FDA Briefing Document

NDA 216951

Drug name: Daprodustat

Applicant: GlaxoSmithKline (GSK) Intellectual Property (No. 2) Limited England

Cardiovascular and Renal Drugs Advisory Committee Meeting

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Division of Nonmalignant Hematology (DNH),

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)

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Table of Contents

Table of Tables

Table of Figures

Glossary

AC	Advisory Committee
ACM	all-cause mortality
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
CI	confidence interval
CKD	chronic kidney disease
CV	cardiovascular
DD	dialysis-dependent
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
(e)GFR	(estimated) glomerular filtration rate
FDA	Food and Drug Administration
Hb	hemoglobin
HD	hemodialysis
HHF	hospitalization for heart failure
IRD	incidence rate difference
ITT	intention-to-treat
IV	intravenous
K-M	Kaplan-Meier
MACE	major adverse cardiovascular event
MI	myocardial infarction
NDD	non-dialysis-dependent
OT	on-treatment
PD	peritoneal dialysis
PRO	patient-reported outcome
PT	preferred term
PY	person-years
RBC	red blood cell
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TEE	thromboembolic event
TESAE	treatment-emergent serious adverse event
US(A)	United States (of America)
VAT	vascular access thrombosis

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss whether the benefits of daprodustat, an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor, outweigh its risks for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis.

1.2 Context for Issues to Be Discussed at the AC

Anemia is a common complication of CKD, develops early in the course of the disease and worsens as CKD progresses. Currently available therapeutic options include iron, erythropoiesis-stimulating agents (ESAs), and red blood cell (RBC) transfusions. ESAs, such as epoetin alfa and darbepoetin alfa, increase RBC mass through the same mechanism as endogenous erythropoietin.

ESA dosing varies from three times a week to monthly, depending on the specific agent and setting. All are administered by intravenous or subcutaneous injection (none can be orally administered). These products have a Boxed Warning for increased mortality; serious cardiovascular and thromboembolic events including stroke and myocardial infarction; and warnings for hypertension, seizures, and thrombotic events including vascular access thrombosis.

If approved daprodustat would be the first orally available treatment for anemia of CKD and the first marketed HIF prolyl hydroxylase inhibitor, which is thought to raise hemoglobin (Hb) by increasing transcription of HIF-responsive genes, including erythropoietin. The daprodustat development program included two large adequate and well-controlled clinical trials, one in subjects with anemia due to CKD who were NDD and another in subjects with anemia of CKD who were DD. These trials compared the effectiveness and safety of daprodustat with approved ESAs.

1.3 Brief Description of Issues for Discussion at the AC

In the head-to-head trials, daprodustat increased Hb to a similar extent as approved ESAs (darbepoietin alfa in the NDD population and darbepoietin alfa or epoetin alfa in the DD population) with similar continued need for RBC transfusions or rescue therapy. There were no other benefits demonstrated on how patients feel, function, or survive. While the oral route of daprodustat provides some convenience over the parenteral ESAs, the advantage of an oral route is unclear for the vast majority of patients undergoing hemodialysis in the US who typically receive an ESA during the dialysis session. In light of the risks of daprodustat that will be discussed below, the oral route also has potential downsides, including risks of inadequate Hb monitoring in some settings (e.g., NDD CKD population), which might lead to worse outcomes (e.g., if Hb is increased too much). There is also the potential for prescribing to

patients with anemia and decreased creatinine clearance who do not currently receive ESAs and some of these patients (e.g., the elderly) might be at greater risk of adverse effects.

In the DD population, notable risks included hospitalization for heart failure (HHF; particularly in patients with a history of heart failure) and bleeding gastric erosions. Daprodustat did not unacceptably increase the risk of major adverse cardiac events (MACE, defined as a composite of all-cause mortality, nonfatal myocardial infarction and nonfatal stroke) or other cardiovascular events compared to darbepoietin alfa or epoetin alfa in the DD population.

