), and one double-blind study in patients receiving a convenient dosing option of three times weekly (TIW) daprodustat (ASCEND-TD). These 4 studies compared daprodustat with active comparator ESA (darbepoetin alfa in ASCEND-ND, and ASCEND-ID, epoetin alfa in ASCEND-TD and both in ASCEND-D). Additionally, there was one double-blind, placebo-controlled study (ASCEND-NHQ) in patients not on dialysis, with the intention of quantifying any improvement in QoL from treating non-dialysis patients.

In view of the increased risk of major adverse cardiovascular events (MACE) with ESA treatment especially when treating to higher hemoglobin (Hgb) targets [Besarab, 1998; Singh, 2006; Pfeffer, 2009], CV safety was considered of cardinal importance in the overall assessment of safety. The 2 large CV outcomes trials that provided the principal assessment of potential CV risk compared the incidence of MACE (defined as death from any cause, non-fatal myocardial infarction [MI] or non-fatal stroke) for daprodustat with that of ESAs. All-cause mortality (ACM, as opposed to CV mortality) within the MACE composite matches the choice in the 3 studies in which the ESA signal was detected (Normal Hematocrit Study, CHOIR, TREAT) and also the subsequent CV outcomes studies in this therapeutic area (EMERALD, PEARL, PIVOTAL, INNO$_2$VATE, PRO$_2$TECT). An independent Clinical Events Classification (CEC) group (blinded to treatment assignment) adjudicated CV events in all 5 Phase 3 studies.

Importantly, completeness of follow-up was high for both CV outcomes studies, such that missing data are not likely to have influenced the conclusions. ASCEND-ND had 98.8% of the theoretical total possible person-years (PY) of follow-up for vital status and 97.3% for CV endpoints, while ASCEND-D had 98.3% of the theoretical total possible PY of follow-up for vital status and 95.3% for CV endpoints. At the end of the studies, vital status was known for >99% of participants in ASCEND-ND and 98% for ASCEND-D.

The increased MACE risk with ESAs may occur both when high absolute levels of Hgb are reached and when the rate of increase is too rapid [Unger, 2010]. Therefore, the daprodustat studies used a cautious dosing algorithm for all treatment groups based on same-day Hgb monitoring. Target Hgb ranges for the majority of the daprodustat global Phase 3 studies were set as 10 to 11 g/dL after discussion with regulatory agencies. Protocols specified an algorithm for uniform supplemental iron treatments for both daprodustat and control groups while participants remained on study treatment, and a common rescue algorithm to ensure consistency of approach across the regions in which the studies were conducted.

The primary safety objective of the CV outcomes studies was to assess non-inferiority (NI) of daprodustat to ESA in first occurrence of MACE. The pre-defined NI margin of 1.25 for the hazard ratio (HR; daprodustat versus ESA) was adopted following agreement from the US FDA and EU EMA. In addition, an Intention-to-Treat (ITT) analysis was pre-specified as the primary analysis for this endpoint, using all event on or after randomization, regardless of treatment status. By following all participants through to the end of study, regardless of patients being on or off treatment, this method respects the principles of randomization and is well recognized as the most unbiased approach to make statistical comparisons and inferences between different treatment policies for both safety and efficacy.

On-treatment analyses of MACE were included as supplementary analyses of the primary ITT analyses. MACE and other adjudicated CV events for both daprodustat and comparator ESA were considered to be on-treatment events if they occurred on or before the date of last dose with a further 28 days post-dose ascertainment window added to capture events of possibly longer latency (circa 28 to 30 days is common when defining the ascertainment window in CV outcomes studies). Using this definition, on-treatment events were systematically undercounted in the treatment group dosed on a less frequent (e.g. 1- to 4-weekly) basis since the definition of ‘on or before the date of last non-zero dose’ fails to capture events that occur within the dosing frequency of the participant’s last dose. On-treatment analyses can be problematic since they are based on the comparison of groups selected by post-randomization events (cessation of study drug), which means they are subject to forms of bias not present with ITT analyses. Alternative, more appropriate definitions for on-treatment were explored post-hoc and are discussed in Section 5.4.3.

Other design considerations for the Phase 3 studies included the fact that they were large enough that randomization ensured that the treatment groups were well-balanced for factors likely to affect outcomes, though inevitably when divided into smaller, non-randomized, subgroups, particularly in the more heterogeneous non-dialysis population, these were not all similarly balanced. Additionally, open-label comparisons may be subject to adverse event (AE) reporting biases but this is less likely to affect more

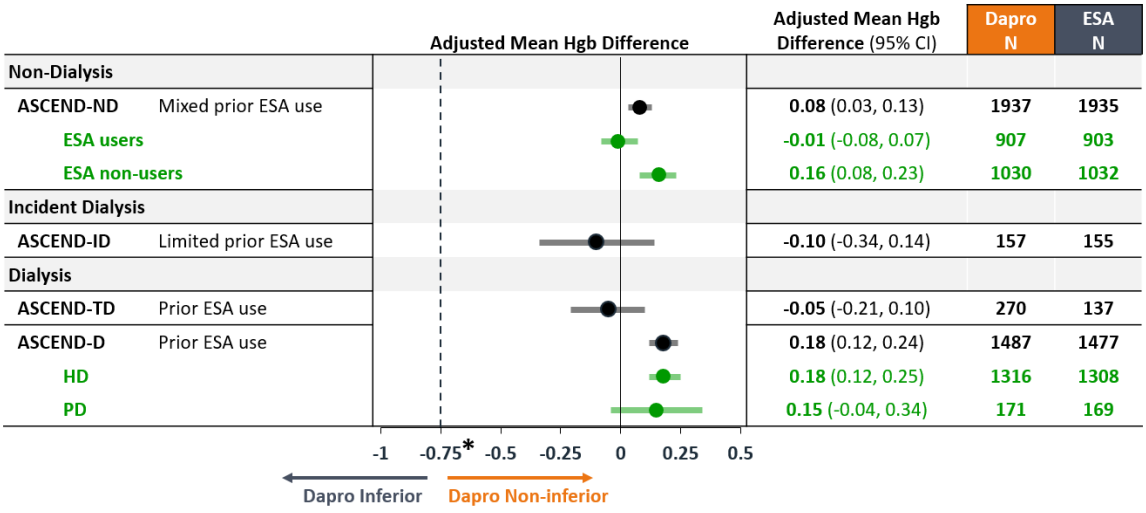
objective measures such as Hgb, other laboratory results, blood pressure (BP), deaths, adjudicated endpoints and serious AEs (defined using specific requirements) and would not have affected the double-blind studies ASCEND-TD and ASCEND-NHQ.

1.4. Efficacy

The primary efficacy objective (change from Baseline in Hgb) was achieved for daprodustat in all 5 global Phase 3 studies. Daprodustat was superior to placebo in ASCEND-NHQ, with a treatment difference in mean Hgb change from baseline to the average during the evaluation period of 1.40 g/dL (95% confidence interval [CI]: 1.23, 1.56; 1-sided p-value <0.0001). In all 4 active-controlled studies, NI to ESA was demonstrated with the lower bound of the 95% CI for the treatment difference in mean Hgb change from baseline to the evaluation period being above the pre-defined NI margin of -0.75 g/dL (daprodustat minus ESA control; Figure 1). Clinical efficacy was achieved in patients receiving dialysis, those new to dialysis (ID), and those not on dialysis regardless of prior ESA use (Figure 1).

In the active-controlled studies the proportion of participants who received transfusions during the evaluation period was generally similar between the daprodustat and ESA groups, as would be expected given the similarity of the achieved Hgb levels. In ASCEND-NHQ study, where separation was observed between the Hgb levels on daprodustat and those on placebo, the proportion of participants requiring a transfusion was 1.3% (4/307) in the daprodustat group and 4.9% (15/307) on placebo.

Figure 1 Active-controlled Studies: Summary of Primary Hemoglobin Endpoint in Global Phase 3 Studies (ITT Population)



HD=hemodialysis, PD=peritoneal dialysis. Note: daprodustat vs darbepoetin alfa in ASCEND-ND and ASCEND-ID; daprodustat vs recombinant human erythropoietin in ASCEND-D and ASCEND-TD.
* Vertical dotted line represents non-inferiority margin (-0.75 g/dL) and applies only to the overall study populations presented in black font.

SF-36 Vitality Domain score was pre-specified as the primary outcome for QoL and was analyzed as a principal secondary endpoint in the placebo-controlled study,

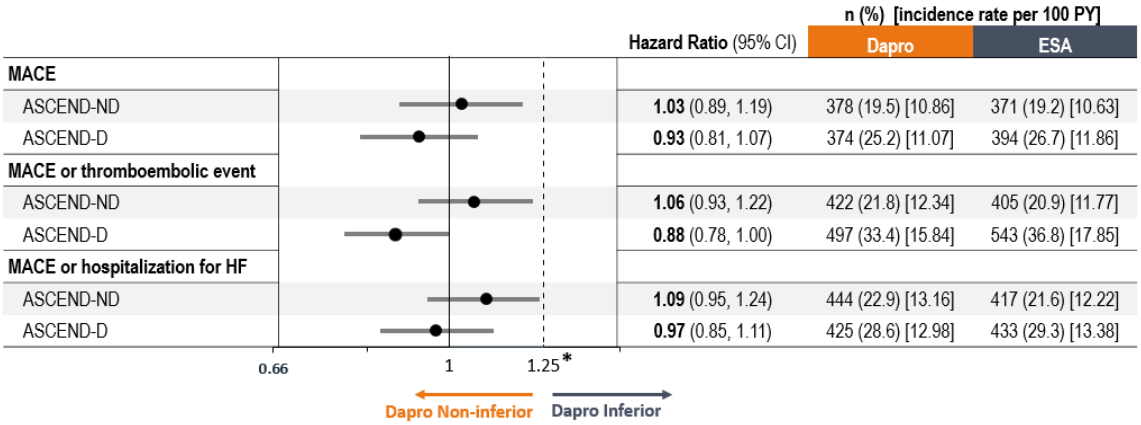
ASCEND-NHQ. Daprodustat significantly increased the SF-36 Vitality Domain score (and so reduced fatigue) compared with placebo (treatment difference: 5.36 points, 95% CI: 2.17, 8.56; 1-sided p-value=0.0005).

1.5. Cardiovascular Safety

The CV outcome trials, ASCEND-D and ASCEND-ND, showed daprodustat to be non-inferior to ESA for the primary safety endpoint of time to first adjudicated MACE using ITT analysis (Figure 2). In both studies, the upper bound of the 2-sided 95% CI for the HR was lower than the prospectively defined NI margin of 1.25.

Results for both principal secondary safety endpoints (time to first MACE or thromboembolic events and time to first MACE or hospitalization for HF) were consistent with those of the primary MACE analysis within each study.

Figure 2 Overall Summary of Analysis of Time to First Occurrence of Adjudicated MACE and Other CV Components (ITT Population)



HF=heart failure; MACE = major adverse cardiovascular event.
Note: ITT analysis; daprodustat vs ESA in ASCEND-D; daprodustat vs darbepoetin in ASCEND-ND. MACE is a composite of all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke. Thromboembolic events defined as vascular access thrombosis, deep vein thrombosis or pulmonary embolism.
* Vertical dotted line represents non-inferiority margin (1.25) and applies only to MACE.

The placebo-controlled ASCEND-NHQ study in non-dialysis participants was not designed with sufficient power to allow for formal statistical comparisons of MACE between treatment groups. However, the data showed no indication of an increased risk with daprodustat over placebo: adjudicated MACE occurred in 15/307 (4.9%) patients assigned to daprodustat and 19/307 (6.2%) assigned to placebo. This result is notable given that patients in the study were treated to higher target Hgb (11 to 12 g/dL) than proposed for the prescribed use of daprodustat in the US (Section 4.3.1).

Studies of 2 other agents in the HIF-prolyl hydroxylase inhibitor (HIF-PHI) class, roxadustat and vadadustat, reported less favorable data in the non-dialysis population than in dialysis patients. The primary safety endpoint of the PRO_2TECT non-dialysis CV outcomes studies, which compared vadadustat with darbepoetin, was analyzed using an ITT analysis and resulted in a HR of 1.17 (95% CI: 1.01, 1.36) [Chertow, 2021], which

contrasts with the HR for ASCEND-ND for daprodustat versus darbepoetin control (HR 1.03, 95% CI: 0.89, 1.19). The non-dialysis assessment for roxadustat was based on a meta-analysis of 3 placebo-controlled studies for which the primary ITT MACE analysis yielded a HR of 1.10 (95% CI: 0.96, 1.27).

On-treatment analyses of time to first MACE were very similar to the primary ITT analysis in the ASCEND-D study. However, the on-treatment results of time to first MACE were not consistent with the primary ITT analysis for the ASCEND-ND study – the HR was 1.4 and the CI did not include unity (Table 1). As discussed above (Section 1.3) and in more detail in the body of this document (Section 5.4.3), the pre-specified on-treatment definitions were fundamentally flawed, because they did not account for the difference in dosing frequency between daily daprodustat and the TIW, weekly, 2-weekly or 4-weekly injected ESA comparators. Further analyses using different on-treatment definitions were performed post-hoc (see definitions in Table 18), including adjustment for the different dosing frequencies (Table 1). The results were more consistent with the primary ITT analysis for ASCEND-ND, with a lower point estimate for the HR than when using the pre-specified definition and 95% CIs that included unity. By contrast, the post-hoc analyses that adjusted for dosing frequency were very consistent with the pre-specified definition for ASCEND-D, likely because the difference in dosing frequency between daily daprodustat and predominantly TIW or weekly ESA control in that study was much less pronounced.

The interpretation of any on-treatment analysis should be considered in the context of the risk of informative censoring (decision to stop treatment could be related to likelihood of a future event) and also the potential exclusion of off-treatment events that are causally linked to prior treatment exposure (events with longer latency). The pre-specified ITT primary analysis remains the most statistically robust and least biased analysis for characterizing the given treatment policy over the period of study follow-up in a manner that respects the randomization and supports statistical inference. Taken together, these primary safety analyses demonstrate daprodustat is non-inferior to ESA for time to first MACE in participants on dialysis and participants not on dialysis.

Table 1 Summary of On-treatment Analysis of Time to First Adjudicated MACE during the Time Period for On-treatment CV Events (ITT Population)

	ASCEND-ND				ASCEND-D			
	Pre-specified (Up to Last Dose + 28d)[c]		Dosing Frequency Adjusted (Up to Last Dose + DF + 28d)[c]		Pre-specified (Up to Last Dose + 28d)[c]		Dosing Frequency Adjusted (Up to Last Dose + DF + 28d)[c]	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)	Dapro (N=1487)	ESA (N=1477)
Number of participants[a]	1937	1933	1937	1933	1482	1474	1482	1474
First adjudicated MACE, n (%)	274 (14.1)	202 (10.5)	275 (14.2)	248 (12.8)	255 (17.2)	271 (18.4)	255 (17.2)	278 (18.9)
Hazard Ratio (95% CI)[b]	**1.40** (1.17, 1.68)		**1.18** (0.99, 1.40)		**0.96** (0.81, 1.14)		**0.94** (0.79, 1.11)	

DF=dosing frequency, MACE=major adverse cardiovascular event.

a. All randomized participants who received at least 1 dose of randomized treatment.

b. Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.

c. Pre-specified (Last dose+28d) and dosing frequency adjusted (Last dose+DF+28d) on-treatment definitions are detailed in Table 18.

Analyses of individual CV endpoints were conducted as additional secondary endpoints. Important methodological limitations exist when analyzing components of composite endpoints separately, which are summarized in recent FDA draft guidance [FDA, 2017]. These include reduced precision due to fewer events and lack of adjustment for multiplicity, as well as lack of accounting for the competing risk of death (for MI, stroke, thromboembolic events, and hospitalization for HF) in the setting of the ASCEND CV outcomes studies. Nevertheless, in-depth investigation was undertaken across all secondary safety endpoints, which identified the need for further post-hoc evaluations related to hospitalization for HF.

Although results from the principal secondary endpoint of time to composite of first MACE or hospitalization for HF did not demonstrate a statistically significant difference between daprodustat and ESA control, this endpoint was designed to provide a broad assessment of CV (i.e. atherosclerotic) risk, with a measure that incorporates HF outcomes. When assessing components within the composite endpoint, the number of ACM events were similar between treatment groups in both ASCEND-D (14.8% daprodustat, 14.6% ESA) and ASCEND-ND (11.6% daprodustat, 12.2% darbepoetin) but a higher number of hospitalization for HF events were observed with daprodustat (20.4% with daprodustat, 13.4% ESA). This led to additional post-hoc analyses specifically targeted to assess for any treatment group effect on HF risk.

These post-hoc analyses demonstrated that in a subgroup of participants in ASCEND-ND with pre-existing HF (13% of the study population), an increased risk of ACM or hospitalization for HF was seen for daprodustat compared with darbepoetin alfa (HR 1.20, 95% CI: 0.89, 1.62). This increase was largely driven by a higher number of

hospitalization for HF events within the composite (20.4% with daprodustat, 13.4% ESA). There was no evidence of an increased risk of ACM or hospitalization for HF with daprodustat in ASCEND-ND in those participants without pre-existing HF, or in the ASCEND-D population, irrespective of pre-existing HF status. Pre-dialysis patients with advanced CKD are uniquely sensitive to fluid overload; this problem is particularly true in the subgroup of patients with a history of HF. In a clinical setting, this vulnerable group of patients are readily identified, and current clinical practice standards dictate frequent monitoring and close supervision of fluid balance in these patients.

1.6. General Safety

Daprodustat was generally well tolerated, with a safety profile based on treatment-emergent (on-treatment) AEs comparable to established ESA treatments, across the spectrum of patients with anemia of CKD. Potential adverse events of special interest (AESIs) and other events of interest (liver safety and those potentially associated with other HIF-PHI agents) were evaluated in the ASCEND program.

The potential for malignancy progression or recurrence was identified as an AESI for daprodustat based on clinical experience with marketed ESAs in patients with cancer, and published links between HIF-1 activity and tumor growth. Consequently, as a precautionary measure, the trials excluded participants with a known active malignancy or recent history of malignancy.

There were no neoplastic or genotoxic findings in the relevant animal studies with daprodustat. In clinical studies, the incidence of treatment-emergent malignancies was sensitive to the treatment-emergent definition because an AE related to cancer was a treatment stopping criterion (relative risk [RR] in ASCEND-ND: RR 1.47, 95% CI: 1.03, 2.10; in ASCEND-D: RR 0.92, 95% CI: 0.62, 1.35; Appendix Table 61). An additional post-hoc analysis was conducted using all participants who took study drug and including all events reported throughout the study follow-up regardless of treatment status (which properly accounts for the potential for long latency between carcinogenesis and the clinical detection of cancers). This analysis showed no meaningful treatment group difference in the incidence of malignancies in each of the CV outcomes studies (in ASCEND-ND: RR 1.03, 95% CI: 0.77, 1.39; in ASCEND-D: RR 0.84, 95% CI: 0.61, 1.16). The RR was consistent with the post-hoc treatment-emergent analysis when adjusted for dosing frequency (ASCEND-ND: RR 1.06, 95% CI: 0.76, 1.46; ASCEND-D: RR 0.88, 95% CI: 0.60, 1.30). The duration and size of these studies was not sufficient to fully characterize the potential for daprodustat to accelerate tumor growth and therefore, this remains an important potential risk.

Hypertension is highly prevalent in patients with CKD, being both a major cause and consequence of impaired renal function. More than 94% of participants had a history of hypertension in the ASCEND studies. Elevated BP is a known effect of ESAs which are labeled accordingly. On review of clinical data, including both investigator-reported AEs and objective endpoints (mean BP changes, BP exacerbations, and change in medications to treat BP), it was concluded that daprodustat had similar effect on BP compared with ESAs. Therefore, there is no greater concern with respect to hypertension for daprodustat than there is for ESAs.

Imbalances in liver-related events have been reported in publicly available information for other HIF-PHI agents. Across the daprodustat development program, 38 participants (19 daprodustat and 19 ESA control) had cases that met biochemical criteria for Hy's Law (alanine aminotransferase [ALT] ≥ 3x upper limit of normal [ULN] and total bilirubin ≥ 2x ULN). A clinically plausible cause of liver injury was present for all 38 participants (40 cases), and there was no signal of drug-induced liver injury (DILI) associated with either daprodustat or ESA control. Following blinded review, an external committee of hepatic experts determined that no case was considered probably related to study drug, and concluded that a hepatotoxicity signal had not been identified among these cases.

Imbalances in seizures and sepsis have also been reported for other HIF-PHI agents. In the ASCEND studies, however, when using the associated standardized MedDRA queries (SMQs) to identify these events, there were no such imbalances.

Gastric and esophageal erosions were identified as an AESI following observations of gastric erosions and ulcers in nonclinical studies following oral or IV administration of daprodustat, primarily in the setting of doses that led to supraphysiologic hematocrit (Hct) in the animals concerned. Gastric erosions in rats have also been associated with repeated administration of ESA at doses that caused similar Hct increases [Woodburn, 2008; Aranesp, 2011]. These animal findings are most likely due to compromised microvascular perfusion that is associated with marked increases in Hct.

The dosing frequency adjusted RR of potential esophageal and gastric erosions observed in ASCEND-ND (RR 1.46, 95% CI: 1.01, 2.09) trended in the opposite direction to that in ASCEND-D (RR 0.73, 95% CI: 0.53, 1.01) due to different rates per 100 PY in the ESA control groups (1.69 versus 3.20). More participants in the daprodustat group of the ASCEND-ND study had stage 5 CKD (37% in daprodustat and 35% in ESA), which is associated with an increased risk of gastric and esophageal erosions and may have affected the results. Most events resolved without discontinuation of study therapy. Further, blinded review by external gastroenterology experts show that while there was a higher number of AESIs reported on daprodustat versus ESA, the proportion of participants with confirmed clinically significant mucosal erosive events without another documented potential cause was similar (<1%) across treatment groups in both dialysis and non-dialysis participants. Thus, based on the totality of data, there does not appear to be an increased risk of esophageal or gastric erosions with daprodustat relative to ESAs.

Daprodustat has been approved in Japan for the treatment of renal anemia since June 2020, leading to an exposure of approximately 41,871 PY as of March 2022. The safety profile of daprodustat has been closely monitored through the initial 6-month post-launch Early Post-Marketing Phase Vigilance (EPPV) period and then through comprehensive pharmacovigilance activities including signal detection. Additional pharmacovigilance activities or risk minimization measures have not been deemed necessary, requested by health authorities or implemented since authorization. The post-marketing data from Japan presented in this document supports the position that daprodustat is generally well tolerated with a safety profile comparable to established ESA treatments across the spectrum of patients with anemia of CKD. No new safety signals have been identified from the post-marketing data, and the benefit-risk profile of daprodustat in Japan continues to be favorable.

1.7. Benefit-Risk

In the active-controlled clinical trials of up to approximately 3.5 years in duration, the dosing regimens tested for daprodustat increased and maintained Hgb to a target range as effectively as injectable ESAs, with similar rates of transfusion. Therefore, daprodustat shares the proven benefits of ESA, including reducing the need for transfusions.

Clinicians avoid transfusions, when possible, because of potential alloimmunization which can have a long-term impact on kidney transplant outcomes. Highly sensitized patients may be less likely to receive a living donor kidney transplant and would be subject to aggressive induction and maintenance immunosuppression therapy to reduce risk of rejection. Blood transfusions also carry the immediate post-transfusion risks of volume overload and hyperkalemia and, although rare, transmission of blood-borne infections. The convenience of an effective oral agent would be expected to improve access to those left untreated for logistical reasons, and provide benefits for health care providers in terms of storage (refrigeration not required), delivery (avoiding parenteral administration, quite often in the provider's office, allows for fewer clinic visits for non-dialysis and peritoneal dialysis patients) and disposal (no biohazard waste associated with used injection devices).

Cardiovascular events and complications are known to be associated with ESAs. Given that daprodustat's pharmacodynamic effect is to increase both endogenous EPO, albeit to a lesser extent than ESAs, and RBC mass, it is not surprising that these were also reported with daprodustat. No increased risk of malignancy was demonstrated with daprodustat compared with ESAs. Furthermore, no signal for increased risk was noted for drug induced liver injury, seizures and sepsis that have been reported for other members of the HIF-PHI class.

The benefit-risk profile of daprodustat in Japan continues to be favorable, and no new safety signals for these patient populations have been identified through post-marketing surveillance.

Benefit-risk in patients on dialysis

Marketed ESAs have been shown to have an increased risk of MACE in clinical trials that targeted physiologically normal levels of Hgb (not now recommended via label or treatment guidelines). It is therefore important that any alternative treatment to ESAs does not have an inferior CV safety profile to ESAs.

The CV outcomes study, ASCEND-D, demonstrated that daprodustat was non-inferior to ESA with respect to the pre-specified primary ITT analysis of the safety endpoint, MACE. For NI studies the effects restricted to the period that participants were on treatment is often of interest; however, the analysis is compromised by defining the period of follow-up based on a post-randomization event (i.e., discontinuation of treatment). Hence, these on-treatment analyses must be interpreted with the appropriate context. Even with these considerations, the on-treatment assessment of MACE for ASCEND-D had results consistent with the primary ITT analysis.

In the past few decades many kidney health organizations globally have strongly advocated for policy and practice changes to increase access to and uptake of home dialysis. This uptake is hindered particularly for those with major logistical difficulties to overcome in attending outpatient clinics to receive parenteral treatments for their anemia. Consequently the convenience of an oral treatment as effective and safe as ESAs would be clearly advantageous in patients on home HD or undergoing peritoneal dialysis.

Benefit-risk in patients not on dialysis

Like ASCEND-D, the CV outcomes study conducted in patients not on dialysis, ASCEND-ND, demonstrated that daprodustat was non-inferior to ESAs with respect to the pre-specified primary ITT analysis of the safety endpoint, MACE. In a subgroup of the non-dialysis population with pre-existing HF there was an observed increase with daprodustat in the risk of being hospitalized for worsening HF. These patients are at high underlying risk of fluid overload, irrespective of drug therapy, and monitoring of their fluid status is an important part of clinical practice. Daprodustat was superior to placebo in improving QoL SF-36 vitality domain score by reducing fatigue in non-dialysis patients.

Patients with CKD anemia not on dialysis experience suboptimal levels of treatment which is exacerbated by the need to travel to clinic to receive parenteral drug administration. This increases the risk of under-treatment leading to correction by transfusion with subsequent fluid overload, hyperkalemia and the need for urgent care, potentially requiring dialysis. Treatment that scrupulously avoids transfusions is important to preserve the option for potentially curative renal transplant, while also reducing fatigue, dyspnea and other limiting symptoms of anemia. An oral treatment still requires close monitoring of Hgb levels but this can be readily achieved via local blood draws without requiring travel to specialist outpatient centers. The availability of an additional, oral therapy would permit more scope for individualizing patient care.

The patient population not on dialysis has the greatest unmet need for an oral treatment that matches the efficacy and safety of current pharmaceutical standard of care, parenterally delivered ESAs, for anemia of CKD.

Conclusion

The efficacy and safety of daprodustat has been demonstrated in 5 placebo-controlled and active-controlled trials, giving consistent evidence supporting its positive benefit-risk when used as an oral treatment option for anemia of CKD in adults receiving, or not receiving, dialysis. The totality of data across the Phase 3 studies, and the available post-marketing data, supports daprodustat having an acceptable safety profile, similar to ESAs. Appropriate pharmacovigilance measures and risk minimization activities will be put in place by GSK.

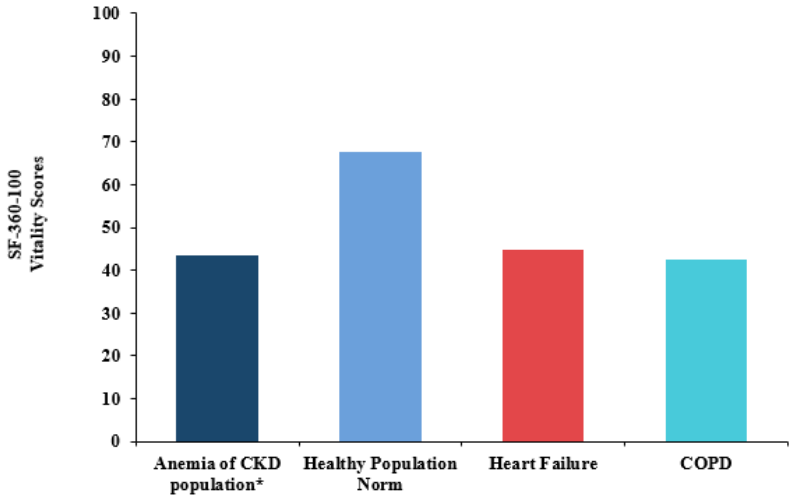
2. BACKGROUND INFORMATION ON THE DISEASE TO BE TREATED

2.1. Nature of the Disease

Anemia is a common manifestation in CKD affecting 15% of CKD patients in the US (estimated 4.8 million) [Stauffer, 2014]. Anemia is characterized by decreased circulating RBC. Anemia occurs in CKD when the body's EPO production is insufficient or when available iron is reduced because of the impaired ability to absorb and mobilize iron through the gut and mobilize it from internal stores. CKD affects a substantial proportion of the US adult general population (15% of US adult general population in 2015-2018) [CDC, 2021]. CKD is progressive; the prevalence of treatable anemia (Hgb <10 g/dL) of CKD increases with each CKD stage: 3a (18.2%), 3b (24.8%), 4 (41.2%), and 5 (72.8%) [Wittbrodt, 2022]. Also, anemia (Hgb <12 g/dL) is present in 86.7% of HD patients and 79.2% of peritoneal dialysis patients [US Renal Data System, 2021]. The presence of anemia and the severity of anemia have been associated with increased risks of mortality, hospitalizations, CV disease, CKD progression, and reduced QoL across multiple studies [Thorp, 2009; Palaka, 2020; Lamerato, 2022].

Untreated anemia increases the risk of CKD progression [Wittbrodt, 2022] and adults with anemia of CKD have a significantly poorer health-related QoL than CKD patients without anemia [de Goeij, 2014; Eriksson, 2016; Azmi, 2018; van Haalen, 2018; Kefale, 2019; Hoshino, 2020; van Haalen, 2020; Shen, 2021; Michalopoulos, 2022] and the general population [Hansen, 2009; Bonner, 2013]. Patients commonly report feeling weak, fatigued, and lacking strength as well as suffering from shortness of breath, difficulty remembering things, and interference with sleep and daily activities [Eriksson, 2016; Mathias, 2020]. When compared with other chronic conditions such as HF and COPD, patients with anemia of CKD have similar QoL which is notably impaired compared with a healthy population norm (Figure 3). This impairment is particularly pronounced in domains of physical functioning, physical role, vitality (fatigue) and general health.

Figure 3 Comparison of Anemia of CKD Mean SF-36 Vitality Domain Scores with Healthy US Population, Heart Failure, and COPD.



CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, SF-36= 36-Item Short Form Survey.
Note: *Finkelstein (2009), anemia of CKD population defined as CKD patients with Hgb<11 g/dL.
Source: [GSK Data on File. 2022N518875_00]

2.2. Current Treatments and Unmet Need

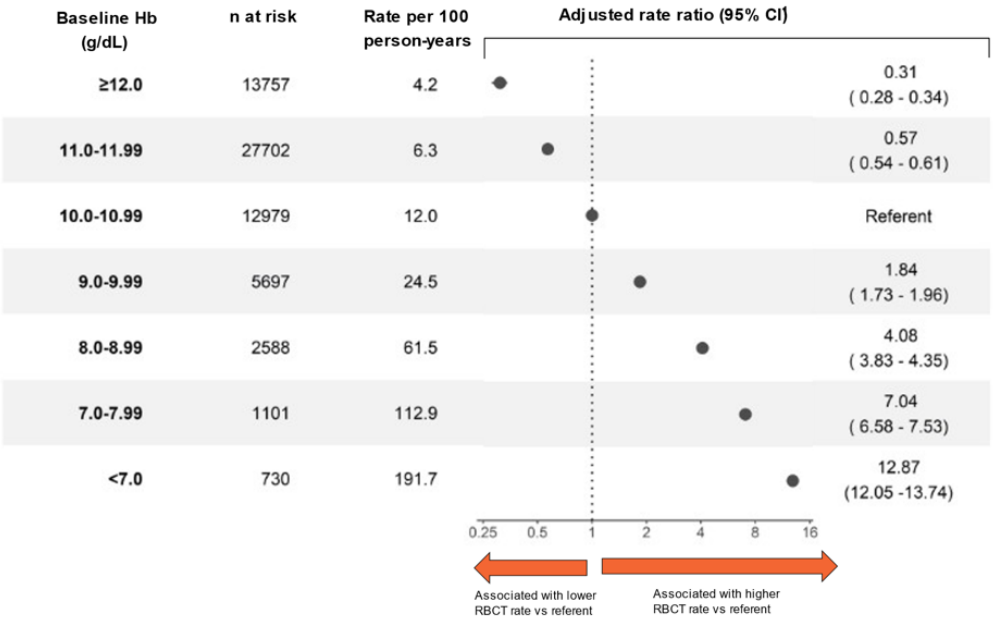
Blood transfusions carry significant short and long-term risks for the patient. Immediate risks post-transfusion include increased risk of volume overload, hospitalization for HF (RR: 1.7, 95% CI: 0.3, 9.2) and hyperkalemia (RR: 12.0, 95% CI: 1.3, 10.9 [Gill, 2015] and, although rare, transmission of blood-borne infections. Additionally, the risk of allosensitization is magnified after transfusions, with one study indicating that 26% to 38% of patients become sensitized after transfusion compared with 2% to 6% of those who were not transfused. Transfusion-induced allosensitization can have a long-term impact on kidney transplant outcomes. Highly sensitized patients may be less likely to receive a living donor kidney transplant and would be subject to aggressive induction and maintenance immunosuppression therapy to reduce risk of rejection [Schinstock, 2019; Clayton, 2017]. Additionally, patients who receive a transfusion while on the transplant wait list in the first 5 years have a nearly 5-fold higher risk of mortality and 11% reduction in the likelihood of receiving a transplant [Obrador, 2013].

ESAs have been approved for treatment of anemia of CKD (Hgb <10 g/dL) since 1989, to decrease RBC transfusions in both non-dialysis and dialysis patients and have been largely successful in reducing the use of transfusions since their introduction in treated patients [Lawler, 2010; Ibrahim, 2008]. However, evidence suggests that, particularly in non-dialysis patients, a substantial proportion of patients do not receive ESA or iron treatment for their anemia. Several studies have shown that from 50% to 74% of non-dialysis US commercially insured [Davis, 2020; Lamerato, 2020; St Peter, 2018] and 66% of Medicare-covered [St. Peter, 2018] CKD stage 3-5 patients with anemia are not receiving treatment with ESA and/or iron [St Peter, 2018]. Also, an international CKD study including the US reported that only 40% of patients treated in nephrology clinics

with persistent Hgb<10 g/dL after 12 months initiated an anemia medication (ESA and/or iron therapy) [Barreto Lopes, 2021].

Despite the risks of transfusions, evidence suggests that, particularly in non-dialysis patients, more patients have been receiving a transfusion than those who have been receiving an ESA. This is true for both commercially insured patients (11% and 12% received ESA and transfusion, respectively) and older Medicare-covered patients (13% and 22% received ESA and transfusion, respectively) [St Peter, 2018]. Recent research on the use of transfusions is currently lacking, so GSK conducted a retrospective cohort study using data from the Optum Clinformatics Data Mart on non-dialysis CKD stage 3-5 patients over the period 2017-2019. Among Medicare Advantage enrollees, an overall rate of 14 transfusions per 100 PY and a strong association with baseline Hgb level were estimated. Patients with Hgb 9-10 g/dL and Hgb 8-9 g/dL were nearly twice and four times more likely to receive a transfusion compared to patients with Hgb 10-11 g/dL, respectively (Figure 4).

Figure 4 Association Between Baseline Hgb and the Rate of RBC Transfusions Observed During Six Months of Follow-up During 2017-2019 (Medicare Advantage)



RBCT=red blood cell transfusion.
1. Adjusted for age, sex, CKD stage, Charlson Comorbidity Index, baseline comorbidities, baseline healthcare resource utilization, prior RBC transfusion use, prior ESA or oral/IV iron use.
Source: [GSK Data on File. 2022N518136_00]

Significant barriers to access exist with current standard of care therapies. ESAs are injectable and often require in-clinic administration. Issues with access are likely to introduce barriers to effective treatment. For example, CKD patients in non-metropolitan areas were less likely to receive an ESA compared to patients living in metropolitan areas [Yan, 2013]. Additionally, the route of administration is an important attribute to patients; 83% of non-dialysis patients say they preferred an oral treatment for

convenience of administration, avoidance of injection pain and drug storage requirements of subcutaneous administration [GSK Data on File 2020N461858_00].

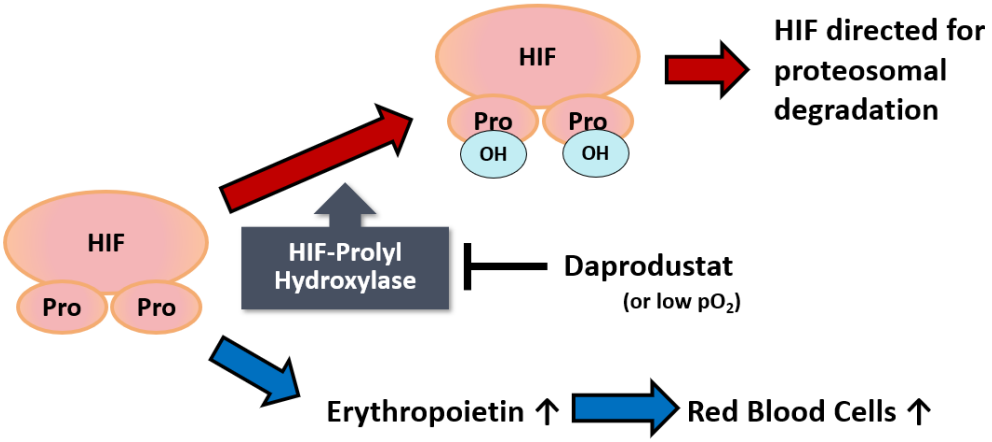
In summary, despite the currently available therapies, GSK considers that treatment of anemia of CKD is suboptimal in many patients. The reasons for suboptimal treatment are multifactorial, and include logistical challenges, AEs associated with current therapies, and limitations of administering injectable formulations that pose a barrier to access while increasing healthcare and patient burden. As a result of this sub-optimal care, patients are undertreated, leading to poor outcomes that include the avoidable use of transfusions, detrimental effects on QoL, and increased potential for other adverse outcomes. Thus, there remains an unmet need for novel, accessible treatment options.

3. BACKGROUND INFORMATION ON THE PRODUCT

3.1. Mode of Action, Toxicological Effects, and Clinical Pharmacology

The HIF pathway regulates the body's adaptive response to hypoxia, including stimulation of erythropoiesis [Haase, 2013]. Under normal oxygen partial pressure, HIF-alpha is hydroxylated by a family of PHD enzymes. Daprodustat is a member of a new class of drugs that inhibit these enzymes leading to a stabilization of HIF-alpha and a consequent increase in endogenous EPO production and erythropoiesis (Figure 5).

Figure 5 Daprodustat Mode of Action



HIF=hypoxia-inducible factor, pO_2=oxygen partial pressure, Pro=proline, OH=hydroxyl.
Note: In the normoxic conditions prolyl-hydroxylase action on HIF direct it for degradation (red arrows). In low oxygen conditions, or with daprodustat, the prolyl-hydroxlyases are inhibited, HIF is stabilized, which stimulates the production of erythropoietin and thus red blood cells (blue arrows).

HIF activation also increases transcription of genes involved in iron metabolism including transferrin, the transferrin receptor, and ferroportin. The net effects are elements of daprodustat's pharmacology that are shared with those of injectable ESAs and reported in other HIF-PHIs including decreases in ferritin and transferrin saturation (TSAT), presumably secondary to increased erythropoiesis.

Anemia of CKD results from a combination of insufficient EPO synthesis, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis [Babitt, 2012] and hence is potentially amenable to treatment with HIF-PHIs such as daprodustat.

Daprodustat displays potent inhibitory activity toward PHD1, 2 and 3 with half-maximal inhibitory concentration (IC50) of 3.5 nM, 22.2 nM and 5.5 nM, respectively [Ariazi, 2017]. While PHD2 inhibition is the primary driver for EPO production and hematopoietic effect, PHD1 and PHD3 inhibition may have distinct impact on inflammation [Aragonés, 2008] and metabolic functions [Walmsley, 2011]. Daprodustat shows little or no inhibitory activity against other dioxygenases including collagen prolyl hydroxylase (IC50 >200,000 nM) which has been implicated in preclinical cardiac safety findings, and factor inhibiting HIF (IC50 of 9800 nM) which may play an important role in vascular endothelial growth factor (VEGF) production [Ariazi, 2017; So, 2014; Wang, 2014]. Because of these context-dependent effects of HIF activation, PHIs with different inhibitor-activity profiles may have different biological effects.

Toxicology

The toxicologic effects observed for daprodustat are predominantly a secondary consequence of increasing red cell mass (Hgb, Hct and RBC generally increased above the upper limit of normal) in normocythemic animals and are consistent with the toxicologic effects reported for marketed ESAs. These effects include polycythemia, generalized vascular congestion, and multi-organ pathology (including heart, kidney, brain, liver, lung, stomach, nerves and vessel walls) subsequent to resultant tissue ischemia and/or thrombosis. These effects are largely mitigated in patients by Hgb monitoring and dose adjustment for maintaining Hgb within target range and controlling rate of rise. Nonclinical findings relevant to AESIs are presented in Section 5.5.5.

Clinical Pharmacology

Daprodustat is readily absorbed and eliminated following oral administration. No accumulation of daprodustat is observed following repeat-dose administration, consistent with its short half-life (~1 to 4 hours). Plasma daprodustat PK is linear and systemic exposures generally increases proportionally to dose over the dose range of 1 mg to 500 mg. Renal dialysis clearance of daprodustat in healthy participants and in participants with stage 3/4 CKD is negligible, likely due to its high plasma protein binding (>99%). No marked difference in daprodustat exposure in stage 5 participants on HD is observed between a dialysis and a non-dialysis day. Daprodustat is extensively metabolized (>99%) via hydroxylation by cytochrome P450 CYP2C8, with a minor contribution by CYP3A4, and concomitant strong inhibitors of CYP2C8 are contraindicated. Daprodustat has 6 predominant circulating metabolites (M) in human plasma, 3 of which (M2, M3 and M13) are major. All 6 metabolites show a clear reduction in oral clearance (and increased AUC values) with increasing severity in CKD stage, leading to an increased plasma exposure compared to participants with normal renal function, and is typically higher in HD participants on a non-dialysis day.

3.2. Proposed Indication

Daprodustat has been developed as a new oral treatment and an alternative to, or replacement for ESA therapies, in patients starting or switching from this treatment, not as an adjunctive treatment. The proposed indication for daprodustat is for the treatment of anemia due to CKD in adult patients on dialysis and not on dialysis. This includes patients newly starting dialysis (ID) and those receiving either HD or peritoneal dialysis.