In contrast, in the NDD population, daprodustat appears to have several other important risks in addition to the risks of heart failure and bleeding gastric erosions. Our findings, based on adjudicated cardiovascular endpoints, show elevated estimated hazard ratios (HRs) for MACE on some analyses (e.g., when evaluated using a supportive on-treatment analysis; when analyzed in the US subgroup of patients; and when analyzed using cardiovascular death instead of all-cause mortality in the MACE composite). We also noted elevated estimated HRs for cardiovascular (CV) mortality, myocardial infarction (MI), stroke, thromboembolic disease, and vascular access thrombosis. Because ESAs such as darbepoietin alfa already carry some of these risks, a further increase in these risks beyond that seen with the ESAs is concerning. Furthermore, these other CV risks (with the exception of stroke) appear higher in the US subgroup of patients compared to the non-US subgroup. The elevated risks in the US subgroup across multiple CV endpoints is noteworthy because daprodustat would be used in the US if FDA approved. Lastly, we also identified a possible increased risk of acute kidney injury (AKI) with daprodustat in the NDD population.

We are seeking the advisory committee's advice and recommendations on these safety issues and whether the benefits of daprodustat outweigh its risks in the NDD and DD populations, and thank you in advance for your service to public health.

1.4 Draft Points for Consideration

As you review the AC Background materials, we ask that you consider the following in advance of the meeting:

Non-Dialysis-Dependent Population

1. Discuss the benefits of daprodustat in the NDD population
2. Discuss the risks of daprodustat in the NDD population, including cardiovascular harm, gastric erosions/hemorrhage, and AKI.
3. Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults not on dialysis?
    - Provide your rationale. If the benefits do not outweigh the risks, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment.

Dialysis Population

1. Discuss the benefits of daprodustat in the DD population.
2. Discuss the risks of daprodustat in the DD population, including the risks of heart failure and gastric erosions/hemorrhage.
3. Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults on dialysis?
    - Provide your rationale. If the benefits do not outweigh the risks, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Anemia of Chronic Kidney Disease

The estimated prevalence of CKD in the U.S. adult population is 15%, with an estimated 17 million people having CKD stages 3 (mild to moderate renal dysfunction, estimated glomerular filtration rate (eGFR) 30 to 59 mL/min/1.73 m^2) to stage 5 (most severe renal dysfunction, kidney failure; eGFR <15 mL/min/1.73 m^2). The prevalence of anemia increases as the GFR declines [1,2]. An estimated 90% of patients requiring dialysis are anemic.

The etiology of anemia of CKD is multifactorial and includes deficiency of erythropoietin (a hormone secreted by the kidneys that increases RBC production), impaired ability to absorb iron (iron deficiency), inability to utilize stored iron (due to chronic disease), blood loss (e.g., through chronic dialysis), and shortened RBC survival. Symptoms of anemia include fatigue, reduced exercise tolerance, and dyspnea.

Currently available therapeutic options for anemia of CKD include iron, ESAs, and RBC transfusions. Patients with CKD are routinely assessed for evidence of iron deficiency and treatment with iron is given if deficient. Approximately 8% of patients with stage 4 CKD and 13% of patients with stage 5 CKD receive an ESA. Use of an ESA in adults with pre-end-stage renal disease (ESRD) ranges from approximately 12% to 17% (3). Most patients with CKD receiving hemodialysis (HD) require ESAs to correct anemia and reduce the need for RBC transfusion and its attendant risks, including the risks of alloreactivity and rejection after kidney transplantation. To place daprodustat into its proper context in the armamentarium of therapies for the anemia of CKD, some general background on ESAs is important.

Erythropoiesis-stimulating Agents

ESAs are a class of recombinant glycoproteins that have an identical or nearly identical primary amino acid sequence to endogenous human erythropoietin and have the same biological

effects as erythropoietin. ESAs bind to and activate the human erythropoietin receptor and stimulate RBC production in bone marrow. ESA use for the treatment of anemia due to CKD in patients on dialysis and not on dialysis has spanned over 30 years.

Currently approved ESAs include epoetin alfa, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and epoetin alfa-epbx (Table 1). Dosing is titrated based on Hb level and can vary from three times a week to monthly, depending on the specific agent and setting. All are either administered by intravenous or subcutaneous injection: none can be orally administered.

Table 1. US-Licensed ESAs for the Treatment of Anemia Due to Chronic Kidney Disease

Product Name Established Name (Trade Name)	Year of Approval
Epoetin alfa (Epogen/Procrit)	1989
Darbepoetin alfa (Aranesp)	2001
Methoxy polyethylene glycol-epoetin beta (Mircera)	2007
Epoetin alfa-epbx (Retacrit)	2018

Source: Clinical Reviewer's table.
Abbreviations: ESA, erythropoiesis-stimulating agent; US, United States

Pertinent Safety Risks of the Drug Class

After the initial approval of an ESA for patients with CKD in 1989, the ESA labeling has undergone significant revisions because of risks that emerged in the postmarketing setting and in subsequent clinical trials (summarized below). These labeling revisions have included the following additions:

- A Boxed Warning for increased mortality and serious cardiovascular (MI and stroke) and thromboembolic events.
- Warnings for hypertension, seizures, and thrombotic events including vascular access thromboses.
- In the dosing and administration section, a reduction in the recommended "target Hb," and a recommendation to discontinue the ESA in patients in whom Hb does not respond adequately over a 12-week dose-escalation period.
- Inclusion of other major adverse reactions of ESA including hypertension, seizures, and pure red cell aplasia.