3.3. Dosage Form, Route and Frequency of Administration, and Dosing Regimen

To reach and maintain target Hgb levels, dose levels of daprodustat can be adjusted on an individual basis in a gradual stepwise fashion to a maximum of 24 mg for the once-daily regimen and 48 mg for the TIW regimen. Similar to ESAs, dose adjustment of daprodustat considers Hgb variability and rates of rise and decline to maintain Hgb within the target range. Following daprodustat initiation and after each dose adjustment, Hgb is monitored every 4 weeks until levels are stable, which allows for appropriate monitoring to minimize the need for blood transfusions or overshoot of Hgb levels.

3.4. Clinical Development Plan and Regulatory Background

3.4.1. Clinical Development Plan

Daprodustat has been evaluated for the treatment of anemia of CKD in a comprehensive program consisting of 16 Phase 1 studies, 10 Phase 2 studies and 5 global Phase 3 studies. A total of 6033 participants were exposed to daprodustat in the clinical development program (34 studies, conducted in healthy volunteers or participants with CKD), with a total of 6691.9 PY of exposure accrued.

The global Phase 3 program comprised 5 studies, which enrolled over 8000 participants across all treatment groups (daprodustat, darbepoetin, epoetin alfa, and placebo). They form the basis for the evaluation of daprodustat within this document (Table 2). The program provides efficacy and safety evaluation of daprodustat for the indications sought and includes studies in participants on long-term dialysis (HD and peritoneal dialysis), those newly starting dialysis (ID), and those not on dialysis. Studies have included participants receiving ESA or its analogs (ESA-users) and participants not currently receiving ESA or its analogues (ESA non-users).

In view of the risk of MACE with ESA treatment when targeting higher Hgb targets, the global Phase 3 program included 2 large CV outcomes trials (as agreed with the FDA) to assess potential risk of MACE for daprodustat compared with ESAs in patients not on dialysis and patients on dialysis. All 5 studies included adult participants (≥18 years) across a spectrum of CKD. Participants were required to be iron replete (ferritin >100 ng/ml, TSAT >20%) at study entry. Participants were excluded from the 4 active-controlled studies if they had other causes of anemia, malignancy within 2 years of screening (aside from localized squamous or basal cell skin carcinoma), or recent CV events (MI, stroke, transient ischemic attack [TIA], HF, or uncontrolled hypertension).

Table 2 Global Phase 3 Studies Overview of Study Design (ASCEND-NHQ, ASCEND-ND, ASCEND ID, ASCEND-D, and ASCEND-TD)

	Non-dialysis Studies		Dialysis Studies		
	ASCEND-NHQ	**ASCEND-ND** *(CV outcomes)*	**ASCEND-ID**	**ASCEND-D** *(CV outcomes)*	**ASCEND-TD**
Population	ND ESA non-user	ND ESA user or non-user	ID[a] ESA non-user	HD or PD ESA user	HD ESA user
Participants randomized	614 (US: 172)	3872 (US: 981)	312 (US: 54)	2964 (US: 846)	407 (US: 107)
Daprodustat dosing	Once daily	Once daily	Once daily	Once daily	TIW
Control dosing	Once daily	q weekly, q 2 weeks, or q 4 weeks	q weekly, q 2 weeks, or q 4 weeks	TIW, q weekly, q 2 weeks, or q 4 weeks	TIW or q weekly
Control	Oral placebo	SC or IV darbepoetin alfa	SC or IV darbepoetin alfa	epoetin alfa IV (HD patients) or darbepoetin alfa SC (PD patients)	IV epoetin alfa
Study duration	28 Weeks	Event driven	52 weeks	Event driven	52 weeks
Blinding	Double- blind	Open-label (sponsor-blind)	Open-label (sponsor-blind)	Open-label (sponsor-blind)	Double-blind, double dummy
Randomization	1:1	1:1	1:1	1:1	2:1 daprodustat: epoetin
Evaluation Period	Weeks 24 to 28	Weeks 28 to 52	Weeks 28 to 52	Weeks 28 to 52	Weeks 28 to 52
Hgb target range	11 to 12 g/dL	10 to 11 g/dL	10 to 11 g/dL	10 to 11 g/dL	10 to 11 g/dL
Hgb at Randomization	8.5 to 10 g/dL	8 to 10 g/dL or 8 to 11 g/dL (on ESA)	8 to 11 g/dL	8 to 11 g/dL[b]	8 to 11 g/dL[b]

HD=hemodialysis, ID=incident dialysis, IV=intravenous, ND=non-dialysis, PD=peritoneal dialysis, q=every, SC=subcutaneous, TIW=three times weekly.

a. Participants were planning to start chronic dialysis within the next 6 weeks (from the date of the screening visit) OR had started and received dialysis (HD or peritoneal dialysis) for end-stage renal disease for a maximum of 90 days immediately prior to randomization and were not expected to stop dialysis during the duration of the trial.

b. >11 to 11.5 g/dL if > minimum ESA dose

3.4.2. Regulatory Status and Advice

Prior to initiation of the global Phase 3 trials, GSK received advice from the US and European regulatory agencies (FDA/EMA) after completion of 2 Phase 2b studies (PHI113633 and PHI113747). FDA advice included the recommendation to evaluate initiation and maintenance therapies within the dialysis-dependent populations.

To provide definitive data on the safety profile of daprodustat compared to ESA, GSK agreed to conduct 2 large CV outcomes trials, one in dialysis and one in non-dialysis patients (ASCEND-D and ASCEND-ND, respectively). The ASCEND-D and ASCEND-ND outcomes trials were originally designed to enroll approximately 3000 participants and 4500 participants, respectively, with follow-up for both trials until

945 adjudicated first MACEs had occurred with a NI margin of 1.20, assuming a true underlying 3% lower RR of MACE for daprodustat compared to ESA control (i.e., HR=0.97). Based on the desire to accelerate trial closure as a result of the coronavirus disease 2019 (COVID-19) pandemic and on emerging data from other oral HIF PHIs, the NI margin for both outcomes studies was changed to 1.25 (protocol amendments submitted to FDA on 05 August 2020) before unblinding of trial data. Increasing the NI margin while maintaining 90% power reduced the target number of first MACE to 664. The original and amended NI margins and target number of first MACE were agreed with the FDA prior to unblinding of the trials, and determined based on clinical judgment, statistical reasoning, regulatory guidance, and review of available literature. Further information on the NI margin of 1.25 is provided in the appendix (Section 10.1).

In September 2021, the FDA requested additional analyses be included in the planned New Drug Application (NDA) to explore different definitions for on-treatment events and the relationship between safety endpoints and dose/Hgb levels. In October 2021, GSK agreed with the European Rapporteur/co-Rapporteur to also include these analyses in the European Marketing Authorization Application.

3.4.2.1. Post-Marketing Experience

Daprodustat has been approved in Japan for the treatment of anemia of CKD in dialysis and non-dialysis patients since June 2020. The cumulative post-marketing exposure to daprodustat from launch in Japan is estimated to be 41,871 PY, as of March 2022. Currently, daprodustat is not licensed anywhere else in the world.

Cumulatively, through 28 June 2022 (the data lock point for the most recent Periodic Update Safety Reports [PSUR] in Japan), there have been 4,091 spontaneous or post-marketing surveillance reports from Japan in the global patient safety database. As the post-marketing experience is described in this document, the limitations of post-marketing data must be acknowledged. Under-reporting of post-marketing data occurs at an unknown rate and the calculations for the population exposed to drug can be inaccurate. The quality of reports of spontaneous data can vary (e.g., sometimes it is unknown if a patient is on dialysis or not) and can be missing key information such as that required for causality assessment. Lastly, there is no timely control group against which to compare the data and these systems may not be well-suited to assess the relationship of a medicine to an event that is common in the treated population [Dal Pan, 2022].

3.5. Study Design

3.5.1. Clinical Trial Methodology

Open-label considerations

- Objective efficacy (centralized laboratory-measured Hgb levels) and safety (adjudicated first MACE) co-primary endpoint measures in the studies were used to minimize potential investigator or participant bias.

- A Sponsor-blinded procedure was implemented in the global Phase 3 studies regarding the study treatment assignment, which was only accessible to the clinical research organization for the studies.
- An external independent data monitoring committee (IDMC) reviewed all efficacy and safety data.
- An external CEC (Duke Clinical Research Institute) group conducted blinded adjudication of all events suspected to meet the definition of MACE as well as other adjudicated CV events (including thromboembolic events, and hospitalization for HF), as well as select CKD progression events for the ASCEND-ND study.
- A Sponsor and Central Study Conduct Team blind to the open-label global Phase 3 studies was implemented to ensure that only the Statistical Data Analysis Center and IDMC had access to unblinded aggregate data.

None of the considerations above were able to control for the impact of an open-label study on spontaneous reporting of safety issues, or on the decision to hospitalize a patient, or apply other interventions, as deemed required by the investigators.

Primary Efficacy Endpoint: All 5 global Phase 3 studies investigated Hgb levels with the same primary efficacy endpoint (mean change from Baseline in Hgb to the average of the values in the evaluation period) for daprodustat versus the control group. This endpoint, which was selected following discussion with the FDA, enabled an evaluation of change through use of a continuous measure with an additional categorical responder-type analysis.

Primary Safety Endpoint: The 2 large CV outcomes studies (ASCEND-ND and ASCEND-D) investigated the same primary safety endpoint: first occurrence of adjudicated MACE during the time period for follow-up of CV events, where MACE was a composite endpoint comprised of ACM, non-fatal MI and non-fatal stroke. Further details on this endpoint and analysis considerations are provided in Section 5.4.1.

NI margin choice for Hgb and MACE: Non-inferiority of daprodustat was evaluated using the following pre-defined NI margins for treatment effect (daprodustat versus ESA) in the ITT population, as agreed with the FDA:

- -0.75 g/dL for the treatment difference for the Hgb primary efficacy endpoint for all 4 active-controlled studies (Appendix 10.1).
- 1.25 for the HR for the MACE primary safety endpoint in the CV outcomes studies (Section 3.4.2; Appendix 10.2).

Principal Secondary Efficacy Endpoints: The first multiplicity-controlled efficacy secondary endpoint for ASCEND-NHQ was the percentage of participants having a Hgb increase of ≥1.0 g/dL from Baseline to evaluation period (Weeks 24 to 28). The second multiplicity-controlled secondary efficacy endpoint for ASCEND-NHQ was mean change in SF-36 Vitality Domain between Baseline and Week 28.

The multiplicity-controlled principal secondary efficacy endpoint for the dialysis studies (ASCEND-D, ASCEND-ID, and ASCEND-TD) was average monthly IV iron dose (mg)/participant to Week 52.

The non-dialysis study ASCEND-ND did not have a principal secondary efficacy endpoint.

Principal Secondary Safety Endpoints: In the 2 large CV outcomes studies (ASCEND-ND and ASCEND-D), superiority tests of first occurrence of adjudicated MACE, MACE or thromboembolic events and, separately, MACE or hospitalization for HF were designated as principal secondary safety analyses. In addition, time to progression of CKD was a pre-specified principal secondary safety endpoint in ASCEND-ND only.

The other ASCEND studies (ASCEND-NHQ, ASCEND-ID, and ASCEND-TD) did not have a principal secondary safety endpoint.

Choice of target range for Hgb, across studies: Target ranges were agreed with regulatory agencies (FDA and EMA).

- The placebo-controlled study ASCEND-NHQ, had identical Hgb target and analysis ranges (11.0 to 12.0 g/dL). The choice of these Hgb ranges was based on the significant QoL improvement versus placebo when Hgb improved by approximately >1.5 to 2 g/dL [Lefebvre, 2006].
- In the 4 active-controlled studies, a target level Hgb during the evaluation period was set as 10.0 to 11.0 g/dL. To account for within-participant variability between methods used for measuring Hgb values (Hgb values assessed by HemoCue point of care devices informed dosing decisions, while Hgb values assessed by a central laboratory were primarily used in reporting), 0.5 g/dL was added to the upper end of the target range to create a defined 'analysis range' of 10.0 to 11.5 g/dL.

Definitions for ITT analyses across studies: Follow-up period definitions for ITT analysis of CV events, ACM, and the definition of treatment-emergent AEs (TEAEs) for all Phase 3 ASCEND studies are provided below in Table 3.

Table 3 Definitions for ITT Analyses for CV Events and All-Cause Mortality, and for TEAEs in All Phase 3 ASCEND Studies

Time Period	Definition
Time period for follow-up of CV events	Included all adjudicated MACE that occurred between randomization and the date of study completion/ withdrawal (plus deaths reported in the clinical database after this time)
Time period for vital status (used for analysis of ACM)	Included all positively adjudicated deaths that occurred on or after randomization. Participants who did not die were censored at their study completion date if they were a study completer or at the later of their date last known to be alive or study withdrawal date if they were a study withdrawal
Treatment-emergent adverse events	Defined as treatment-emergent if they occurred on or between treatment start date and the last non-zero dose date + 1 day

ACM=all-cause mortality; CV=cardiovascular; MACE=major adverse cardiovascular event; TEAE=treatment-emergent adverse event.
Note: Post-hoc dosing frequency adjusted on-treatment definitions are detailed in Table 18.

For CV outcome studies (ASCEND-D and ASCEND-ND), a modified ITT (mITT) post-hoc analysis (on and off treatment) was presented for malignancies (Section 5.5.5.2), including all participants who took study drug and including all events reported throughout the study follow-up regardless of treatment status.

QoL Endpoints and Methodology Considerations:

SF-36 Vitality Domain

The SF-36 (v2 acute version) is a 36-item, generic measure of aspects of health status that is considered important in describing and monitoring individuals suffering from a disease or illness 'during the past week' [Maruish, 2011]. The SF-36 comprises 8 domains which are widely used as endpoints in clinical trials and have supported previous FDA labeling claims [Ware Jr, 2000; Parfrey, 2005; Aymé, 2017]. The SF-36 is the most commonly used PRO measure of health-related QoL in populations of patients with anemia due to CKD. The SF-36 Vitality domain, which is recognized as the most relevant domain within the instrument, is commonly used as a alpha-controlled outcome measure in studies in this population [van Nooten, 2010; Staibano, 2020].

Fatigue, one of the key defining symptoms of anemia of CKD, is assessed through the SF-36 Vitality Domain by evaluating states of feeling full of life, having a lot of energy, feeling worn out, and feeling tired, with low scores indicating poorer health states [Maruish, 2011]. The SF-36 Vitality Domain was chosen as a multiplicity-controlled hierarchical secondary endpoint in the ASCEND-NHQ owing to the clinical importance of improving symptoms related to this domain. The validity of the SF-36 Vitality Domain for the assessment of fatigue was also supported by qualitative and quantitative psychometric evidence submitted to the FDA as part of the NDA. When assessing the effectiveness of the anemia of CKD treatment, assessment of fatigue is central to the understanding of the value of the treatment to patients.

Other Trial Design Considerations: Consistent rescue therapy algorithms and iron management criteria were utilized for both treatment groups in each of the 5 global Phase 3 studies. This provided consistency across participants, minimized the chance that participants had inadequate response to treatment for their anemia for an extended period of time, and ensured participants remained iron replete.

3.5.2. Statistical Considerations

Estimation Model for Primary Efficacy Endpoint: The primary efficacy analysis in all 5 global Phase 3 studies was based on the ITT Population and used on and off treatment, observed and multiply-imputed Hgb values in an analysis of covariance (ANCOVA) model including treatment, baseline Hgb value, and pre-specified prognostic randomization stratification factors (region in all studies except ASCEND-ID, dialysis type in both ASCEND-D and ASCEND-ID, dialysis planned/unplanned in ASCEND-ID only, and current ESA use in ASCEND-ND only). Handling of missing data for the active-controlled studies is described below in 'Data Imputation for Efficacy Endpoints'. For the ASCEND-NHQ, a missing not at random assumption was used for multiple

imputation of missing Hgb values according to a participant's treatment status (on- versus off-treatment) and superiority was established if the 1-sided p-value was <0.025. For the active-controlled studies, a missing at random assumption was considered appropriate, as off-treatment Hgb values were expected to be similar to on-treatment Hgb values, since patients would usually take commercially available ESA medication during such times in order to control their Hgb. Non-inferiority was to be declared if the lower bound of the 95% CI was no smaller than -0.75 g/dL.

Cox Proportional Hazards regression model for primary safety endpoint: In the CV outcomes studies, time to first occurrence of adjudicated MACE was analyzed using a Cox Proportional Hazards regression model, adjusting for treatment and the prognostic randomization stratification factors (region in both studies, dialysis type in ASCEND-D only and of ESA use at randomization in ASCEND-ND only). The HR for daprodustat versus ESA was estimated, and NI was established based on a pre-specified upper bound margin of 1.25. Sensitivity analyses involved tipping point analyses that assessed the impact of missing follow-up (from participants who withdrew during the study and did not have a MACE before withdrawal or a known death after withdrawal). Tipping point analyses identify a number of different scenarios (i.e., assumptions about missing data in the 2 treatment groups) where the conclusion drawn from the primary analysis would no longer hold.

Considerations Relating to Multiplicity: Multiplicity procedures were pre-specified in all 5 global Phase 3 studies to control the study-wise Type 1 error rate as follows:

- For placebo-controlled study ASCEND-NHQ, a 3-step hierarchical strategy was used to control for multiplicity. The primary and 2 principal secondary endpoints were controlled by a step-down procedure (mean change from Baseline in Hgb, then percentage of participants having a Hgb increase of ≥1.0 g/dL from Baseline, then mean change in the SF-36 Vitality Domain), gated by achieving superiority at a 1-sided 2.5% significance level.
- For active-controlled studies ASCEND-D and ASCEND-ND, the co-primary endpoints (efficacy endpoint of change from Baseline in Hgb values, and safety endpoint of time to first adjudicated MACE) were first evaluated for NI by comparing the pre-defined lower or upper limit of each 2-sided 95% CI to the appropriate NI margin. Conditional on both co-primary endpoints achieving NI (i.e., passing a gatekeeper approach), the family of MACE and other principal secondary endpoints were formally tested for superiority using the closed test Holm-Bonferroni multiplicity procedure.
- For active-controlled studies ASCEND-TD and ASCEND-ID, a 2-step hierarchical strategy was used. The primary endpoint (mean change from Baseline in Hgb) was tested first for NI, using the lower limit of the 2-sided 95% CI. Conditional on the primary endpoint achieving NI, the single principal secondary endpoint was tested for superiority using a 1-sided 2.5% significance level.

Imputation Strategy for SF-36 Vitality Domain Scores in ASCEND-NHQ: In the ASCEND-NHQ study, the second principal secondary endpoint (mean change in the SF-36 Vitality Domain score) was based on a hypothetical strategy for the intercurrent events of death prior to the end of evaluation period and randomized treatment

discontinuation prior to the end of the evaluation period. Observed on-treatment values were used to impute values after these intercurrent events. Imputation based on only on-treatment values was chosen since this was a placebo-controlled study, which allowed participants to receive standard of care while off-treatment. In addition, a missing at random assumption was used for imputing missing values prior to end of treatment.

Data Imputation for Efficacy Endpoints:

ASCEND-NHQ: both observed and multiply-imputed values are presented for primary (mean change from Baseline in Hgb to the average of the values in the evaluation period) and principal secondary efficacy endpoints (Table 4).

Table 4 Observed and Imputed Values for Primary and Principal Secondary Efficacy Endpoints in ASCEND-NHQ

	Dapro (N=307)	Placebo (N=307)
Primary Efficacy Endpoint: Post Randomization Hgb Change from Baseline to EP[a], n (%)		
Patients with no imputed Hgb values	259 (84)	239 (78)
Patients with partially-imputed Hgb values	12 (4)	27 (9)
Patients with all imputed Hgb values	36 (12)	41 (13)
Principal Secondary Efficacy Endpoint: Participants with Hgb Increase ≥1 g/dL from Baseline to EP[a], n (%)		
Patients with no imputed Hgb values	252 (82)	217 (71)
Principal Secondary Efficacy Endpoint: Mean Change in SF-36 Vitality Domain between Baseline and Week 28, n (%)		
Patients with imputed baseline or Week 28 SF-36 data	97 (32)	117 (38)

EP=evaluation period, SF-36=36-Item Short Form Survey.
a. Post-randomization values include on and off treatment values.

Active-controlled studies: Plots of Hgb data across visits are presented using only observed data. Statistical analyses of Hgb change from Baseline were performed using both observed and multiply-imputed values for missing data during the evaluation period. Rubin's rules [Rubin, 1987] were used to combine results of imputed datasets to provide a single estimated treatment difference and associated 95% CI. Additional supplementary and sensitivity analyses (including Per Protocol analysis of evaluable Hgb data i.e., on-treatment values not affected by the use of non-randomized ESA or transfusions) were also conducted.

The ASCEND-ND study began close out 1 month after the last participant was randomized, and hence some participants did not reach the Evaluation Period. A total of 361 (19%) participants receiving daprodustat and 357 (18%) participants receiving darbepoetin alfa had no Hgb values during the Evaluation Period in this study. For the other active-controlled studies, the amount of missing data ranged from 7% to 11% and were similar across treatment groups in all dialysis studies (ASCEND-D, ASCEND-ID and ASCEND-TD). In the dialysis studies, all participants had the opportunity to complete the Evaluation Period prior to closure of the study.

ITT and additional on-treatment analysis for primary safety endpoint:

The ITT analysis (on-study period for follow-up of CV events) was pre-specified and agreed upon with FDA as the primary safety analysis to evaluate the NI of MACE for daprodustat compared with ESA. This method respects the randomization and is well recognized as the most unbiased approach to make statistical inferences regarding treatment policy in CV outcomes trials (in which participants may be followed for considerable time after permanent treatment discontinuation). While problematic in that such analyses are not supported by a valid randomization, on-treatment analyses are nevertheless frequently conducted with the objective of evaluating outcomes that may reasonably be attributed to the presence of randomized treatment. The 2 large CV outcomes studies included on-treatment analyses of MACE as supplementary analyses of the primary ITT analyses.

The issues with on-treatment analyses are well documented. Various authors [Granger, 2005; Greenland, 2008; DeMets, 2019; Yang, 2019] outline that the exclusion of follow-up time from the analysis (as would apply for an on-treatment analysis) violates the randomization principle of an ITT analysis and creates a situation where an observed difference between groups cannot reliably be attributed to study treatment. For example, on-treatment comparisons between groups may be confounded by non-comparable patient populations since participants who discontinue do so informatively; thus, those who remain reflect self-selecting subgroups of patients. This self-selection can be particularly notable in open-label trials, where investigators may employ different reasons or thresholds for discontinuing treatment for the agents being compared [Snapinn, 2004].

The ITT approach, which evaluates the effect of a treatment policy, is not subject to these types of bias. However, in the setting of a NI trial, an ITT analysis has its own limitations given that the inclusion of off-treatment events may dilute or obscure a possible causal association. While important to acknowledge these limitations, the ITT analysis remains the most methodologically robust approach for statistical comparisons [Fleming, 2011], and the one by which the CV outcomes studies were prospectively designed and powered for, in agreement with FDA.

In addition to the general limitations of on-treatment analyses, the ASCEND studies had a significant flaw in the pre-specified on-treatment definition that failed to account for the different dosing regimens for patients on daprodustat compared with other ESAs (particularly 4-week dosing regimens of darbepoetin alfa; refer to Section 5.4.3). The pre-specified definition for TEAEs also failed to account for the dosing frequency differences. Therefore, post-hoc definitions adjusting for dosing frequency were applied in post-hoc TEAE analyses (Table 18).

4. PLACEBO-CONTROLLED STUDY ASCEND-NHQ

In the double-blind, placebo-controlled ASCEND-NHQ study, non-dialysis participants were randomized to receive either daprodustat or matching placebo tablets. Participants were not provided with the results of the point of care HemoCue Hgb assessment during the study. Investigators, investigational site staff, and participants were also blinded to select central laboratory results (i.e., Hgb, Hct, hepcidin, RBC count, and reticulocyte

count) during the study. All dose adjustments were made programmatically for both the daprodustat and the matching placebo group, based on the point of care HemoCue Hgb value measured at least every 4 weeks. Thus, the investigator and participants remained blinded to the dose being administered during the study.

In addition, the double-blind, placebo-controlled design of the ASCEND-NHQ study was designed to assess a reduction of fatigue and improvement of QoL in non-dialysis participants with the following considerations: 1) QoL assessments were conducted prior to all study-related activities including point of care HemoCue Hgb assessments, and the previous results of the PROs were blinded to participants, investigators and investigational site staff in the study to ensure minimal bias, 2) treatment allocation was blinded so did not impact measurement of responses to PROs, and 3) comparison to placebo allowed assessment of the impact of daprodustat on QoL study participants.

4.1. Participant Disposition and Demographics

4.1.1. Participant Disposition and Discontinuation

The proportion of participants who discontinued randomized study treatment because they met protocol-defined stopping criteria was higher in the placebo group than in the daprodustat group (Table 5). This imbalance was due to the higher proportion of participants needing rescue in the placebo group compared to daprodustat (placebo: 8% [26/307] versus daprodustat: <1% [2/307]).

Table 5 ASCEND-NHQ: Participant Disposition in the Placebo-controlled Study (ITT Population)

	ASCEND-NHQ (N=614)	
	Dapro (N=307)	Placebo (N=307)
Study Completion Status, n (%)		
Completed	300 (98)	290 (94)
Withdrawn	7 (2)	17 (6)
Prematurely discontinued randomized treatment	53 (17)	96 (31)
Died while taking randomized treatment	0	2 (<1)
Primary reason for all randomized treatment discontinuation[a]		
Adverse event	22 (7)	24 (8)
Protocol deviation	0	1 (<1)
Participant reached protocol-defined stopping criteria[a]	14 (5)	41 (13)
Decision by participant/proxy	10 (3)	25 (8)
Other[b]	7 (2)	5 (2)

a. Protocol-defined stopping criteria included: renal transplant, transition to dialysis, rescue, cancer, prohibited medication.
b. Other includes lost to follow up, sponsor terminated, site closed, investigator discretion.

4.1.2. Demographics and Baseline Disease Status

The participants enrolled in ASCEND-NHQ study are representative of CKD patients with anemia not on dialysis in the US, which is one of the proposed populations for treatment with daprodustat. The proportion of Black or African American participants per

treatment group in the US region was above 40% (Table 6). Demographic profiles were as anticipated for the non-dialysis indication in which patients have high prevalence of concomitant conditions e.g., hypertension and diabetes. Baseline characteristics including renal characteristics, Hgb levels, CV and diabetes characteristics, BP values, and markers of iron metabolism were generally similar between treatment groups.

Table 6 ASCEND-NHQ: Key Baseline Demographic and Disease Characteristics

	ASCEND-NHQ (N=614)	
	Dapro (N=307)	Placebo (N=307)
Age in years, mean (SD)	65.3 (13.43)	66.6 (12.93)
Female, n (%)	176 (57)	178 (58)
Ethnicity, n (%)		
Hispanic or Latino	104 (34)	103 (34)
Race, n (%)		
American Indian or Alaskan Native	34 (11)	34 (11)
Asian	30 (10)	28 (9)
Black or African American	44 (14)	47 (15)
Native Hawaiian or Other Pacific Islander	0	1 (<1)
White	197 (64)	195 (64)
Other	2 (<1)	2 (<1)
US Region [a]	86	86
Black or African American	36 (42)	42 (49)
CKD stage		
≤3	95 (31)	89 (29)
4	139 (45)	137 (45)
5	73 (24)	81 (26)
Hgb mean (SD)	9.73 (0.635)	9.71 (0.729)
Prior ESA Use, n (%)	0	0
History of: n (%)		
Diabetes [b]	187 (61)	188 (61)
Stroke	28 (9)	19 (6)
MI	27 (9)	29 (9)
Cancer	11 (4)	12 (4)
Heart failure [c]	47 (15)	46 (15)
CV Disease [d]	133 (43)	133 (43)
Thromboembolic events	16 (5)	18 (6)
Current medical condition: hypertension	278 (91)	282 (92)

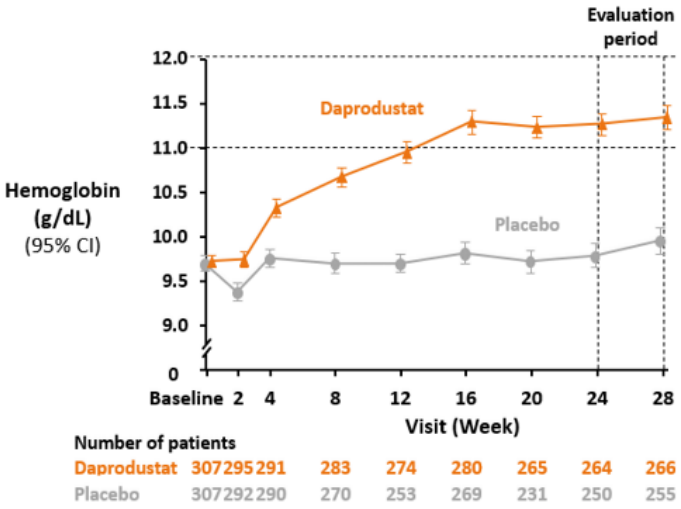
a. Number of participants in US region used for denominator for sub-category.
b. History of diabetes was defined as having a yes response to at least one record of the medical history terms that contains “diabetic” or “diabetes”.
c. History of Heart Failure was defined as having a medical condition of “heart failure” at enrolment.
d. CV disease history defined as the following in medical history: angina pectoris, MI, stroke, coronary artery disease, transient ischemic attack, heart failure, atrial fibrillation, cardiac arrest, and/or valvular heart disease.

4.2. Clinical Efficacy

4.2.1. Hemoglobin Values

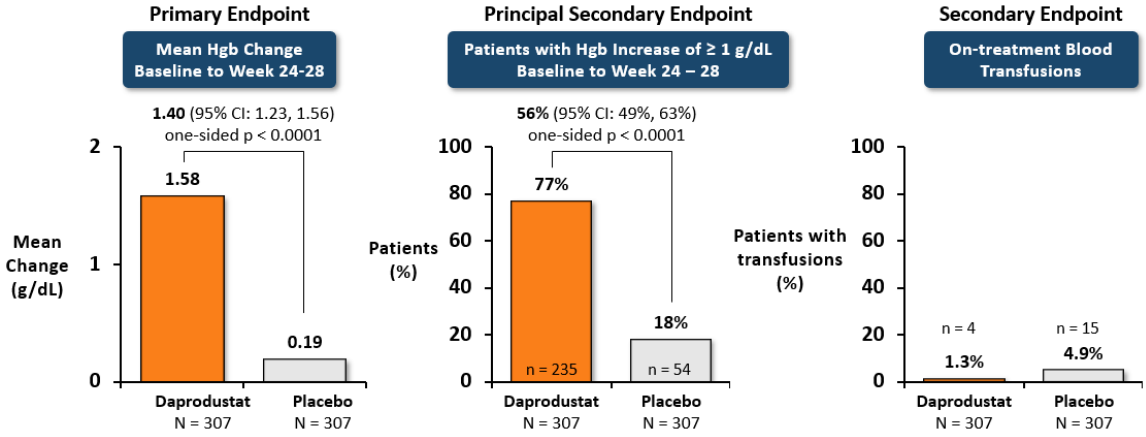
In the ASCEND-NHQ study, daprodustat-treated participants showed an increase in mean Hgb within 4 weeks of treatment initiation (Figure 6). Daprodustat demonstrated statistical superiority to placebo in the primary efficacy analysis of mean Hgb change from Baseline to the average over the evaluation period (Weeks 24 to 28; Figure 7, left). Pre-specified supplementary analysis conducted for the primary endpoint using observed on and off treatment values and observed on-treatment values support the results of the primary analysis. Superiority of daprodustat to placebo was also demonstrated in the principal secondary endpoint of percentage of participants with a Hgb increase ≥1 g/dL from Baseline to the evaluation period, representing evidence of a clinically meaningful benefit (Figure 7, center). Blood transfusions were required by 1.3% (4/307) participants in the daprodustat group and 4.9% (15/307) on placebo (Figure 7, right).

Figure 6 ASCEND-NHQ: Post-Randomization Observed Hgb Data by Visit (ITT Population)



Note: Error bars indicate 95% CI. The dashed vertical lines represent the Evaluation Period (Week 24 to Week 28). The dashed horizontal lines represent the target range for Hgb.

Figure 7 ASCEND-NHQ: Efficacy Endpoints of Hgb (ITT Population)



Note: **Primary endpoint:** Post-randomization values include on and off treatment values. Hgb values during the Evaluation Period (Week 24 to Week 28) include both observed and imputed values. Difference: One-sided p-value based on test of null hypothesis: (daprodustat – placebo) ≤0 versus alternative: difference >0. Superiority was established if the 1-sided p-value <0.025.
Principal Secondary Endpoint: On and off treatment values post-randomization and imputed values from primary endpoint. Difference: Cochran-Mantel-Haenszel chi-squared test adjusting for treatment and region. One-sided p-value based on test of null hypothesis: (daprodustat-placebo) ≤0 versus alternative: difference >0.
Secondary Endpoint: Definition for on treatment transfusion: Treatment Start Date < Date ≤ Treatment Stop Date + 1 day.

4.2.2. Fatigue and Quality of Life

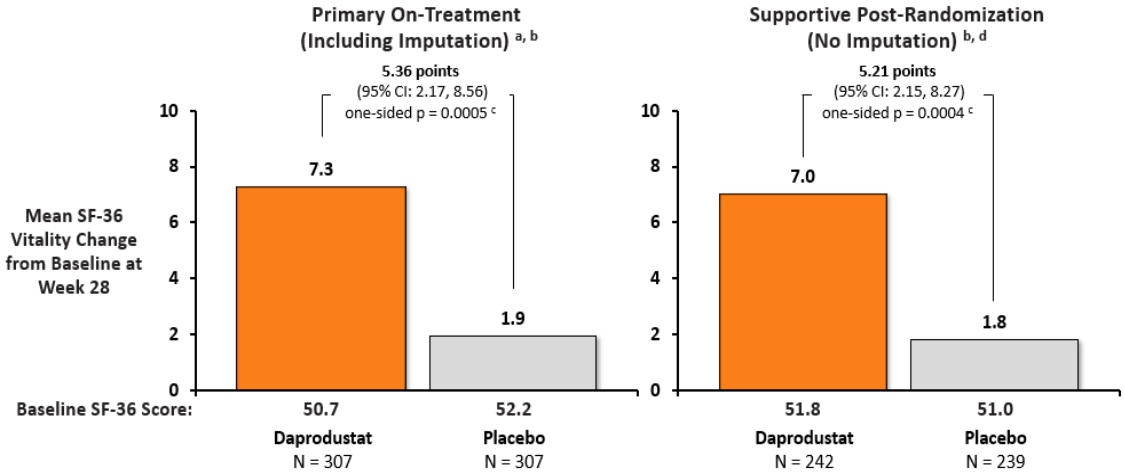
Based on a multiplicity-controlled principal secondary endpoint SF-36 vitality domain analysis, daprodustat was superior to placebo in reducing fatigue and improving QoL in non-dialysis participants.

Validation of SF-36 Vitality Domain score is described in Section 3.5.1. The statistical analysis of the SF-36 vitality data, comprising the second principal secondary endpoint (mean change in SF-36 Vitality Domain score) and the imputation strategy, is described in Section 3.5.2.

4.2.2.1. SF-36 Vitality Domain: Change from Baseline

Daprodustat was superior to placebo in improving SF-36 Vitality scores in non-dialysis participants (Figure 8, left), reflecting an improvement in energy levels and reduction in fatigue. Additionally, the effect of imputed data was investigated through a sensitivity analysis using only on-treatment observed values (with no imputation); results for this analysis were consistent with the primary on-treatment and imputed SF-36 analysis. A supportive post-randomization analysis (with no imputation) also showed similar results to the primary on-treatment analysis including imputation (Figure 8, right).

Figure 8 ASCEND-NHQ: Analyses of SF-36 Vitality Domain-Scores at Week 28 (ITT Population): Mean Change from Baseline



SF-36=36-Item Short Form Survey.
Note: Mean SF-36 Vitality Domain uses a 0-100 scoring.
a. On-treatment SF-36 analyses include imputed values for participants with intercurrent events (death or treatment discontinuation) or participants with missing data.
b. Based on an ANCOVA model with terms for treatment, baseline score, and region.
c. One-sided p-value based on test of null hypothesis (daprodustat-placebo) ≤0 versus alternative: difference >0. Superiority for the difference between the daprodustat and placebo treatment groups was established if the 1-sided p-value is less than 0.025.
d. Post-randomization SF-36 measurements (which includes on and off treatment values) are included.

4.2.2.2. SF-36 Vitality Domain: Responder Analysis

A 6-point minimum clinically important difference (MCID) in SF-36 vitality score, considered to represent a meaningful within-patient change, was identified through a systematic literature review and distribution-based and anchor-based methodologies. In the ASCEND-NHQ study, participants achieving the MCID (6-point or more change) between baseline and Week 28 follow-up are categorized as "responders" (Section 3.5.1). In the pre-specified responder analysis (proportion of participants with an improvement of ≥6 points in the on-treatment SF-36 Vitality Domain score from Baseline at Week 28), daprodustat was superior to placebo at Week 28 (58% compared with 40%, 1-sided p-value: 0.0049). The main approach for these analyses used on-treatment observed values and imputed values based on the on-treatment values.

4.3. Clinical Safety

4.3.1. Cardiovascular Safety

The ASCEND-NHQ study in non-dialysis participants was not designed nor sufficiently powered for formal statistical comparisons of MACE (ACM, non-fatal MI, and non-fatal stroke) between treatment groups. The first occurrence of adjudicated MACE was similar between the daprodustat and placebo treatment groups (Table 7), even though target Hgb values in this study were higher than that of the active-controlled studies (as deemed

appropriate in order to obtain a robust assessment of the treatment effect of daprodustat versus placebo on change in Hgb and incremental gain in QoL [Lefebvre, 2006].

Table 7 ASCEND-NHQ: First Occurrence of Adjudicated MACE (ITT Population)

Adjudicated Event Type n (%)	Dapro (N=307)	Placebo (N=307)
First MACE	15 (4.9)	19 (6.2)
First MACE (on-treatment)[a]	12 (3.9)	15 (4.9)
First MACE or TEE or hospitalization for HF	27 (8.8)	29 (9.4)

HF=heart failure, MACE= major adverse cardiovascular event; TEE=thromboembolic events.
Note: ASCEND-NHQ was not designed or powered to assess MACE. Hence, no statistical analyses were conducted. TEE defined as deep vein thrombosis, vascular access thrombosis, or pulmonary embolism.
a. On-treatment was defined as the last non-zero dose date + 28 days (Table 18), and was conducted as a post-hoc analysis for this study (ASCEND-NHQ).

4.3.2. General Safety

The ASCEND-NHQ study was shorter (28 weeks) than the active-controlled studies (≥52 weeks), but permitted an appraisal of which adverse events (AEs) may be associated with daprodustat and those which reflect background events attributable to a disease carrying appreciable morbidity. The overall incidence of TEAEs was generally balanced between treatment groups (Table 8). The incidences of serious TEAEs and TEAEs leading to discontinuation of study drug were similar in the 2 groups.

Table 8 ASCEND-NHQ: Overview of TEAEs (Safety Population)

ASCEND-NHQ	Dapro n (%) (N=308)	Placebo n (%) (N=306)	Risk Difference (%)
Any TEAE	213 (69)	216 (71)	-1.43
Any TEAE leading to discont. of RT	22 (7)	28 (9)	-2.01
Any Serious TEAE	62 (20)	68 (22)	-2.09

RT=randomized treatment, TEAE=treatment-emergent adverse event.
TE period for AEs: Treatment Start Date ≤ AE Start/Worsening Date ≤ Last Non-Zero Dose Date + 1 day.

The common (≥5%) TEAEs across the study were diarrhea, hypertension, and edema peripheral. TEAEs with a frequency ≥3% in either treatment group are presented in Table 9. Nausea was more frequently reported in daprodustat-treated participants, while fatigue, anemia, and cough were more frequent in placebo-treated participants. The higher incidence of fatigue in the placebo group is consistent with the results of the SF-36 Vitality Domain analysis described in Section 4.2.2.

Table 9 ASCEND-NHQ: TEAEs (≥3% in either group) by Preferred Term (Safety Population)

	Dapro n (%) (N=308)	Placebo n (%) (N=306)	Difference (%)	Relative Risk (95% CI)
Any TEAE	**213 (69)**	**216 (71)**	**-1.43**	**0.98 (0.88,1.09)**
Diarrhoea	25 (8)	17 (6)	2.56	1.46 (0.81,2.65)
Hypertension	23 (7)	16 (5)	2.24	1.43 (0.77,2.65)
Oedema peripheral	12 (4)	21 (7)	-2.97	0.57 (0.28,1.13)
Urinary tract infection	13 (4)	15 (5)	-0.68	0.86 (0.42,1.78)
Arthralgia	9 (3)	13 (4)	-1.33	0.69 (0.30,1.59)
Headache	12 (4)	8 (3)	1.28	1.49 (0.62,3.59)
Nasopharyngitis	11 (4)	9 (3)	0.63	1.21 (0.51,2.89)
Nausea	14 (5)	5 (2)	2.91	2.78 (1.01,7.63)
Upper respiratory tract infection	8 (3)	11 (4)	-1.00	0.72 (0.29,1.77)
Fatigue	2 (<1)	15 (5)	-4.25	0.13 (0.03,0.57)
Anaemia	3 (<1)	12 (4)	-2.95	0.25 (0.07,0.87)
Constipation	3 (<1)	10 (3)	-2.29	0.30 (0.08,1.07)
Cough	2 (<1)	10 (3)	-2.62	0.20 (0.04,0.90)

TEAEs leading to treatment discontinuation: All events leading to treatment discontinuation were reported in <1% of participants in either treatment group (Table 10).

Table 10 ASCEND-NHQ: TEAEs Leading to Treatment Discontinuation (≥2 Participants) by Preferred Term (Safety Population)

	Dapro n (%) (N=308)	Placebo n (%) (N=306)	Difference (%)
Any TEAE leading to discontinuation	**22 (7)**	**28 (9)**	**-2.01**
Renal failure	2 (<1)	2 (<1)	0.00
Diarrhoea	3 (<1)	0	0.97
End stage renal disease	1 (<1)	2 (<1)	-0.33
Anaemia	1 (<1)	1 (<1)	0.00
Atrial fibrillation	2 (<1)	0	0.65
Azotaemia	1 (<1)	1 (<1)	0.00
Covid-19	2 (<1)	0	0.65
Decreased appetite	0	2 (<1)	-0.65
Nausea	1 (<1)	1 (<1)	0.00

TEAE=treatment-emergent adverse event.

Serious TEAEs: The most frequently reported serious TEAEs were AKI (acute kidney injury) and anemia (Table 11). Renal safety in ASCEND-NHQ is discussed in Section 5.5.8.1.