ESA use in patients with CKD can increase the risk of MACE. Clinical trials have established that targeting higher rather than lower Hb levels increases the risk of MACE, although the ideal Hb target that best balances benefits and risks has not been identified for any of the ESAs.

- The US Normal Hematocrit trial (4) was the first in a series of randomized, controlled trials designed to test the hypothesis that a higher target hematocrit in subjects receiving hemodialysis (HD) would result in improved outcomes. In this trial, 1233 patients with ESRD on HD with symptomatic heart failure or ischemic heart disease were randomized to either partial treatment of anemia (hematocrit of 30±3%) or full correction (hematocrit of 42±3%). The primary endpoint was time to death or first

nonfatal MI. The trial was terminated at the third interim analysis for futility and potential harm in the full anemia correction group. There were 202 primary endpoint events in the full correction group compared to 164 events in the partial correction group: risk ratio 1.3 (95% confidence interval [CI] 0.9, 1.9). Also, 39% of subjects in the full anemia correction group had vascular access thrombosis compared to 29% of subjects in the partial treatment arm.

- The CHOIR study (5) was a randomized, active-controlled clinical trial in patients with NDD-CKD that aimed to show superiority of full anemia correction by ESA administration in terms of CV events and death. In this trial, 1432 patients with CKD and anemia (Hb <11 g/dL) received epoetin alfa and were randomly assigned to a target Hb of either 13.5 g/dL or 11.3 g/dL. The primary endpoint was a composite of death, MI, hospitalization for heart failure, or stroke. The study was prematurely stopped for futility after an interim analysis at a median study duration of 16 months because it was considered unlikely that benefit would be demonstrated for the primary composite CV endpoint. There were 125 events among 715 subjects in the high-Hb group versus 97 events among 717 subjects in the low-Hb group (hazard ratio [HR], 1.34; 95% CI 1.03, 1.74; [P=0.03]), with death and hospitalization for heart failure accounting for 75% of the events.
- The CREATE study (6) in 603 patients with CKD stages 3 to 5 (26% with diabetes) failed to demonstrate the superiority of full anemia correction (Hb target 13.0 to 15.0 g/dL) with respect to CV events, as compared to partial correction of anemia (Hb target 11.0 to 12.5 g/dL), when starting ESA therapy at an earlier stage than ESRD.
- Subsequently, TREAT, by far the largest trial, examined CV and renal outcomes in 4038 patients with stages 3 and 4 CKD (7). TREAT was the only large placebo-controlled study to assess CV outcomes. Patients received either darbepoetin alfa to achieve a Hb target of 13.0 g/dL or matching placebo with rescue darbepoetin alfa when the Hb concentration was <9.0 g/dL. The HR for the first coprimary endpoint, the composite of death or a CV event, was 1.05 (95% CI 0.94, 1.17). The HR for the second coprimary endpoint, death or ESRD, was 1.06 (P=NS). There was, however, a nearly two-fold increased risk of stroke (HR 1.92; 95% CI 1.38, 2.68) with darbepoetin alfa compared to placebo. In addition, venous thromboembolic events occurred at a significantly higher incidence in the darbepoietin alfa arm (2.0%) compared to the placebo arm (1.1%, P=0.02).

As a result of these concerns, FDA convened the Cardiovascular and Renal Drugs Advisory Committee in 2010 to discuss whether the ESA indication for the treatment of anemia due to chronic kidney disease should be withdrawn in the NDD patient population. Votes were strongly in favor of continued marketing: 1 “yes”, 15 “no”, and 1 abstention.