Table 11 ASCEND-NHQ: Serious TEAEs (≥1% in either group) by Preferred Term (Safety Population)

	Dapro n (%) (N=308)	Placebo n (%) (N=306)	Difference (%)	Relative Risk (95% CI)
Any Serious TEAE	**62 (20)**	**68 (22)**	**-2.09**	**0.91 (0.67,1.23)**
Acute kidney injury	5 (2)	5 (2)	-0.01	0.99 (0.29,3.40)
Anaemia	2 (<1)	8 (3)	-1.97	0.25 (0.05,1.16)
Renal failure	2 (<1)	6 (2)	-1.31	0.33 (0.07,1.63)
Urinary tract infection	2 (<1)	4 (1)	-0.66	0.50 (0.09,2.69)
Cardiac failure	4 (1)	1 (<1)	0.97	3.97 (0.45,35.35)
Cardiac failure acute	0	4 (1)	-1.31	NA

TEAEs of Special Interest: The incidence of AESIs was generally low and there were no clinically meaningful imbalances between treatment groups (Table 12).

Table 12 ASCEND-NHQ: Overview of Treatment-Emergent AESIs (Safety Population)

Category	Daprodustat (N=308)		Placebo (N=306)	
	n (%)	Rate per 100 PY[a]	n (%)	Rate per 100 PY[a]
Worsening of hypertension	31 (10)	21.82	26 (8)	19.78
Death, MI, stroke, HF, PE, DVT, thromboembolic events, thrombosis of vascular access[b]	26 (8)	18.13	23 (8)	17.09
Proliferative retinopathy, macular edema, choroidal neovascularization	3 (<1)	2.03	9 (3)	6.63
Esophageal and gastric erosions	2 (<1)	1.35	3 (<1)	2.19
Cancer-related mortality and tumor progression and recurrence	1 (<1)	0.67	2 (<1)	1.46
Pulmonary artery hypertension	3 (<1)	2.03	0	0
Exacerbation of rheumatoid arthritis	2 (<1)	1.35	0	0
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	0	0	0	0

AESI=adverse event of special interest, DVT=deep vein thrombosis, HF=heart failure, MI=myocardial infarction, PE=pulmonary embolism.

Note: Rate per 100 PY = 100 x (number of participants with event/person-years)

a. Calculated as 100 X (number of participants with events / participant years).

b. Potential TEAEs of special interest in this category were assessed in ASCEND-NHQ, ASCEND-ID and ASCEND-TD studies. In the CV outcomes studies, these events were not assessed as TEAEs of special interest, but adjudicated as CV endpoints and most aligned with the composite CV endpoint of "MACE or thromboembolic event or hospitalization for HF (refer to Table 7)".

5. ACTIVE-CONTROLLED STUDIES

5.1. Exposure, Participant Disposition and Demographics

5.1.1. Exposure

Exposure within each of the 2 large CV outcomes studies was similar across the daprodustat and comparator treatment groups (Table 13; Table 14). More than 50% of participants received at least 18 months of treatment in the ASCEND-ND study rising to more than 2 years of treatment in the ASCEND-D study. Exposure within the smaller ASCEND studies was also similar between the treatment groups within each study (Table 14).

Table 13 Cardiovascular Outcomes Studies: Summary of Extent of Exposure to Daprodustat for Global Phase 3 (Safety Population)

Duration of Exposure (Months, n [%])	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1933)	Dapro (N=1482)	ESA (N=1474)
≤6 months	398 (21)	356 (18)	218 (15)	204 (14)
>6 to ≤12 months	314 (16)	337 (17)	178 (12)	167 (11)
>12 to ≤18 months	300 (15)	302 (16)	125 (8)	122 (8)
>18 to ≤24 months	266 (14)	241 (12)	129 (9)	149 (10)
>24 to ≤30 months	255 (13)	265 (14)	407 (27)	392 (27)
>30 to ≤36 months	205 (11)	221 (11)	307 (21)	304 (21)
>36 to ≤42 months	156 (8)	166 (9)	107 (7)	122 (8)
>42 to ≤48 months	41 (2)	40 (2)	11 (<1)	14 (<1)
>48 months	2 (<1)	5 (<1)	-	-

Table 14 Active-controlled Studies: Extent of Exposure in Months for Global Phase 3 (Safety Population)

ASCEND-ND		ASCEND-D		ASCEND-ID		ASCEND-TD	
Dapro (N=1937)	Darbe (N=1933)	Dapro (N=1482)	ESA (N=1474)	Dapro (N=157)	Darbe (N=155)	Dapro (N=270)	ESA (N=136)
Mean (SD) exposure in months							
18.48 (12.040)	18.97 (12.121)	21.96 (11.627)	22.35 (11.540)	10.24 (3.301)	10.70 (2.977)	9.94 (3.562)	9.93 (3.639)
Median (IQR) exposure in months							
17.45 (7.43, 28.06)	17.51 (8.28, 28.58)	25.79 (10.78, 31.08)	25.82 (11.99, 31.31)	11.96 (9.63, 11.99)	11.96 (11.79, 12.06)	11.99 (7.75, 11.99)	11.99 (8.20, 11.99)

IQR=interquartile range (i.e., 25%, 75% percentiles)

5.1.2. Participant Disposition and Discontinuation

The proportion of participants who permanently discontinued randomized treatment was similar in both treatment groups in the active-controlled studies (Table 15).

Table 15 Active-controlled Studies: Participant Disposition in the Active-controlled Studies (ITT Population)

	ASCEND-ND		ASCEND-D		ASCEND-ID		ASCEND-TD	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)	Dapro (N=157)	Darbe (N=155)	Dapro (N=270)	ESA (N=137)
Study Completion Status, n (%)								
Completed[a]	1873 (97)	1870 (97)	1370 (92)	1366 (92)	155 (99)	151 (97)	269 (>99)	135 (99)
Withdrawn	64 (3)	65 (3)	117 (8)	111 (8)	2 (1)	4 (3)	1 (<1)	2 (1)
Randomized Treatment (RT) Status, n (%)								
Prematurely discontinued RT	727 (38)	726 (38)	785 (53)	781 (53)	45 (29)	39 (25)	78 (29)	39 (28)
Died while taking RT	156 (8)	166 (9)	114 (8)	119 (8)	11 (7)	6 (4)	7 (3)	3 (2)
Primary reason for all RT discontinuation								
Adverse event	254 (13)	222 (11)	233 (16)	236 (16)	19 (12)	9 (6)	28 (10)	11 (8)
Protocol deviation	14 (<1)	20 (1)	9 (<1)	5 (<1)	0	6 (4)	0	0
Stopping criteria met[b]	151 (8)	161 (8)	237 (16)	222 (15)	8 (5)	9 (6)	23 (9)	14 (10)
Decision by participant/ proxy	281 (15)	288 (15)	258 (17)	275 (19)	17 (11)	14 (9)	23 (9)	11 (8)
Other[c]	27 (1)	35 (2)	48 (3)	43 (3)	1 (<1)	1 (<1)	4 (1)	3 (2)

RT=randomized treatment.

a. Participants were considered to have completed the study if they completed all visits through the End of Study visit irrespective of whether they discontinued randomized treatment. Participants who died while on study were also considered to have completed the study.

b. Protocol-defined stopping criteria include: kidney transplant, rescue, pregnancy, cancer, liver chemistry, prohibited medication, transition to dialysis (France only), worsening kidney function due to Autosomal Dominant Polycystic Kidney Disease, change in dialysis modality (e.g., for sites in France).

c. Other includes lost to follow up, sponsor terminated, site closed, investigator discretion.

5.1.3. Demographics and Baseline Disease Status

The participants enrolled are representative of CKD patients with anemia not on dialysis and on dialysis (HD and peritoneal) in the US, which are the proposed populations for treatment with daprodustat. In the ASCEND-ND and ASCEND-D studies, Black or African American participants comprised 33% to 39% of the participants in the US region (Table 16).

Demographic profiles were as anticipated for the non-dialysis and dialysis indications in which patients have high prevalence of concomitant conditions e.g., hypertension and diabetes. Baseline characteristics including renal characteristics, ESA use (ASCEND-D and ASCEND-TD only), Hgb levels, CV and diabetes characteristics, BP values, and markers of iron metabolism were generally similar between treatment groups within each global Phase 3 study. Some small differences were noted (higher proportion of stage 5 CKD participants in the daprodustat group in ASCEND-ND and higher incidence of history of thromboembolic events in the daprodustat group in ASCEND-D).

Table 16 Active-controlled Studies: Key Baseline Demographic and Disease Characteristics (ITT Population)

	ASCEND-ND (N=3872)		ASCEND-D (N=2964)		ASCEND-ID (N=312)		ASCEND-TD (N=407)	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)	Dapro (N=157)	Darbe (N=155)	Dapro (N=270)	ESA (N=137)
Age in years, mean (SD)	64.8 (14.03)	64.9 (13.83)	57.2 (14.29)	57.3 (14.65)	53.7 (14.31)	55.8 (15.70)	59.4 (14.16)	55.8 (15.34)
Female, n (%)	1102 (57)	1071 (55)	636 (43)	630 (43)	61 (39)	57 (37)	121 (45)	56 (41)
Ethnicity, n (%)								
Hispanic	430 (22)	467 (24)	367 (25)	371 (25)	50 (32)	50 (32)	69 (26)	33 (24)
Race, n (%)								
American Indian or Alaskan Native	88 (5)	100 (5)	19 (1)	32 (2)	5 (3)	2 (1)	1 (<1)	1 (<1)
Asian	525 (27)	537 (28)	176 (12)	181 (12)	26 (17)	31 (20)	20 (7)	9 (7)
Black or African American	183 (9)	185 (10)	228 (15)	233 (16)	16 (10)	13 (8)	49 (18)	32 (23)
Native Hawaiian or Other Pacific Islander	7 (<1)	7 (<1)	26 (2)	25 (2)	0	0	1 (<1)	0
White	1098 (57)	1055 (55)	995 (67)	982 (66)	110 (70)	107 (69)	195 (72)	94 (69)
Other	36 (2)	51 (3)	43 (3)	24 (2)	0	2 (1)	4 (1)	1 (<1)
US Region[a]	492	489	425	421	29	25	71	36
Black or African American	160 (33)	161 (33)	168 (40)	162 (38)	13 (45)	11 (44)	38 (54)	24 (67)
CKD stage								
≤3	345 (18)	371 (19)	-	-	-	-	-	-
4	875 (45)	894 (46)	-	-	-	-	-	-
5	716 (37)	670 (35)	-	-	-	-	-	-
Missing	1 (<1)	0	-	-	-	-	-	-
Hgb mean (SD), g/dL	9.87 (0.940)	9.85 (0.948)	10.35 (0.970)	10.39 (0.981)	9.46 (1.002)	9.49 (0.97)	10.44 (0.83)	10.59 (0.926)
Prior ESA Use, n (%)	907 (47)	903 (47)	1487 (100)	1477 (100)	0	0	270 (100)	137 (100)
History of: n (%)								
Diabetes[b]	1084 (56)	1134 (59)	615 (41)	617 (42)	70 (45)	70 (45)	105 (39)	53 (39)
Stroke	128 (7)	128 (7)	96 (6)	110 (7)	7(4)	9 (6)	26 (10)	19 (14)
MI	133 (7)	136 (7)	133 (9)	147 (10)	12(8)	9 (6)	31 (11)	9 (7)

	ASCEND-ND (N=3872)		ASCEND-D (N=2964)		ASCEND-ID (N=312)		ASCEND-TD (N=407)	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)	Dapro (N=157)	Darbe (N=155)	Dapro (N=270)	ESA (N=137)
Cancer	100(5)	86 (4)	74 (5)	72 (5)	3 (2)	4 (3)	13 (5)	10 (7)
Heart Failure[c]	265 (14)	254 (13)	267 (18)	254 (17)	19 (12)	17 (11)	50 (19)	22 (16)
CV Disease[d]	716 (37)	716 (37)	666 (45)	665 (45)	47 (30)	45 (29)	110 (41)	54 (39)
Thromboembolic events	80 (4)	70 (4)	273 (18)	242 (16)	13 (8)	8 (5)	52 (19)	36 (26)
Current medical condition: hypertension	1828 (94)	1829 (95)	1366 (92)	1373 (93)	146 (93)	146 (94)	238 (88)	123 (90)
Baseline Dialysis Type								
Hemodialysis	-	-	1316 (89)	1308 (89)	126 (80)	126 (81)	270 (100)	137 (100)
Peritoneal dialysis	-	-	171 (11)	169 (11)	31 (20)	29 (19)	-	-

MI=myocardial infarction.

a. Number of participants in US region used for denominator for sub-category.

b. History of diabetes was defined as having a yes response to at least one record of the medical history terms that contains “diabetic” or “diabetes”.

c. History of Heart Failure was defined as having a medical condition of “heart failure” at enrolment.

d. History of CV disease was defined as having a yes response to any of the following medical history conditions: angina pectoris, myocardial infarction, stroke, coronary artery disease, transient ischemic attack, heart failure, atrial fibrillation, cardiac arrest, and/or valvular heart disease.

5.2. Clinical Efficacy

Results from the 4 global Phase 3 active-controlled studies have demonstrated that, regardless of prior ESA use, treatment with daprodustat can achieve and maintain Hgb within a given target range, as an indication of clinical efficacy in patients receiving dialysis, those new to dialysis and those not on dialysis, and regardless of prior ESA use. Daprodustat met the primary efficacy endpoint (change from Baseline in Hgb) in all 4 global Phase 3 active-controlled studies, demonstrating NI to conventionally used ESA or its analogs using an evaluation period across Weeks 28 to 52. The lower boundary of the 95% CI for the treatment difference over the evaluation period in all 4 active-controlled studies was above the prospectively defined NI margin of -0.75 g/dL, regardless of dosing regimen (once daily and TIW) (Figure 1).

5.2.1. Hemoglobin Values

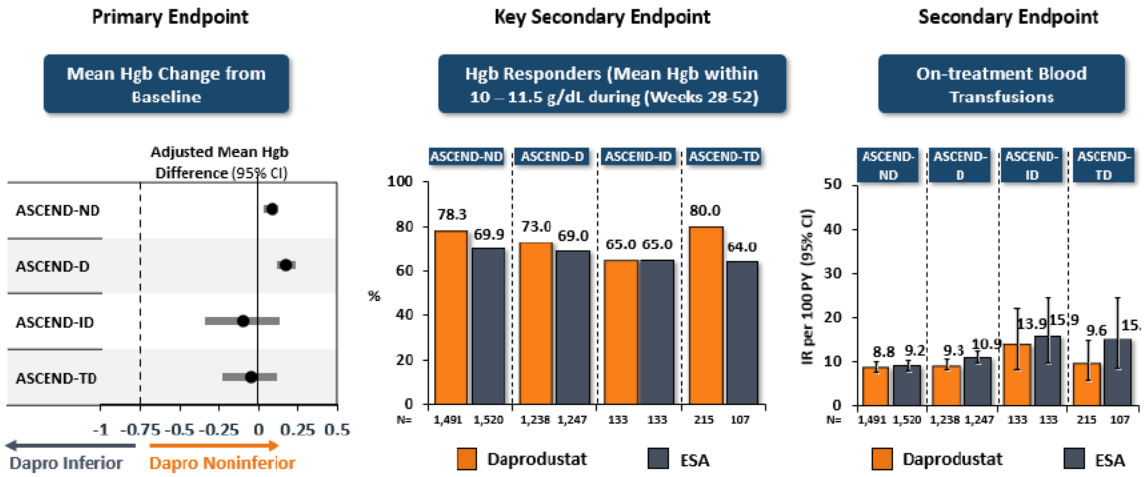
Evidence of efficacy of daprodustat in non-dialysis (ASCEND-ND) and dialysis (ASCEND-D, ASCEND-ID, and ASCEND-TD) participants compared with ESAs has been demonstrated. Non-inferiority of daprodustat to ESA control was demonstrated in the primary ITT analysis in all 4 active-controlled Phase 3 studies (Figure 9, left).

The results of the following additional analyses were also consistent with the primary analysis conclusion in ASCEND-D, including a supplemental shorter evaluation period (Weeks 28 to 36) analysis using evaluable Hgb values only.

Daprodustat maintained mean Hgb in the target range (Table 2), with similar mean Hgb values compared with ESA control during that period, indicating an appropriate start dose and titration algorithm for daprodustat in both non-dialysis and dialysis populations (Figure 10).

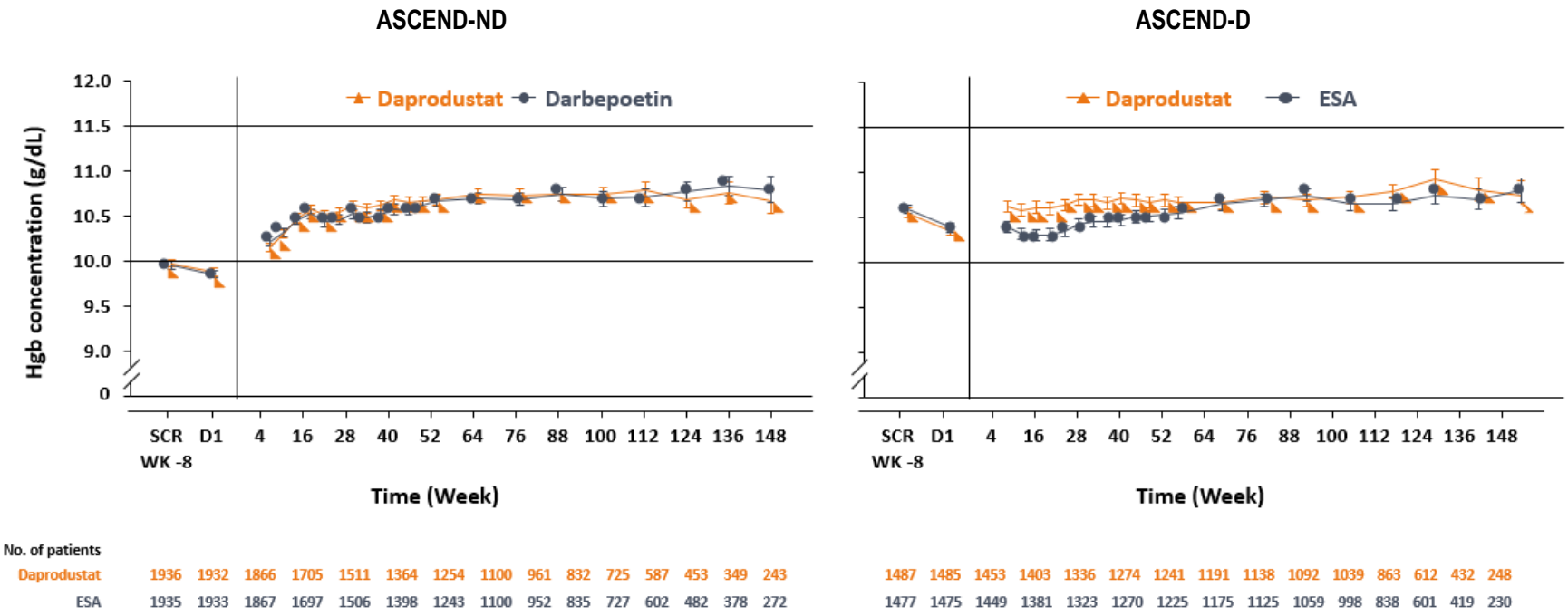
Hgb responders (participants with mean Hgb within the analysis range during the evaluation period: 10 to 11.5 g/dL) for daprodustat were also nominally (not adjusted for multiplicity) statistically superior to darbepoetin alfa in the ASCEND-ND study (Figure 9, center). A similar difference for Hgb responders was observed between the 2 treatment groups regardless of ESA status at Baseline in the ASCEND-ND study. Furthermore, the percentage of time Hgb remained within the analysis range demonstrated nominal NI (using a pre-specified margin of -15%) to darbepoetin alfa in the ASCEND-ND study (Hodges-Lehmann estimate of median treatment difference: 4.57%, 95% CI: 2.04, 7.11). For the ASCEND-D study, daprodustat was generally comparable to ESA control in the percentage of Hgb responders during the evaluation period (Weeks 28 to 52). Of note, daprodustat TIW was nominally statistically superior to ESA for the proportion of responders and percentage of time Hgb was within the responder range.

Figure 9 Active-controlled Studies: Efficacy Endpoints (ITT Population)



Note: **Primary endpoint:** Post-randomization values include on and off treatment observed and imputed values. Based on an ANCOVA model with terms for treatment, Baseline Hgb, dialysis type (ASCEND-D), region, and current ESA use (ASCEND-ND). **Secondary endpoint:** Treatment group comparisons based on Cochran-Mantel-Haenszel chi-squared test adjusted for region (all studies), current ESA use (ASCEND-ND) and dialysis type (ASCEND-D).

Figure 10 Post-Randomization Observed Hgb Data by Visit (ITT Population)



SCR=screening. Note: Error bars indicate 95% CI. Baseline and visits on or before Day 1 (D1) include only pre-treatment values.

The proportion of participants with any Hgb excursions (<7.5 g/dL or ≥12 g/dL) during the evaluation period (Weeks 28 to 52) of each study is presented in Table 17. A discussion of thrombosis in the context of excessive erythropoiesis is provided in Section 5.5.5.3.

Table 17 Active-controlled Studies: Participants with any Hgb Excursions during the Evaluation Period (ITT Population)

	ASCEND-ND		ASCEND-D		ASCEND-ID		ASCEND-TD	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)	Dapro (N=157)	Darbe (N=155)	Dapro TIW (N=270)	ESA (N=137)
Participants with Evaluable Central Lab Hgb during the Evaluation Period								
n	1490	1515	1238	1245	133	133	215	107
Hgb value <7.5 g/dL during Evaluation Period								
n (%)	17 (1)	19 (1)	23 (2)	30 (2)	5 (4)	5 (4)	3 (1)	2 (2)
Hgb value ≥12 g/dL during Evaluation Period								
N (%)	345 (23)	342 (23)	430 (35)	332 (27)	36 (27)	49 (37)	31 (14)	23 (21)

Note: Evaluable values are on-treatment values not taken within the 8 weeks following a red blood cell or whole blood transfusion or a post-randomization non-randomized ESA treatment.

5.2.2. Efficacy in Subgroups

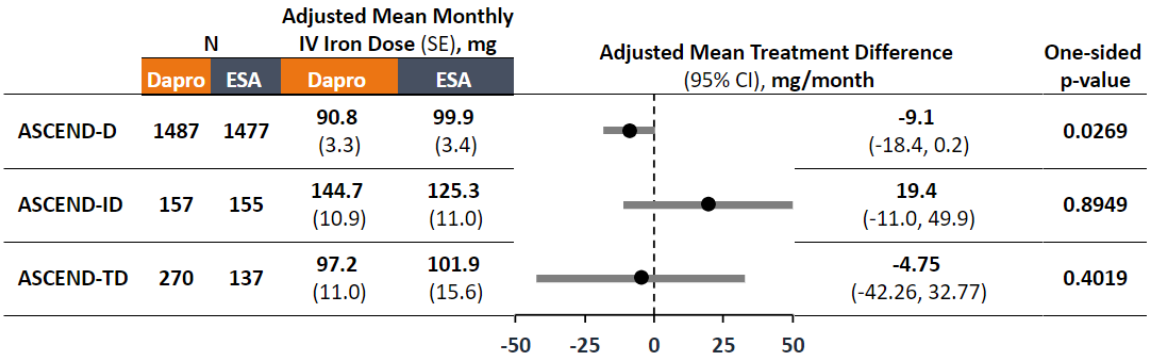
Overall, there was little or no statistical heterogeneity between the 22 subgroups studied. In the 2 large CV outcome studies, daprodustat was determined to be as effective as ESA controls (epoetin alfa and darbepoetin alfa), regardless of age, sex, race, body weight, dialysis type (HD, peritoneal dialysis [in ASCEND-D and ASCEND-ID], or non-dialysis), CKD stage (ASCEND-ND), prior ESA use (ASCEND-ND), and Baseline Hgb.

In non-dialysis participants (ASCEND-ND), daprodustat was as effective as ESA whether the participant was using an ESA at Baseline or not (Figure 1). In dialysis participants (ASCEND-D), daprodustat was as effective as ESA whether participants were receiving HD or peritoneal dialysis (Figure 1).

5.2.3. Iron Use

The global Phase 3 protocols specified an algorithm for supplemental iron treatments for both daprodustat and control groups while participants remained on study treatment. Results from the principal secondary analyses of the on-treatment monthly IV iron dose (mg/month) from Day 1 to Week 52 in the ASCEND-D, ASCEND-ID, and ASCEND-TD studies showed little or no difference between daprodustat and ESA in the mean IV iron dose (Figure 11). This endpoint was not analyzed in the participants in the ASCEND-ND study.

Figure 11 ASCEND-D, ASCEND-ID and ASCEND-TD: Mean IV Iron Dose in mg/month (ITT Population)



Note: Iron data after a participant has received a blood transfusion is excluded from the analysis. This was a post-hoc analysis in ASCEND-TD.

5.2.4. Fatigue and Quality of Life

The SF-36 Vitality Domain was a secondary endpoint (not multiplicity controlled) in the active-controlled studies. Change in the SF-36 Vitality Domain scores were similar between daprodustat and ESA in both dialysis (ASCEND-D and ASCEND-ID) and non-dialysis participants (ASCEND-ND) at Weeks 28 and 52. A linear mixed model repeated measures analysis of the change in SF-36 Vitality Domain scores in all populations studied (dialysis and non-dialysis) showed no statistically significant difference in improvements between daprodustat and ESA. These results were in line with expectations for these open-label, NI trials, since patients were treated to the same target Hgb level, which was limited and uniform between daprodustat and ESA control groups, as defined by protocol.

5.3. Clinical Safety – General Methods

All the active-controlled global Phase 3 studies used the same Hgb target range (10 to 11 g/dL, Section 3.5.1) and the same protocol-specified dose levels and frequencies in all territories to avoid the potential for difficulty in interpretation of safety data that might have arisen from varying target and actual-achieved levels of Hgb.

Details on study design and statistical considerations are provided in Section 3.5.1 and Table 3, including information on the pre-specified ITT analysis (time period for follow-up of CV events) for the primary safety endpoint. Considerations relating to on-treatment analyses for the primary safety endpoint (which are also relevant for the pre-specified definition of TEAEs) are provided in Section 5.4.3. Post-hoc analyses (as defined in Table 18) were conducted to address a bias in the pre-specified on-treatment definitions which did not account for different dosing frequencies in the active control groups compared with once-daily daprodustat.

Table 18 Pre-specified and Post-hoc Definitions for On-treatment CV events and Treatment-emergent Adverse Events

Event	Definition
On-treatment CV events	Treatment Start Date ≤ Date of Event ≤ Earlier of Date of Study Completion/withdrawal and:
Pre-specified	LDD **+ 28 days**[a]
Post-hoc, adjusted for DF[b]	LDD **+ DF**[b]
Post-hoc, adjusted for DF + 28 days	LDD **+ DF**[b] **+ 28 days**[a]
Post-hoc, anchored on date of decision to stop treatment	Date of decision to stop randomized treatment
Post-hoc, anchored on date of decision to stop treatment + 28 days	Date of decision to stop randomized treatment **+ 28 days**[a]
Treatment-emergent adverse events	Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Date of:
Pre-specified	LDD **+ 1 day**
Post-hoc, adjusted for DF[b]	LDD **+ DF**[b]

TE=treatment-emergent; LDD=last non-zero dose date; DF=dosing frequency.
Note: No dosing frequency adjusted analyses were conducted for ASCEND-NHQ since daprodustat and the placebo comparator were dosed at same frequency.
a. An ascertainment window of 28 days after on-treatment period was selected to allow for capture of CV events with long latency.
b. A participant's dosing frequency at their last dose of randomized treatment was used. Dosing frequency for daily doses = 1 day; TIW doses = 2 days; weekly doses = 7 days; every 2 weeks = 14 days; every 4 weeks = 28 days.

5.4. Cardiovascular Safety

5.4.1. Endpoints and Analysis Considerations

The primary safety objective of each CV outcomes study was to assess NI of daprodustat to ESA in first occurrence of MACE, where MACE was a composite endpoint consisting of ACM, non-fatal MI and non-fatal stroke. A pre-defined NI margin of 1.25 for the HR (daprodustat versus ESA) was adopted following regulatory Agency discussions (refer to Section 3.4.2). Patients with CKD are at a high risk of death and, while CV causes are prominent, other leading causes of death (e.g., infection) represent an important competing risk for CV outcomes. As such, the MACE criteria agreed with the FDA includes ACM, rather than mortality only attributed to CV causes.

The multiplicity-adjusted principal secondary CV analyses were superiority evaluations of first occurrence of MACE, MACE or thromboembolic events, and MACE or hospitalization due to HF.

Each MACE component (ACM, MI [fatal and non-fatal], and stroke [fatal and non-fatal]) was also evaluated separately. Other individual CV events comprised CV mortality, hospitalization due to HF, and thromboembolic events. An external blinded committee (CEC) independently adjudicated these CV events.

5.4.2. Non-Inferiority Assessment of MACE (ITT Analysis During the Time Period for Follow-up of CV Events) – ASCEND-ND and ASCEND-D

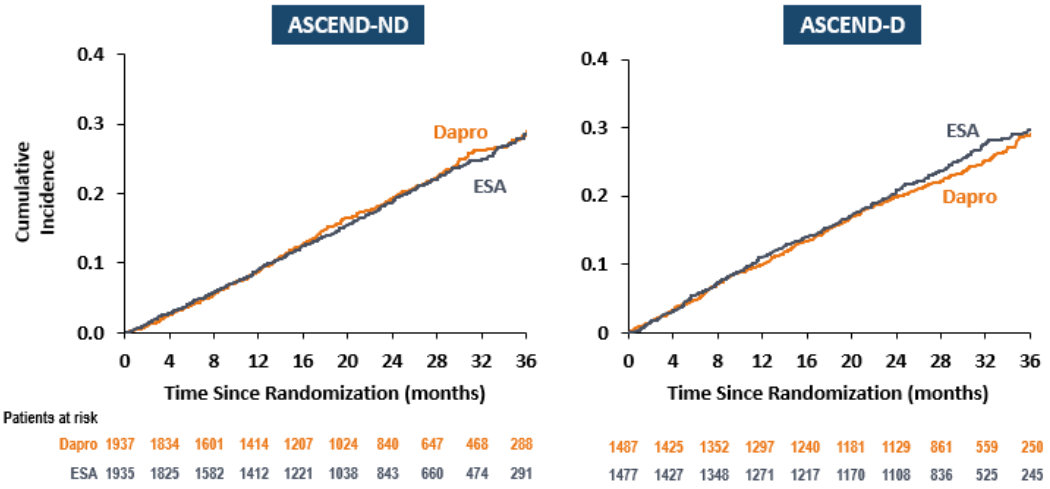
The large CV outcomes studies (ASCEND-ND and ASCEND-D) showed that daprodustat was non-inferior to ESA for the primary safety endpoint of time to first adjudicated MACE during the time period for follow-up of CV events (defined in Table 3). In both studies, the upper boundary of the 2-sided 95% CI for the HR for first MACE was lower than the prospectively defined NI margin of 1.25 (Table 19, Figure 12).

Table 19 Summary of Analysis of Time to First Adjudicated MACE during the Time Period for Follow-up of CV Events (ITT Population)

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
First adjudicated MACE, n (%)	378 (19.5)	371 (19.2)	374 (25.2)	394 (26.7)
Rate per 100 PY (95% CI)	10.86 (9.80, 12.02)	10.63 (9.58, 11.77)	11.07 (9.98, 12.26)	11.86 (10.72, 13.09)
Diff in rate per 100 PY (95% CI) [a]	0.23 (-1.31, 1.77)		-0.78 (-2.41, 0.84)	
Hazard Ratio (95% CI) [b, c]	**1.03** (0.89, 1.19)		**0.93** (0.81, 1.07)	

MACE= major adverse cardiovascular event.
Note: Rate per 100 PY = 100 x (number of participants with event/person-years)
a. A rate difference <0 indicates a lower risk with daprodustat compared to ESA/darbepoetin alfa.
b. Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.
c. Non-inferiority was established if the upper limit of the 2-sided 95% CI for the hazard ratio (daprodustat vs ESA) was less than the pre-specified margin of 1.25.

Figure 12 Kaplan-Meier Plot of Time to First Adjudicated MACE for the Primary ITT Analysis during the Time Period for Follow-up of CV Events



MACE=major adverse cardiovascular event.

Additional Analyses

All pre-specified supplementary analyses in both CV outcomes studies (comprising on-treatment MACE analyses, removal of COVID-19 MACE, inclusion of additional covariates, and removal of events recorded after the protocol-defined number of MACE [ASCEND-D study only]) were consistent with the results of the primary safety analysis with the exception of on-treatment MACE in the non-dialysis study ASCEND-ND (Section 5.4.3.1).

Evaluation of Missing Data

In the CV outcomes studies, a similar proportion of participants on daprodustat and ESA had unknown (missing) CV status at the end of both studies (5% each treatment group in ASCEND-ND, 11% each in ASCEND-D). Unknown vital status at end of study was low in both treatment groups (<1% each in ASCEND-ND, 2% each in ASCEND-D). As a result, ASCEND-ND had 98.8% of the theoretical total possible PY of follow-up for vital status and 97.3% for CV endpoints, while ASCEND-D had 98.3% of the theoretical total possible PY of follow-up for vital status and 95.3% for CV endpoints.

A tipping point analysis was conducted to assess the impact of the missing data (from participants who withdrew during the study and did not have a MACE before withdrawal or a known death after withdrawal). Tipping point analyses identify a number of different scenarios (i.e., assumptions about missing data in the 2 treatment groups) where the conclusion drawn from the primary analysis would no longer hold. One such scenario identifies the resulting assumptions about MACE risk in missing data from the daprodustat group required to tip the NI conclusion when the missing data in the ESA control group is assumed to be missing at random. In this scenario, the tipping point analyses estimated that participants with missing MACE events in the daprodustat group would have to be postulated to be more than 2.72 times higher than the observed daprodustat hazard rate (ASCEND-ND), and more than 7-fold higher than the observed hazard rate in ASCEND-D for a conclusion of NI (daprodustat versus rhEPO) to no longer hold. This magnitude of difference seems implausible, suggesting that missing data did not alter the conclusion of NI in these 2 CV outcomes studies.

5.4.3. On-Treatment MACE

5.4.3.1. Pre-specified Analysis of On-Treatment MACE (Events up to Last Dose Date + 28 Days)

The results of the pre-specified on-treatment MACE analysis were consistent with the results of the primary ITT analysis for ASCEND-D, but not for ASCEND-ND (Table 20). In addition to the general limitations of on-treatment analyses summarized in Section 3.5.2, the approach taken for the pre-specified on-treatment definition in these studies had a fundamental flaw that prohibits an interpretation consistent with the intent of these supplementary analyses.

Table 20 Summary of Pre-specified On-treatment Analysis of Time to First Adjudicated MACE (ITT Population)

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
Events up to Last Dose Date + 28 days				
Number of participants[a]	1937	1933	1482	1474
First adjudicated MACE, n (%)	274 (14.1)	202 (10.5)	255 (17.2)	271 (18.4)
Rate per 100 PY (95% CI)	9.95 (8.80, 11.20)	7.18 (6.22, 8.24)	9.86 (8.69, 11.15)	10.39 (9.19, 11.71)
Diff in rate per 100 PY (95% CI)[b]	2.77 (1.23, 4.30)		-0.53 (-2.26, 1.20)	
Hazard Ratio (95% CI)[c]	**1.40** (1.17, 1.68)		**0.96** (0.81, 1.14)	

Note: Rate per 100 PY = 100 x (number of participants with event/person-years)
Note: The pre-specified on-treatment definition is detailed in Table 18.
a. All randomized participants who received at least 1 dose of randomized treatment.
b. A rate difference <0 indicates a lower risk with daprodustat compared to ESA/darbepoetin alfa.
c. Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.

On-treatment definition considerations

On-treatment definitions often have 2 components: 1) a period of time reflective of the active receipt of randomized treatment; 2) an ascertainment window reflecting a subsequent period of time to capture treatment-related events that may occur after treatment discontinuation, e.g., events with a longer latency or serious events of potentially causal interest that follow less serious treatment-ending events.

In outcome studies with a placebo comparator group which is dosed at the same frequency as the active treatment, the follow-up period for on-treatment analyses only needs to consider the equal active treatment period in the treatment groups, in addition to an ascertainment window. In previous trial designs, ascertainment windows either for TEAEs or safety endpoints have ranged from 7, 30 and 38 days following last dose, with some analyses exploring ascertainment windows as far out as 90 days after last dose administered [Wiviott, 2019; Husain, 2019; Zinman, 2017; Scirica, 2013]. Although longer ascertainment windows have the potential to detect events with longer latency, they also have the potential for confounding, particularly in trials assessing anemia in CKD patients where participants are likely to initiate alternative anemia therapy after stopping randomized treatment. These considerations and variable approaches illustrate the intrinsic difficulty in selecting an ascertainment window that appropriately captures the events described in point 2) above, while minimizing the potential for confounding (e.g., due to possible initiation of other treatments).

Defining an appropriate on-treatment period is further complicated by the need to define a suitable active treatment period when the treatment groups had different dosing regimens. In the 2 large CV outcomes studies, daprodustat was dosed once daily, in contrast to the ESA comparator group, which was dosed either TIW, once weekly, once every 2 weeks, or once every 4 weeks. In the ASCEND program, on-treatment CV events

for MACE and other adjudicated CV endpoints were defined for both daprodustat and comparator ESA as events occurring on or before the date of last dose and added to this was a further 28 days post-dose ascertainment window. If both groups were dosed daily, the comparison of the 2 groups would not be biased. However, the situation of a differing dosing frequency in the comparator group leads to systematic bias when counting events occurring on or before the date of last dose, because events that occur within the dosing frequency of the participant's last dose are not counted. In turn, not taking account of dosing frequency for the ESA comparator group may initiate the ascertainment window too early, thereby reducing counts of latent or other events which may be causally-linked to ESA treatment discontinuation.

The bias introduced for participants dosed daily versus those dosed less frequently can be substantial. The bias grows the closer the event of interest is to the date of stopping dosing. When treatment is stopped principally because of the occurrence of some AE, as indeed was the case in the ASCEND program, such that the 2 events are highly correlated in time, the bias can be extreme. For example, when considering an AE that leads to discontinuation of study treatment and then the following day results in an endpoint of interest (e.g., stroke), the stroke would be counted as occurring during the active dosing period for a once daily dose regimen, but occurring after the active dosing period for a regimen dosed TIW, once weekly, or any longer duration of frequency. Note that this dosing frequency-induced bias is not unique to the ASCEND program nor to the specific interventions studied. The bias would be introduced even if placebo daily dosing were randomized against less frequent dosing regimens of placebo, for the same reasons of differing dosing frequencies outlined in the example above.

This situation is further complicated in the ASCEND program because, across studies, there is a differing extent of disparity in the dosing frequencies between treatment groups. In ASCEND-D, 89% of participants receiving ESA control were receiving TIW or weekly ESA at the time of their last dose of treatment, compared with daily daprodustat. However, in ASCEND-ND approximately 78% of participants receiving darbepoetin alfa control were receiving darbepoetin alfa once every 4 weeks at the time of their last dose of treatment compared with daily daprodustat. Therefore, the scope for bias in on-treatment analyses that do not account for dosing frequency is substantially higher in ASCEND-ND as compared with ASCEND-D.

Hence, to account for this important flaw in the pre-specified on-treatment definition, a post-hoc analysis was performed that accounted for dosing frequency (Section 5.4.3.2). Another post-hoc approach for defining 'on-treatment' was also explored, which was anchored on the date of the decision to stop following the dosing algorithm instead of the last dose date (Section 5.4.3.3). These adjustments more accurately accounted for an active randomized treatment period in the face of differing dosing regimens and ensured that the ascertainment window was initiated at an appropriate and comparable timepoint for both treatment groups. Although these post-hoc analyses produce a less biased evaluation of events than the pre-specified definition (which did not account for differing dosing frequency across treatment groups), all on-treatment analyses have limitations and potential biases, particularly in the setting of open-label trials. Hence, the on-treatment analyses should be interpreted in this context.

5.4.3.2. Post-hoc Dosing Frequency Adjusted Analysis of On-treatment MACE

The post-hoc dosing frequency adjusted results were more consistent with the primary ITT analysis (Table 19). They yielded a lower point estimate for the HR than the pre-specified method, and with 95% CIs that included unity (Table 21, Figure 14).

Table 21 Summary of Post-hoc On-treatment Analysis of Time to First Adjudicated MACE (ITT Population)

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
Number of participants[a]	1937	1933	1482	1474
Events Up to Last Dose Date + DF				
First adjudicated MACE, n (%)	192 (9.9)	189 (9.8)	177 (11.9)	207 (14.0)
Rate per 100 PY (95% CI)	7.28 (6.29, 8.39)	6.75 (5.82, 7.79)	7.09 (6.09, 8.22)	8.14 (7.07, 9.33)
Diff in rate per 100 PY (95% CI)[b]	0.53 (-0.88, 1.94)		-1.05 (-2.58, 0.47)	
Hazard Ratio (95% CI)[c]	**1.09** (0.89, 1.33)		**0.88** (0.72, 1.07)	
Events Up to Last Dose Date + DF + 28 days				
First adjudicated MACE, n (%)	275 (14.2)	248 (12.8)	255 (17.2)	278 (18.9)
Rate per 100 PY (95% CI)	9.97 (8.83, 11.22)	8.59 (7.55, 9.73)	9.86 (8.68, 11.14)	10.59 (9.38, 11.91)
Diff in rate per 100 PY (95% CI)[b]	1.38 (-0.21, 2.97)		-0.73 (-2.47, 1.00)	
Hazard Ratio (95% CI)[c]	**1.18** (0.99, 1.40)		**0.94** (0.79, 1.11)	

DF=dosing frequency, MACE=major adverse cardiovascular event, PY=person-years.
Note: Rate per 100 PY = 100 x (number of participants with event/person-years)
Note: Post-hoc dosing frequency adjusted on-treatment definitions are detailed in Table 18.
a. All randomized participants who received at least 1 dose of randomized treatment.
b. A rate difference <0 indicates a lower risk with daprodustat compared to ESA/darbepoetin alfa.
c. Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.

5.4.3.3. On-Treatment MACE Anchored on Date of Decision to Stop Treatment

The date of decision to stop treatment (i.e., the date a participant decided to stop following the treatment dosing algorithm) was also explored as another potential anchor date for an on-treatment definition. While not a true physical dosing stop date, the ASCEND studies captured the date of decision to stop treatment to address the question of the comparative effect of daprodustat versus the ESA control, while participants continued to take the dose of randomized treatment designated by the protocol-defined dosing algorithm to maintain Hgb within the predefined target range (10.0 to 11.0 g/dL). This analysis provides an approximation to a setting where ESA (and daprodustat) could have both been dosed daily, in a double-dummy, double-blind, randomized controlled trial. However, analysis of data using an on-treatment definition anchored on the date of decision to stop treatment does have some limitations. For example, when the decision to stop treatment is close to the date of the last dose (within a few days), the time between treatment start and the date of decision to stop treatment could still miss an event that

occurred while the patient remained on treatment in accordance with the frequency of their dosing regimen. Nevertheless, adopting the use of the decision to stop treatment to define on-treatment periods also enables a treatment comparison that accounts for the important bolus of events that can be associated with the decision of a participant or investigator to stop randomized treatment. In CV outcomes studies, this is typical and corresponds with treatment-terminating events (notably death). Further, anchoring an ascertainment window to this on-treatment period permits capturing other events that are more likely to be related to study drug, as adverse outcomes leading to treatment discontinuation may be highly predictive of more serious events to follow (e.g., participant experiences either angina, or a TIA, resulting in a decision to stop randomized treatment, and soon after progresses to have a MI or stroke [adjudicated events]).

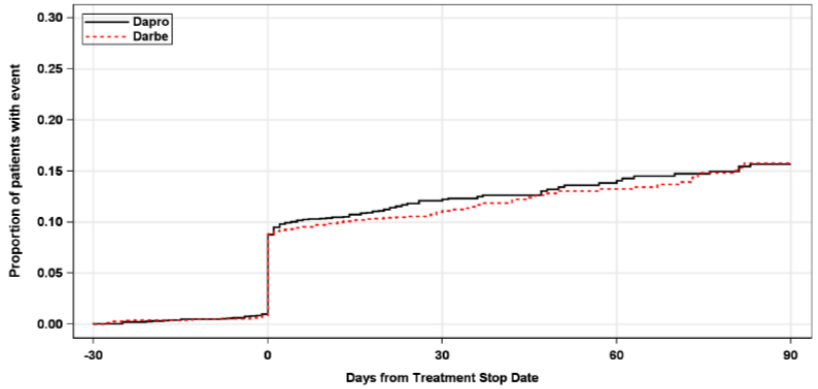
The distribution of events that occurred between the 30 days before and up to 90 days after each anchor date in the 2 large CV outcomes studies, including this bolus of events around the decision to stop date, is illustrated in Figure 13. For all plots, the MACE rate is constant for the 30 days prior to the anchor dates, and the curves are similar between days 60 to 90 after this anchor date. In addition, the slope is far greater following the last dose/decision to stop date than before, illustrating that sicker patients discontinue treatment, and as a result, the difference in on-treatment periods between the treatment groups (relative to decision to stop date) is consequential.

When the date of decision to stop treatment is used as the anchor date (Figure 13 A – ASCEND-ND), a substantial spike occurs in MACE corresponding with the date of decision to stop treatment for both treatment groups. This is expected, given that the majority of first events in the MACE composite were deaths, leading to randomized treatment being stopped.

When using last dose date as an anchor date (Figure 13 B – ASCEND-ND), only a daily dosing regimen (daprodustat, in this instance) would be temporally correlated with the decision to stop treatment, while a 4-weekly dosing regimen (as is the case for darbepoetin alfa in the majority of participants in ASCEND-ND) would not, and so anchoring an on-treatment definition to last dose date would result in missed events for the treatment group with 4-weekly dosing (consistent with analyses of on-treatment MACE in the darbepoetin alfa group when anchoring to last dose date, as compared with the decision to stop treatment; Figure 14). The time between a participant's last dose date and date of decision to stop treatment was further dissociated when considering those receiving a 'zero dose' (i.e., not receiving any study treatment during this time), which was possible per the dosing algorithm in cases where Hgb was too high, or a dose was needed below the lowest available dose. In these instances, if a participant switched to 'zero dose' as defined by the dosing algorithm, and some days after died in the study, their event would be counted as occurring after the last dose date, but within a period anchored by the decision to stop treatment which would be set to the date when the participant died. Given the therapeutic/supratherapeutic context of such a case, assessing these events as 'on-treatment' would be more in keeping with the objective of these supplementary analyses.

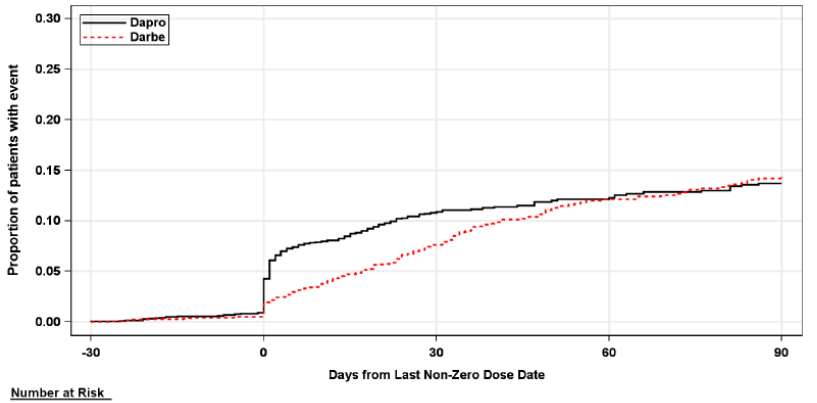
Figure 13 Plot of Time to First Occurrence of Adjudicated MACE (ITT Population)

A: ASCEND-ND: Time to First MACE in Relation to Decision to Stop Treatment Date



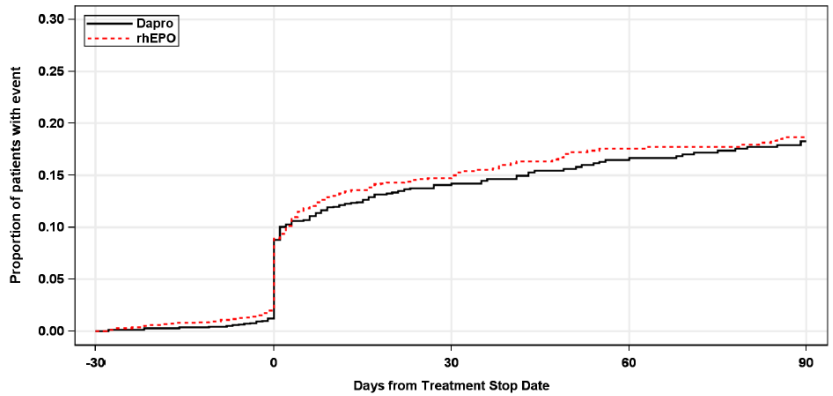
Number at Risk					
Dapro	1854	1836	781	389	352
Darbe	1857	1841	702	396	355

B: ASCEND-ND: Time to First MACE in Relation to Last Non-Zero Dose Date



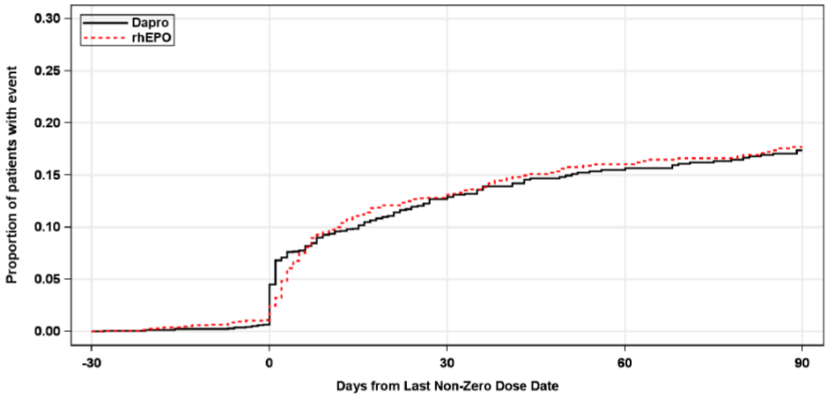
Number at Risk					
Dapro	1857	1840	1018	634	566
Darbe	1864	1855	1326	726	584

C: ASCEND-D: Time to First MACE in Relation to Decision to Stop Treatment Date



Number at Risk					
Dapro	1398	1381	656	478	456
rhEPO	1366	1338	656	457	437

D: ASCEND-D: Time to First MACE in Relation to Last Non-Zero Dose Date



Number at Risk					
Dapro	1400	1391	797	611	568
rhEPO	1374	1358	918	581	535

Post-hoc analyses for time to first MACE were conducted for both CV outcome studies anchored on the date of decision to stop treatment, with and without including the 28-day ascertainment window. Observed results are consistent with the dosing frequency adjusted on-treatment analysis and the ITT analysis (Table 22).

Table 22 Summary of Post-hoc On-treatment Analysis of Time to First Adjudicated MACE (ITT Population); Anchored on Date of Decision to Stop Treatment

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
Number of participants[a]	1937	1933	1482	1474
Events up to Date of decision to stop treatment				
First adjudicated MACE, n (%)	246 (12.7)	240 (12.4)	207 (14.0)	229 (15.5)
Rate per 100 PY (95% CI)	8.47 (7.45, 9.60)	8.06 (7.07, 9.15)	7.89 (6.85, 9.04)	8.71 (7.62, 9.91)
Diff in rate per 100 PY (95% CI)[b]	0.41 (-1.06, 1.88)		-0.81 (-2.37, 0.74)	
Hazard Ratio (95% CI)[c]	**1.06** (0.89, 1.27)		**0.91** (0.76, 1.10)	
Events up to Date of decision to stop treatment + 28 days				
First adjudicated MACE, n (%)	302 (15.6)	268 (13.9)	276 (18.6)	304 (20.6)
Rate per 100 PY (95% CI)	10.01 (8.91, 11.20)	8.69 (7.68, 9.80)	10.19 (9.02, 11.46)	11.20 (9.98, 12.54)
Diff in rate per 100 PY (95% CI)[b]	1.32 (-0.22, 2.85)		-1.02 (-2.76, 0.72)	
Hazard Ratio (95% CI)[c]	**1.16** (0.99, 1.37)		**0.92** (0.78, 1.08)	

MACE=major adverse cardiovascular event, PY=person-years.
Note: Rate per 100 PY = 100 x (number of participants with event/person-years)
a. All randomized participants who received at least 1 dose of randomized treatment.
b. A rate difference <0 indicates a lower risk with daprodustat compared to ESA/darbepoetin alfa.
c. Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.

5.4.3.4. Summary of On-Treatment MACE Analyses

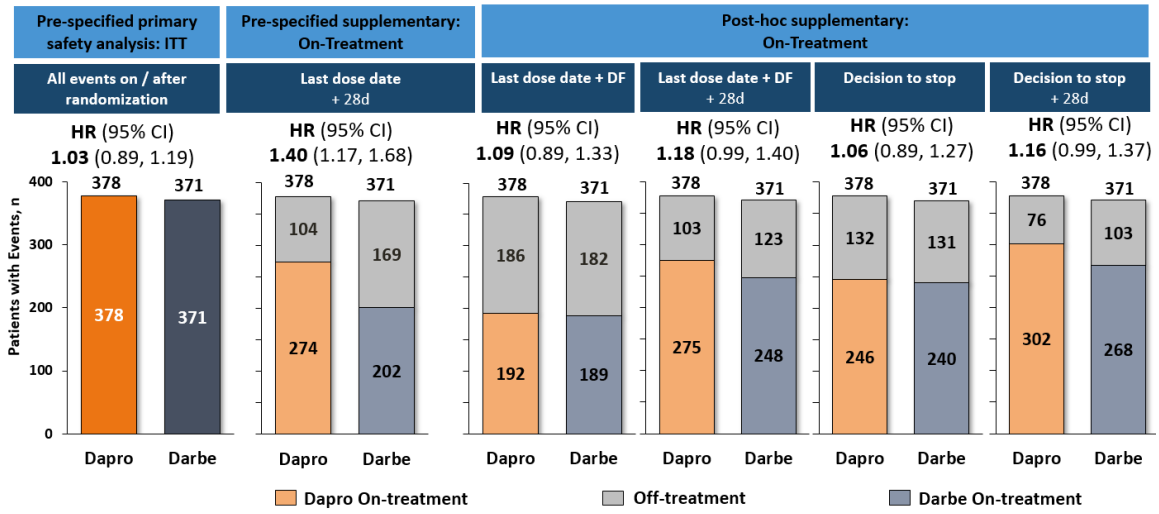
Different definitions of the on-treatment period address different clinical questions of interest, but the interpretation of any on-treatment analysis should be considered in the appropriate context due to the risk of informative censoring (i.e., decision to stop treatment could be related to perceived likelihood of a future event) and also the potential exclusion of off-treatment events that are causally linked to prior treatment exposure (i.e., events with longer latency).

The pre-specified on-treatment analysis in the ASCEND program used for CV events did not account for the differential dosing frequency across treatment groups, and in so doing, serious bias was introduced by statistical artifact. Modifying the on-treatment definition for the CV outcome studies to include a participant's dosing frequency corrects for some of this bias, most notably for ASCEND-ND which had the most disparate dosing frequencies, as does the use of the decision to stop treatment (Figure 14). The HR

of 1.40, estimated from the pre-specified on-treatment analyses, is subject to significant bias which is reduced for post-hoc on-treatment analyses with HRs estimated between 1.09 to 1.18.

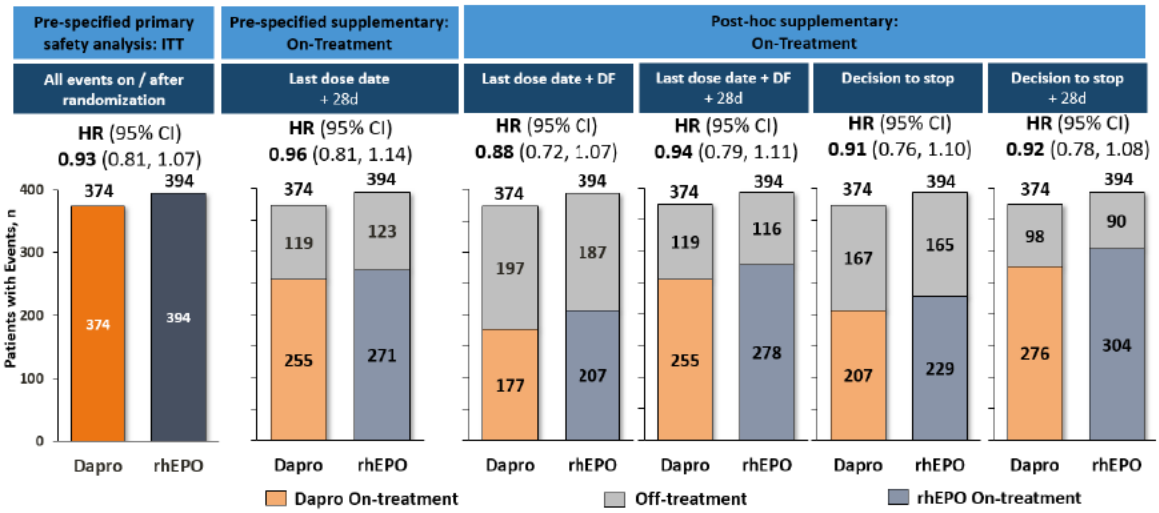
The results of these post-hoc on-treatment analyses provide on-treatment evaluations that have less bias and are more consistent with the primary ITT safety analysis for MACE, though still subject to the known limitations of all such on-treatment analyses. These limitations are illustrated in this study by the high sensitivity of classifying outcomes as occurring on-treatment, that is very dependent on the specific on-treatment definition used. As such, the pre-specified ITT primary analysis remains the most statistically robust and least biased analysis for characterizing the given treatment policy over the period of study follow-up in a manner that respects the randomization and supports statistical inference. Literature supports this view, given on-treatment analyses can overestimate or underestimate events [DeMets, 2019; Fleming, 2011; Yang, 2019], the latter of which was observed in this investigation. Taken together, these primary safety analyses demonstrate daprodustat is non-inferior to ESA for time to first MACE in patients on dialysis and not on dialysis.

Figure 14 On- and Off-Treatment MACE in ASCEND-ND: Sensitivity to On-treatment Definition



DF= dosing frequency; HR=hazard ratio.
Note: For top panel pre-specified and post-hoc definitions, refer to Table 18.

Figure 15 On- and Off-Treatment MACE in ASCEND-D: Sensitivity to On-treatment Definition



DF= dosing frequency; HR=hazard ratio.
Note: For top panel pre-specified and post-hoc definitions, refer to Table 18.

5.4.4. MACE in ASCEND-ID and ASCEND-TD

The 52-week studies ASCEND-ID and ASCEND-TD were neither designed nor sufficiently powered for a formal statistical demonstration of NI of daprodustat to ESA control in time to first MACE. Therefore, adjudicated MACE data from each of these studies, as well as individual CV components and CV events were summarized only and there were no statistical analyses of RR. First occurrence of adjudicated MACE was similar between the daprodustat and ESA control treatment groups in both studies (Table 23).

Table 23 First Occurrence of Adjudicated MACE during the Time Period for Follow-up of CV Events (ITT Population)

	ASCEND-ID		ASCEND-TD	
	Daprodustat (N=157)	Darbe (N=155)	Daprodustat (N=270)	ESA (N=137)
First Adjudicated MACE				
Number participants, n (%)	157	155	270	137
First MACE	**19 (12.1)**	**15 (9.7)**	**33 (12.2)**	**14 (10.2)**
Incidence rate per 100 PY (95% CI)	11.65 (7.02, 18.20)	9.24 (5.17, 15.24)	12.30 (8.46, 17.27)	10.02 (5.48, 16.81)
Absolute rate difference per 100 PY (95% CI)[a]	**2.41** (-4.61, 9.43)		**2.28** (-4.44, 9.00)	

MACE=major adverse cardiovascular event, MI=myocardial infarction.
Note: Rate per 100 PY = 100 x (number of participants with event/person-years)
a. A rate difference <0 indicates a lower risk with daprodustat compared to ESA.

5.4.5. Adjudicated First MACE or Thromboembolic Events and Adjudicated First MACE or Hospitalization for Heart Failure

Results for the principal secondary safety endpoints, time to first MACE or thromboembolic events, time to first MACE or hospitalization for HF, were consistent with those of the primary MACE analysis in both non-dialysis and dialysis participants (Table 24). A further discussion of MACE is provided in Section 5.4.2 and hospitalization for HF is provided in Section 5.4.7.5.

Table 24 Principal Secondary Safety Endpoints during the Time Period for Follow-up of CV Events (ITT Population)

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
First Adjudicated MACE or thromboembolic event				
First MACE or thromboembolic events, n (%)	422 (21.8)	405 (20.9)	497 (33.4)	543 (36.8)
Rate per 100 PY (95% CI)	12.34 (11.19, 13.57)	11.77 (10.65, 12.98)	15.84 (14.48, 17.30)	17.85 (16.38, 19.42)
Diff in rate per 100 PY (95% CI)[a]	0.57 (-1.08, 2.21)		-2.01 (-4.06, 0.04)	
Hazard Ratio (95% CI)[b]	**1.06** (0.93, 1.22)		**0.88** (0.78, 1.00)	
First Adjudicated MACE or hospitalization for HF				
First MACE or hospitalization for heart failure, n (%)	444 (22.9)	417 (21.6)	425 (28.6)	433 (29.3)
Rate per 100 PY (95% CI)	13.16 (11.97, 14.44)	12.22 (11.08, 13.46)	12.98 (11.77, 14.27)	13.38 (12.15, 14.70)
Diff in rate per 100 PY (95% CI)[a]	0.94 (-0.76, 2.63)		-0.40 (-2.16, 1.36)	
Hazard Ratio (95% CI)[b]	**1.09** (0.95, 1.24)		**0.97** (0.85, 1.11)	

MACE=major adverse cardiovascular event, PY=person-years.
Note: Rate per 100 PY = 100 x (number of participants with event/person-years)
a. A rate difference <0 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.
b. HR estimated using Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. HR <1 indicates lower risk with daprodustat compared with ESA/darbepoetin alfa.

5.4.6. Subgroup Analyses – ASCEND-ND and ASCEND-D

For both the ASCEND-ND and ASCEND-D studies, the risk of composite MACE was generally consistent across subgroups (Appendix Figure 25 and Appendix Figure 26, respectively. This included age, sex, weight, region, ESA use at randomization (for non-dialysis), Baseline Hgb category, CKD stage (for non-dialysis), dialysis type (HD or peritoneal dialysis; for dialysis), and hypo-responder status (for dialysis). Results of the subgroup analysis in the ASCEND-ND study indicated some heterogeneity across geographic regions (treatment by subgroup interaction: p-value=0.0760). Some heterogeneity across regions and by history of CV disease was observed in the ASCEND-D study (treatment by subgroup interaction: p-value=0.0608 and p-value=0.0844, respectively).

Heterogeneity across geographic regions was also observed in the ASCEND-ND study for the principal secondary endpoints of MACE or thromboembolic events and MACE or hospitalization for HF, which was not observed in ASCEND-D. In subgroup analyses of the 3 endpoints in ASCEND-ND, HRs were generally lower in the Asia-Pacific and Western Europe/Canada/Australia+New Zealand/Israel subgroups and higher in the Eastern Europe/South Africa, Latin America, and US subgroups, with point estimates approximately equal magnitude below and above 1, respectively. This may have resulted from random imbalance in baseline risk factors within these regions: for example, in the US subgroup there was a clinically relevant imbalance between treatment groups in the US for baseline CKD Stage 5 (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73m^2; 27% daprodustat versus 21% darbepoetin) and history of HF (21% for daprodustat versus 17% for darbepoetin) (Appendix Table 55). Declining eGFR confers a substantial and exponential increase in risk of adverse CV and HF outcomes, even with small absolute reductions in eGFR [He, 2017; House, 2019; McAlister, 2012]. Similarly, the differences in prevalence of pre-existing HF or prior venous thromboembolism (both of which were higher in the daprodustat treatment group at baseline, as compared to ESA comparator, Appendix Table 55) indicate clinically important imbalances in powerful predictors of subsequent HF hospitalization or thromboembolic events, respectively. Baseline imbalance in eGFR would, in turn, be expected to drive differences in vascular access, which was observed and represents an imbalance in the denominator when assessing thromboembolic events.

Taken together, the evidence available does not support an increased risk of first occurrence of MACE, MACE or thromboembolic events, or MACE or hospitalization for HF for the daprodustat group relative to the ESA control group for any one region or for those participants with a history of CV disease in either of the CV outcomes studies. Additional to the pre-specified subgroups, further analyses were performed to explore a subgroup of interest (participants with pre-existing HF at enrolment) on outcomes specific to HF: these results are described in more detail in Section 5.4.7.5.4.

5.4.7. Individual Adjudicated Events

Analyses of individual CV events (ACM, MI, stroke, thromboembolic events, and hospitalization for HF) were conducted as additional secondary endpoints to provide a comprehensive evaluation of CV safety data obtained in the trials. These analyses are subject (to varying degrees) to the following statistical limitations: a) reduced precision of the HR estimate due to fewer events and b) lack of adjustment for competing risks for endpoints other than ACM and c) lack of adjustment for multiplicity. This is consistent with the limitations cited in FDA draft guidance on Multiple Endpoints [FDA, 2017], which states that results for each component of a composite endpoint should be included in study reports, but in a manner that avoids overstating their role in interpretation. The guidance states that such analyses should be considered descriptive only and not alter conclusions for statistical significance of a composite primary endpoint.

Under conditions of NI of daprodustat, both trials could be expected to deliver HR point estimates for the primary safety endpoint of MACE around unity: this could result in both studies with estimates below unity, both above unity, or one trial below and the other above unity. Inferences based on statistical tests performed for individual adjudicated

events outside of the primary or principal secondary composite endpoints should be made in the context of these limitations/considerations, particularly when considering further subgrouping of these individual CV events based on demographic and potential risk factors.

Cardiovascular Outcome Studies – ASCEND-ND and ASCEND-D

Analysis of time to first CV event of the individual components of the primary composite MACE and the additional composite endpoints (MACE or thromboembolic events and MACE or hospitalization for HF; Section 5.4.5) yielded results within each study that were generally similar between treatment groups (Table 25). With the exception of hospitalization for HF (discussed further in Section 5.4.7.5), the HR point estimates for all individual events were less than unity in the ASCEND-D trial and greater than unity in the ASCEND-ND trial. For events occurring with lower frequency (stroke and thromboembolic events), point estimates deviated from unity to a greater extent, but with wide and overlapping CIs (Table 25). As described, since secondary CV safety endpoints are either constituents of MACE, or associated with overlapping risk factors, these safety endpoints are highly correlated. Clustering of constituent endpoints around the point estimate of their composite would therefore be expected and entirely consistent with confirmation of NI as demonstrated by the primary safety analysis.

Table 25 Analysis of Time to First Occurrence of Other Secondary Endpoints Related to Adjudicated MACE during the Time Period for Follow-up of CV Events (ITT Population)

	ASCEND-ND			ASCEND-D		
	Dapro (N=1937)	Darbe (N=1935)	Dapro versus Darbe	Dapro (N=1487)	ESA (N=1477)	Dapro versus ESA
	n (%)	n (%)	HR (95% CI)[a]	n (%)	n (%)	HR (95% CI)[b]
All-cause mortality[c]	301 (15.5)	298 (15.4)	**1.03** (0.87, 1.20)	294 (19.8)	300 (20.3)	**0.96** (0.82, 1.13)
CV mortality[d]	109 (5.6)	92 (4.8)	**1.20** (0.91, 1.58)	117 (7.9)	121 (8.2)	**0.95** (0.74, 1.23)
MI (fatal or non-fatal)	103 (5.3)	97 (5.0)	**1.06** (0.80, 1.40)	114 (7.7)	137 (9.3)	**0.81** (0.63, 1.04)
Stroke (fatal or non-fatal)	45 (2.3)	34 (1.8)	**1.33** (0.87, 2.07)	43 (2.9)	51 (3.5)	**0.84** (0.56, 1.25)
TEE [e] (fatal or non-fatal)	64 (3.3)	51 (2.6)	**1.27** (0.88, 1.84)	185 (12.4)	215 (14.6)	**0.84** (0.69, 1.02)
VAT	44 (2.3)	31 (1.6)		162 (10.9)	195 (13.2)	
DVT	14 (<1)	19 (<1)		17 (1.1)	14 (<1)	
PE	6 (<1)	1 (<1)		6 (<1)	6 (<1)	
Hospitalization for HF (fatal or non-fatal)	140 (7.2)	115 (5.9)	**1.22** (0.95, 1.56)	112 (7.5)	101 (6.8)	**1.10** (0.84, 1.45)

DVT=deep vein thrombosis, HF=heart failure, HR=hazard ratio, MI=myocardial infarction, PE=pulmonary embolism, TEE=thromboembolic events, VAT=vascular access thrombosis.

a. Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, ESA use at randomization and region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with darbepoetin.

b. Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type and region as covariates.

c. Time to all-cause mortality was assessed during the time period for vital status.

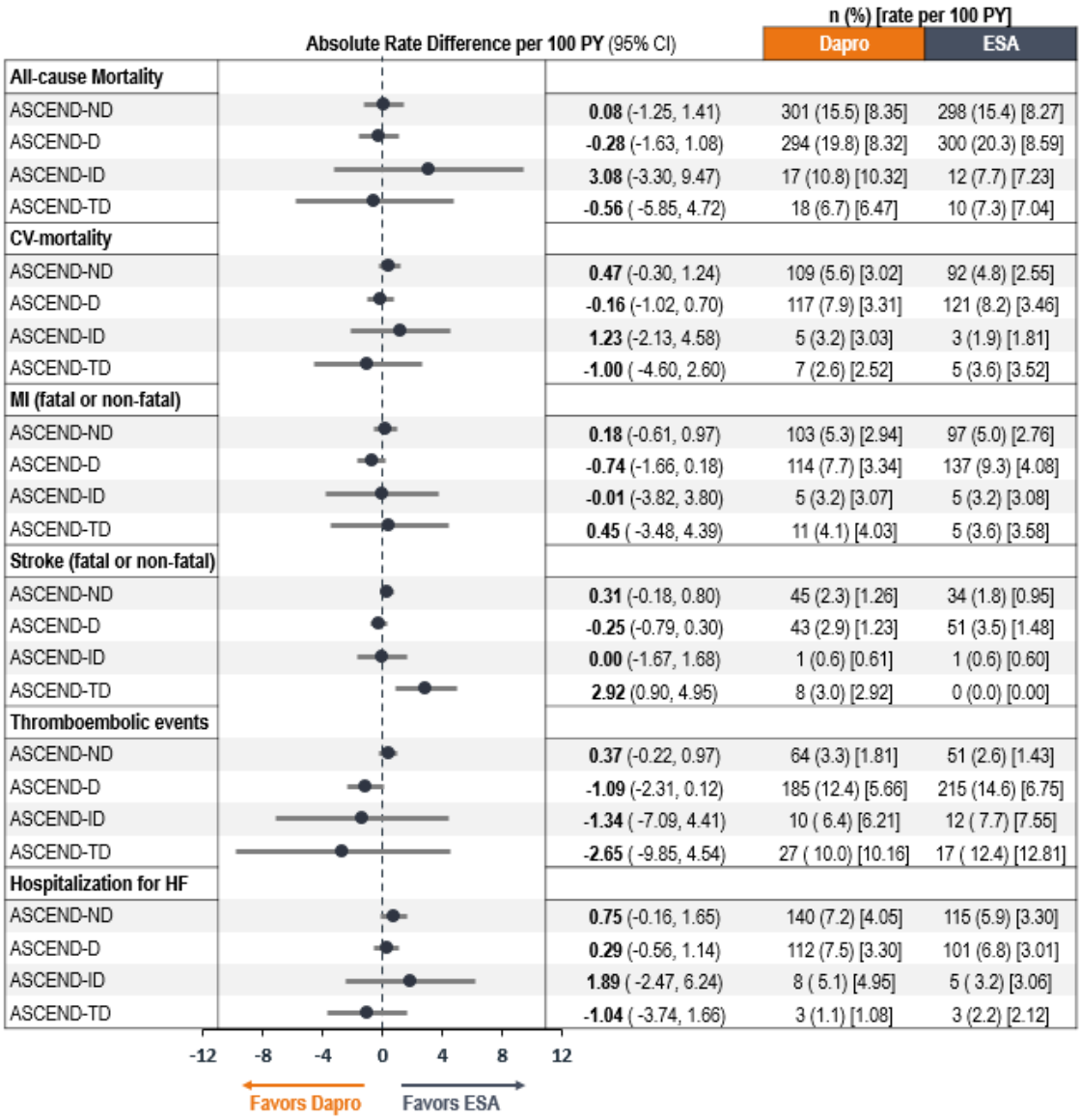
d. CV mortality included all deaths judged to have a CV primary cause as well as deaths with undetermined primary cause - either presumed sudden death or presumed CV death (refer to Table 26 for causes of death).

e. TEE defined as VAT, DVT or PE.

All Active-Controlled Studies

The first occurrence of individual CV events across all 4 active-controlled studies is presented in Figure 16. To aid clinical interpretation and comparison of these events across studies of differing size and duration of follow-up, incidences rates and absolute rate differences per 100 PY with their 95% CIs are presented. Interpretation of the ASCEND-ID and ASCEND-TD study results should consider that these studies had shorter follow-up and were not specifically designed or sufficiently powered to formally assess CV safety.

Figure 16 Absolute Rate Difference for First Occurrence of Individual CV Events by Study (Active-Controlled Studies)



HF=heart failure, MI=myocardial infarction.
Note: CV mortality included all deaths judged to have a CV primary cause as well as deaths with undetermined primary cause either presumed sudden death or presumed CV death (refer to Table 26 for causes of death).
Statistical analyses of relative risk were not pre-specified or conducted in ASCEND-ID and ASCEND-TD as these studies were not designed or sufficiently powered to formally assess CV safety.
TEE defined as VAT, DVT or PE
ESA controls were darbepoetin alfa (ASCEND-ND, ASCEND-ID), epoetin alfa (ASCEND-TD) or both (ASCEND-D).
Rate per 100 PY = 100 x (number of participants with event/person-years)

5.4.7.1. Mortality

Adjudicated causes of death in the CV outcomes studies were generally similar between treatment groups (Table 26). In both studies, the leading cause of death was infection.

Table 26 Adjudicated Causes of Death during the Time Period for Vital Status (ITT Population)

	ASCEND-ND			ASCEND-D		
	dapro n(%) (N=1937)	darbe n(%) (N=1935)	Difference (%)	dapro n(%) (N=1487)	ESA n(%) (N=1477)	Difference (%)
Deaths	**301 (15.5)**	**298 (15.4)**	**0.14**	**294 (19.8)**	**300 (20.3)**	**-0.54**
Cause of Death						
Cardiovascular	**89 (4.6)**	**70 (3.6)**	**0.98**	**96 (6.5)**	**91 (6.2)**	**0.29**
Sudden cardiac death	34 (1.8)	31 (1.6)	0.15	47 (3.2)	39 (2.6)	0.52
Heart failure/cardiogenic shock	20 (1.0)	13 (0.7)	0.36	14 (0.9)	11 (0.7)	0.20
Stroke	14 (0.7)	11 (0.6)	0.15	13 (0.9)	15 (1.0)	-0.14
Acute myocardial infarction	9 (0.5)	9 (0.5)	0.00	12 (0.8)	9 (0.6)	0.20
Other cardiovascular causes	5 (0.3)	1 (0.1)	0.21	6 (0.4)	4 (0.3)	0.13
Cardiovascular hemorrhage	2 (0.1)	1 (0.1)	0.05	1 (0.1)	6 (0.4)	-0.34
Non-cardiovascular	**149 (7.7)**	**148 (7.6)**	**0.04**	**132 (8.9)**	**155 (10.5)**	**-1.62**
Infection (includes sepsis)	90 (4.6)	90 (4.7)	0.00	77 (5.2)	90 (6.1)	-0.92
Renal	20 (1.0)	22 (1.1)	-0.10	15 (1.0)	15 (1.0)	-0.01
Malignancy	11 (0.6)	14 (0.7)	-0.16	15 (1.0)	19 (1.3)	-0.28
Gastrointestinal	6 (0.3)	1 (0.1)	0.26	7 (0.5)	7 (0.5)	0.00
Hemorrhage [a]	6 (0.3)	1 (0.1)	0.26	5 (0.3)	6 (0.4)	-0.07
Pulmonary	6 (0.3)	5 (0.3)	0.05	3 (0.2)	4 (0.3)	-0.07
Undetermined	**63 (3.3)**	**80 (4.1)**	**-0.88**	**66 (4.4)**	**54 (3.7)**	**0.78**
Unknown death	43 (2.2)	58 (3.0)	-0.78	45 (3.0)	24 (1.6)	1.40
Presumed sudden death	11 (0.6)	11 (0.6)	0.00	11 (0.7)	15 (1.0)	-0.28
Presumed cardiovascular death	9 (0.5)	11 (0.6)	-0.10	10 (0.7)	15 (1.0)	-0.34

Note: CV and Non-CV causes of death occurring in ≥0.3% in any group are presented. The analysis of time to CV mortality (presented in Table 25 and Figure 16) includes all deaths indicated as having a CV primary cause of death as well as deaths with an undetermined primary cause of death that are indicated to be either presumed sudden death or presumed CV death.

a. Excluding hemorrhagic strokes and bleeding in the setting of coronary revascularization.

5.4.7.2. Myocardial Infarction

The proportion of participants with first occurrence of adjudicated MI (fatal or non-fatal) was generally similar between treatment groups in each of the CV outcomes studies, with an absolute treatment rate difference (daprodustat minus ESA) of <0.2 events per 100 PY (Figure 16). The smaller dialysis studies (ASCEND-ID and ASCEND-TD) supported results observed in the larger CV outcomes studies with treatment rate differences of ≤0.45 events per 100 PY.

In the post-marketing spontaneous reports from Japan, there were 20 events of MI in 20 patients, with a reporting rate of 0.05 events per 100 PY. The average age of the patients was 82 years and the reported gender was 35% female, 55% male, and 10% unknown. Of the reported cases, 4 (20%) were fatal. A GSK internal analysis of healthcare data from Japan reveals an incidence rate of 0.04 to 0.36 events per 100 PY in CKD patients not on dialysis, and 1.64 events per 100 PY in CKD patients on dialysis [GSK Data on File 2022N519895_00; GSK Data on File 2022N519896_00; GSK Data on File 2022N519897_00]. The reporting rate from our spontaneous post-marketing data is lower than observed incidence rates in clinical practice in Japan.

5.4.7.3. Stroke

Across the ASCEND Phase 3 program, few participants experienced a fatal or non-fatal stroke in each study (Table 25).

In ASCEND-ND, ASCEND-D, and ASCEND-ID, the incidence of first adjudicated strokes was similar between treatment groups, with an absolute treatment rate difference (daprodustat minus ESA) of <0.4 events per 100 PY (Figure 16).

In the ASCEND-TD study, which evaluated TIW dosing in dialysis participants, the imbalance in first adjudicated strokes was an outlier (Figure 16), with strokes reported in 8/270 participants treated with daprodustat and 0/137 participants in the ESA control group. Even when considering the 2:1 randomization and resulting small sample size in the control group, the observation of zero strokes with ESA treatment is unexpected and below the incidence rate observed in the literature [Power, 2012]. Important factors when considering these data therefore include the reduced precision in the HR estimate, the different randomization schedule (2:1 daprodustat to control), and the absence of an association of stroke events with daprodustat dose or Hgb levels. Despite the potential for higher individual doses to be administered in the ASCEND-TD study (i.e., 2x the daily dose in ASCEND-D, up to 48 mg), participants who experienced stroke events in ASCEND-TD were on similar doses of daprodustat to those in ASCEND-D; in ASCEND-TD the median dose prior to the stroke was 4 mg TIW and the median dose during the first year in ASCEND-D among all patients was 6 mg QD. Of note, the ASCEND-D study represents a much larger evaluable population with dialysis, where fewer stroke events occurred in the daprodustat group than in the ESA control

The totality of data across the Phase 3 program does not support an increased risk of stroke with daprodustat compared to ESAs. Further, post-marketing data from Japan showed there were 92 events of stroke in 92 patients, with a reporting rate of 0.22 events per 100 PY. The average age of the patients was 82 years and the reported gender was 46% female, 40% male, and 14% unknown. Of the reported cases, 7% were fatal. GSK internal analyses of healthcare data from Japan reveals an incidence of 0.64 to 1.77 events per 100 PY in Japanese CKD patients not on dialysis, and 0.95 events per 100 PY in CKD patients on dialysis. The reporting rate from our spontaneous post-marketing data is lower than observed incidence rates in clinical practice in Japan [GSK Data on File 2022N519895_00, GSK Data on File 2022N519896_00, GSK Data on File 2022N519897_00].

5.4.7.4. Thromboembolic Events

The adjudicated composite of thromboembolic events measured in the CV outcomes studies comprised deep vein thrombosis (DVT), pulmonary embolism (PE), and vascular access thrombosis (VAT). As compared with ESA controls, there was a lower incidence of thromboembolic events in the daprodustat group in ASCEND-D (12.4% daprodustat, 14.6% ESA) and a higher incidence in ASCEND-ND (3.3% daprodustat, 2.6% ESA, Figure 16). The overall rate per 100 PY in the ASCEND-ND population was substantially lower (1.81 daprodustat, 1.43 ESA) than in ASCEND-D (5.66 daprodustat, 6.75 ESA), driven by more VAT events across the dialysis population, as would be expected given the prevalence of vascular access in that population.

DVT and PE are typically considered together in the context of venous thromboembolism, given their shared pathology and clinical relatedness. In ASCEND-ND, the incidence of DVT and PE combined was similar in the 2 treatment groups (Table 25). The imbalance in thromboembolic events in ASCEND-ND (not favoring daprodustat, absolute incidence rate difference of <0.4 events per 100 PY) and ASCEND-D (not favoring ESA control, absolute incidence rate difference of >1 event per 100 PY) resulted from differences in VAT events, in different directions (Figure 16, Table 25).

When evaluating VAT events, it is important to consider the proportion and time in which participants are at risk of VAT, neither of which were controlled for in the ASCEND-ND study. For enrolment in ASCEND-ND, participants should not have been receiving or scheduled to start dialysis within 90 days of study start. As a result, only a minority of participants had vascular access at enrolment (daprodustat: 114 [5.9%], darbepoetin: 104 [5.4%]). Further, during the study there was a higher number of participants initiating HD with new vascular access in the daprodustat group (daprodustat: 474 [24.5%], darbepoetin: 459 [23.7%]), which represents a higher denominator at risk of VAT, irrespective of drug therapy. This is of note, as the criteria for VAT were broad (the absence of bruit or thrill and/or the inability to successfully initiate dialysis via the arteriovenous fistula or arteriovenous graft after the successful surgical procedure) and did not require objective imaging confirmation for adjudication. Therefore, VAT events will include patency failure events, which in the context of recent access formation, occur at a high rate and are recognized to be driven by risk factors unrelated to underlying thrombotic risk or any potential drug effect [Dember, 2008; Dixon, 2009; Jain, 2009; Lok, 2012; MacRae, 2016; Irish, 2017].

The clinical context of VAT events in the ASCEND-ND population (patients with new vascular access initiated during the study) is therefore similar to that in the ASCEND-ID population. In this context, the ASCEND-ID study is more suitable to assess for a treatment group difference in VAT as it was prospectively designed for a randomized treatment group comparison, and participants were stratified by dialysis type (and hence risk of VAT). In the ASCEND-ID study (N=312), the incidence of participants with thromboembolic events was similar between groups (10 [6.4%] daprodustat versus 12 [7.7%] darbepoetin), with a similar number with VAT (9 [5.7%] daprodustat versus 11 [7.1%] darbepoetin).

ASCEND-D offers the most robust study to assess for any treatment effect on the risk of VAT for participants with established vascular access (with 89% of the population on HD at randomization, with vascular access and a prospective study design for a randomized comparison of treatment groups). ASCEND-D also offers the most extensive dataset for evaluable VAT events in a single study from across the daprodustat program. A post-hoc analysis of time to first VAT showed that there were over 4.5-fold more first VAT events in ASCEND-D, as compared to ASCEND-ND (Appendix Table 52). In ASCEND-D, there was a lower incidence of participants with first VAT in the daprodustat group, 164 (11.0%), compared with the ESA control, 201 (13.6%), with a 95% CI for HR that excluded 1.

Our experience from the post-marketing setting in Japan is consistent with the totality of data across the Phase 3 studies and demonstrates that daprodustat has a similar safety profile for the risk of thromboembolic events, as compared to the respective ESA controls. In the post-marketing spontaneous reports from Japan, thromboembolic events were defined as a compilation of DVT, PE, and VAT. There were 51 events of thromboembolic events in 51 patients, with a reporting rate of 0.12 events per 100 PY. The average age of the patients was 78 years and the reported gender was 33% female, 43% male, and 24% unknown. Of the reported cases, 2% were fatal. GSK internal analyses of healthcare data from Japan reveals an incidence rate of 1.12 to 1.4 events per 100 PY in CKD patients not on dialysis, and 0.31 events per 100 PY in CKD patients on dialysis [GSK Data on File 2022N519895_00; GSK Data on File 2022N519896_00; GSK Data on File 2022N519897_00]. The reporting rate from our spontaneous post-marketing data is lower than observed incidence rates in clinical practice in Japan.

5.4.7.5. Heart Failure

As part of the assessment of CV safety for daprodustat, time to the composite of first MACE or hospitalization for HF was included as a principal secondary endpoint in the ASCEND-D and ASCEND-ND studies. This was designed to provide a measure that integrates an assessment of HF, with the risk of atherosclerotic CV disease. Data on hospitalization for HF as an individual endpoint was also examined as part of the other secondary endpoints. With regard to these endpoints and consistent with draft guidance from FDA on Multiple Endpoints in Clinical Trials [FDA, 2017], these analyses should be considered descriptive and do not reflect formal hypothesis testing or alter conclusions on statistical significance of composite primary endpoints (or principal secondary endpoints, adjusted for multiplicity). This is of particular importance for time to event analyses for hospitalization for HF, which censor patients at death, and in doing so, introduce a fundamental flaw of censoring a highly informative event in the population (i.e., the most serious adverse effect in HF - sudden cardiac death).