Current Clinical Practice

The international 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of Anemia and Chronic Kidney Disease (8)

recommends addressing all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. The guideline recommends balancing the potential benefits of reducing blood transfusions and improving anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension) (recommendation 1B). For adults with NDD-CKD and Hb concentrations <10.0 g/dL, the decision whether to initiate ESA therapy should be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy, and the presence of symptoms attributable to anemia (recommendation 2C). For adults with NDD-CKD and Hb concentrations ≥10.0 g/dL, ESA therapy is not recommended (recommendation 2D). For adults with stage 5 CKD on dialysis, ESA therapy is recommended when Hb is between 9.0 and 10.0 g/dL (recommendation 2B), and the KDIGO Guideline advises against use to maintain Hb above 11.5 g/dL (recommendation 2C).

2.2 Pertinent Drug Development and Regulatory History

HIF-prolyl hydroxylase inhibitors represent a new class of orally administered tablets. The Applicant states the following in the mechanism of action section of their proposed daprodustat label:

"Daprodustat stimulates endogenous erythropoiesis and modulates iron metabolism through inhibition of HIF-prolyl-4-hydroxylases. This activity results in the stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes, including erythropoietin and transferrin."

Daprodustat is developed as a film-coated tablet for oral administration. The proposed recommended starting dose is based on whether the patient is on dialysis, the Hb level, and current use of ESA therapy. For patients being switched from ESA treatment to daprodustat, the starting dose of daprodustat is based on the dose regimen of ESA therapy at the time of substitution.

A summary of key communications between FDA and the Applicant is provided in the Appendix.

3 Summary of Issues for the AC

3.1 Efficacy Issues

The efficacy of daprodustat to raise Hb is not in question. Summaries of the efficacy data in the NDD and DD populations are provided below.

3.1.1 Sources of Data

Daprodustat's evidence of safety and effectiveness for the treatment of anemia due to CKD in adults is based primarily on five adequate and well-controlled trials (the ASCEND program) (Table 2).

Table 2. Clinical Studies in the ASCEND Program

	Non-Dialysis Studies			Dialysis Studies	
Study name/number	ASCEND-ND 200808	ASCEND-NHQ 205270	ASCEND-D 200807	ASCEND-TD 204837	ASCEND-ID 201410
Population	ND ESA user or non-user	ND	HD or PD ESA user	HD ESA user	Incident dialysis (ID) ESA non-user
Daprodustat dosing	Once daily	Once daily	Once daily	Three times a week	Once daily
Control	SC darbepoietin alfa	Oral placebo	IV epoetin alfa for HD subjects or SC darbepoetin alfa for PD subjects	IV epoetin alfa	SC or IV darbepoetin alfa
Number of participants	4500	600	3000	402	300
Blinding	Open-label (sponsor blind)	Double-blind	Open-label (sponsor blind)	Double-blind, double dummy	Open-label (sponsor blind)
Randomization	1:1	1:1	1:1	2:1	1:1
Stratification	Region Current ESA use Participation in ABPM substudy	Region	Dialysis type (HD or PD) Region Participation in ABPM substudy	Region	Dialysis type (HD or PD) Dialysis start planned or unplanned
Evaluation period	Weeks 28-52	Weeks 24-28	Weeks 28-52	Weeks 28-52	Weeks 28-52
Hb target range	10-11 g/dL	11-12 g/dL	10-11 g/dL	10-11 g/dL	10-11 g/dL

Source:
Abbreviations: ABPM, ambulatory blood pressure monitoring; Hb, hemoglobin; HD, hemodialysis; ID, incident dialysis; IV, intravenous; ND, non-dialysis; PD, peritoneal dialysis; ESA, erythropoiesis-stimulating agent; SC, subcutaneous

The two trials that are the focus of this AC meeting are ASCEND-ND and ASCEND-D, which are event-driven, multicenter, multinational, open-label, active-controlled, randomized, parallel-group trials.

ASCEND-ND assessed the efficacy and safety of daprodustat once daily compared to darbepoetin alfa in the NDD population. Subjects not currently receiving ESAs and subjects currently receiving ESAs were included. Those on an ESA continued their ESA therapy during the screening and run-in periods.

ASCEND-D assessed the efficacy and safety of daprodustat once daily compared to intravenous (IV) epoetin alfa in subjects on HD and compared to SC darbepoetin alfa in subjects on peritoneal dialysis (PD). Subjects switched their ESA to these study drugs on the day of randomization.

Please see Table 3 for details on the study designs of ASCEND-ND and ASCEND D.

The three additional, much smaller CKD studies are considered supportive and not discussed in detail in this background document.