Although results from these secondary endpoints did not convincingly demonstrate a clear treatment group difference, the data observed prompted additional post-hoc analyses aimed at identifying any treatment effect specific to HF risk. The analyses utilized the appropriate endpoints (time to first occurrence, or recurrent analysis of the composite of ACM or hospitalization for HF) and subgroups (those with or without pre-existing HF). These are presented alongside the pre-specified secondary analyses below.

5.4.7.5.1. MACE or Hospitalization for HF

Hospitalization for HF was adjudicated by an independent adjudication committee blinded to treatment allocation. Criteria for adjudication as hospitalization for HF events were:

- Admission to hospital with a primary diagnosis of HF
- Length of stay >24h, or discharge date post-dates admission date
- New or worsening symptoms of HF
- Two clinical symptoms, or one clinical symptom and one laboratory finding
- Intensification of treatment

The incidence rates observed for MACE or hospitalization for HF were generally similar between treatment groups in both studies, although in the ASCEND-ND trial, there were more events in the daprodustat group (Figure 16, Table 27). When assessing the components within the composite endpoint, the number of ACM events were similar between treatment groups in both ASCEND-D (14.8% daprodustat, 14.6% ESA) and ASCEND-ND (11.6% daprodustat, 12.2% darbepoetin): the higher number of composite events with daprodustat in ASCEND-ND was principally due to differences in non-fatal hospitalization for HF.

When evaluating time to first hospitalization for HF alone, there was a higher number of events in the daprodustat group compared with the control group in both studies, with 25 and 11 excess events in the daprodustat versus ESA groups in the ASCEND-ND and ASCEND-D trial, respectively (Table 27).

Post-hoc recurrent event analyses were performed utilizing a Negative Binomial Model (which assumes each individual has their own underlying rate of events) to determine the rate ratio between trial groups, thereby assessing the burden of morbidity conferred by risk of recurrent hospitalization (consistent with the approach employed in recent HF trials [Clagget, 2018]. Results of the recurrent event analyses for each endpoint (Table 27) are summarized below.

- For the principal secondary endpoint of MACE or hospitalization for HF: Results of the recurrent event analysis (rate ratio) were consistent with results from the time to first event analysis (HR) for both studies.
- For the individual endpoint of hospitalization for HF: In the ASCEND-D trial, when accounting for recurrent events, there was no increase with daprodustat (rate ratio 1.03, 95% CI: 0.76, 1.40), while in ASCEND-ND, an increase was seen in the rate ratio for recurrent hospitalization for HF (rate ratio 1.45, 95% CI: 1.09, 1.94).

Table 27 Analyses of Composite Endpoint (MACE or Hospitalization for HF) and Hospitalization for HF (ITT Population)

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
First Adjudicated MACE or hospitalization for HF				
First MACE or hospitalization for HF, n (%)	444 (22.9)	417 (21.6)	425 (28.6)	433 (29.3)
All-cause Mortality	225 (11.6)	237 (12.2)	220 (14.8)	215 (14.6)
Non-fatal MI	86 (4.4)	81 (4.2)	92 (6.2)	112 (7.6)
Non-fatal Stroke	26 (1.3)	17 (0.9)	28 (1.9)	33 (2.2)
Non-fatal hospitalization for HF	107 (5.5)	82 (4.2)	85 (5.7)	73 (4.9)
Rate per 100 PY (95% CI)	13.16 (11.97, 14.44)	12.22 (11.08, 13.46)	12.98 (11.77, 14.27)	13.38 (12.15, 14.70)
Diff in rate per 100 PY (95% CI)[a]	0.94 (-0.76, 2.63)		-0.40 (-2.16, 1.36)	
Hazard Ratio (95% CI)[b]	**1.09** (0.95, 1.24)		**0.97** (0.85, 1.11)	
Recurrent MACE or Hospitalization for HF (Post-hoc)				
Rate Ratio (95% CI)[c]	**1.09** (0.93, 1.29)		**0.90** (0.76, 1.07)	
First Adjudicated hospitalization for HF				
First hospitalization for HF, n (%)	140 (7.2)	115 (5.9)	112 (7.5)	101 (6.8)
Rate per 100 PY (95% CI)	4.05 (3.41, 4.78)	3.30 (2.73, 3.96)	3.30 (2.72, 3.97)	3.01 (2.45, 3.65)
Diff in rate per 100 PY (95% CI)[a]	0.75 (-0.16, 1.65)		0.29 (-0.56, 1.14)	
Hazard Ratio (95% CI)[b]	**1.22** (0.95, 1.56)		**1.10** (0.84, 1.45)	
Recurrent Hospitalization for HF (Post-hoc)				
Rate Ratio (95% CI)[c]	**1.45** (1.09, 1.94)		**1.03** (0.76, 1.40)	

HF=heart failure, MACE=major adverse cardiovascular event, MI=myocardial infarction, PY=person-years.
Note: Rate per 100 PY = 100 x (number of participants with event/person-years)

a. A rate difference <0 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.

b. HR estimated using Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. HR <1 indicates lower risk with daprodustat compared with ESA/darbepoetin alfa.

c. Ratio of model estimated rates (Dapro/ESA) and CI are based on a negative binomial model with treatment, dialysis type (ASCEND-D only), prior ESA use (ASCEND-ND only), and region as covariates and the logarithm of follow-up time in years as an offset variable. Rate ratio <1 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.

5.4.7.5.2. Further Characterization of Outcomes Specific to HF (Post-hoc)

Data collected in case record forms linked with adjudicated events were reviewed in post-hoc summaries. In the ASCEND-ND trial, the majority of first hospitalization for HF events occurred prior to dialysis initiation (daprodustat 106/140 [76%] and darbepoetin 95/115 [83%]), with 16 more first hospitalization for HF events in the daprodustat group attributed by the investigator to fluid overload as the primary cause, rather than specifically to HF (45/140 [32%] versus 29/115 [25%], respectively). While concordance between investigator-reported and adjudicated hospitalization for HF events was broadly similar between trial groups, the proportion of evaluated events that was positively adjudicated was higher in the daprodustat group relative to the darbepoetin

group in the ASCEND-ND trial (daprodustat, 46.5%; darbepoetin, 35.9%), but similar in the ASCEND-D trial (daprodustat, 32.9%; ESA, 30.6%).

In the ASCEND-ND trial, a greater percentage of patients in the daprodustat group had CKD stage 5 (37% in daprodustat versus 35% in darbepoetin) and a smaller percentage had CKD stage 3 (18% daprodustat versus 19% in darbepoetin) at baseline (Table 16). Given the strong association of eGFR decline with HF risk, this small difference in CKD stage reflects a clinically meaningful difference in eGFR not favoring daprodustat. As the population with low eGFR is uniquely predisposed to fluid overload associated with uremia, there is clinical uncertainty over the nature of hospitalization for HF events. There may have been a higher proportion of events relating to fluid-driven presentation in the daprodustat group, resulting from the imbalance in baseline CKD.

Given that patients with HF are at a high risk of death, the rate of death occurring in patients experiencing a hospitalization for HF event during trial participation is an important measure of the clinical implications of hospitalization for HF events. In the ASCEND-ND trial, of the patients experiencing a hospitalization for HF event, there was a similar number of subsequent deaths (daprodustat 47/140 [33.6%], darbepoetin 45/115 [39.1%]). This suggests that the imbalance observed between groups may be attributed to an excess of less prognostically significant events, consistent with the broad spectrum of clinical presentations that could be positively adjudicated as hospitalization for HF events.

5.4.7.5.3. Analysis of Time to ACM or First Hospitalization for HF (Post-hoc)

Death is a key informative event in the evaluation of risk related to HF, as patients are at high risk of sudden cardiac death from the underlying HF, which can be greater than the risk of progressive decompensation or cardiac pump failure [Wang, 2010]. A composite endpoint of ACM or hospitalization for HF is therefore more suitable than hospitalization for HF alone in assessing HF risk, as it accounts for the competing risk of death, captures the most clinically important outcome of hospitalization-free survival, and is consistent with the accepted approach of evaluating HF outcomes in CKD populations [Singh, 2006; Swedberg, 2013; Eckardt, 2021]. In contrast, hospitalization for HF alone introduces bias by censoring participants at time of death, who would otherwise be at high risk of hospitalization. This is particularly problematic in those participants with a history of HF, where censoring becomes highly informative due to an increased likelihood that a death is related to the underlying HF of a participant.

In the ASCEND-D trial, time to first occurrence of ACM or hospitalization for HF was similar for daprodustat and ESA control (Figure 18). This composite endpoint included 11 more hospitalization for HF events in the daprodustat group, but 14 more deaths in the ESA treatment group (Appendix Table 54). In the ASCEND-ND trial, there was a higher number of ACM or first hospitalization for HF events in the daprodustat group (393 versus 368). This difference in events was driven by a higher number of hospitalizations for HF in the daprodustat group relative to the darbepoetin group (140 versus 115; Appendix Table 54).

In the ASCEND-D trial, multiple occurrences (2 or more) of the composite of ACM or hospitalization for HF were reported for 55 participants in the daprodustat group and

53 participants in the ESA group. When accounting for recurrent events, there was no increase seen in HF risk in models for ACM or hospitalization for HF (rate ratio 0.97, 95% CI: 0.82, 1.15). In the ASCEND-ND trial, multiple occurrences (2 or more) of the composite of ACM or hospitalization for HF were reported for 68 participants on daprodustat and 50 participants on darbepoetin. When accounting for recurrent events, the increase observed for occurrence of first events was preserved in the rate ratio for recurrent events of ACM or hospitalization for HF (rate ratio 1.11, 95% CI: 0.94, 1.32).

Recurrent event analyses were therefore consistent with the time to first event analyses for the composite endpoint of ACM or hospitalization for HF.

5.4.7.5.4. Analysis by History of HF Subgroups (Post-hoc)

To further characterize HF outcomes, a clinically recognizable subgroup of patients with a history of HF was identified by medical conditions at enrollment. This group represented approximately 13% of the study population in ASCEND-ND, and 17% of the study population in ASCEND-D. Participants with a history of HF would be expected to be most sensitive to any treatment risk for HF complications, and therefore this subgroup was subject to additional post-hoc analyses.

The HR point estimates for analyses by history of HF subgroup are summarized in Table 28 for a) MACE or hospitalization for HF, b) hospitalization for HF alone, and c) the more methodologically appropriate and clinically complete composite endpoint of ACM or hospitalization for HF (Figure 17).

Table 28 Summary of Time to First Hospitalization for HF and its Composite Endpoints by History of HF Subgroup (ITT Population)

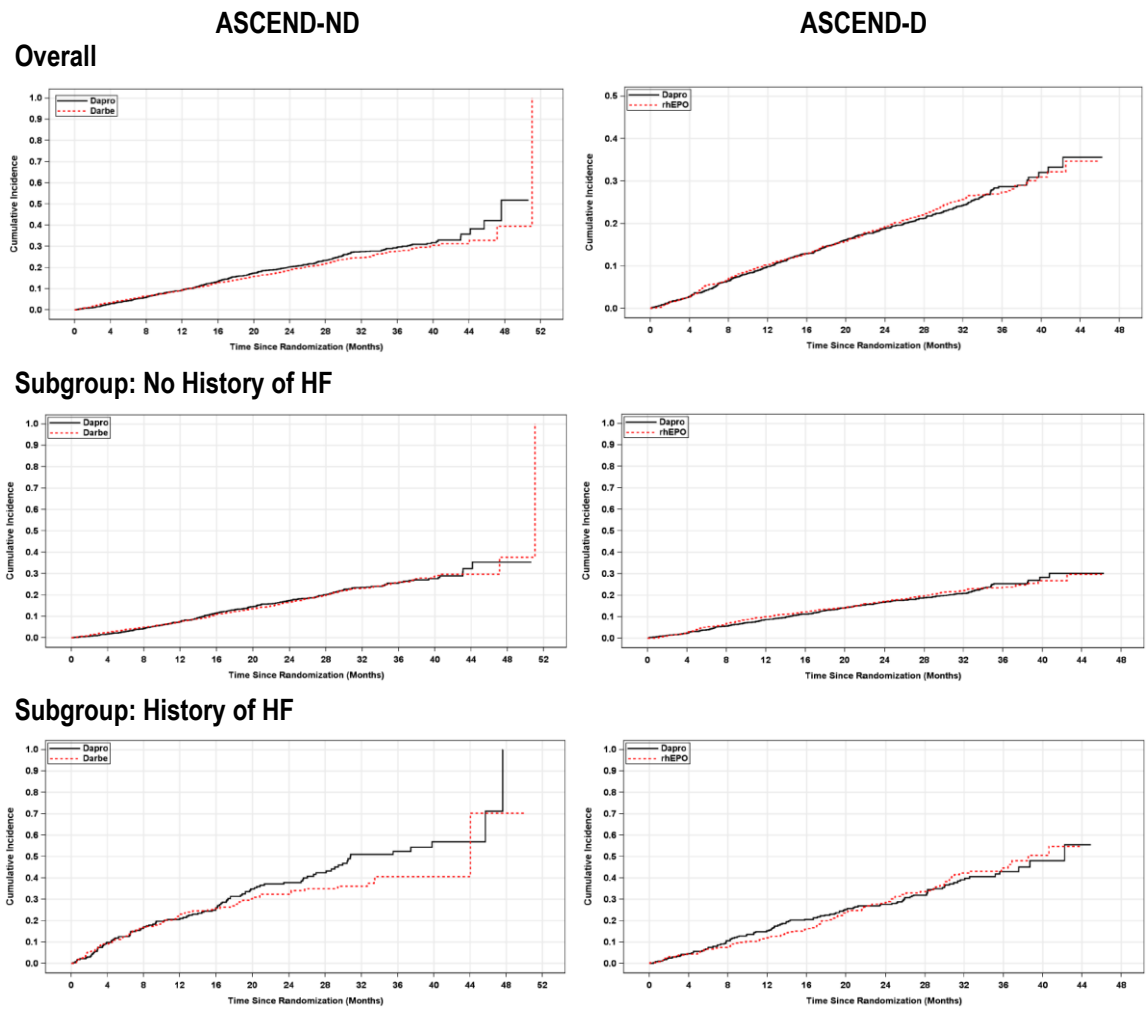
Endpoint	History of HF subgroup[a]	Dapro n/N (%)	ESA control n/N (%)	Hazard Ratio (95% CI)
ASCEND-ND				
Time to first MACE or hospitalization for HF	No	331/1671 (19.8)	334/1679 (19.9)	1.02 (0.88, 1.19)
	Yes	113/265 (42.6)	83/254 (32.7)	1.22 (0.92, 1.62)
Time to first hospitalization for HF	No	86/1671 (5.1)	81/1679 (4.8)	1.08 (0.79, 1.46)
	Yes	54/265 (20.4)	34/254 (13.4)	1.37 (0.89, 2.11)
Time to first ACM or hospitalization for HF	No	289/1671 (17.3)	292/1679 (17.4)	1.02 (0.87, 1.21)
	Yes	104/265 (39.2)	76/254 (29.9)	1.20 (0.89, 1.62)
ASCEND-D				
Time to first MACE or hospitalization for HF	No	306/1220 (25.1)	318/1222 (26.0)	0.95 (0.81, 1.11)
	Yes	119/267 (44.6)	115/254 (45.3)	1.03 (0.80, 1.33)
Time to first hospitalization for HF	No	65/1220 (5.3)	69/1222 (5.6)	0.93 (0.66, 1.30)
	Yes	47/267 (17.6)	32/254 (12.6)	1.52 (0.97, 2.38)
Time to first ACM or hospitalization for HF	No	260/1220 (21.3)	263/1222 (21.5)	0.98 (0.82, 1.16)
	Yes	103/267 (38.6)	103/254 (40.6)	0.99 (0.76, 1.31)

ACM=all-cause mortality, HF=heart failure, MACE=major adverse cardiovascular event.
a. History of Heart Failure was defined as having a medical condition of “heart failure” at enrolment

These analyses demonstrate that in the dialysis population from ASCEND-D, there was no evidence of an increased risk of ACM or hospitalization for HF for daprodustat compared with ESA, irrespective of whether patients had pre-existing HF (history of HF) (Figure 18). Further, in ASCEND-ND, there was no evidence of an increased risk of ACM or hospitalization for HF for daprodustat compared with darbepoetin alfa in those participants without pre-existing HF (subgroup with no history of HF). However, in the subgroup with pre-existing HF (13% of the study population), an increased risk of ACM or hospitalization for HF was seen for daprodustat compared with darbepoetin alfa (HR 1.20, 95% CI: 0.89, 1.62). This increase was largely driven by a higher number of hospitalization for HF events within the composite (20.4% with daprodustat, 13.4% ESA, Appendix Table 54).

Results were similar when the subgroup analysis was performed using a 4-term cardiac subgroup (which included HF, left ventricular systolic dysfunction, left ventricular diastolic dysfunction or pulmonary hypertension) that was pre-specified as one of 20 subgroup categories to assess homogeneity of treatment effect, with the majority of events in this broader subgroup derived from those with HF at baseline.

Figure 17 Kaplan-Meier Plots of Time to First Occurrence of ACM or Hospitalization for HF, Overall and by History of HF Subgroups (ITT Population)



HF=heart failure. Note: Y-axes are not drawn to the same scale.

5.4.7.5.5. Post-marketing Data for Heart Failure

Overall, the reporting rate of HF in the Japan post-marketing data is low; there were 128 events of HF in 121 patients, with a reporting rate of 0.29 events per 100 PY. The average age of the patients was 86 years and the reported gender was 45% female, 40% male, and 15% unknown. Of the reported cases, 46% were fatal. Fifty-five patients (45%) had reported a prior history of HF, and 80 patients (66%) reported risk factors for CV diseases. In terms of dialysis status: 21% were on dialysis, 36% were not on dialysis, and the dialysis status of 43% was not known. GSK internal analyses of healthcare data from Japan reveals an incidence rate of 1.21 to 1.78 events per 100 PY in CKD patients not on dialysis, and 1 event per 100 PY in CKD patients on dialysis [GSK Data on File 2022N519895_00; GSK Data on File 2022N519896_00; GSK Data on File 2022N519897_00]. The reporting rate from our spontaneous post-marketing data is lower than observed incidence rates in clinical practice in Japan.

5.4.7.5.6. Summary of Heart Failure Risk

Post-hoc analyses specifically designed to assess hospitalization for HF risk while appropriately accounting for patient survival and the recognized risk of sudden death (the most severe risk/complication from HF) using the composite endpoint of time to ACM or first hospitalization for HF, demonstrate that any potential increase in HF risk for daprodustat compared with ESA control is confined to the non-dialysis patient population in the ASCEND-ND trial with a history of HF. In conjunction with a lack of non-clinical findings for cardiac toxicity, a lack of any adverse changes on left ventricular ejection fraction (LVEF) with echocardiography at up to 24 weeks exposure in Phase 2 studies, and the evidence presented here from the ASCEND CV outcomes trials, the totality of data provides significant evidence that there is no increased risk of incident HF with daprodustat. A summary for each population is displayed in Figure 18 and provided below.

Dialysis patients

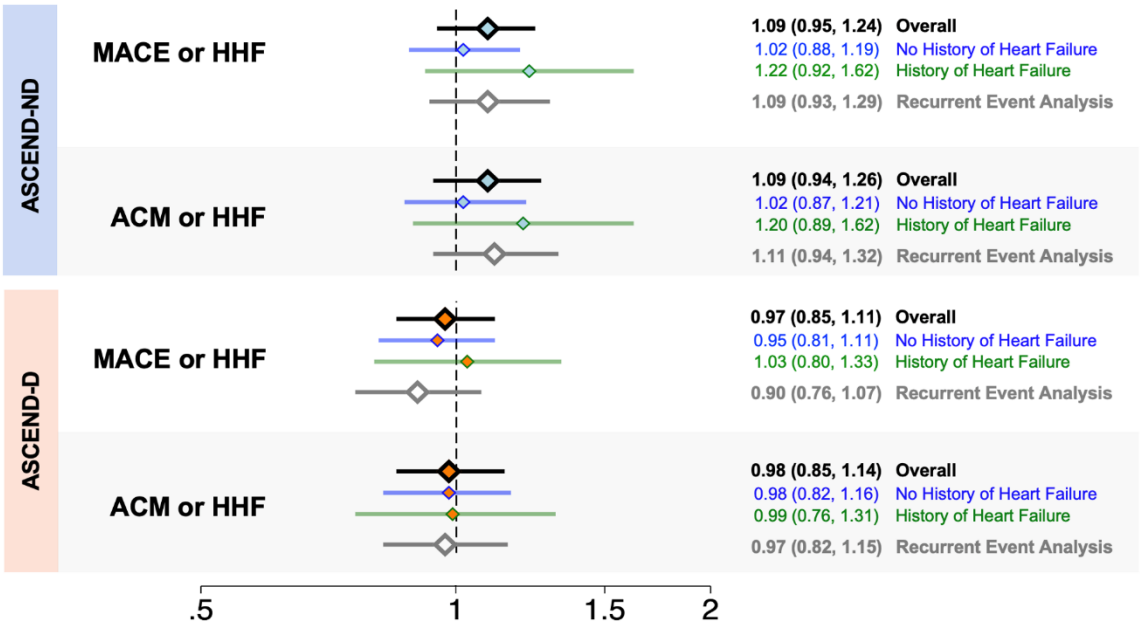
- There was no evidence of an increased risk of ACM or hospitalization for HF for daprodustat compared with ESA, irrespective of whether patients had pre-existing HF.

Non-dialysis patients

- Without pre-existing HF: There was no evidence of an increased risk of ACM or hospitalization for HF for daprodustat compared with darbepoetin alfa.
- With pre-existing HF: An increased risk of ACM or hospitalization for HF was seen for daprodustat compared with darbepoetin alfa (HR 1.20, 95% CI: 0.89, 1.62).

Pre-dialysis patients with advanced CKD and co-existing HF are uniquely sensitive to fluid overload, irrespective of drug therapy. In a clinical setting, this vulnerable group of patients are readily identified, and current clinical practice standards dictate frequent monitoring and close supervision of fluid balance in these patients.

Figure 18 Summary of Analysis of Time to First Occurrence of Hospitalization for HF and the Composite Endpoints by History of HF Subgroups (ITT Population)



ACM=all-cause mortality, HHF=Hospitalization for HF, MACE=major adverse cardiovascular event
Note: Estimates of the Hazard Ratio with 95% CI are shown, except for recurrent event analyses which represent the estimates and confidence intervals for the Negative Binomial Rate Ratio.

5.5. General Safety

5.5.1. Overview of TEAEs

An overview of TEAEs in the 4 active-controlled studies is presented in Table 29. The AEs for these studies are summarized using the definition for treatment-emergent adjusting for dosing frequency (see Sections 5.3 and 5.4.3). AE summaries and analyses captured all investigator-reported events, independent of any adjudication. When adjusted for dosing frequency, the incidence of TEAEs across the ASCEND studies was generally similar, although AEs leading to treatment discontinuation were more frequent in the daprodustat group (Table 29; Table 32). **Refer to Appendix 10.7 for a presentation of the pre-specified AE data.**

Table 29 Active-controlled Studies: Overview of TEAEs (Safety Population); Dosing Frequency Adjusted

	Dapro n (%)	ESA n (%)	Risk Difference (%)
Non-dialysis			
ASCEND-ND	**(N=1937)**	**(N=1933)**	
Any TEAE	1545 (80)	1559 (81)	-0.89
Any TEAE leading to discont. of RT	247 (13)	201 (10)	2.35
Any Serious TEAE	850 (44)	817 (42)	1.62
Dialysis			
ASCEND-D	**(N=1482)**	**(N=1474)**	
Any TEAE	1307 (88)	1275 (86)	1.69
Any TEAE leading to discont. of RT	216 (15)	195 (13)	1.35
Any Serious TEAE	773 (52)	790 (54)	-1.44
ASCEND-TD	**(N=270)**	**(N=136)**	
Any TEAE	205 (76)	108 (79)	-3.49
Any TEAE leading to discont. of RT	23 (9)	10 (7)	1.17
Any Serious TEAE	82 (30)	49 (36)	-5.66
ASCEND-ID	**(N=157)**	**(N=155)**	
Any TEAE	120 (76)	116 (75)	1.59
Any TEAE leading to discont. of RT	14 (9)	7 (5)	4.40
Any Serious TEAE	52 (33)	57 (37)	-3.65

DF=dosing frequency, RT=randomized treatment.

Note: Studies ASCEND-ND, ASCEND-D, and ASCEND-ID were open-label. Study ASCEND-TD was double-blind. Dosing frequency adjusted (Last dose+DF) treatment-emergent definition is detailed in Table 18. ESA controls were darbepoetin alfa (ASCEND-ND, ASCEND-ID), epoetin alfa (ASCEND-TD) or both (ASCEND-D).

5.5.2. Common Treatment-emergent Adverse Events

When adjusted for dosing frequency, the incidence of common (≥5%) TEAEs in both ASCEND-D and ASCEND-ND studies was generally similar between the daprodustat and ESA control groups (Table 30 and Table 31). The treatment group difference in the incidence of each common AE was <2%. The most frequently reported AEs across the studies were characteristic of the study populations (e.g., hypertension).

Table 30 ASCEND-ND: Common (≥5%) TEAEs (Safety Population); Dosing Frequency Adjusted

ASCEND-ND Common TEAEs	Dapro n (%) (N=1937)	Darbe n (%) (N=1933)	Risk difference (%)	Relative risk (95% CI)
Hypertension	257 (13)	279 (14)	-1.17	0.92 (0.79 ,1.08)
Urinary tract infection	187 (10)	190 (10)	-0.18	0.98 (0.81 ,1.19)
Oedema peripheral	199 (10)	176 (9)	1.17	1.13 (0.93 ,1.37)
Hyperkalaemia	151 (8)	153 (8)	-0.12	0.98 (0.79 ,1.22)
Diarrhoea	150 (8)	151 (8)	-0.07	0.99 (0.80 ,1.23)
Chronic kidney disease	134 (7)	129 (7)	0.24	1.04 (0.82 ,1.31)
Nasopharyngitis	118 (6)	134 (7)	-0.84	0.88 (0.69 ,1.12)
Pneumonia	109 (6)	124 (6)	-0.79	0.88 (0.68 ,1.13)
Constipation	128 (7)	96 (5)	1.64	1.33 (1.03 ,1.72)
Fall	111 (6)	95 (5)	0.82	1.17 (0.89 ,1.52)
Anaemia	109 (6)	86 (4)	1.18	1.26 (0.96 ,1.67)
Back pain	85 (4)	110 (6)	-1.30	0.77 (0.59 ,1.02)
Nausea	103 (5)	87 (5)	0.82	1.18 (0.89 ,1.56)
Upper respiratory tract infection	98 (5)	92 (5)	0.30	1.06 (0.81 ,1.40)
Acute kidney injury	102 (5)	87 (5)	0.77	1.17 (0.89 ,1.55)

Note: Dosing frequency adjusted (Last dose+DF) treatment-emergent definition is detailed in Table 18. ESA control was darbepoetin alfa in ASCEND-ND.

Table 31 ASCEND-D: Common (≥5%) TEAEs (Safety Population); Dosing Frequency Adjusted

ASCEND-D Common TEAEs	Dapro n (%) (N=1482)	ESA n (%) (N=1474)	Risk difference (%)	Relative risk (95% CI)
Hypertension	243 (16)	243 (16)	-0.09	0.99 (0.85 ,1.17)
Diarrhoea	167 (11)	187 (13)	-1.42	0.89 (0.73 ,1.08)
Headache	116 (8)	140 (9)	-1.67	0.82 (0.65 ,1.04)
Dialysis hypotension	141 (10)	113 (8)	1.85	1.24 (0.98 ,1.57)
Pneumonia	123 (8)	126 (9)	-0.25	0.97 (0.77 ,1.23)
Hypotension	120 (8)	110 (7)	0.63	1.09 (0.85 ,1.39)
Nasopharyngitis	114 (8)	104 (7)	0.64	1.09 (0.84 ,1.41)
Arthralgia	102 (7)	112 (8)	-0.72	0.91 (0.70 ,1.17)
Fluid overload	96 (6)	110 (7)	-0.98	0.87 (0.67 ,1.13)
Cough	101 (7)	103 (7)	-0.17	0.98 (0.75 ,1.27)
Upper respiratory tract infection	102 (7)	100 (7)	0.10	1.01 (0.78 ,1.32)
Bronchitis	93 (6)	101 (7)	-0.58	0.92 (0.70 ,1.20)
Anaemia	80 (5)	105 (7)	-1.73	0.76 (0.57 ,1.00)
Arteriovenous fistula thrombosis	85 (6)	99 (7)	-0.98	0.85 (0.64 ,1.13)
Hyperkalaemia	91 (6)	91 (6)	-0.03	0.99 (0.75 ,1.32)
Fall	85 (6)	91 (6)	-0.44	0.93 (0.70 ,1.24)
Nausea	83 (6)	87 (6)	-0.30	0.95 (0.71 ,1.27)
Urinary tract infection	82 (6)	87 (6)	-0.37	0.94 (0.70 ,1.26)
Vomiting	84 (6)	83 (6)	0.04	1.01 (0.75 ,1.35)
Arteriovenous fistula site complication	68 (5)	94 (6)	-1.79	0.72 (0.53 ,0.97)
Pain in extremity	85 (6)	76 (5)	0.58	1.11 (0.82 ,1.50)
Back pain	66 (4)	90 (6)	-1.65	0.73 (0.54 ,0.99)
Dyspnoea	69 (5)	84 (6)	-1.04	0.82 (0.60 ,1.11)
Atrial fibrillation	57 (4)	82 (6)	-1.72	0.69 (0.50 ,0.96)
Pyrexia	57 (4)	77 (5)	-1.38	0.74 (0.53 ,1.03)

Note: Dosing frequency adjusted (Last dose+DF) treatment-emergent definition is detailed in Table 18. ESA controls were darbepoetin alfa or epoetin alfa in ASCEND-D.

5.5.3. TEAEs Leading to Treatment Discontinuation

While the incidence of TEAEs leading to treatment discontinuation in the ASCEND-ND and ASCEND-D studies was higher in the daprodustat group compared with the ESA group (Table 32), the imbalance was not driven by any particular pattern of preferred term (PT) (incidence <1% of participants in either treatment group for all terms). The majority of events are accounted for by the adjudicated MACE endpoints (Section 5.4). Events associated with sepsis/septic shock are discussed in Section 5.5.6. Events associated with renal failure are discussed in Section 5.5.8.

Table 32 TEAEs Leading to Discontinuation of Randomized Treatment by Preferred Term (Safety Population); Dosing Frequency Adjusted

	Dapro n (%)	ESA n (%)	Risk difference (%)
ASCEND-ND	**(N=1937)**	**(N=1933)**	
Any TEAE leading to discont.	**247 (13)**	**201 (10)**	2.35
Death	11 (<1)	12 (<1)	-0.05
COVID-19	10 (<1)	7 (<1)	0.15
Pneumonia	9 (<1)	8 (<1)	0.05
Cardiac arrest	5 (<1)	9 (<1)	-0.21
Acute myocardial infarction	6 (<1)	7 (<1)	-0.05
Myocardial infarction	10 (<1)	3 (<1)	0.36
Azotaemia	8 (<1)	4 (<1)	0.21
ASCEND-D	**(N=1482)**	**(N=1474)**	
Any TEAE leading to discont.	**216 (15)**	**195 (13)**	1.35
Cardiac arrest	18 (1)	16 (1)	0.13
Sepsis	12 (<1)	6 (<1)	0.40
Death	8 (<1)	6 (<1)	0.13
Septic shock	3 (<1)	10 (<1)	-0.48
Cerebrovascular accident	4 (<1)	7 (<1)	-0.20
Cardio-respiratory arrest	6 (<1)	4 (<1)	0.13
COVID-19	5 (<1)	4 (<1)	0.07

Note: The 7 most frequently reported preferred terms are presented. Data are adjusted for dosing frequency (refer to Table 18 for definition). ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

5.5.4. Serious TEAEs

Fatal events were captured as adjudicated ACM during the time period for vital status (presented in Section 5.4.7.1). Adjudicated causes of death are presented in Table 26 for the CV outcomes studies.

When adjusted for dosing frequency, treatment group differences for serious TEAEs in both CV outcomes studies were <2% overall, and for each PT. Although an imbalance was noted in the incidence of SAEs related to kidney function in ASCEND-ND (Table 33), no difference in CKD progression was observed between the treatment groups based on renal endpoints (Section 5.5.8.3) or adjudicated renal deaths (Table 26). See Section 5.5.8 for further discussion of renal safety.

Table 33 Serious TEAEs by Preferred Term (Safety Population); Dosing Frequency Adjusted

	Dapro n (%)	ESA n (%)	Risk difference (%)
ASCEND-ND	**(N=1937)**	**(N=1933)**	
Any serious TEAE	**850 (44)**	**817 (42)**	**1.62**
Pneumonia	78 (4)	89 (5)	-0.58
Chronic kidney disease	86 (4)	60 (3)	1.34
Acute kidney injury	70 (4)	50 (3)	1.03
Azotaemia	54 (3)	42 (2)	0.62
End stage renal disease	48 (2)	41 (2)	0.36
COVID-19	39 (2)	41 (2)	-0.11
Urinary tract infection	33 (2)	40 (2)	-0.37
ASCEND-D	**(N=1482)**	**(N=1474)**	
Any serious TEAE	**773 (52)**	**790 (54)**	-1.44
Pneumonia	86 (6)	87 (6)	-0.10
Arteriovenous fistula thrombosis	36 (2)	58 (4)	-1.51
Fluid overload	42 (3)	45 (3)	-0.22
Sepsis	29 (2)	40 (3)	-0.76
Anaemia	26 (2)	42 (3)	-1.10
Acute myocardial infarction	30 (2)	34 (2)	-0.28
Atrial fibrillation	23 (2)	35 (2)	-0.82

Note: The 7 most frequently reported preferred terms are presented. Data are adjusted for dosing frequency (refer to Table 18 for definition). ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

5.5.5. TEAEs of Special Interest

Potential AESIs in the global Phase 3 program were defined based on clinical and nonclinical data with daprodustat, its mechanism of action, and/or the known safety profile of ESAs. AESIs were programmatically identified using pre-defined Terms of Interest lists comprised of a broad range of MedDRA PTs potentially corresponding to each AESI. The reported events were not adjudicated.

AESI Overview: For both CV outcomes studies, the incidence of AESIs was generally similar between the daprodustat and ESA control groups (Table 34).

Table 34 Incidence and Relative Risk of Treatment-emergent AESI (Safety Population); Dosing Frequency Adjusted

	Dapro n (%)	ESA n (%)	Difference (%)	Relative Risk (95% CI)
ASCEND-ND	**(N=1937)**	**(N=1933)**		
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	5 (0.3)	3 (0.2)	0.10	1.66 (0.40, 6.95)
Cardiomyopathy	6 (0.3)	7 (0.4)	-0.05	0.86 (0.29, 2.54)
Pulmonary artery hypertension	15 (0.8)	9 (0.5)	0.31	1.66 (0.73, 3.79)
Cancer-related mortality and tumor progression and recurrence	72 (3.7)	68 (3.5)	0.20	1.06 (0.76, 1.46)
Esophageal and gastric erosions	70 (3.6)	48 (2.5)	1.13	1.46 (1.01, 2.09)
Proliferative retinopathy, macular edema, choroidal neovascularization	54 (2.8)	46 (2.4)	0.41	1.17 (0.79, 1.73)
Exacerbation of rheumatoid arthritis	2 (0.1)	4 (0.2)	-0.10	0.50 (0.09, 2.72)
Worsening of hypertension	344 (17.8)	372 (19.2)	-1.49	0.92 (0.81, 1.05)
				0.1 1 10
ASCEND-D	**(N=1482)**	**(N=1474)**		
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	20 (1.3)	11 (0.7)	0.60	1.81 (0.87, 3.76)
Cardiomyopathy	15 (1.0)	16 (1.1)	-0.07	0.93 (0.46, 1.88)
Pulmonary artery hypertension	9 (0.6)	12 (0.8)	-0.21	0.75 (0.32, 1.77)
Cancer-related mortality and tumor progression and recurrence	47 (3.2)	53 (3.6)	-0.42	0.88 (0.60, 1.30)
Esophageal and gastric erosions	60 (4.0)	82 (5.6)	-1.51	0.73 (0.53, 1.01)
Proliferative retinopathy, macular edema, choroidal neovascularization	38 (2.6)	36 (2.4)	0.12	1.05 (0.67, 1.65)
Exacerbation of rheumatoid arthritis	2 (0.1)	1 (0.1)	0.07	1.99 (0.18, 21.91)
Worsening of hypertension	293 (19.8)	304 (20.6)	-0.85	0.96 (0.83, 1.11)
				0.1 1 10

Note: Data are adjusted for dosing frequency (refer to Table 18 for definition). ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

5.5.5.1. Esophageal and Gastric Erosions

Nonclinical Gastrointestinal Findings

In toxicology studies, glandular stomach erosions and ulcers with hemorrhage were observed in normocythemic mice, rats, dogs, and monkeys following oral or IV administration of daprodustat at doses that led to increased hematopoiesis, rapid increases in Hct and/or supraphysiologic Hct in animals. The most likely basis for the erosions and ulcers observed with daprodustat is compromised microvascular perfusion that is associated with marked increases in Hct. Gastric erosions in rats have also been associated with repeated administration of ESA at doses that caused similar Hct increases [Woodburn, 2008; Aranesp, 2011].

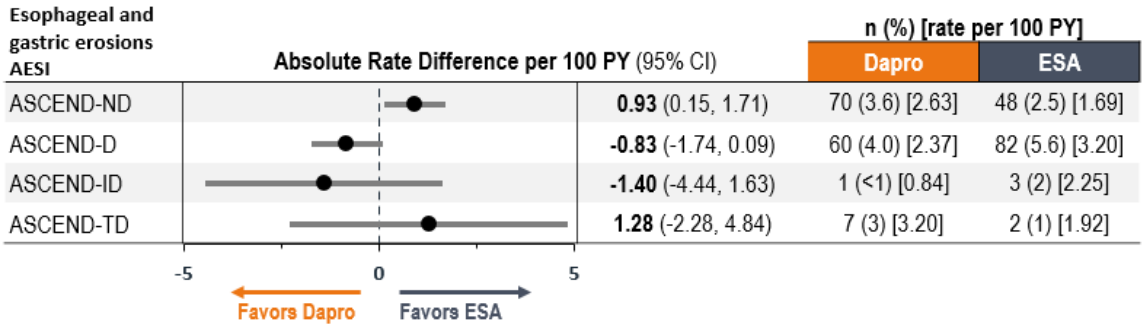
Clinical Findings

Esophageal and gastric erosions were investigated as an AESI across the ASCEND program based on the observations in nonclinical studies.

- Events were identified with MedDRA high level terms (HLTs) reflective of ulceration and/or perforation and PTs that were nonspecific in nature (e.g., GI hemorrhage) but that could be associated with an erosive event.
- AEs were not adjudicated and diagnostic confirmation with upper endoscopy was not required.

Across the active-controlled studies, the rate of potential esophageal and gastric erosions was variable (Figure 19). The rates of this AESI were similar in the daprodustat groups in ASCEND-ND and ASCEND-D (2.63 per 100 PY and 2.37 per 100 PY, respectively; Figure 19), and the difference in relative risk (1.46 and 0.73; Table 34) between the studies was driven by a marked difference in rates in the ESA control groups (1.69 per 100 PY and 3.20 per 100 PY, respectively). The rates in the TD and ID studies are associated with a high level of uncertainty due to small numbers. Although ASCEND-ND had a higher rate of potential esophageal and gastric erosions in the daprodustat group relative to darbepoetin alfa, the rate of this AESI was not increased for daprodustat relative to placebo in the double-blind, placebo-controlled ASCEND-NHQ study in non-dialysis participants (2.19 per 100 PY in placebo, 1.35 per 100 PY in daprodustat; Table 12).

Figure 19 Active-controlled ASCEND Studies: Treatment-emergent Potential Esophageal and Gastric Erosions AESI (Safety Population); Dosing Frequency Adjusted



Note: Data are adjusted for dosing frequency (refer to Table 18 for definition). ESA controls were darbepoetin alfa (ASCEND-ND, ASCEND-ID), epoetin alfa (ASCEND-TD) or both (ASCEND-D).
Rate per 100 PY = 100 x (number of participants with event/person-years).

No specific reason was identified for the imbalance in events of esophageal and gastric erosions AESI by PT (Table 35), including gastrointestinal (GI) hemorrhage. The majority of events were confounded by comorbidities and most events resolved despite continuing therapy in both treatment groups. Within the AESI category, the most frequently reported event in both CV outcome studies was ‘Gastrointestinal haemorrhage’ (Table 35).

Table 35 Treatment-emergent Potential Esophageal and Gastric Erosions AESI for ≥10 Participants by Preferred Term (Safety Population); Dosing Frequency Adjusted

Esophageal and gastric erosions AESI by preferred term, n (%)	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1933)	Dapro (N=1482)	ESA (N=1474)
GI haemorrhage	20 (1)	9 (<1)	16 (1)	22 (1)
Gastritis erosive	14 (<1)	8 (<1)	14 (<1)	14 (<1)
Upper GI haemorrhage	14 (<1)	10 (<1)	4 (<1)	6 (<1)
Gastric ulcer	4 (<1)	6 (<1)	7 (<1)	12 (<1)

GI=gastrointestinal. Note: Data are adjusted for dosing frequency (refer to Table 18 for definition). ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

GI hemorrhage may arise from lesions in the upper (esophagus, stomach, duodenum) or lower (small intestine, colon) GI tract and can range in seriousness. Definitive determination of the bleeding source typically requires endoscopic evaluation, which was left to the clinical judgment of the site investigators. Of the participants who experienced "GI haemorrhage" in ASCEND-ND, the event was considered an SAE for 60% (12/20) of participants in the daprodustat group and 78% (7/9) of participants in the darbepoetin group.

Serious AESIs of esophageal and gastric erosions (ASCEND-ND: 62/3870 [1.6%]; ASCEND-D: 72/2956 [2.4%]) were reviewed by 2 independent external gastroenterologists with prior experience in adjudication. The primary aim of the analysis was to determine the prevalence of confirmed clinically-significant gastrointestinal mucosal erosive events in ASCEND-ND and ASCEND-D. A number of limitations of the available data were highlighted including most notably (i) lack of endoscopy in ~20% of participants despite the serious nature of these AESIs, where further endoscopic investigation would be indicated, and (ii) lack of reported *H. pylori* results in the majority, despite the recognized importance of *H. pylori* in gastroduodenal ulcer disease.

Based on the external gastroenterologists' assessment, the proportion of participants with serious AESI of esophageal and gastric erosions might have been expected to be higher given the frequent usage of aspirin and NSAID (38% to 70%), other antiplatelet agents (6% to 22%), and anticoagulants (13% to 24%) and the low use of prophylactic co-therapy to prevent erosions (30% to 39%). Following their review, the proportion of participants with confirmed clinically significant mucosal erosive events without another documented potential cause was low (<1%) across treatment groups in both dialysis and non-dialysis patients (ASCEND-ND: 8/1487, 0.54% daprodustat versus 1/1477, 0.07% darbepoetin; ASCEND-D: 0.36% in both treatment groups). Of the 8 participants on daprodustat, 7 were on anti-coagulants, anti-platelet agents or steroids and none had test results for *H. pylori*. The lack of *H. pylori* test results (for a treatable infection strongly linked to peptic ulcer disease including erosions) in these participants makes interpretation of a cause of erosive GI disease problematic. Further, antithrombotic therapy may have played a role in precipitating GI bleeding in 4 of these 8 daprodustat participants. The independent external gastroenterologists concluded that "In light of the fact that no difference was seen in clinically significant disease without another cause in

ASCEND-D, the difference in ASCEND-ND could be due to the play of chance or represent a true difference between study groups in the risk of erosive disease. In the absence of sufficient historical information and diagnostic evaluation to allow for adequate assessment in most cases, possible causes of the observed difference in events in ASCEND ND, including the role of daprodustat, remain uncertain".

The post-marketing spontaneous reports from Japan was also evaluated with respect to gastric erosions. There were 47 events of gastric erosions in 43 patients, with a reporting rate of 0.10 events per 100 PY. The average age of the patients was 80 years old and the reported gender was 40% female, 45% male, and 15% unknown. Of the reported cases, 7% (3 patients) were fatal. GSK internal analyses of healthcare data from Japan reveals an incidence rate of 0.23 to 0.51 events per 100 PY in CKD patients not on dialysis, and 1.65 events per 100 PY in CKD patients on dialysis [GSK Data on File 2022N519895_00; GSK Data on File 2022N519896_00; GSK Data on File 2022N519897_00]. The reporting rate from our spontaneous post-marketing data is lower than observed incidence rates in clinical practice in Japan.

The totality of the data suggests that daprodustat is not associated with an increased risk of gastric or esophageal erosions:

- The rate of esophageal and gastric erosions was variable across studies. This rate was similar in the daprodustat groups in both CV outcomes studies, with a marked difference in rates in the ESA control groups between studies.
- More participants in the daprodustat group of the ASCEND-ND study had stage 5 CKD (37% daprodustat versus 35% ESA), which is associated with an increased risk of gastric and esophageal erosions.
- The majority of events were confounded by comorbidities and resolved despite continuing study therapy.
- Review by external gastroenterology experts show that while there was a higher number of AESIs reported on daprodustat versus ESA, the proportion of participants with confirmed clinically significant mucosal erosive events **without** another documented potential cause was low (<1%) across treatment groups in both dialysis and non-dialysis participants.
- There was no signal for gastric erosions following review of post-marketing spontaneous reports from Japan.

5.5.5.2. Cancer-related Mortality and Tumor Progression and Recurrence

Cancer-related events were identified as an AESI based on theoretical considerations of HIF-related biology. While no causal relationship has been demonstrated, HIF-alpha overexpression is observed in a broad range of human cancers and has been shown to correlate with poor prognosis.

VEGF, a key mediator in tumor angiogenesis, can be activated by HIF-1. Daprodustat was determined to be non-genotoxic in preclinical assays and has shown both no evidence of increased carcinogenicity from lifetime animal studies and no consistent effect on plasma VEGF levels at clinically relevant doses.

Nonclinical Carcinogenicity Findings

Weight of evidence from in vitro and in vivo genotoxicity studies, together with results of chronic toxicity studies and from rat and mouse carcinogenicity studies, supports that daprodustat does not represent a genotoxic or carcinogenic risk for humans:

- Results of a standard battery of genetic toxicity assays showed that neither daprodustat nor its three major circulating human metabolites are genotoxic.
- Chronic toxicity studies (6-month rat and 9-month monkey) showed no treatment-related preneoplastic findings, no effects on reproductive organs that would suggest hormonal perturbations, no evidence of immunosuppression, and no proliferative changes other than the expected pharmacologic effect of bone marrow erythroid hyperplasia.
- There were no treatment-related neoplastic findings in rat or mouse lifetime carcinogenicity studies at doses yielding systemic exposures >256X above estimated human area under the concentration time curve (AUC) at the maximum recommended human dose (MRHD). The mouse study included concomitant administration of the 3 major circulating human metabolites (M2, M3, and M13), since these metabolites are not produced by rats or mice following administration of daprodustat.

Clinical Findings

Although labeled as ‘cancer-related mortality and tumor progression and recurrence’, this AESI category captures all potential AEs of malignant cancers and is not restricted to progression, recurrence, or mortality.

The pre-specified analyses (Appendix Table 61) of treatment-emergent malignancies was sensitive to the systematic dosing frequency bias (in precisely the same way as described for prespecified on-treatment MACE) because the occurrence of an AE related to cancer was mandated as a treatment stopping criterion. A post-hoc analysis conducted to take into account differential dosing frequency resulted in HRs that did not suggest an increased rate of malignancy with daprodustat (Table 36). In addition, a post-hoc mITT analysis was conducted (Table 36) using all participants who took study drug including all events reported throughout the study follow-up (which properly accounts for the long latency between carcinogenesis and the clinical detection of cancers). This analysis showed no evidence of a treatment difference in the incidence of this AESI in each of the CV outcomes studies.

Table 36 Cancer-related Mortality and Tumor Progression and Recurrence (Safety Population)

	Events up to date of	Dapro n (%)	ESA n (%)	Relative Risk (95% CI)
ASCEND-ND		**(N=1937)**	**(N=1933)**	
TE, DF adjusted	Last Dose + DF	72 (3.7)	68 (3.5)	**1.06** (0.76, 1.46)
mITT, on and off trt	End of study	87 (4.5)	84 (4.3)	**1.03** (0.77, 1.39)
ASCEND-D		**(N=1482)**	**(N=1474)**	
TE, DF adjusted	Last Dose + DF	47 (3.2)	53 (3.6)	**0.88** (0.60, 1.30)
mITT, on- and off-trt	End of study	65 (4.4)	77 (5.2)	**0.84** (0.61, 1.16)

DF=dosing frequency, TE=treatment-emergent, mITT=modified intention-to-treat, trt=treatment.
Note: Definitions for TE (DF adjusted) are detailed in Table 18. On and off-treatment events were assessed in the mITT analysis: Treatment Start Date ≤ AE Start Date/AE Worsening Date. ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

A review of AE terms found no obvious trend in the type or location of cancer in either treatment group (Table 37), other than the expected observation that the most common events were skin cancers (non-melanomatous skin cancer was not an exclusion or stopping criterion).

Following the FDA suggestion that further evaluation was needed to assess a potential malignancy signal with a focus on GI and skin neoplasms, a review by an oncologist external to GSK identified no safety concern for GI or non-melanomatous skin cancers. However, an imbalance in events of melanoma was noted across the Phase 3 program in participants receiving daprodustat (2 events each in ASCEND-D and ASCEND-ND, 1 event in ASCEND-TD) compared with none in the active comparator group. Despite the imbalance, the incidence rate of melanoma reported in both ASCEND-D and ASCEND-ND (0.06 per 100 PY in each) aligned with background rates observed in the CKD population for both dialysis (0.00558 to 0.092 per 100 PY) and non-dialysis (0.04 to 0.12 per 100 PY) populations [Wang, 2016; Wong, 2016; Au, 2019]. Review of the available information for the melanoma events across the Phase 3 program did not support a causal effect for daprodustat.

In the ITT analysis of adjudicated ACM, malignancy-related deaths were balanced between treatment groups in both CV outcome studies (Table 26). The overall rates of cancer in ASCEND-D and ASCEND-ND were 1.89 per 100 PY and 2.50 per 100 PY, respectively. These rates are aligned with background rates for the CKD dialysis and non-dialysis populations [Butler, 2015; Wong, 2016; Cheung, 2019; Chen, 2020].

In the post-marketing spontaneous reports from Japan, there were 108 events of malignancies in 89 patients, with a reporting rate of 0.21 events per 100 PY. The average age of the patients was 80 years old and the reported gender was 24% female, 56% male, and 19% unknown. Twelve patients (13%) reported a fatal outcome. The types of malignancies reported were similar to those reported in the CV outcomes studies. GSK internal analyses of healthcare data from Japan reveals an incidence rate of 0.17 to 2.43 events per 100 PY in CKD patients not on dialysis, and 1.44 events per 100 PY in CKD patients on dialysis [GSK Data on File 2022N519895_00; GSK Data on File 2022N519896_00; GSK Data on File 2022N519897_00]. The reporting rate from

our spontaneous post-marketing data is lower than or consistent with observed incidence rates in clinical practice in Japan.

The totality of data in the CV outcomes studies supports the conclusion that daprodustat did not increase the risk of malignancy compared to ESA. However, given the long latency of cancer, this remains an important potential risk.

Table 37 AESI of Cancer-related Mortality and Tumor Progression and Recurrence by Preferred Term (Safety Population)

Safety Population mITT approach	ASCEND-ND				ASCEND-D			
	Dapro N=1937		Darbe N=1933		Dapro N=1482		ESA N=1474	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Overall Cancer AEs	87 (4)	2.50	84 (4)	2.40	65 (4)	1.89	77 (5)	2.26
Neoplasms, malignant	80 (4)	2.29	75 (4)	2.14	57 (4)	1.66	69 (5)	2.02
Skin	22 (1)	0.62	15 (<1)	0.42	7 (<1)	0.20	14 (<1)	0.40
Site unspecified	11 (<1)	0.31	9 (<1)	0.25	3 (<1)	0.09	5 (<1)	0.14
Renal	3 (<1)	0.08	6 (<1)	0.17	10 (<1)	0.29	4 (<1)	0.12
Breast	8 (<1)	0.22	5 (<1)	0.14	3 (<1)	0.09	4 (<1)	0.11
Colorectal	5 (<1)	0.14	5 (<1)	0.14	4 (<1)	0.11	3 (<1)	0.09
Blood and lymphatic system disorders	5 (<1)	0.14	10 (<1)	0.28	6 (<1)	0.17	6 (<1)	0.17
Marrow depression and hypoplastic anemia	5 (<1)	0.14	10 (<1)	0.28	6 (<1)	0.17	6 (<1)	0.17

mITT=modified intention-to-treat.
Note: On and off-treatment events were assessed in the mITT analysis: Treatment Start Date ≤ AE Start Date/AE Worsening Date. ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D). Rate per 100 PY = 100 x (number of participants with event/person-years).
Adapted from: [Singh, 2022]

5.5.5.3. Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis

Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis is a known complication of treatment with recombinant EPO and its derivatives. Both the rate of rise and the attained Hgb have been implicated in thromboembolic risk associated with ESAs.

Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis was investigated as an AESI based on the mechanism of action of daprodustat and observations in nonclinical studies (i.e., in animal studies, excessive erythropoiesis [Hgb/Hct > upper limit normal] attributed to daprodustat was associated with vascular congestion/inflammation, microthrombi, and tissue ischemia in a number of organs). The risk of this toxicologic effect is largely mitigated by Hgb monitoring and dose adjustment algorithms for maintaining Hgb levels within target range.

The 2 reporting criteria for thrombosis and/or tissue ischemia in the setting of excessive erythropoiesis were:

- an AE PT on the thrombosis and/or tissue ischemia Terms of Interest list,
  - "thrombosis" not limited to DVT, PE, VAT
  - "tissue ischemia" comprised of all MedDRA terms that include "ischaemia" or "ischaemic"

and

- an associated Hgb value ≥13 g/dL or Hgb increase >2 g/dL over 2 weeks or >4 g/dL over 4 weeks (excessive erythropoiesis)

This AESI was infrequent in both CV outcomes studies, and therefore, results comparing incidence rates between treatment groups should be interpreted in this context. More events of thrombosis and/or tissue ischemia secondary to excessive erythropoiesis occurred in the daprodustat group than in the ESA group in ASCEND-D (Table 34). It should be noted that the incidence of treatment-emergent thrombosis and/or tissue ischemia (the first criterion) in the ASCEND-D study was similar in the 2 treatment groups while a higher proportion of participants in the daprodustat group had excessive erythropoiesis due to meeting the Hgb criterion (Table 38).

Therefore, in ASCEND-D, the observed treatment group difference in this AESI appears to be driven by a higher incidence of excessive erythropoiesis in the daprodustat group rather than an increase in thrombosis or tissue ischemia related AEs. This assessment is consistent with the incidence of on-study adjudicated thromboembolic events, which was balanced between treatment groups (Section 5.4.7.4), and a higher proportion of participants with a Hgb value ≥12 g/dL during the evaluation period in the daprodustat group (35%) compared to ESA (27%). The observation is also consistent with the Hgb increase (mean change from Baseline during the evaluation period), which was greater for daprodustat compared with ESA (Figure 1).

Table 38 Treatment-emergent Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis (Safety Population); Dosing Frequency Adjusted

	ASCEND-ND		ASCEND-D	
	Dapro n (%)	Darbe n (%)	Dapro n (%)	ESA n (%)
	N=1937	N=1933	N=1482	N=1474
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis[a]	**5 (<1)**	**3 (<1)**	**20 (1)**	**11(<1)**
Participants meeting criteria: Hgb ≥13 g/dL	2	2	16	6
Participants meeting criteria: Hgb increase >2 g/dL over 2 weeks or >4 g/dL over 4 weeks	3	2	6	6
TE thrombosis and/or tissue ischemia	172 (9)	139 (7)	288 (19)	318 (22)
Participants meeting criteria for excessive erythropoiesis[a]	254 (13)	297 (15)	371 (25)	304 (21)

TE=treatment-emergent.

Note: Dosing frequency adjusted data are presented (refer to Table 18 for definition). Participants who met more than 1 criterion are counted under each category that applies. ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

a. Excessive erythropoiesis is identified from randomization to the DF adjusted treatment-emergent end date + 15 days.

5.5.5.4. Hypertension

GSK took a multi-factorial approach in evaluating the effect of daprodustat on BP across the ASCEND Phase 3 program utilizing objective and subjective measures including changes in BP over the study period, BP exacerbations, AESI of "worsening of hypertension", and changes in BP medications. Across the 2 large CV outcomes studies (ASCEND-D and ASCEND-ND), daprodustat had a similar effect on BP compared with ESA across each of these parameters (Table 39).

Table 39 Evaluation of Blood Pressure Parameters (Safety Population)

	ASCEND-D		ASCEND-ND	
	Daprodustat (N=1487)	ESA (N=1477)	Daprodustat (N=1937)	Darbepoetin (N=1935)
On-treatment BP (mmHg)[a]				
Systolic, n	1487	1477	1937	1935
Baseline, mean (SD)	134.6 (22.53)	134.7 (22.04)	136.3 (17.37)	136.0 (17.13)
End of Treatment, mean (SD)	134.2 (22.43)	134.3 (23.67)	135.0 (18.68)	135.0 (18.66)
Diastolic, n	1487	1477	1937	1935
Baseline, mean (SD)	74.0 (13.98)	73.5 (13.44)	73.7 (10.84)	73.7 (11.16)
End of Treatment, mean (SD)	72.9 (13.41)	72.3 (13.40)	73.4 (11.42)	73.3 (11.70)
On-treatment BP Exacerbation Events[b]				
Participants with on-treatment Post-dialysis BP, N	1470	1458	1919	1884
Post-dialysis BP Exacerbations, n (%)	988 (67.2)	998 (68.4)	939 (48.9)	1012 (53.7)
Post-hoc Dosing Frequency Adjusted Treatment-emergent potential AESI of Worsening Hypertension				
Worsening Hypertension, N	1482	1474	1937	1933
n (%)	293 (19.8)	304 (20.6)	344 (17.8)	372 (19.2)
Summary of Subjects with Changes in On-Treatment BP Medications to End of Treatment				
Number of Participants	1326	1317	1865	1879
No change, n (%)	622 (47)	673 (51)	799 (43)	852 (45)
At least one change, n (%)	704 (53)	644 (49)	1066 (57)	1027 (55)
Increase, n (%)	299 (23)	271 (21)	608 (33)	573 (30)
Decrease, n (%)	588 (44)	536 (41)	902 (48)	861 (46)
Switch, n (%)	199 (15)	201 (15)	364 (20)	383 (20)

BP=blood pressure; CI=confidence interval; SD=standard deviation

Note: ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

a. In ASCEND-ND, for patients who have transitioned to dialysis, only post-dialysis BP values are used.

b. Defined as an increase in SBP of ≥25 mmHg from baseline or SBP ≥180 mmHg or an increase in DBP of ≥15 mmHg from baseline or DBP ≥110 mmHg.

5.5.6. TEAEs Potentially Associated with other HIF-PHIs

As part of GSK's process, TEAEs potentially associated with other HIF-PHI agents based on the emerging safety profiles of related molecules were assessed by post-hoc evaluations of Terms of Interest lists using the pooled data from the ASCEND-D and ASCEND-ND studies. No clinically meaningful differences between treatment groups were noted (Table 40).

Table 40 Pooled Studies ASCEND-ND and ASCEND-D: TEAEs of Seizures, Sepsis, Fractures, and Hepatotoxicity (Safety Population); Dosing Frequency Adjusted

	Dapro		ESA		Rate Difference (per 100PY)
	n (%)	Rate/ 100PY	n (%)	Rate/ 100PY	
TEAEs of	(N=3419)		(N=3407)		
Seizures	26 (<1)	0.49	28 (<1)	0.51	-0.02
Fractures	188 (5)	3.69	188 (6)	3.51	0.18
Sepsis/septic shock	114 (3)	2.18	162 (5)	2.99	-0.81
Hepatotoxicity	89 (3)	1.71	93 (3)	1.71	0

Note: TEAEs presented are based on MedDRA SMQs (narrow). ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).
Rate per 100 PY = 100 x (number of participants with event/person-years)

5.5.7. Liver Safety

In the pooled CV outcomes studies, the rate of investigator-reported AEs of hepatotoxicity was similar in the daprodustat and ESA control groups (Table 40).

In the ASCEND program, 4154 participants were exposed to daprodustat, and 4004 participants were exposed to the ESA control. A total of 69 participants on daprodustat met liver stopping and/or monitoring criteria versus 81 on ESA (control group).

In total, across the daprodustat development program, 38 participants (19 daprodustat and 19 ESA control) met biochemical criteria for Hy's Law (Table 41). A clinically plausible cause of liver injury was present for all 38 participants (40 cases), and there was no signal of DILI associated with either daprodustat or ESA control. Of note, ESA is not associated with liver safety issues.

GSK provided blinded narratives of the 38 participants who experienced an event that met the biochemical criterial for potential Hy's Law defined as ALT ≥3x ULN and total bilirubin ≥2x ULN to an external daprodustat hepatic assessment committee (DHAC). The DHAC determined that no case was considered "*possibly, probably, highly likely, or definitely related to study drug*", and it was the committee's *"...overall impression...that no hepatotoxicity signal had been identified among these cases.*"

Table 41 ASCEND Global Phase 3 Studies: Etiology of Liver Injury in Cases Meeting Biochemical Criteria for Hy's Law* (Safety Population)

Period	Daprodustat Cases (Participants)	ESA Control Cases (Participants)
Total	20 (19)	20 (19)
On-treatment [a]	12 (12)	16 (16)
Biliary	6	8
Drug-induced (not IP) [b]	1	2
Viral hepatitis	2 [e]	2
Alcohol	0	1 [e]
Other [c]	3	3
Post-treatment [d]	8 (8)	4 (4)
Biliary	2	1
Drug-induced (not IP) [f]	1	0
Viral hepatitis	1 [e]	0
Alcohol	0	1 [e]
Sepsis	1	2
Congestive hepatopathy	1	0
Other [c]	2	0

IP= investigational product.

*GSK defined Hy's Law as ALT ≥3 x ULN and total bilirubin ≥2 x ULN. One of these 40 cases only met Hy's Law criteria with an AST that was ≥3 x ULN (instead of an ALT≥3 x ULN, as per GSK's definition) and total bilirubin ≥2 x ULN. The case was included in this table for completeness, however, only the 39 cases that met GSK's criteria for Hy's Law were sent for evaluation by the Daprodustat Hepatic Assessment Committee (DHAC).

Note: ESA controls were darbepoetin alfa (ASCEND-ND), and darbepoetin alfa or epoetin alfa (ASCEND-D).

a. On-treatment dosing frequency-adjusted: if the date of the laboratory assessment occurred from the treatment start date to the last non-zero dose date + dosing frequency (dosing frequency for daily doses = 1 day; TIW doses = 2 days; weekly doses = 7 days; every 2 weeks = 14 days; every 4 weeks = 28 days).

b. Allopurinol; atorvastatin.

c. Cases in this category have more than one potential etiology. Examples include combinations of potential etiologies such as drug-induced (not investigational product), biliary, sepsis, and ischemia.

d. Post-treatment period is defined as the period after the on-treatment dosing frequency adjusted period. The study day at liver event onset for post-treatment liver events ranged from 129 to 949 days.

e. One participant is counted once in the on-treatment row and once in the respective post-treatment row.

f. Herbal medication, type unknown

In the post-marketing spontaneous reports from Japan, there were 26 events in 22 patients in the Hepatobiliary SOC. Internal review of the available information in these spontaneous cases indicated that none of them were suggestive of drug-induced liver injury (5 cases were confounded by hepatic, gallbladder or pancreatic cancer; 7 cases reported bile duct stone, cholecystitis, cholelithiasis, acute cholangitis and/or cholangitis; 7 cases were confounded by previous medical history of liver disease, 2 lacked information on the temporal association between daprodustat exposure and onset of event; and in 1 case, a patient reported hyperbilirubinemia 1 month and 25 days after starting daprodustat which improved subsequently despite continuation of treatment with daprodustat).

5.5.8. Renal Safety

A comprehensive discussion of the renal safety including all relevant data on non-dialysis patients (ASCEND-NHQ and ASCEND-ND) is presented in this section. Based on the totality of data across non-clinical and clinical studies (including an analysis of AEs, eGFR and CKD progression), there has been no indication that daprodustat increases the risk of AKI and no evidence of nephrotoxicity. Internal review of all serious events of AKI in ASCEND-ND determined most cases as multifactorial, and reflective of etiologies seen in clinical practice in Japan including, but not limited to, infection, dehydration, and/or congestive HF.

5.5.8.1. Non-Clinical Studies

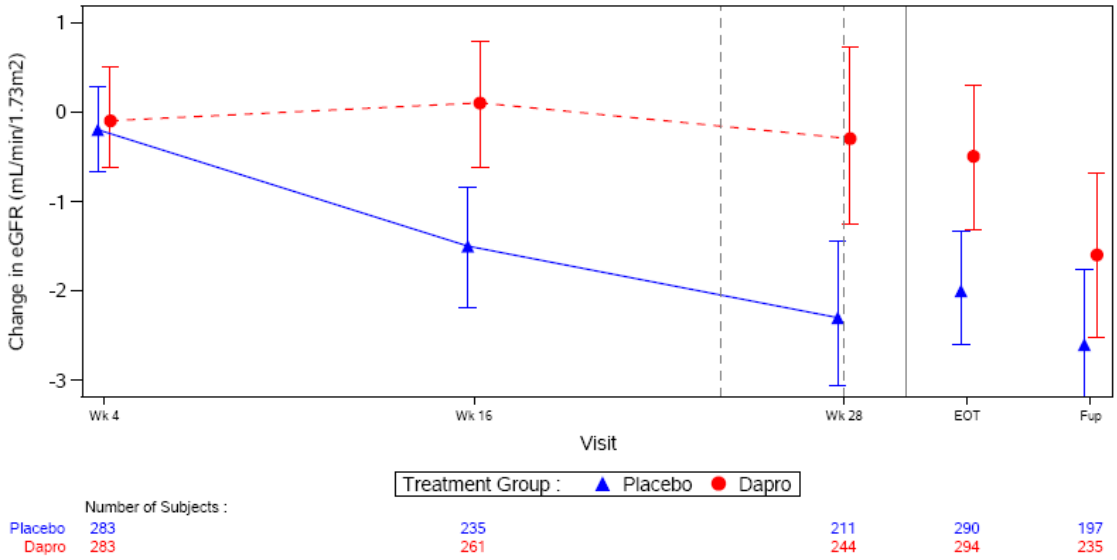
The daprodustat toxicology program was conducted in multiple species with dosing durations up to 2 years and there was no direct daprodustat-mediated nephrotoxicity observed. The main toxicology finding in animals associated with daprodustat was generalized vascular congestion, thrombosis and multi-organ pathology (including heart, kidney, brain, liver, lung, stomach, and vessel walls). These effects were secondary to compromised blood flow and vascular perfusion in organs as a result of daprodustat pharmacology in normocythemic animals leading to non-physiologic high Hct values and inferred increased blood viscosity.

5.5.8.2. ASCEND-NHQ

There was no signal for nephrotoxicity or adverse renal outcomes due to daprodustat in the double-blind, placebo-controlled ASCEND-NHQ study.

Mean baseline eGFR was similar between the treatment groups (24.4 mL/min/1.73m^2 for daprodustat and 23.6 mL/min/1.73m^2 for placebo). Mean eGFR decreased at Week 28 for both treatment groups with a greater decrease for the placebo group (-2.3 mL/min/1.73m^2) compared with the daprodustat group (-0.3 mL/min/1.73m^2). The 95% CIs for change from baseline at Week 28 for the placebo and daprodustat groups did not overlap (Figure 20). There were fewer TEAEs in the Renal and Urinary SOC for participants randomized to daprodustat compared with placebo (24 [8%] and 35 [11%], respectively).

Figure 20 ASCEND-NHQ: Line Plot of On-treatment eGFR Change from baseline (ITT Population)



Note: Error bars indicate 95% confidence interval. The dashed vertical lines represent the evaluation period (Week 24 to Week 28)

Day 1 value was the data collected on the randomization date (Day 1 visit). Baseline value was the latest non-missing pre-dose assessment on or before the randomization date. This was generally expected to be the pre-dose value from the Day 1 visit, unless it is missing.

End of treatment value was the latest value on or before the treatment stop date + 1 day.

In addition, using the FDA's terms for defining AKI (Appendix 10.9), there was no evidence of an increase in AEs for participants randomized to daprodustat compared to those randomized to placebo (Table 42). None of these events were reported as drug-related by the investigator.

Table 42 ASCEND-NHQ: Serious TEAEs using FDA Modified Serious Acute Kidney Injury Definition (Safety Population)

	Placebo N=306 n (%)	Daprodustat N=308 n (%)
Serious Adverse Events		
Renal & Urinary disorders SOC	21 (7)	14 (5)
Acute kidney injury	5 (2)	5 (2)
Nephropathy toxic	0	1 (<1)

5.5.8.3. ASCEND-ND

Progression of CKD

In ASCEND-ND, time to first occurrence of CKD progression was a pre-specified principal secondary endpoint restricted to the subset of participants (N=2,485) with

Baseline eGFR ≥15 mL/min/1.73m^2. Progression of CKD was defined as participants with a 40% decline in eGFR, participants clinically indicated for dialysis or transitioned to chronic dialysis for at least 90 days, or participants in receipt of a kidney transplant. CKD progression was generally similar between the treatment groups and daprodustat did not significantly reduce the time to progression of CKD compared with darbepoetin (subdistribution HR 0.98, 95% CI: 0.84, 1.13; Appendix Table 53).

A summary of all events of CKD progression is presented in Table 43. The component profile of CKD progression was similar between treatment groups; chronic dialysis was the most frequent component of CKD progression.

Table 43 ASCEND-ND: Summary of All Events of CKD Progression (ITT Population)

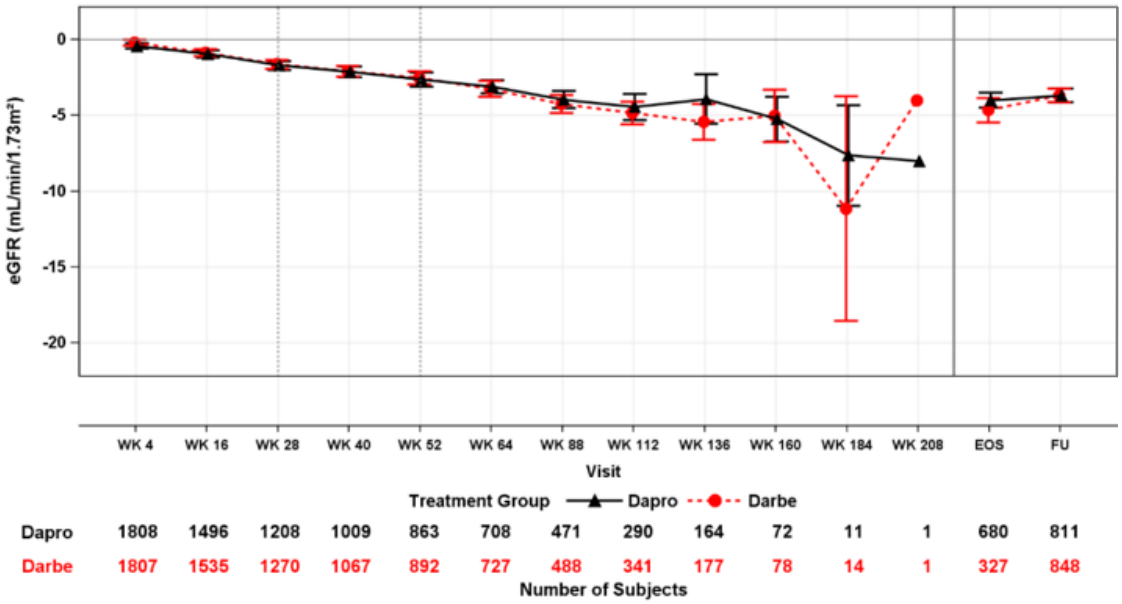
	Dapro (N=1937)		Darbe (N=1935)	
	Number (%) of Participants	Number of Events	Number (%) of Participants	Number of Events
Number (%) of Participants [a]	1220	-	1265	-
CKD Progression [b]	343 (28.1)	464	359 (28.4)	501
Confirmed 40% eGFR decline	175 (14.3)	175	195 (15.4)	195
Chronic dialysis [c]	252 (20.7)	266	259 (20.5)	279
Kidney transplant	23 (1.9)	23	27 (2.1)	27

a. All randomized participants with baseline eGFR ≥15 mL/min/1.73m^2.
b. Participants with more than one event are counted under each event type.
c. The chronic dialysis component includes subjects who initiate chronic dialysis for ≥90 days (non-adjudicated), positively adjudicated cases of dialysis less than 90 days with expected chronicity, and positively adjudicated cases where dialysis was indicated for a chronic condition but not provided.

On-treatment eGFR

Decline in eGFR (inclusive of all participants regardless of baseline eGFR) was similar in the daprodustat group compared to darbepoetin alfa group (Figure 21). Mean Baseline eGFR was similar between the daprodustat group (mean [SD] 20.1 [11.28] mL/min/1.73m^2) and the darbepoetin group (mean [SD] 20.7 [11.05] mL/min/1.73m^2). Change from Baseline eGFR in on-treatment eGFR by visit to the end of study was similar between treatment groups.

Figure 21 ASCEND-ND: Line Plot of Change from Baseline in On-treatment eGFR by Visit (ITT Population)



eGFR= estimated glomerular filtration rate, EOS=end of study, FU=follow-up.
Note: Error bars indicate 95% Confidence Interval. The dashed vertical lines represent the evaluation period (Week 28 to Week 52). Follow-up visit includes only post-treatment values.

Acute Kidney Injury

Acute Kidney Injury is defined as an increase in serum creatinine of at least 1.5-fold, with or without decreased urine output [KDIGO, 2012]. Dosing frequency adjusted treatment-emergent AKI events (using the MedDRA PT Acute Kidney Injury) were similar in both treatment groups, but there was a 1% difference in serious AKI events (Table 44). To further investigate this difference, the FDA provided an expanded list of terms to assess AKI (Appendix 10.9). Using this definition, the same difference of 1% was observed for AKI (Table 44).

Table 44 ASCEND-ND: Treatment-emergent AKI Events (Using the MedDRA Preferred Term Acute Kidney Injury and the FDA Expanded List of Terms) (Safety Population); Dosing Frequency Adjusted

	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)
Based on MedDRA PT AKI terms		
TEAEs of AKI	102 (5)	87 (5)
Serious TEAEs of AKI	70 (4)	50 (3)
Based on the FDA's Expanded List of Terms for AKI	0	0
Serious TEAEs of AKI	77 (4)	56 (3)
AKI	70	50
Anuria	0	1
Cardiorenal syndrome	2	2
Oliguria	1	0
Renal tubular necrosis	1	0
Tubulointerstitial nephritis	1	2

AKI=acute kidney disease.PT=preferred term, TEAE=treatment-emergent adverse event.

Baseline Characteristics

To further investigate the 1% difference in serious AKI events, the relationship of serious AKI (based on FDA PTs) with baseline characteristics was assessed. It is widely recognized that reduced eGFR is a risk factor for AKI. In ASCEND-ND, few serious AKI events occurred in participants with CKD stages 1 to 3 (Table 45). Events mainly occurred in participants with CKD stage 4 and 5, a population at higher risk of developing AKI.

Table 45 ASCEND-ND: Summary of Characteristics of Serious TEAEs of Acute Kidney Injury based on FDA Definition (Safety Population); Dosing Frequency Adjusted

	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)
Participants with Serious AKI Event	77 (4)	56 (3)
First serious AKI events by Baseline CKD stage (Based on eGFR)		
Stage 1: ≥90 mL/min/1.73m^2	0	0
Stage 2: 60-89 mL/min/1.73m^2	0	0
Stage 3: 30-<60 mL/min/1.73m^2	9 (<1)	11 (<1)
Stage 4: 15-<30 mL/min/1.73m^2	42 (2)	26 (1)
Stage 5: <15 mL/min/1.73m^2	26 (1)	19 (<1)

AKI=acute kidney disease, eGFR=estimated glomerular filtration rate.

Because serious AKI events were skewed toward CKD Stage 4 and 5 participants, baseline risk between the two treatment groups was investigated. When controlling for baseline CKD stage, the HRs and 95% CIs were similar (Table 46). However, the small

number of participants who experienced a serious AKI event in comparison to the total number of participants in the study may make the HR a less reliable measure for estimating serious AKI risk. Therefore, a more granular review of patient baseline characteristics known to be associated with risk of AKI was undertaken.

Table 46 ASCEND-ND: Summary of Analysis of Time to First Occurrence of Serious Acute Kidney Injury[a] During Different Time Periods (Safety Population)

Serious AKI events during time period (events up to)	Dapro (N=1937) n (%) [rate/ 100 PY]	Darbe (N=1933) n (%) [rate/100 PY]	Absolute rate diff/ 100 PY (95% CI)	Hazard Ratio (95% CI)
OT (LDD+DF)	77 (4.0) [2.90]	56 (2.9) [1.98]	0.92 (0.09, 1.75)	**1.45** (1.03, 2.05)
OT (LDD+DF), controlling for baseline CKD Stage	77 (4.0) [2.90]	56 (2.9) [1.98]	0.92 (0.09, 1.75)	**1.43** (1.01, 2.02)

OT=on-treatment, DF=dosing frequency, LDD=last non-zero dose date

Note: Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, current ESA use at randomization, and region as covariates. A hazard ratio < 1 indicates a lower risk with daprodustat compared to darbepoetin alfa.

Note: Baseline CKD stage categorical variable used with three levels (2+3, 4, and 5)a. Using an FDA query similar to the MedDRA query "Acute Kidney Injury, Narrow".

a. Included MedDRA Preferred Terms are listed in Appendix 10.9

Looking at baseline CKD, there was a higher percentage of participants at Grade 4/5 for the daprodustat group than for the darbepoetin group. At the most serious category of Grade 5 CKD, there was a clinically relevant difference at baseline with more Stage 5 participants in the daprodustat group (Table 47). Age is also known to be a risk factor for AKI events. At baseline in ASCEND-ND study, there was 1% more participants in the ≥75-year-old age group in the daprodustat group than in the darbepoetin group (Table 47).

Table 47 ASCEND-ND: Summary of Baseline Characteristics Known to be Associated with Risk of AKI (Safety Population)

Risk Category	Dapro N=1937	Darbe N=1933
CKD Stage 4/5 at enrolment, n (%)	Stage 4: 875 (45.2) Stage 5: 716 (37.0) **Total: 1591 (82.1)**	Stage 4: 894 (46.2) Stage 5: 669 (34.6) **Total: 1563 (80.9)**
Patients ≥ 75 years of age, n (%)	**502 (25.9)**	**481 (24.9)**

Review of AKI Adverse Events

To investigate the 1% difference in serious AKI events, the AKI events in both groups (including all terms from FDA's definition) were also assessed to identify if another etiology (e.g., infection, dehydration) was likely.

To differentiate serious AKI events from CKD progression, CKD progression events were flagged if the AKI event occurred within 90 days prior to protocol defined CKD progression or any time thereafter. Additionally, AEs reported in proximity to the AKI event were assessed (e.g., infection or dehydration) to contextualize the event. Narratives were also reviewed for additional case details.

As noted in Table 48, of the 77 daprodustat cases, 22 cases of AKI were adjudicated as CKD progression events (2 participants with Stage 3; 20 participants with Stage 4). Twenty-six participants already met eGFR criteria of end-stage kidney disease (ESKD). There were 29 (37.7%) participants remaining with AKI cases of clinical importance. After reviewing the narratives and AEs that occurred around the time of the AKI event, all 29 cases had an alternative etiology such as dehydration, infection, hemorrhage, or a multifactorial etiology (Table 49, which provides the preferred terms and underlying causes of the daprodustat serious AKI events in the ASCEND-ND study).

Also as noted in Table 48, of the 56 darbepoetin cases, 13 cases of AKI were adjudicated as CKD progression events (2 in participants with Stage 3, 11 participants with Stage 4). Nineteen participants already met eGFR criteria of ESKD. There were 24 (42.9%) participants remaining. After reviewing the narratives and AEs that occurred around the time of the AKI event, 22 of the 24 cases had alternative underlying causes similar to those of the daprodustat cases including infection, dehydration, other underlying illnesses or a combination of medical issues (Table 49). Two of the cases had insufficient information to determine an alternative etiology.

Table 48 ASCEND-ND: Summary of Participants with Baseline eGFR <15, CKD Progression During Study and/or Death (Safety Population)

	Daprodustat N=77	Darbepoetin N=56
Participants with eGFR <15/ CKD progression and/or Death	**48 (62.3%)**	**33 (58.9%)**
Cases with eGFR <15 [a]	27	22
Cases Adjudicated as CKD progression	22	13
Events associated with Death	6	2
Participants without eGFR <15/ CKD progression and/or Death	29 (37.7%)	23 (41.1%)

eGFR=estimated glomerular filtration rate. Note: Participants may be included in more than one subcategory for 'Participants with eGFR <15/ CKD progression and/or death'.

a. Stage 5 at baseline or had eGFR <15 during the course of the study

Table 49 ASCEND-ND: Summary of Preferred Terms and Underlying Causes of Serious TEAEs of Acute Kidney Injury based on FDA Definition (Safety Population); Dosing Frequency Adjusted

	Daprodustat	Darbepoetin
FDA composite "serious AKI"	**77**	**56**
Acute kidney injury	**70**	**50**
ESKD (eGFR < 15 at baseline)	23	15
Adjudicated CKD progression	19	12
Dehydration	12	8
Infection	7	3
Dehydration/Infection	5	3
Hemorrhage	1	
Obstruction	1	
Other	1	6
Concomitant meds	1	
Heart Failure		1
Insufficient Information		2
Cardiorenal syndrome	**2**	**2**
ESKD (eGFR < 15 at baseline)	1	1
Adjudicated CKD progression	1	1
Nephropathy toxic	**2**	**1**
ESKD (eGFR < 15 at baseline)	1	1
Adjudicated CKD progression	1	
Oliguria	**1**	
ESKD (eGFR < 15 at baseline)	1	
Tubulointerstitial nephritis	**1**	**2**
ESKD (eGFR < 15 at baseline)	1	2
Renal tubular necrosis	**1**	
Adjudicated CKD progression	1	
Anuria		**1**
ESKD (eGFR < 15 at baseline)		1

AKI=acute kidney injury, eGFR=estimated glomerular filtration rate, ESKD=End stage kidney disease
Note: Preferred term in bold; Etiology (from SAE narrative) indented below PT; Participants are assigned to a single category.

AKI Associated Adverse Health Outcomes

AKI is considered an important clinical outcome because it is associated with adverse health outcomes, notably death and ESKD. In the ASCEND-ND study, the difference identified between treatment groups in AKI is derived from AE reports rather than an adjudicated AKI endpoint. However, both of the outcomes for which AKI is a risk factor, ACM and ESKD, were subject to predefined adjudicated secondary safety analyses. Neither ACM (HR 1.03, 95% CI: 0.87, 1.20) nor CKD progression (HR 0.98, 95% CI: 0.84, 1.13) differed between the study treatment groups.

Japan Post-Marketing Data

In our Japan post-marketing data, the number of cases of AKI (using the FDA definition) were small: 8 events in 8 patients with a reporting rate of 0.019 events per 100 PY. The average age of the patients was 80 years old and the reported gender was 50% female, 37.5% male, and 12.5% unknown. None were fatal. Seven of the cases occurred in the setting of other clinical conditions that could lead to AKI such as dehydration or infection, and one case had insufficient information for assessment. Incidence rates of AKI in clinical practice in Japan were not available.

5.5.8.4. Conclusion

The totality of evidence on renal safety described above is supportive of the following conclusions:

- There was no obvious signal for nephrotoxicity or adverse renal outcomes for daprodustat against placebo.
- There was no difference between daprodustat and darbepoetin alfa in the principal secondary endpoint of time to progression of CKD nor in the decline of eGFR (regardless of baseline eGFR) in non-dialysis participants.
- The daprodustat group had a slightly larger percentage of participants over 75 years of age (1% difference) and with Grade 4/5 CKD at baseline (1.2% difference), both of which are risk factors for AKI. Although these differences are very small, they may contribute to the 1% difference in serious AKI events between treatment groups.
- There is no obvious pattern associated with daprodustat treatment in the occurrence of AKI in CKD patients. Serious AKI events were infrequent (rate <1 per 100 PY in either treatment group of ASCEND-ND) and were driven by other comorbidities.
- In non-dialysis participants, there was no difference between daprodustat and darbepoetin alfa in adverse health outcomes, death and ESKD, for which AKI is a risk factor.
- Pro-active pharmacovigilance activities in Japan have not identified a signal for nephrotoxicity with daprodustat in the post-marketing setting.

6. CARDIOVASCULAR RISK BY POST-RANDOMIZATION DOSE AND HGB

6.1. Summary of Analyses, Results, and Limitations

6.1.1. Summary of Analyses

The following analyses were undertaken to evaluate the relationship between post-randomization dose and Hgb and safety events in ASCEND-D and ASCEND-ND:

Pre-specified

1. Landmark analysis at Week 4 to evaluate the relationship between Hgb change at Week 4 and occurrence of future MACE using forward selection method
2. Time dependent covariate analysis to evaluate the relationship between post-randomization Hgb value and change in Hgb value and occurrence of MACE
3. MACE rates across post-randomization Hgb quintiles and Hgb change quintiles
4. MACE across post-randomization dose quartiles

Post-hoc

1. Post-hoc revised landmark analyses for darbepoetin participants in the ASCEND-ND study using pre-specified analysis model including covariates Week 4 Hgb category and Hgb change at Week 4 category
2. FDA requested exploratory analyses to examine relationship between post-randomization dose categories and Hgb quintiles and adjudicated outcomes (time to first MACE, all-cause mortality, CV mortality, fatal/non-fatal stroke, non-fatal MI, thromboembolic event and hospitalization for HF) as well as 18 FDA specified AE groupings
   a) Post-randomization dose categories included average weekly dose while receiving treatment, average weekly dose in the 2 and 4 weeks preceding the event, and average weekly dose at the time of the event. The rationale for using dose categories instead of dose quintiles is discussed below in Section 6.2.1.1.
   b) Hgb quintiles just prior to the event and Hgb rates of change in the 4 weeks and 12 weeks (rates of increase and decrease evaluated separately) preceding the event were examined.

6.1.2. Summary of Results

- **Dose:** Consistent findings across all the analyses included an apparent association between higher post-randomization dose and adjudicated outcomes including MACE. The association between higher dose and CV outcomes has previously been reported in observational studies in the dialysis population [Zhang, 2004; Bae, 2015] and in the non-dialysis population in TREAT [Solomon, 2010]. These studies also found that patients in the higher dose categories had greater burden of CV disease at baseline [Zhang, 2004; Solomon, 2010].
- **Hgb:** Consistent findings across all the analyses included an apparent association between lower post-randomization Hgb and adjudicated outcomes including MACE. The association between lower achieved Hgb and CV events was also shown in TREAT [Solomon, 2010] and reported in an observational study in dialysis [Locatelli, 2004]. There was no indication of an association between high post-randomization Hgb and adjudicated safety outcomes including MACE. The lack of an association between higher post-randomization Hgb values and CV outcomes is consistent with randomized controlled studies of ESA (e.g., Normal Hematocrit Study and CHOIR) where higher achieved Hgb was not associated with greater morbidity/mortality despite the finding that those randomized to a higher Hgb target

had greater mortality/morbidity [FDA Advisory Committee Briefing Document, 2007].

- **Similarity between daprodustat and ESA:** The relationships between post-randomization dose as well as post-randomization Hgb and adjudicated outcomes were similar for daprodustat and ESA comparator in both ASCEND-D and ASCEND-ND. The similarity of the findings for daprodustat and ESA comparator thus support the findings from the primary hypothesis and suggest that the CV risk of daprodustat is similar to that of ESAs and can be managed by controlling target Hgb.

6.1.3. Summary of Limitations

All the analyses listed above have major methodological limitations as a result of groups being selected for comparison on the basis of post-randomization events (such as post-randomization changes in dose and Hgb response to the randomized treatment), which limits the ability to infer causality based on these analyses. In addition, there were too few events in individual dose categories and Hgb quintiles for some adjudicated CV outcomes, leading to a higher degree of uncertainty in the conclusions. The limitation of having few events was further exacerbated in the FDA requested Hgb rate of change quintiles analyses as events without the minimum of two values needed to calculate a slope of change in Hgb were not included in these analyses. For the Hgb rate of change in the 4 weeks prior to event, 90% of the events did not have an associated slope of change and for the Hgb rate of change in the 12 weeks prior to event, 50% to 60% (percentage varying slightly for each event of interest) of the events did not have an associated slope of change in Hgb.

6.2. FDA Dose Category and Hgb Quintiles Analyses

As described prior, the FDA requested post-hoc analyses by dose category and Hgb quintiles for many adjudicated outcomes as well as AE groupings. Below, we discuss in further detail some of the findings from these analyses by using the time to first adjudicated MACE (the primary safety endpoint) as an example.

6.2.1. Cardiovascular Risk by Average Weekly Dose Categories

6.2.1.1. Dose Categories

Due to the skewed distribution of daprodustat doses taken across the study population, use of quintiles would have collapsed a large range of doses into the high- and low-dose quintiles while the intermediate doses would have a small range, which would make discerning a dose response more difficult. Five dose categories were therefore chosen in a manner that attempted to balance the representation of a range of doses across the categories, while having sufficient amount of observation time in each dose category to permit meaningful examination of the data.

Dose categories were calculated using the time period when participants were on randomized study treatment and following the dosing algorithm; this included those on a zero dose, i.e., on dose hold or required a dose below lowest available dose. The average weekly dose at the time of the event of interest was defined as the dose on the day the event of interest occurs, converted to an average weekly dose, and assigned to a dose

category as outlined in Table 50. The average weekly dose in the 2 weeks prior and 4 weeks prior to the event of interest was also calculated and assigned to a dose category. The number of events per 100 PY was generated for each of the 5 average weekly dose categories.

Table 50 Average Dose Categories for CV Risk Analyses

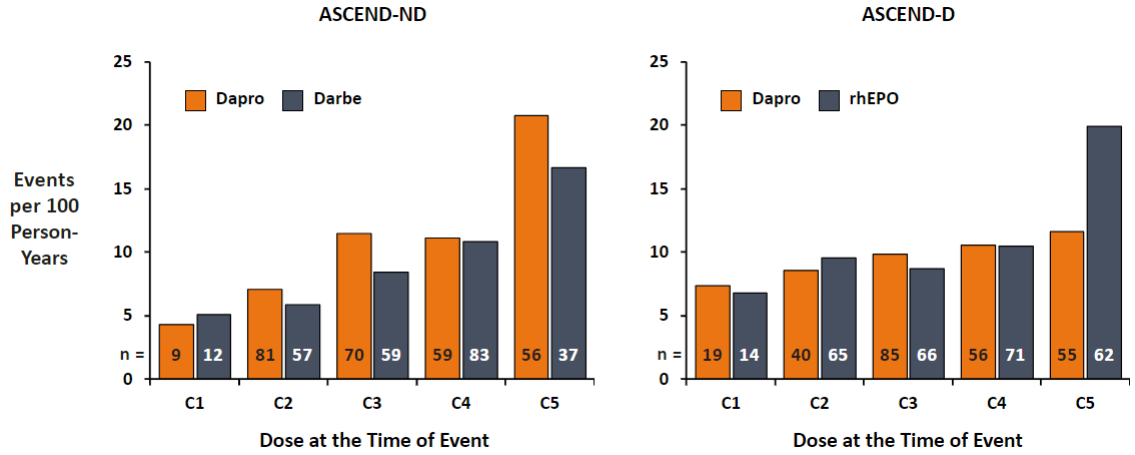
	ASCEND-D		ASCEND-ND	
	Weekly dose of Daprodustat	Weekly dose of ESA	Weekly dose of Daprodustat	Weekly dose of ESA
Category 1	0 mg	0 U	0 mg	0 µg
Category 2	>0 mg to <28 mg	>0 U to <5000 U	>0 mg to <28 mg	>0 µg to <15 µg
Category 3	28 mg to <56 mg	5000 U to <10000 U	28 mg to <42 mg	15 µg to <25 µg
Category 4	56 mg to <84 mg	10000 to <18000 U	42 mg to <70 mg	25 µg to <75 µg
Category 5	≥84 mg	≥18000 U	≥70 mg	≥75 µg

6.2.1.2. Adjudicated MACE by Dose Category

There was an association of increasing MACE with higher dose categories evident in ASCEND-ND and ASCEND-D for both daprodustat and the ESA comparator. Figure 22 depicts the association with average weekly dose at the time of event, and the average weekly dose in the 2-weeks prior and 4-weeks prior to event followed the same pattern (not shown). Note that the daprodustat dose in categories 3 to 5 is greater in the ASCEND-D than the ASCEND-ND study (Table 50).

The results of analyses for other adjudicated safety outcomes were generally consistent with findings for MACE except for thromboembolic events in ASCEND-D, where no association was seen for either treatment group.

Figure 22 Dosing Frequency Adjusted On-treatment CV Period Adjudicated MACE by Dose Categories Based on the Dose at the Time of the Event (Events per 100 Person-Years)



Note: On-treatment CV period is defined as the treatment start date to the earlier of last non-zero dose or study withdrawal + dosing frequency + 28 days
The numbers inside the bars represent the numbers of events.

6.2.2. Cardiovascular Risk by Hgb

6.2.2.1. Hgb Quintile Ranges

The Hgb quintile ranges for each analysis were similar between treatment groups across ASCEND-D and ASCEND-ND. The quintiles used for the analysis of Hgb just prior to adjudicated MACE for the dosing frequency on-treatment CV period are shown in Table 51.

Table 51 ASCEND-ND: Hemoglobin (Hgb) Quintile Ranges (g/dL) Used for Assessment of Hgb Just Prior to Adjudicated MACE; Dosing Frequency Adjusted On-treatment CV Period

ASCEND-D	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
Daprodustat	≤9.8	>9.8 to 10.4	>10.4 to 10.8	>10.8 to 11.4	>11.4
rhEPO	≤9.6	>9.6 to 10.2	>10.2 to 10.7	>10.7 to 11.3	>11.3
ASCEND-ND					
Daprodustat	≤9.7	>9.7 to 10.3	>10.3 to 10.7	>10.7 to 11.2	>11.2
Darbepoetin	≤9.7	>9.7 to 10.2	>10.2 to 10.7	>10.7 to 11.2	>11.2

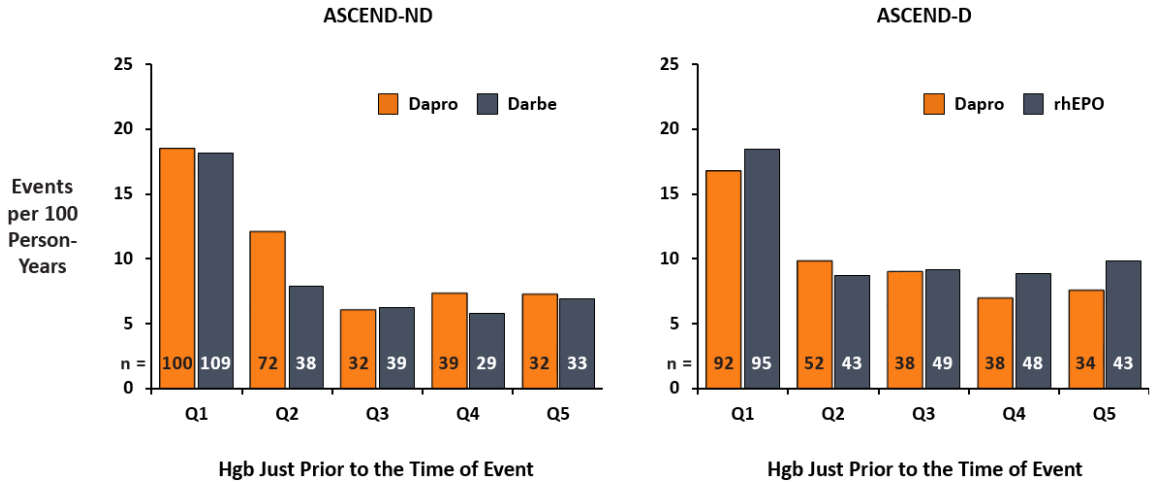
6.2.2.2. Adjudicated MACE by Hgb Quintiles

The highest MACE risk was noted in the lowest Hgb quintiles, where an association of events was observed with low Hgb just prior to the event in ASCEND-ND and ASCEND-D. Results were similar for daprodustat and the ESA controls. There was no indication of increased risk of MACE with Hgb values in the higher quintiles for either treatment group in either study (Figure 23).

For the other adjudicated safety outcomes, the findings were generally similar to MACE for both daprodustat and the ESA comparators, with higher event rates seen with lower Hgb just prior to the event. There were no associations of events with high Hgb, for either daprodustat or the ESA controls, which support the appropriateness of the Hgb targets and dosing algorithms used in the Phase 3 program.

Analyses exploring the relationship between adjudicated safety outcomes and rates of decrease in Hgb and rates of increase in Hgb in the 12 weeks prior to the CV events were performed but could not be interpreted as 50% to 60% (percentage varying slightly for each event of interest) of the events did not have an associated slope of change in Hgb in the 12-weeks prior to the event since there were fewer than 2 Hgb values in the associated time intervals. This was due to the protocol-defined study visit schedule changing from every 4 weeks to every 12 weeks after the first year in the study. Hgb values were not imputed in these cases, such that any event that did not have an associated Hgb slope was excluded from the summary.

Figure 23 Dosing Frequency Adjusted On-treatment CV Period Adjudicated MACE by Hgb Quintiles Based on the Hgb Value Just Prior to the Event (Events per 100 Person-Years)



Note: On-treatment CV period is defined as the treatment start date to the earlier of last non-zero dose or study withdrawal + dosing frequency + 28 days
The numbers inside the bars represent the numbers of events.

7. POST-MARKETING

Following launch in Japan, as a routine condition of approval, daprodustat completed an EPPV Period, which ran from 26 August 2020 to 25 February 2021. During this time, heightened efforts are made to facilitate timely collection of spontaneous AEs from health care professionals. The final report of the EPPV concluded that no new findings affecting the safety profile of daprodustat were identified, and that no additional risks or new safety measures were thought to be necessary. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) has accepted these conclusions.

Additionally, a post-marketing surveillance (PMS) “Special Drug Use Investigation”, which is a standard requirement for new chemical entities in Japan, commenced in September 2020. The objective of this surveillance is to prospectively monitor and collect physician reports of safety events related to daprodustat in daily clinical practice in Japan. As of August 2022, 1,674 patients have been enrolled in this surveillance program which is anticipated to complete in 2026.

Cumulatively, through 28 June 2022 (the data lock point for the most recent PSUR), there have been 4,091 spontaneous or post-marketing surveillance reports from Japan. The safety of daprodustat is regularly monitored through routine pharmacovigilance activities including:

- Systematic and proactive review of aggregate safety data with trend analysis to detect increased frequency of reporting and qualitative and quantitative methodologies to detect safety signals.

- Broad contextualization of the safety data within epidemiology event rates as was presented in various clinical sections of this document.
- Ongoing awareness and review of important individual cases, including reports with a fatal outcome.
- Systematic review of the literature.

In summary, the analysis of post-marketing data from Japan carried out by GSK, has thus far been consistent with the known safety profile of the drug as described in the Japan Product Information, and has not identified any new safety signals. Additional pharmacovigilance activities or risk minimization measures have not been deemed necessary, requested by health authorities or implemented since authorization. No new safety signals have been identified from the post-marketing data, and the benefit-risk profile of daprodustat in Japan continues to be favorable.

8. BENEFIT-RISK

Benefit-risk is discussed at the end of the Executive Summary (Section 1.7) and below.

In the active-controlled clinical trials of up to approximately 3.5 years in duration, the dosing regimens tested for daprodustat increased and maintained Hgb to a target range as effectively as injectable ESAs, with similar rates of transfusion. Therefore, daprodustat shares the proven benefits of ESA, including reducing the need for transfusions.

Clinicians avoid transfusions, when possible, because of potential alloimmunization which can have a long-term impact on kidney transplant outcomes. Highly sensitized patients may be less likely to receive a living donor kidney transplant and would be subject to aggressive induction and maintenance immunosuppression therapy to reduce risk of rejection. Blood transfusions also carry the immediate post-transfusion risks of volume overload and hyperkalemia and, although rare, transmission of blood-borne infections. The convenience of an effective oral agent would be expected to improve access to those left untreated for logistical reasons, and provide benefits for health care providers in terms of storage (refrigeration not required), delivery (avoiding parenteral administration, quite often in the provider's office, allows for fewer clinic visits for non-dialysis and peritoneal dialysis patients) and disposal (no biohazard waste associated with used injection devices).

Cardiovascular events and complications are known to be associated with ESAs. Given that daprodustat's pharmacodynamic effect is to increase both endogenous EPO, albeit to a lesser extent than ESAs, and RBC mass, it is not surprising that these were also reported with daprodustat. No increased risk of malignancy was demonstrated with daprodustat compared with ESAs. Furthermore, no signal for increased risk was noted for drug induced liver injury, seizures and sepsis that have been reported for other members of the HIF-PHI class.

The benefit-risk profile of daprodustat in Japan continues to be favorable, and no new safety signals for these patient populations have been identified through post-marketing surveillance.

Benefit-risk in patients on dialysis

Marketed ESAs have been shown to have an increased risk of MACE in clinical trials that targeted physiologically normal levels of Hgb (not now recommended via label or treatment guidelines). It is therefore important that any alternative treatment to ESAs does not have an inferior CV safety profile to ESAs.

The CV outcomes study, ASCEND-D, demonstrated that daprodustat was non-inferior to ESA with respect to the pre-specified primary ITT analysis of the safety endpoint, MACE. For NI studies the effects restricted to the period that participants were on treatment is often of interest; however, the analysis is compromised by defining the period of follow-up based on a post-randomization event (i.e., discontinuation of treatment). Hence, these on-treatment analyses must be interpreted with the appropriate context. Even with these considerations, the on-treatment assessment of MACE for ASCEND-D had results consistent with the primary ITT analysis.

In the past few decades many kidney health organizations globally have strongly advocated for policy and practice changes to increase access to and uptake of home dialysis. This uptake is hindered particularly for those with major logistical difficulties to overcome in attending outpatient clinics to receive parenteral treatments for their anemia. Consequently the convenience of an oral treatment as effective and safe as ESAs would be clearly advantageous in patients on home HD or undergoing peritoneal dialysis.

Benefit-risk in patients not on dialysis

Like ASCEND-D, the CV outcomes study conducted in patients not on dialysis, ASCEND-ND, demonstrated that daprodustat was non-inferior to ESAs with respect to the pre-specified primary ITT analysis of the safety endpoint, MACE. In a subgroup of the non-dialysis population with pre-existing HF there was an observed increase with daprodustat in the risk of being hospitalized for worsening HF. These patients are at high underlying risk of fluid overload, irrespective of drug therapy, and close monitoring of their fluid status is an important part of clinical practice. Daprodustat was superior to placebo in improving QoL SF-36 vitality domain score by reducing fatigue in non-dialysis patients.

Patients with CKD anemia not on dialysis experience suboptimal levels of treatment which is exacerbated by the need to travel to clinic to receive parenteral drug administration. This increases the risk of under-treatment leading to correction by transfusion with subsequent fluid overload, hyperkalemia and the need for urgent care, potentially requiring dialysis. Treatment that scrupulously avoids transfusions is important to preserve the option for potentially curative renal transplant, while also reducing fatigue, dyspnea and other limiting symptoms of anemia. An oral treatment still requires close monitoring of Hgb levels but this can be readily achieved via local blood draws without requiring travel to specialist outpatient centers. The availability of an additional, oral therapy would permit more scope for individualizing patient care.

The patient population not on dialysis has the greatest unmet need for an oral treatment that matches the efficacy and safety of current pharmaceutical standard of care, parenterally delivered ESAs, for anemia of CKD.

Conclusion

The efficacy and safety of daprodustat has been demonstrated in 5 placebo-controlled and active-controlled trials, giving consistent evidence supporting its positive benefit-risk when used as an oral treatment option for anemia of CKD in adults receiving, or not receiving, dialysis. The totality of data across the Phase 3 studies, and the available post-marketing data, supports daprodustat having an acceptable safety profile, similar to ESAs.

Proper use of daprodustat, including patient selection, dosing and monitoring, and precautionary guidance related to risks, can be largely managed via product labeling. GSK intends to communicate and mitigate the risk of worsening HF in those patients with pre-existing HF who are not on dialysis through the product labeling (US prescribing information and medication guide), including language in the 'Warnings and Precautions' and 'Adverse Reactions' sections. Prescriber education materials will be provided to assist with further risk mitigation in non-dialysis patients with history of HF. In addition, enhanced pharmacovigilance activities will be conducted in the form of targeted follow-up questionnaires to gather additional data about spontaneous reports of malignancies.

9. REFERENCES

Aragonés J, Schneider M, Geyte KV, et al. Deficiency or inhibition of oxygen sensor Phd1 induces hypoxia tolerance by reprogramming basal metabolism. Nat Genet. 2008 Feb;40(2):170-80.

Aranesp, FDA Drug Approval Package, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/103951_aranesp_toc.cfm

Ariazi J, Duffy KJ, Adams DF, et al. Discovery and preclinical characterization of GSK1278863 (Daprodustat), a small molecule hypoxia inducible factor-prolyl hydroxylase inhibitor for anemia. J Pharmacol Exp Ther. 2017 Dec;363(3):336-47.

Au EH, Chapman JR, Craig JC, et al. Overall and Site-Specific Cancer Mortality in Patients on Dialysis and after Kidney Transplant. J Am Soc Nephrol. 2019 Feb 14;30(3):471–80.

Aymé S, Bockenhauer D, Day S, et al. Common elements in rare kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney international. 2017;92(4):796-808.

Azmi S, Goh A, Muhammad NA, et al. The cost and quality of life of Malaysian type 2 diabetes mellitus patients with chronic kidney disease and anemia. Value Health Reg Issues. 2018;15:42-9.

Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol. 2012;23(10):1631-34.

Badve SV, Beller EM, Cass A, et al. Interventions for erythropoietin- resistant anemia in dialysis patients. Cochrane Database Syst Rev. 2013;(8):CD006861.

Bae MN, Kim SH, Kim YO, et al. Association of erythropoietin- stimulating agent responsiveness with mortality in hemodialysis and peritoneal dialysis patients. PLoS One. 2015;10(11):e0143348.

Barreto Lopes M, Tu C, Zee J, et al. A real-world longitudinal study of anemia management in non-dialysis-dependent chronic kidney disease patients: a multinational analysis of CKDopps. Sci Rep. 2021;11(1):1784.

Besarab A, Bolton WK, Browne JK. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584-90.

Bonner A, Caltabiano M, Berlund L. Quality of life, fatigue, and activity in Australians with chronic kidney disease: a longitudinal study. Nursing & health sciences. 2013;15(3):360-367.

Briefing Document for the Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee (CRDAC), September 11, 2007. Accessed 14 July 2022. Available from: https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4315b1-04-AMGEN.pdf

Butler AM, Olshan AF, Kshirsagar AV, et al. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009. Am J Kidney Dis. 2015 May;65(5):763-72.

Claggett B, Pocock S, Wei LJ, et al. Comparison of time-to-first event and recurrent-event methods in randomized clinical trials. Circulation. 2018;138(6):570-577.

Clayton PA, Coates PT. Are sensitized patients better off with a desensitization transplant or waiting on dialysis? Kidney Int. 2017;91(6):1266-8.

Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2021. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2021

[cited 2022 August 11]. Available from: https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.

Chen X, Li Y, Ding X, et al. Incidence, risk, and prognosis of cancer in patients on chronic hemodialysis. Blood Purif. 2020;49(3):310-21.

Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non–dialysis-dependent CKD. N Engl J Med. 2021;384:1589-600.

Cheung CY, Tang SCW. Oncology in nephrology comes of age: A focus on chronic dialysis patients. Nephrology (Carlton). 2019;24(4):380-86.

Committee For Medicinal Products For Human Use (CHMP). Guideline on the Choise of the Non-Inferiority Margin.2006. Accessed 15 September 2022. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf

Dal Pan GP, Lindquist M, Gelperin K. Postmarketing spontaneous pharmacovigilance reporting systems, in Textbook of Pharmacoepidemiology, Third Edition, Edited by Strom BL, Kimmel SE, Hennessy S. New York: John Wiley & Sons Ltd, 2022.

Davis J, Suehs B, Xu Y, et al. Understanding Treatment of Severe Anemia due to CKD: A Descriptive Study in Non-Dialysis Medicare Advantage Prescription Drug Plan Patients. Kidney Week 2020 (online); Abstract PO0273. Available at https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3439498 (cited 10 August 2022).

de Goeij MCM, Meuleman Y, Van DS, et al. Haemoglobin levels and health-related quality of life in young and elderly patients on specialized predialysis care. Nephrol Dial Transplant. 2014;29(7):1391-98.

Dember LM, Beck GJ, Allon M, et al. Dialysis Access Consortium Study Group. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA. 2008;299(18):2164-71.

DeMets DL, Cook T. Challenges of Non-Intention-to-Treat Analyses. JAMA. 2019;321(2):145-6.

Dixon BS, Beck GJ, Vazquez MA, et al. Effect of Dipyridamole plus aspirin on hemodialysis graft patency. N Engl J Med 2009;360:2191-201.

Drüeke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071-84.

Eckardt KU, Agarwal R, Aswad A, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. N Engl J Med 2021;384:1601-12.

Eriksson D, Goldsmith D, Teitsson S, Jackson J, van Nooten F. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anaemia. BMC Nephrol. 2016;17(1):1-10.

Fleming TR, Odem-Davis K, Rothmann MD, et al. Some essential considerations in the design and conduct of non-inferiority trials. Clinical Trials 2011;8:432-39.

Food and Drug Administration (FDA). Non-inferiority clinical trials to establish effectiveness. Guidance for Industry. 2010. Accessed: 15 September 2022. Available from: https://www.fda.gov/media/78504/download

Food and Drug Administration (FDA). Multiple endpoints in clinical trials. Guidance for Industry. 2017. Accessed: 15 September 2022. Available from: https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf

Gaillard HM, Hamilton GC. Hemoglobin/hematocrit and other erythrocyte parameters. Emerg Med Clin North Am. 1986;4:15-40.

Gill K, Fink JC, Gilbertson DT, et al. Red blood cell transfusion, hyperkalemia, and heart failure in advanced chronic kidney disease. Pharmacoepidemiol Drug Saf. 2015;24:654–62.

Granger BB, Swedberg K, Ekman I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet. 2005;366(9502):2005-11.

Greenland S, Lanes S, Jara M. Estimating effects from randomized trials with discontinuations: the need for intent-to-treat design and G-estimation. Clin Trials. 2008;5(1):5-13.

GSK Data on File 2022N519897_00. Events of special interest in Japanese dialysis patients. 2022.

GSK Data on File 2022N519896_00. Events of interest in patients with anaemia of CKD and receiving an erythropoiesis stimulating agent in Japan: an insurance claims analysis. 2022.

GSK Data on File 2022N519895_00. Assessment of event rates in patients with anaemia of CKD and receiving an erythropoiesis stimulating agent in Japan: a claims analysis. 2022.

GSK Data on File 2022N518875_00. Between Population Comparison in SF-36 0-100 Vitality Scores. 2022.

GSK Data on File 2020N461858_00. Patient and physician preferences for treatments of anemia in chronic kidney disease: insights from the qualitative pilot of a choice experiment (2022 ASN selected abstract). 2022.

GSK Data on File 2022N518136_00. Quantifying the frequency of red blood cell transfusions in US Medicare Advantage patients in Chronic Kidney Disease stage 3-5 by hemoglobin levels during 2017-2019 (Summary extract from 218794). 2022.

Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. Blood Rev. 2013;27(1):41-53.

Hansen RA, Chin H, Blalock S, et al. Predialysis chronic kidney disease: Evaluation of quality of life in clinic patients receiving comprehensive anemia care. Res Social Adm Pharm. 2009;5(2):143-53.

He J, Shlipak M, Anderson A, et al. Risk Factors for Heart Failure in Patients With Chronic Kidney Disease: The CRIC (Chronic Renal Insufficiency Cohort) Study. J Am Heart Assoc. 2017;6(5):1-9.

Hoshino J, Muenz D, Zee J, et al. Associations of hemoglobin levels with health-related quality of life, physical activity, and clinical outcomes in persons with stage 3-5 nondialysis CKD. J Renal Nutrition. 2020;30(5):404-14.

House AA, Wanner C, Sarnak MJ, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2019;95:1304–17.

Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841-51.

Ibrahim HN, Ishani A, Foley RN, Guo H, Liu J, Collins AJ. Temporal Trends in Red Blood Transfusion Among US Dialysis Patients, 1992-2005. Am J Kidney Dis. 2008;52(6):1115-21.

Irish AB, Viecelli AK, Hawley CM, et al. Effect of fish oil supplementation and aspirin use on arteriovenous fistula failure in patients requiring hemodialysis. A randomized clinical trial. JAMA Intern Med. 2017;177(2):184-93.

Jain G, Allon M, Saddekni S. Does heparin coating improve patency or reduce infection of tunneled dialysis catheters? Clin J Am Soc Nephrol. 2009;4:1787–90.

Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2012;3(1):136-50.

Keane WF, Brenner BM, de Zeeuw D, et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. Kidney Int. 2003;63 (4):1499-507.

Kefale B, Alebachew M, Tadesse Y, et al. Quality of life and its predictors among patients with chronic kidney disease: A hospital-based cross sectional study. PLoS One. 2019 Feb 27;14(2):e0212184.

Lamerato L, James G, van Haalen H, et al. Epidemiology and outcomes in patients with anemia of CKD not on dialysis from a large US healthcare system database: a retrospective observational study. BMC Nephrol. 2022;23:166

Lawler EV, Bradbury BD, Fonda JR, Gaziano J.M, Gagnon DR. Transfusion Burden among Patients with Chronic Kidney Disease and Anemia. Clin J Am Soc Nephrol. 2010;5:667– 672.

Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. Kidney Int. 2009;75(1):15-24.

Lefebvre P, Vekeman F, Sarokhan B, et al. Relationship between hemoglobin level and quality of life in anemic patients with chronic kidney disease receiving epoetin alfa. Curr Med Res Opin. 2006;22(10):1929-37.

Locatelli F, Pisoni RL, Combe C, et al. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant. 2004;19(1):121-32. [Erratum, Nephrol Dial Transplant 2004;19:1666].

Lok CE, Moist L, Hemmelgarn BR, et al. Fish Oil Inhibition of Stenosis in Hemodialysis Grafts (FISH) Study Group. Effect of fish oil supplementation on graft patency and cardiovascular events among patients with new synthetic arteriovenous hemodialysis grafts: a randomized controlled trial. JAMA. 2012;307(17):1809-16.

McAlister FA, Ezekowitz J, Tarantini L, et al. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: Impact of the New Chronic Kidney Disease-Epidemiology Collaboration Group Formula Circulation. 2012;5(3):309-14.

MacRae JM, Dipchand C, Oliver M, et al. Canadian Society of Nephrology Vascular Access Work Group. Arteriovenous access failure, stenosis, and thrombosis. Can J Kidney Health Dis. 2016;3:1-11.

Maruish ME, (Ed). User's manual for the SF-36v2 Health Survey In. 3rd ed: Lincoln, RI: QualityMetric Incorporated; 2011.

Mathias SD, Blum SI, Sikirica V, et al. Symptoms and impacts in anemia of chronic kidney disease. J Patient Rep Outcomes. 2020;4(1):64.

Michalopoulos SN, Gauthier-Loiselle M, Aigbogun MS, et al. Patient and care partner burden in CKD patients with and without anemia: A US-Based Survey. Kidney Medicine. 2022;4(4):100439.

Obrador GT, Macdougall IC. Effect of red cell transfusions on future kidney transplantation. Clin J Am Soc Nephrol. 2013;8(5):852-60.

Palaka E, Grandy S, van Haalen H, et al. The impact of CKD anaemia on patients: incidence, risk factors, and clinical outcomes—a systematic literature review. Int J Nephrol. 2020;1;2020:7692376.

Parfrey PS, Foley RN, Wittreich BH, et al. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol. 2005;16(7):2180-9.

Pfeffer M, Burdmann EA, Chen C-Y, et al. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. N Engl J Med 2009;361:2019-32.

Power A, Chan K, Singh SK, et al. Appraising Stroke Risk in Maintenance Hemodialysis Patients: A Large Single-Center Cohort Study. Am J Kidney Dis. 2012;59(2):249-57.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. John Wiley and Sons, 1987.

Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. Pharmacoeconomics. 1999;15(2):141-55.

Schinstock CA, Smith BH, Montgomery RA, et al. Managing highly sensitized renal transplant candidates in the era of kidney paired donation and the new kidney allocation system: Is there still a role for desensitization? Clin Transplant. 2019;33(12):e13751.

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.

Seliger S, Fox KM, Gandra SR, Bradbury B, Hsu VD, Walker L, Chiou CF, Fink JC. Timing of erythropoiesis-stimulating agent initiation and adverse outcomes in nondialysis CKD: a propensity-matched observational study. Clin J Am Soc Nephrol. 2010 May;5(5):882-8.

Shen Y, Wang J, Yuan J, et al. Anemia among Chinese patients with chronic kidney disease and its association with quality of life - Results from the Chinese cohort study of chronic kidney disease (C-STRIDE). BMC Nephrol. 2021;22(1):64.

Singh AK, Szczech, L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355:2085-98. doi: 10.1056/NEJMoa065485.

Singh AK, Carroll K, McMurray JJV, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. N Engl J Med. 2021;385(25):2313-24.

Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the treatment of anemia in patients undergoing dialysis. N Engl J Med. 2021;385(25):2325-35.

Singh AK, Wanner C, Wiecek AJ, et al. Daprodustat is not associated with an increased risk of cancer: results from the ASCEND-ND and ASCEND-D Trials. NDT. 2022;37 (Suppl.3):i377–i393.

Snapinn SM, Jiang Q, Iglewicz B. Informative noncompliance in endpoint trials. Curr Control Trials Cardiovasc Med. 2004;5(1):5.

So JH, Kim JD, Yoo KW, et al. FIH-1, a Novel interactor of mindbomb, functions as an essential anti-angiogenic factor during zebrafish vascular development. PLoS One. 2014 Oct 27;9(10):e109517.

Solomon SD, Uno H, Lewis EF, et al, for the TREAT Investigators. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010; 363:1146-55.

St Peter WL, Guo H, Kabadi S, et al. Prevalence, treatment patterns, and healthcare resource utilization in Medicare and commercially insured non-dialysis-dependent chronic kidney disease patients with and without anemia in the United States. BMC Nephrol. 2018;19(1):67.

Staibano P, Perelman I, Lombardi J, et al. Patient-centred outcomes in anaemia and renal disease: a systematic review. Kidney Diseases. 2020;6(2):74-84

Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One. 2014;9(1):e84943.

Swedberg K , Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med. 2013; 368:1210-19.

Thorp ML, Johnson ES, Yang X, et al. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. Nephrology (Carlton). 2009;14(2):240-6.

Unger EF, Thompson AM, Blank MJ et al. Erythropoiesis-stimulating agents — time for a reevaluation. N Engl J Med 2010; 362: 189-192.

United States Renal Data System Chapter 1: Incidence, prevalence, patient characteristics, and treatment modalities. Ann Arbor, MI: USRDS Coordinating Center; 2021 [cited 2021 September 27]. Available at: https://adr.usrds.org/2021/chronic-kidney-disease/1-ckd-in-the-general-population.

United States Renal Data System. Chapter 3: Morbidity and Mortality in Patients with CKD. Ann Arbor, MI: USRDS Coordinating Center; 2021 [cited 2022 August 10]. Available at: https://adr.usrds.org/2021/chronic-kidney-disease/3-morbidity-and-mortality-in-patients-with-ckd

van Haalen H, Jackson J, Salehi H, et al. Health state utility of patients with chronic kidney disease and anemia: analysis of EQ-5D in a real world population. 2018. Oxford Univ Press Great Clarendon St, Oxford OX2 6DP, England, 456-7.

van Haalen H, Jackson J, Spinowitz B, et al. Impact of chronic kidney disease and anemia on health-related quality of life and work productivity: analysis of multinational real-world data. BMC Nephrol. 2020;21(1):88.

van Nooten FE, Green J, Brown R, et al. Burden of illness for patients with non-dialysis chronic kidney disease and anemia in the United States: review of the literature. J Med Econ. 2010;13(2):241-56.

Walmsley SR, Chilvers ER, Thompson AA, et al. Prolyl hydroxylase 3 (PHD3) is essential for hypoxic regulation of neutrophilic inflammation in humans and mice. J Clin Invest 2011 Mar;121(3):1053-63.

Wang AYM, Lam CWK, Chan IHS, et al. Sudden cardiac death in end-stage renal disease patients. A 5-year prospective analysis. Hypertension. 2010;56:210-16.

Wang E, Zhang C, Polavaram N, et al. The role of factor inhibiting HIF (FIH-1) in inhibiting HIF-1 transcriptional activity in glioblastoma multiforme. PLoS One. 2014;9(1):e86102.

Wang CC, Tang CH, Wang CY, et al. Risk of skin cancer in patients on chronic haemodialysis: a nationwide, population-based study in Taiwan. Br J Dermatol. 2016 Dec;175(6):1175-82.

Ware Jr JE. SF-36 health survey update. Spine. 2000;25(24):3130-39.

Westgard QC. Desirable Specifications for Total Error, Imprecision, and Bias derived from intra- and inter-individual biologic variation. 2014. Accessed 15 September 2022]. Available from: https://www.westgard.com/biodatabase1 htm

Wittbrodt ET, James G, Kumar S, et al. Contemporary outcomes of anemia in US patients with chronic kidney disease, Clin Kidney J. 2022;15(2):244-252.

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.

Wong G, Staplin N, Emberson J, et al. Chronic kidney disease and the risk of cancer: an individual patient data meta-analysis of 32,057 participants from six prospective studies. BMC Cancer. 2016;16:488.

Woodburn KW, Schatz PJ, Fong KL, et al. Preclinical safety and pharmacology of Hematide, a peptidic erythropoiesis stimulating agent (ESA), in rats and monkeys. Drug Chem Toxicol. 2008;31(2):229-44.

Yan G, Cheung AK, Ma JZ, et al. The Associations between Race and Geographic Area and Quality-of-Care Indicators in Patients Approaching ESRD. Clin J Am Soc Nephrol. 2013;8:610–18.

Yang F, Wittes J, Pitt B. Beware of on-treatment safety analyses. Clin Trials. 2019;16(1):63-70.

Zhang Y, Thamer M, Stefanik K, et al. Epoetin requirements predict mortality in hemodialysis patients. Am J Kidney Dis. 2004;44(5):866-76.

Zinman B, Inzucchi SE, Lachin JM, et al. Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. Stroke. 2017;48(5):1218-25.

10. APPENDICES

10.1. Hgb Non-inferiority Margin

The NI margin for the primary the Hgb primary efficacy endpoint was -0.75 g/dL for all 4 active-controlled studies, based upon a combination of factors established on statistical reasoning, clinical judgement, and regulatory guidance:

a. NI margin less than a Hgb change that would result in a clinically meaningful difference to the patient. An Hgb change of at least 1 g/dL defined as clinically meaningful Hgb response according to literature [Leaf, 2009; Samsa, 1999];

b. NI margin considers the percentage of the efficacy of ESA preserved by the margin, based on regulatory guidance for designing NI trials [FDA, 2010; CHMP, 2006], which takes into account the Hgb level permitted in the trials and the effect on Hgb if placebo was included;

c. NI margin greater than a change in Hgb that could be due to variability, which protects against the trials resulting in a false negative conclusion [Gaillard, 1986; Westgard, 2011].

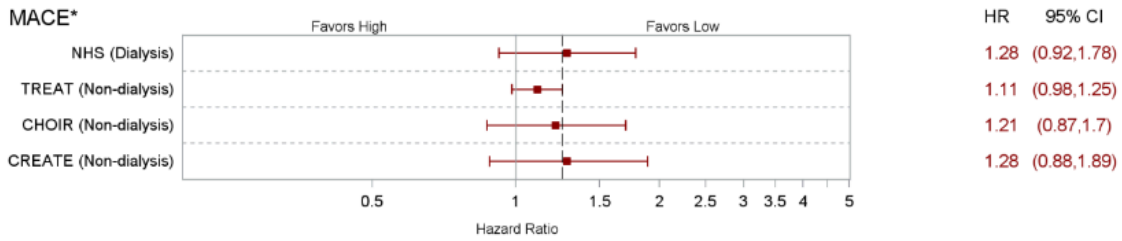
d. NI margins that have been used in past trials of ESAs for the comparative assessment of Hgb efficacy in patients with anemic of CKD patients (Darbepoetin alfa, Peginesatide, and Epoetin-beta).

10.2. MACE Non-inferiority Margin

The NI margin for the assessment of MACE in the CV Outcomes studies, was 1.25 (HR), supported by a review of evidence for harm reported in historical randomized trials of ESA in dialysis and non-dialysis CKD patients with anemia. The review focused on the 4 large ESA trials designed to investigate whether using ESA to raise Hgb concentrations to achieve higher targets would improve clinical outcomes: Normal Hematocrit Study (NHS) [Besarab, 1998], Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial (CHOIR) [Singh, 2006], Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin-beta (CREATE), [Drüeke, 2006], Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) [Pfeffer, 2009].

The results from these studies supported the choice of 1.25 as the NI margin for the assessment of MACE in ASCEND-D and ASCEND-ND (Figure 24; vertical dotted line). The 1.25 threshold was lower than the MACE point estimates for NHS and CREATE, similar to the point estimate for CHOIR and at or markedly lower than all estimated upper bounds for MACE risk.

Figure 24 Forest Plots: MACE Results of NHS, CHOIR, CREATE and TREAT Trials



Note: X-axis on log10 scale. Reference line at 1.25
*For NHS only myocardial infarction and death. For CREATE any CV first event.

10.3. Adjudicated Vascular Access Thrombosis

Table 52 Time to First Adjudicated Vascular Access Thrombosis (ITT Population)

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
First adjudicated VAT, n (%)	46 (2.4)	31 (1.6)	164 (11.0)	201 (13.6)
Censored, n (%)	1891 (97.6)	1904 (98.4)	1323 (89.0)	1276 (86.4)
Incidence rate per 100 PY (95% CI)	1.29 (0.95, 1.72)	0.87 (0.59, 1.23)	4.98 (4.24, 5.80)	6.27 (5.43, 7.20)
Diff in rate per 100 PY (95% CI)[a]	0.43 (-0.06, 0.91)		-1.29 (-2.45, -0.14)	
Hazard Ratio (95% CI)[b]	**1.49** (0.94, 2.35)		**0.80** (0.65, 0.98)	
1-sided superiority p-value[c]	0.9569		0.0153	

VAT=vascular access thrombosis, PY=person-years.

a. A rate difference <0 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.

b. HR estimated using Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. HR <1 indicates lower risk with daprodustat compared with ESA/darbepoetin alfa.

c. One-sided p-value based on Wald test of null hypothesis: HR (Dapro/ESA) ≥1 vs alternative: HR <1.

10.4. Time to Progression of CKD in ASCEND-ND

Table 53 ASCEND-ND: Time to First Occurrence of CKD Progression (ITT Population)

	Number (%) of Participants	
	Dapro (N=1937)	**Darbe (N=1935)**
Number of participants [a]	1220	1265
CKD Progression	343 (28.1)	359 (28.4)
Confirmed 40% eGFR decline	173 (14.2)	191 (15.1)
Chronic dialysis	162 (13.3)	158 (12.5)
Kidney transplant	8 (0.7)	10 (0.8)
Incidence Rate per 100 PY (95% CI)	17.55 (15.74, 19.51)	17.76 (15.97, 19.70)
Absolute Rate Difference per 100 PY (95% CI)	-0.21 (-2.82, 2.40)	
Subdistribution Hazard Ratio (95% CI) [b]	**0.98** (0.84, 1.13)	

eGFR=estimated glomerular filtration rate, PY=person-years.

Note: Rate per 100 PY = 100 x (number of participants with event/person-years)

a. All randomized participants with Baseline eGFR $\geq$15 mL/min/1.73 m^2.

b. Subdistribution hazard ratio is estimated using Fine & Gray's proportional subdistribution hazard regression model to account for death as a competing risk, with treatment group, baseline ESA use, and region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared to darbepoetin.

10.5. Adjudicated ACM or Hospitalization for HF

Table 54 Time to First Occurrence of ACM or Hospitalization for HF, Overall and by History of HF Subgroups (ITT Population)

	ASCEND-ND		ASCEND-D	
	Dapro (N=1937)	Darbe (N=1935)	Dapro (N=1487)	ESA (N=1477)
First Adjudicated ACM or hospitalization for HF				
First ACM or hospitalization for HF, n (%)	393 (20.3)	368 (19.0)	363 (24.4)	366 (24.8)
All-cause Mortality	253 (13.1)	253 (13.1)	251 (16.9)	265 (17.9)
Non-fatal hospitalization for HF	140 (7.2)	115 (5.9)	112 (7.5)	101 (6.8)
Rate per 100 PY (95% CI)	11.36 (10.27, 12.54)	10.57 (9.51, 11.70)	10.69 (9.62, 11.85)	10.89 (9.81, 12.07)
Diff in rate per 100 PY (95% CI)[a]	0.80 (-0.76, 2.36)		-0.21 (-1.77, 1.36)	
Hazard Ratio (95% CI)[b]	**1.09** (0.94, 1.26)		**0.98** (0.85, 1.14)	
History of Heart Failure Subgroup: No				
First ACM or hospitalization for HF, n (%)	289/1671 (17)	292/1679 (17)	260/1220 (21)	263/1222 (22)
All-cause Mortality	203 (12)	211 (13)	195 (16)	194 (16)
Non-fatal hospitalization for HF	86 (5)	81 (5)	65 (5)	69 (6)
Hazard Ratio (95% CI)[b]	**1.02** (0.87, 1.21)		**0.98** (0.82, 1.16)	
History of Heart Failure Subgroup: Yes				
First ACM or hospitalization for HF, n (%)	104/265 (39)	76/254 (30)	103/267 (39)	103/254 (41)
All-cause Mortality	50 (19)	42 (17)	56 (21)	71 (28)
Non-fatal hospitalization for HF	54 (20)	34 (13)	47 (18)	32 (13)
Hazard Ratio (95% CI)[b]	**1.20** (0.89, 1.62)		**0.99** (0.76, 1.31)	

ACM=all-cause mortality, HF=heart failure, MACE=major adverse cardiovascular event, PY=person-years.
Note: Rate per 100 PY = 100 x (number of participants with event/person-years)
a. A rate difference <0 indicates a lower risk with daprodustat compared with ESA/darbepoetin alfa.
b. HR estimated using Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and region as covariates. HR <1 indicates lower risk with daprodustat compared with ESA/darbepoetin alfa.

10.6. Demographics and Baseline Characteristics by Region (US vs Non-US)

Table 55 Summary of Demographics and Baseline Characteristics by Region (US vs Non-US) (ITT Population)

	ASCEND-ND (N=3872)				ASCEND-D (N=2964)			
	US		Non-US		US		Non-US	
	Dapro (N=492)	Darbe (N=489)	Dapro (N=1445)	Darbe (N=1446)	Dapro (N=425)	ESA (N=421)	Dapro (N=1062)	ESA (N=1056)
Age (Years), mean (SD)	67.5 (13.06)	67.5 (12.98)	63.9 (14.24)	64.0 (14.00)	58.2 (13.23)	58.1 (13.03)	56.8 (14.68)	57.0 (15.24)
Gender, n (%)								
Male	222 (45)	219 (45)	613 (42)	645 (45)	240 (56)	244 (58)	611 (58)	603 (57)
Female	270 (55)	270 (55)	832 (58)	801 (55)	185 (44)	177 (42)	451 (42)	453 (43)
High Level Race, n (%)								
American Indian or Alaskan Native	1 (<1)	3 (<1)	87 (6)	97 (7)	6 (1)	10 (2)	13 (1)	22 (2)
Asian	8 (2)	20 (4)	517 (36)	517 (36)	20 (5)	17 (4)	156 (15)	164 (16)
Black or African American	160 (33)	161 (33)	23 (2)	24 (2)	168 (40)	162 (38)	60 (6)	71 (7)
Native Hawaiian/Pacific Islander	3 (<1)	0	4 (<1)	7 (<1)	8 (2)	4 (<1)	18 (2)	21 (2)
White	320 (65)	303 (62)	778 (54)	752 (52)	217 (51)	224 (53)	778 (73)	758 (72)
Mixed Race	0	2 (<1)	36 (2)	49 (3)	6 (1)	4 (<1)	37 (3)	20 (2)
Baseline Hgb (g/dL), mean (SD)	9.64 (0.897)	9.62 (0.868)	9.94 (0.942)	9.93 (0.962)	10.2 (0.88)	10.3 (0.84)	10.4 (1.00)	10.4 (1.03)
Baseline BMI (kg/m^2), mean (SD)	30.36 (7.243)	29.93 (7.020)	26.94 (5.884)	26.73 (5.717)	30.89 (7.954)	30.45 (7.803)	26.61 (5.915)	26.92 (6.027)
Baseline CKD stage, n (%)								
Stage 2	4 (<1)	1 (<1)	5 (<1)	7 (<1)	-	-	-	-
Stage 3	102 (21)	125 (26)	234 (16)	238 (16)	-	-	-	-
Stage 4	255 (52)	259 (53)	620 (43)	635 (44)	-	-	-	-
Stage 5	131 (27)	104 (21)	585 (40)	566 (39)	-	-	-	-
Baseline eGFR (mL/min/1.73m^2), median (Q1, Q3)	20 (14, 28)	21 (16, 30)	17 (11, 25)	17 (12, 26)	-	-	-	-

	ASCEND-ND (N=3872)				ASCEND-D (N=2964)			
	US		Non-US		US		Non-US	
	Dapro (N=492)	Darbe (N=489)	Dapro (N=1445)	Darbe (N=1446)	Dapro (N=425)	ESA (N=421)	Dapro (N=1062)	ESA (N=1056)
Hospitalization within 6 months prior to screening, n (%)	47 (10)	29 (6)	205 (14)	182 (13)	42 (10)	46 (11)	157 (15)	167 (16)
History of, n (%)								
Diabetes[a]	332 (67)	344 (70)	752 (52)	790 (55)	288 (68)	280 (67)	327 (31)	337 (32)
Stroke	41 (8)	39 (8)	87 (6)	89 (6)	36 (8)	44 (10)	60 (6)	66 (6)
Cancer	46 (9)	30 (6)	55 (4)	56 (4)	24 (6)	15 (4)	50 (5)	57 (5)
Heart Failure[b]	103 (21)	83 (17)	162 (11)	171 (12)	108 (25)	105 (25)	159 (15)	149 (14)
Coronary Artery Disease	133 (27)	134 (27)	236 (16)	266 (18)	134 (32)	119 (28)	213 (20)	215 (20)
PE	6 (1)	6 (1)	12 (<1)	10 (<1)	12 (3)	8 (2)	9 (<1)	12 (1)
DVT	27 (5)	17 (3)	23 (2)	20 (1)	27 (6)	20 (5)	37 (3)	24 (2)
Vitamin K Antagonist Use, n (%)	28 (6)	13 (3)	43 (3)	42 (3)	24 (6)	23 (5)	56 (5)	48 (5)
Vascular Access at Baseline, n (%)	22 (5)	26 (5)	92 (6)	78 (5)	-	-	-	-
First Dialysis Vascular Access During the Study, n (%)	118 (24)	91 (19)	356 (25)	368 (25)	-	-	-	-

BMI=body mass index, DVT= deep vein thrombosis, eGFR= estimated glomerular filtration rate, PE=pulmonary embolism.

a. History of diabetes was defined as having a yes response to at least one record of the medical history terms that contains “diabetic” or “diabetes”.

b. History of heart failure was defined as having a medical condition of “heart failure” at enrolment.

10.7. General Safety

Table 56 ASCEND-ND: Common (≥5%) TEAEs (Safety Population); Pre-specified and Dosing Frequency Adjusted Definitions

	Up to Last Dose + 1d (pre-specified) [a]				Up to Last Dose + DF [a]			
ASCEND-ND Common TEAEs	Dapro n (%) (N=1937)	rhEPO n (%) (N=1933)	Risk difference (%)	Relative risk (95% CI)	Dapro n (%) (N=1937)	rhEPO n (%) (N=1933)	Risk difference (%)	Relative risk (95% CI)
Hypertension	257 (13)	272 (14)	-0.80	0.94 (0.80 ,1.10)	257 (13)	279 (14)	-1.17	0.92 (0.79 ,1.08)
Urinary tract infection	187 (10)	179 (9)	0.39	1.04 (0.86 ,1.27)	187 (10)	190 (10)	-0.18	0.98 (0.81 ,1.19)
Oedema peripheral	199 (10)	166 (9)	1.69	1.20 (0.98 ,1.46)	199 (10)	176 (9)	1.17	1.13 (0.93 ,1.37)
Hyperkalaemia	151 (8)	144 (7)	0.35	1.05 (0.84 ,1.30)	151 (8)	153 (8)	-0.12	0.98 (0.79 ,1.22)
Diarrhoea	150 (8)	139 (7)	0.55	1.08 (0.86 ,1.34)	150 (8)	151 (8)	-0.07	0.99 (0.80 ,1.23)
Chronic kidney disease	134 (7)	113 (6)	1.07	1.18 (0.93 ,1.51)	134 (7)	129 (7)	0.24	1.04 (0.82 ,1.31)
Nasopharyngitis	118 (6)	133 (7)	-0.79	0.89 (0.70 ,1.13)	118 (6)	134 (7)	-0.84	0.88 (0.69 ,1.12)
Pneumonia	109 (6)	109 (6)	-0.01	1.00 (0.77 ,1.29)	109 (6)	124 (6)	-0.79	0.88 (0.68 ,1.13)
Constipation	128 (7)	90 (5)	1.95	1.42 (1.09 ,1.84)	128 (7)	96 (5)	1.64	1.33 (1.03 ,1.72)
Fall	111 (6)	91 (5)	1.02	1.22 (0.93 ,1.59)	111 (6)	95 (5)	0.82	1.17 (0.89 ,1.52)
Anaemia	109 (6)	79 (4)	1.54	1.38 (1.04 ,1.83)	109 (6)	86 (4)	1.18	1.26 (0.96 ,1.67)
Back pain	85 (4)	109 (6)	-1.25	0.78 (0.59 ,1.03)	85 (4)	110 (6)	-1.30	0.77 (0.59 ,1.02)
Nausea	103 (5)	84 (4)	0.97	1.22 (0.92 ,1.62)	103 (5)	87 (5)	0.82	1.18 (0.89 ,1.56)
Upper respiratory tract infection	98 (5)	91 (5)	0.35	1.07 (0.81 ,1.42)	98 (5)	92 (5)	0.30	1.06 (0.81 ,1.40)
Acute kidney injury	102 (5)	81 (4)	1.08	1.26 (0.95 ,1.67)	102 (5)	87 (5)	0.77	1.17 (0.89 ,1.55)

DF=dosing frequency, TEAE=treatment-emergent adverse event

a. Pre-specified (Last dose+1d) and dosing frequency adjusted (Last dose+DF) treatment-emergent definitions are detailed in Table 18.

Table 57 ASCEND-D: Common (≥5%) TEAEs (Safety Population); Pre-specified and Dosing Frequency Adjusted Definitions

	Up to Last Dose + 1d (pre-specified) [a]				Up to Last Dose + DF [a]			
ASCEND/D Common AEs	Dapro n (%) (N=1482)	rhEPO n (%) (N=1474)	Risk difference (%)	Relative risk (95% CI)	Dapro n (%) (N=1482)	rhEPO n (%) (N=1474)	Risk difference (%)	Relative risk (95% CI)
Hypertension	243 (16)	241 (16)	0.05	1.00 (0.85 ,1.18)	243 (16)	243 (16)	-0.09	0.99 (0.85 ,1.17)
Diarrhoea	167 (11)	182 (12)	-1.08	0.91 (0.75 ,1.11)	167 (11)	187 (13)	-1.42	0.89 (0.73 ,1.08)
Headache	116 (8)	140 (9)	-1.67	0.82 (0.65 ,1.04)	116 (8)	140 (9)	-1.67	0.82 (0.65 ,1.04)
Dialysis hypotension	141 (10)	110 (7)	2.05	1.27 (1.00 ,1.62)	141 (10)	113 (8)	1.85	1.24 (0.98 ,1.57)
Pneumonia	123 (8)	118 (8)	0.29	1.04 (0.81 ,1.32)	123 (8)	126 (9)	-0.25	0.97 (0.77 ,1.23)
Hypotension	120 (8)	106 (7)	0.91	1.13 (0.88 ,1.45)	120 (8)	110 (7)	0.63	1.09 (0.85 ,1.39)
Nasopharyngitis	114 (8)	104 (7)	0.64	1.09 (0.84 ,1.41)	114 (8)	104 (7)	0.64	1.09 (0.84 ,1.41)
Arthralgia	102 (7)	111 (8)	-0.65	0.91 (0.71 ,1.18)	102 (7)	112 (8)	-0.72	0.91 (0.70 ,1.17)
Fluid overload	96 (6)	110 (7)	-0.98	0.87 (0.67 ,1.13)	96 (6)	110 (7)	-0.98	0.87 (0.67 ,1.13)
Cough	101 (7)	101 (7)	-0.04	0.99 (0.76 ,1.30)	101 (7)	103 (7)	-0.17	0.98 (0.75 ,1.27)
Upper respiratory tract infection	102 (7)	100 (7)	0.10	1.01 (0.78 ,1.32)	102 (7)	100 (7)	0.10	1.01 (0.78 ,1.32)
Bronchitis	93 (6)	100 (7)	-0.51	0.92 (0.70 ,1.22)	93 (6)	101 (7)	-0.58	0.92 (0.70 ,1.20)
Anaemia	80 (5)	100 (7)	-1.39	0.80 (0.60 ,1.06)	80 (5)	105 (7)	-1.73	0.76 (0.57 ,1.00)
Arteriovenous fistula thrombosis	85 (6)	98 (7)	-0.91	0.86 (0.65 ,1.14)	85 (6)	99 (7)	-0.98	0.85 (0.64 ,1.13)
Hyperkalaemia	91 (6)	89 (6)	0.10	1.02 (0.77 ,1.35)	91 (6)	91 (6)	-0.03	0.99 (0.75 ,1.32)
Fall	85 (6)	91 (6)	-0.44	0.93 (0.70 ,1.24)	85 (6)	91 (6)	-0.44	0.93 (0.70 ,1.24)
Nausea	83 (6)	85 (6)	-0.17	0.97 (0.72 ,1.30)	83 (6)	87 (6)	-0.30	0.95 (0.71 ,1.27)
Urinary tract infection	82 (6)	85 (6)	-0.23	0.96 (0.71 ,1.29)	82 (6)	87 (6)	-0.37	0.94 (0.70 ,1.26)
Vomiting	84 (6)	78 (5)	0.38	1.07 (0.79 ,1.45)	84 (6)	83 (6)	0.04	1.01 (0.75 ,1.35)
Arteriovenous fistula site complicatic	68 (5)	93 (6)	-1.72	0.73 (0.54 ,0.99)	68 (5)	94 (6)	-1.79	0.72 (0.53 ,0.97)
Pain in extremity	85 (6)	76 (5)	0.58	1.11 (0.82 ,1.50)	85 (6)	76 (5)	0.58	1.11 (0.82 ,1.50)
Back pain	66 (4)	89 (6)	-1.58	0.74 (0.54 ,1.01)	66 (4)	90 (6)	-1.65	0.73 (0.54 ,0.99)
Dyspnoea	69 (5)	82 (6)	-0.91	0.84 (0.61 ,1.14)	69 (5)	84 (6)	-1.04	0.82 (0.60 ,1.11)
Atrial fibrillation	57 (4)	79 (5)	-1.51	0.72 (0.51 ,1.00)	57 (4)	82 (6)	-1.72	0.69 (0.50 ,0.96)
Pyrexia	57 (4)	76 (5)	-1.31	0.75 (0.53 ,1.04)	57 (4)	77 (5)	-1.38	0.74 (0.53 ,1.03)

DF=dosing frequency, TEAE=treatment-emergent adverse event

a. Pre-specified (Last dose+1d) and dosing frequency adjusted (Last dose+DF) treatment-emergent definitions are detailed in Table 18.

Table 58 Incidence and Relative Risk of Treatment-emergent AESI (Safety Population); Pre-specified and Dosing Frequency Adjusted Definitions

	Up to Last dose + 1d (pre-specified) [a]				Up to Last dose + DF [a]			
	Dapro n (%)	rhEPO n (%)	Difference (%)	Relative Risk (95% CI)	Dapro n (%)	rhEPO n (%)	Difference (%)	Relative Risk (95% CI)
ASCEND-ND	**(N=1937)**	**(N=1933)**			**(N=1937)**	**(N=1933)**		
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	5 (0.3)	3 (0.2)	0.10	1.66 (0.40, 6.95)	5 (0.3)	3 (0.2)	0.10	1.66 (0.40, 6.95)
Cardiomyopathy	6 (0.3)	7 (0.4)	-0.05	0.86 (0.29, 2.54)	6 (0.3)	7 (0.4)	-0.05	0.86 (0.29, 2.54)
Pulmonary artery hypertension	15 (0.8)	9 (0.5)	0.31	1.66 (0.73, 3.79)	15 (0.8)	9 (0.5)	0.31	1.66 (0.73, 3.79)
Cancer-related mortality and tumor progression and recurrence	72 (3.7)	49 (2.5)	1.18	1.47 (1.03, 2.10)	72 (3.7)	68 (3.5)	0.20	1.06 (0.76, 1.46)
Esophageal and gastric erosions	70 (3.6)	41 (2.1)	1.49	1.70 (1.16, 2.49)	70 (3.6)	48 (2.5)	1.13	1.46 (1.01, 2.09)
Proliferative retinopathy, macular edema, choroidal neovascularization	54 (2.8)	44 (2.3)	0.51	1.22 (0.83, 1.81)	54 (2.8)	46 (2.4)	0.41	1.17 (0.79, 1.73)
Exacerbation of rheumatoid arthritis	2 (0.1)	4 (0.2)	-0.10	0.50 (0.09, 2.72)	2 (0.1)	4 (0.2)	-0.10	0.50 (0.09, 2.72)
Worsening of hypertension	344 (17.8)	363 (18.8)	-1.02	0.95 (0.83, 1.08)	344 (17.8)	372 (19.2)	-1.49	0.92 (0.81, 1.05)
				0.1 1 10				0.1 1 10
ASCEND-D	**(N=1482)**	**(N=1474)**			**(N=1482)**	**(N=1474)**		
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	20 (1.3)	11 (0.7)	0.60	1.81 (0.87, 3.76)	20 (1.3)	11 (0.7)	0.60	1.81 (0.87, 3.76)
Cardiomyopathy	15 (1.0)	16 (1.1)	-0.07	0.93 (0.46, 1.88)	15 (1.0)	16 (1.1)	-0.07	0.93 (0.46, 1.88)
Pulmonary artery hypertension	9 (0.6)	12 (0.8)	-0.21	0.75 (0.32, 1.77)	9 (0.6)	12 (0.8)	-0.21	0.75 (0.32, 1.77)
Cancer-related mortality and tumor progression and recurrence	47 (3.2)	51 (3.5)	-0.29	0.92 (0.62, 1.35)	47 (3.2)	53 (3.6)	-0.42	0.88 (0.60, 1.30)
Esophageal and gastric erosions	60 (4.0)	81 (5.5)	-1.45	0.74 (0.53, 1.02)	60 (4.0)	82 (5.6)	-1.51	0.73 (0.53, 1.01)
Proliferative retinopathy, macular edema, choroidal neovascularization	38 (2.6)	35 (2.4)	0.19	1.08 (0.69, 1.70)	38 (2.6)	36 (2.4)	0.12	1.05 (0.67, 1.65)
Exacerbation of rheumatoid arthritis	2 (0.1)	1 (0.1)	0.07	1.99 (0.18, 21.91)	2 (0.1)	1 (0.1)	0.07	1.99 (0.18, 21.91)
Worsening of hypertension	293 (19.8)	302 (20.5)	-0.72	0.96 (0.84, 1.11)	293 (19.8)	304 (20.6)	-0.85	0.96 (0.83, 1.11)
				0.1 1 10				0.1 1 10

DF=dosing frequency

a. Pre-specified (Last dose+1d) and dosing frequency adjusted (Last dose+DF) treatment-emergent definitions are detailed in Table 18.

Table 59 TEAEs Leading to Discontinuation of Randomized Treatment by Preferred Term (Safety Population); Pre-specified and Dosing Frequency Adjusted Definitions

ASCEND-ND

	Up to Last Dose + 1d (pre-specified) [a]			Up to Last Dose + DF [a]		
	Dapro n (%) (N=1937)	rhEPO n (%) (N=1933)	Risk difference (%)	Dapro n (%) (N=1937)	rhEPO n (%) (N=1933)	Risk difference (%)
Any TEAE leading to discont.	**247 (13)**	**94 (5)**	7.89	**247 (13)**	**201 (10)**	2.35
Death	11 (<1)	3 (<1)	0.41	11 (<1)	12 (<1)	-0.05
COVID-19	10 (<1)	4 (<1)	0.31	10 (<1)	7 (<1)	0.15
Pneumonia	9 (<1)	4 (<1)	0.26	9 (<1)	8 (<1)	0.05
Cardiac arrest	5 (<1)	4 (<1)	0.05	5 (<1)	9 (<1)	-0.21
Acute myocardial infarction	6 (<1)	3 (<1)	0.15	6 (<1)	7 (<1)	-0.05
Myocardial infarction	10 (<1)	0	0.52	10 (<1)	3 (<1)	0.36
Azotaemia	8 (<1)	2 (<1)	0.31	8 (<1)	4 (<1)	0.21

ASCEND-D

	Up to Last Dose + 1d (pre-specified) [a]			Up to Last Dose + DF [a]		
	Dapro n (%) (N=1482)	rhEPO n (%) (N=1474)	Risk difference (%)	Dapro n (%) (N=1482)	rhEPO n (%) (N=1474)	Risk difference (%)
Any TEAE leading to discont.	**216 (15)**	**124 (8)**	6.16	**216 (15)**	**195 (13)**	1.35
Cardiac arrest	18 (1)	8 (<1)	0.67	18 (1)	16 (1)	0.13
Sepsis	12 (<1)	4 (<1)	0.54	12 (<1)	6 (<1)	0.40
Death	8 (<1)	2 (<1)	0.40	8 (<1)	6 (<1)	0.13
Septic shock	3 (<1)	6 (<1)	-0.20	3 (<1)	10 (<1)	-0.48
Cerebrovascular accident	4 (<1)	5 (<1)	-0.07	4 (<1)	7 (<1)	-0.20
Cardio-respiratory arrest	6 (<1)	2 (<1)	0.27	6 (<1)	4 (<1)	0.13
COVID-19	5 (<1)	2 (<1)	0.20	5 (<1)	4 (<1)	0.07

Note: The 7 most frequently reported preferred terms are presented. DF=dosing frequency, Pre-specified (Last dose+1d) and dosing frequency adjusted (Last dose+DF) treatment-emergent definitions are detailed in Table 18.

Table 60 Serious TEAEs by Preferred Term (Safety Population); Pre-specified and Dosing Frequency Adjusted Definitions

ASCEND-ND

	Up to Last Dose + 1d (pre-specified) [a]			Up to Last Dose + DF [a]		
	Dapro n (%) (N=1937)	rhEPO n (%) (N=1933)	Risk difference (%)	Dapro n (%) (N=1937)	rhEPO n (%) (N=1933)	Risk difference (%)
Any serious TEAE	**850 (44)**	**703 (36)**	7.51	**850 (44)**	**817 (42)**	**1.62**
Pneumonia	78 (4)	75 (4)	0.15	78 (4)	89 (5)	-0.58
Chronic kidney disease	86 (4)	49 (3)	1.90	86 (4)	60 (3)	1.34
Acute kidney injury	70 (4)	47 (2)	1.18	70 (4)	50 (3)	1.03
Azotaemia	54 (3)	35 (2)	0.98	54 (3)	42 (2)	0.62
End stage renal disease	48 (2)	36 (2)	0.62	48 (2)	41 (2)	0.36
COVID-19	39 (2)	33 (2)	0.31	39 (2)	41 (2)	-0.11
Urinary tract infection	33 (2)	36 (2)	-0.16	33 (2)	40 (2)	-0.37

ASCEND-D

	Up to Last Dose + 1d (pre-specified) [a]			Up to Last Dose + DF [a]		
	Dapro n (%) (N=1482)	rhEPO n (%) (N=1474)	Risk difference (%)	Dapro n (%) (N=1482)	rhEPO n (%) (N=1474)	Risk difference (%)
Any serious TEAE	**773 (52)**	**748 (51)**	1.41	**773 (52)**	**790 (54)**	-1.44
Pneumonia	86 (6)	81 (5)	0.31	86 (6)	87 (6)	-0.10
Arteriovenous fistula thrombosis	36 (2)	57 (4)	-1.44	36 (2)	58 (4)	-1.51
Fluid overload	42 (3)	45 (3)	-0.22	42 (3)	45 (3)	-0.22
Sepsis	29 (2)	37 (3)	-0.55	29 (2)	40 (3)	-0.76
Anaemia	26 (2)	41 (3)	-1.03	26 (2)	42 (3)	-1.10
Acute myocardial infarction	30 (2)	31 (2)	-0.08	30 (2)	34 (2)	-0.28
Atrial fibrillation	23 (2)	35 (2)	-0.82	23 (2)	35 (2)	-0.82

DF=dosing frequency.
Note: The 7 most frequently reported preferred terms are presented.
a. Pre-specified (Last dose+1d) and dosing frequency adjusted (Last dose+DF) treatment-emergent definitions are detailed in Table 18.

Table 61 Cancer-related Mortality and Tumor Progression and Recurrence (Safety Population); Pre-specified and Dosing Frequency Adjusted Definitions

	Events up to date of	Dapro n (%)	ESA n (%)	Relative Risk (95% CI)
ASCEND-ND		**(N=1937)**	**(N=1933)**	
TE, pre-specified	Last Dose + 1d	72 (3.7)	49 (2.5)	**1.47** (1.03, 2.10)
TE, DF adjusted	Last Dose + DF	72 (3.7)	68 (3.5)	**1.06** (0.76, 1.46)
mITT, on and off trt	End of study	87 (4.5)	84 (4.3)	**1.03** (0.77, 1.39)
ASCEND-D		**(N=1482)**	**(N=1474)**	
TE, pre-specified	Last Dose + 1d	47 (3.2)	51 (3.5)	**0.92** (0.62, 1.35)
TE, DF adjusted	Last Dose + DF	47 (3.2)	53 (3.6)	**0.88** (0.60, 1.30)
mITT, on and off trt	End of study	65 (4.4)	77 (5.2)	**0.84** (0.61, 1.16)

DF=dosing frequency, TE=treatment-emergent, mITT=modified intention-to-treat, trt=treatment.
Note: Definitions for TE (pre-specified and DF adjusted) are detailed in Table 18. On and off-treatment events were assessed in the mITT analysis: Treatment Start Date ≤ AE Start Date/AE Worsening Date.

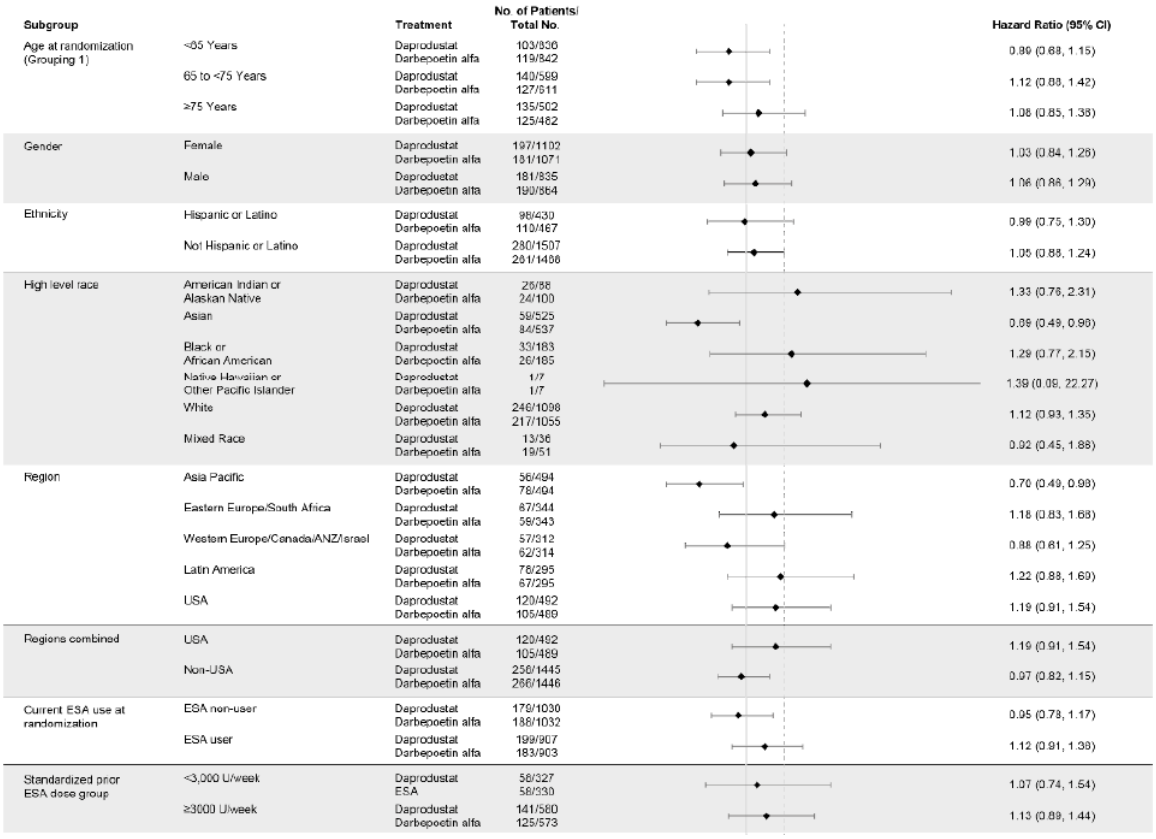
Table 62 Pooled Studies ASCEND-ND and ASCEND-D: TEAEs of Seizures, Sepsis, Fractures, and Hepatotoxicity (Safety Population); Pre-specified and Dosing Frequency Adjusted Definitions

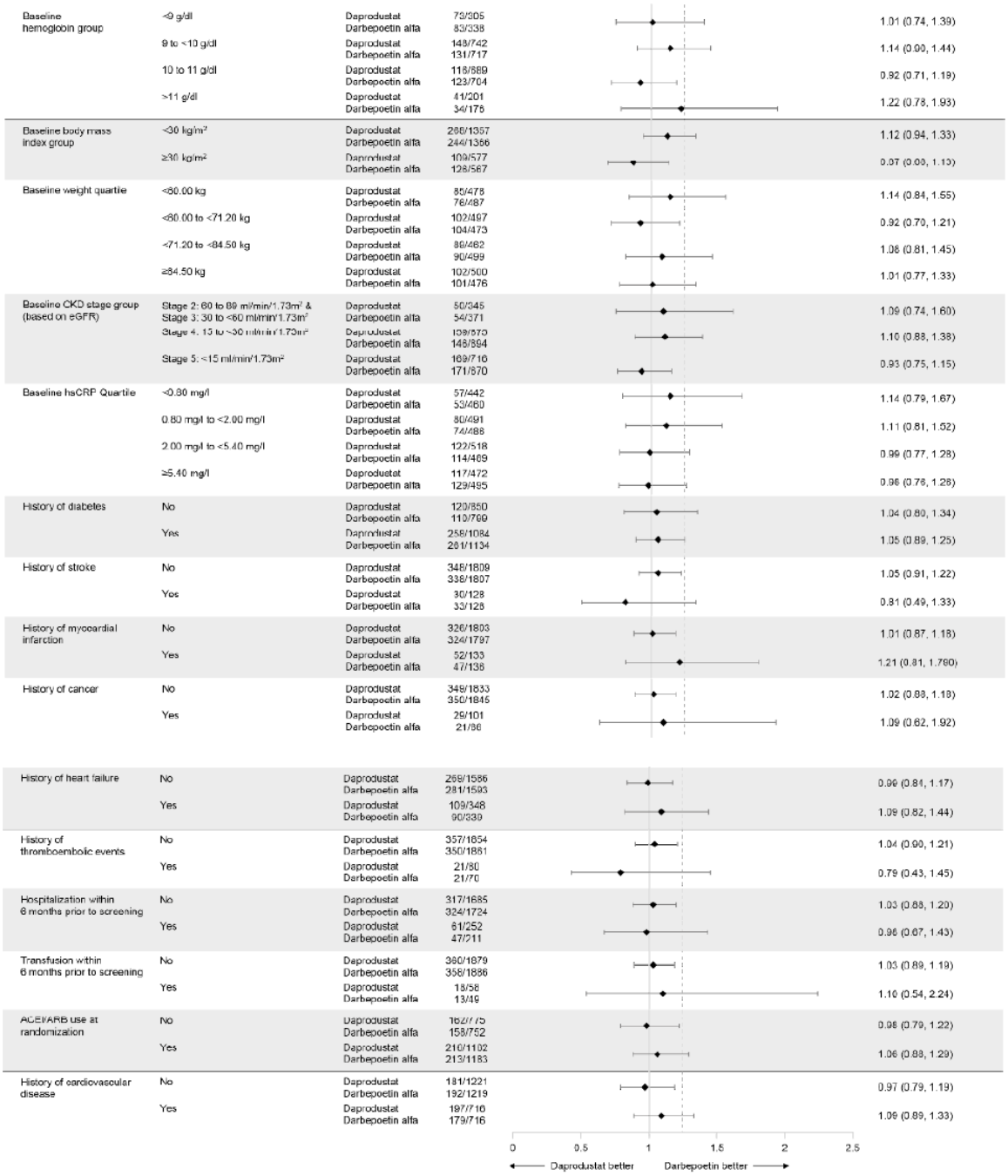
	Up to Last Dose + 1d (pre-specified) [a]			Up to Last Dose + DF [a]		
TEAEs of	Dapro n (%) (N=3419)	rhEPO n (%) (N=3407)	Rate Difference (per 100PY)	Dapro n (%) (N=3419)	rhEPO n (%) (N=3407)	Rate Difference (per 100PY)
Seizures	26 (<1)	25 (<1)	0.02	26 (<1)	28 (<1)	-0.02
Fractures	188 (5)	175 (5)	0.34	188 (5)	188 (6)	0.18
Sepsis/septic shock	114 (3)	142 (4)	-0.51	114 (3)	162 (5)	-0.81
Hepatotoxicity	89 (3)	85 (2)	0.11	89 (3)	93 (3)	0

Note: TEAEs presented are based on MedDRA SMQs (narrow). Data are adjusted for dosing frequency (refer to Table 18 for definition).
Rate per 100 PY = 100 x (number of participants with event/person-years).

10.8. Subgroup Analyses of Time to First Adjudicated MACE

Figure 25 Study ASCEND-ND: Forest Plots by Subgroup for MACE (ITT Population)

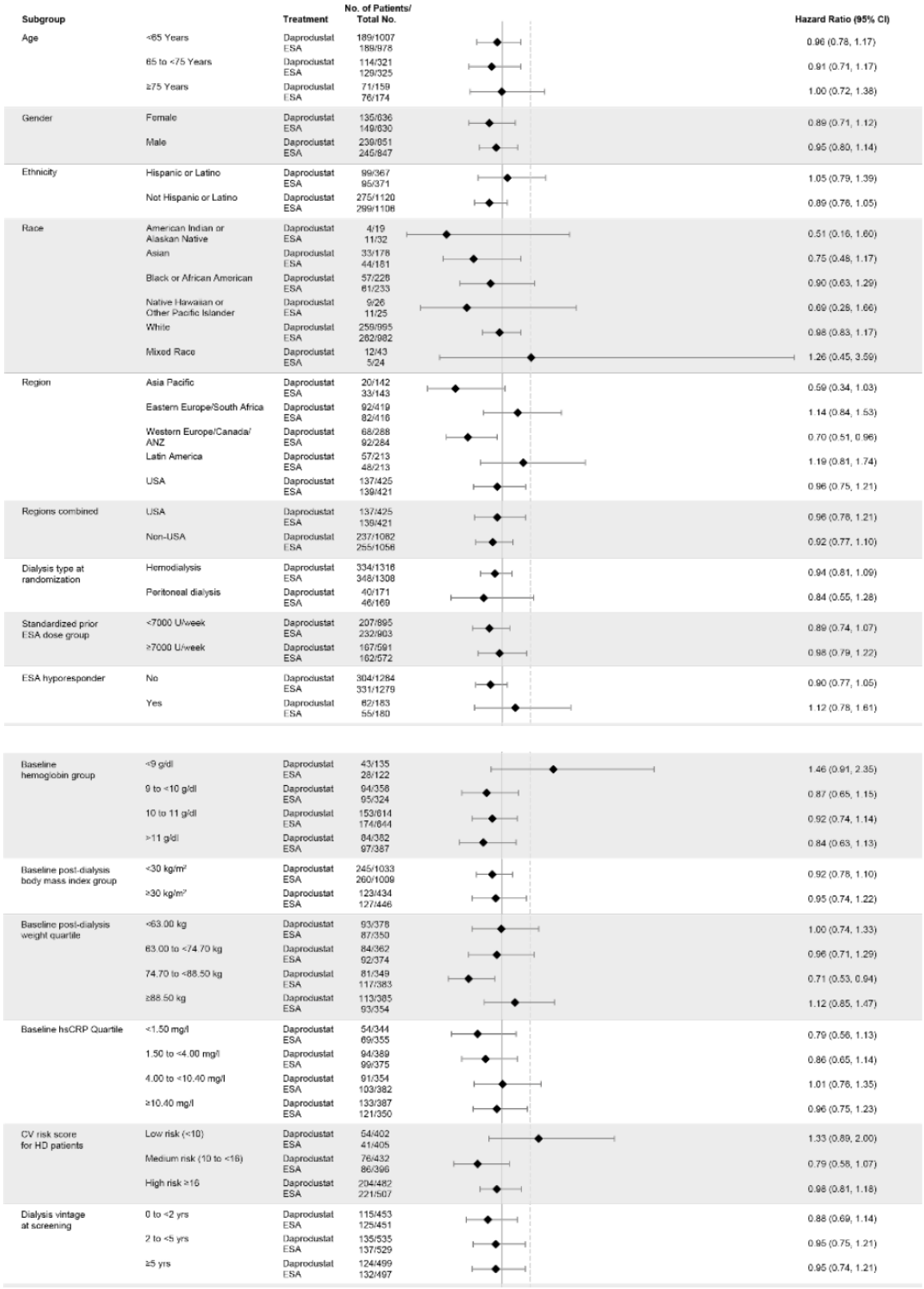


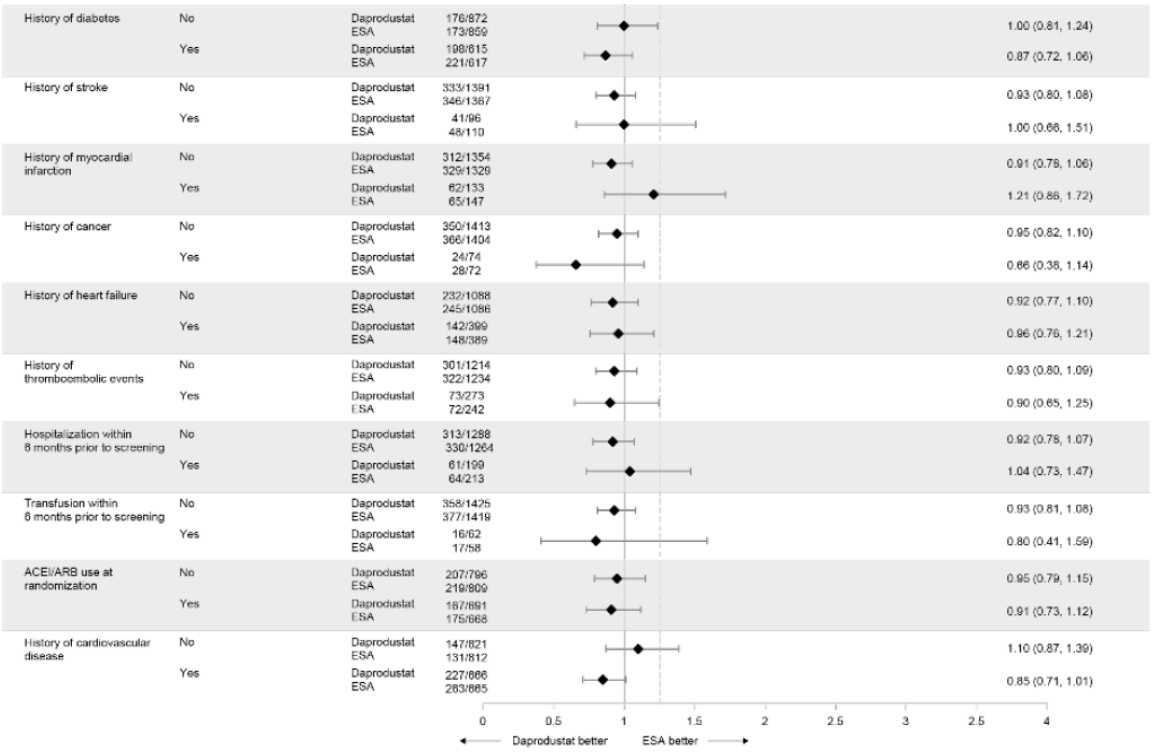


Source: Reproduced from: [Singh, 2021]

Note: History of heart failure subgroup defined as having a yes response to any of the following 4 pre-defined terms for medical history conditions at enrolment: heart failure, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, and pulmonary hypertension.

Figure 26 Study ASCEND-D: Forest Plots by Subgroup for MACE (ITT Population)





Source: Reproduced from: [Singh, 2021]

Note: History of heart failure subgroup defined as having a yes response to any of the following 4 pre-defined terms for medical history conditions at enrolment: heart failure, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, and pulmonary hypertension.

10.9. FDA MedDRA queries, included terms for Acute Kidney Injury, Narrow

- Acute kidney injury
- Acute phosphate nephropathy
- Acute prerenal failure
- Anuria
- Cardiorenal syndrome
- Continuous haemodiafiltration
- Crush syndrome
- Crystal nephropathy
- Delayed foetal renal development
- Frasier syndrome
- GRACILE syndrome
- Haemolytic uraemic syndrome
- Hepatorenal failure
- Nephritis
- Nephropathy toxic
- Oliguria
- Pancreatorenal syndrome
- Postoperative renal failure
- Postrenal failure
- Prerenal failure
- Renal failure acute
- Renal injury
- Renal ischaemia
- Renal tubular injury
- Renal tubular necrosis
- Traumatic anuria
- Tubulointerstitial nephritis
- Urate nephropathy
- Urine output decreased