- ASCEND-NHQ was a double-blind, placebo-controlled study in a non-dialysis population with anemia with objectives of providing evidence of efficacy, safety and improved quality of life versus placebo.
- ASCEND ID was a 1-year, open-label, active-controlled study that evaluated subjects with anemia associated with CKD who were not regularly using an ESA and who were initiating dialysis (unplanned or planned) to provide evidence for the efficacy and safety of daprodustat in the incident dialysis population.
- ASCEND-TD was a 1-year, double-blind, active-controlled study that enrolled subjects who were HD dependent (hemodiafiltration and hemofiltration with HD) who had anemia of CKD and were being treated with ESAs or its analogues to provide support for a three times a week dosing regimen.

3.1.2 Study Designs of ASCEND-ND and ASCEND-D

ASCEND-ND randomized subjects if they had CKD stage 3, 4, or 5 (per Kidney Disease Outcomes Quality Initiative using CKD-EPI) and were not currently receiving dialysis or scheduled to start dialysis within 90 days at screening. ASCEND-ND included subjects with no prior exposure to ESA and subjects with prior ESA exposure. At randomization, subjects were required to have hemoglobin levels of 8 to 10 g/dL if not using an ESA, and hemoglobin levels of 8 to 11 g/dL if using an ESA. Subjects were considered prior ESA users if they were using ESAs for at least six weeks prior to the screening visit. Those on an ESA at the screening visit continued the ESA until randomization (Table 3).

ASCEND-D included randomized subjects undergoing dialysis (hemodialysis [HD] at least two times weekly or peritoneal dialysis [PD] at least five times weekly) for at least 90 days prior to screening and who had received an ESA[1] (continuously for at least 6 weeks at screening). ASCEND-D required hemoglobin levels of 8 to 12 g/dL at screening and 8 to 11 g/dL at randomization.

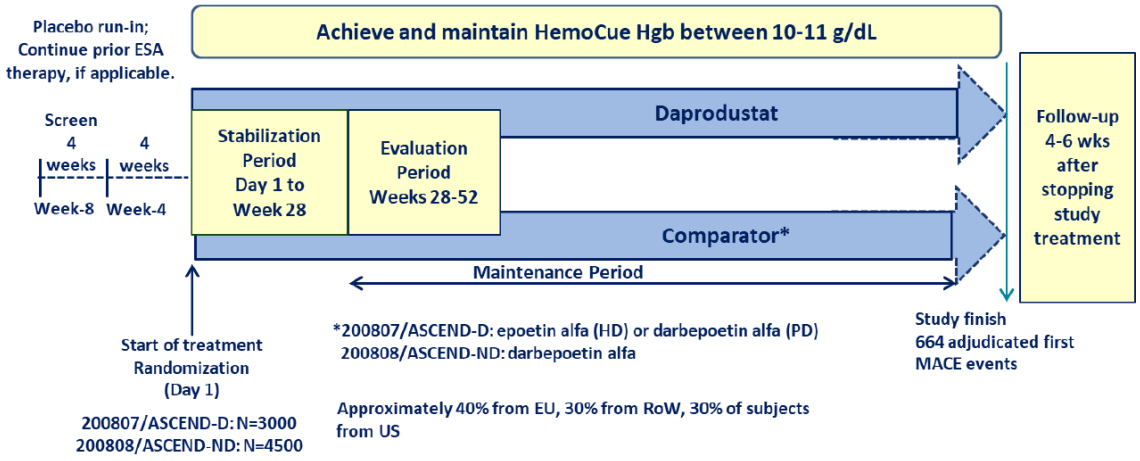
Both studies required ferritin to be >100 ng/mL at screening and transferrin saturation >20% at screening.

For both studies, subjects were excluded if they had anemia that was unrelated to CKD, cancer, New York Heart Association Class IV heart failure at enrollment, or MI, acute coronary syndrome, stroke, transient ischemic attack, or gastrointestinal bleed ≤4 weeks prior to screening through to randomization (Day 1). Subjects with uncontrolled hypertension, liver disease (alanine aminotransferase >2× the upper limit of normal, bilirubin >1.5× the upper limit of normal), or malignancy within 2 years prior to screening were excluded.

[1] Minimum ESA dose: epoetins: 1500 units IU/week intravenous or 1000 U/week SC; darbepoetin alfa: 20 µg/4 weeks; methoxy PEG-epoetin: 30 µg/month SC/IV

The trials consisted of five periods: screening, placebo run-in, stabilization period, evaluation period, and long-term follow-up (Figure 1). The subjects were evaluated at least every 4 weeks during the first year of the trial and at least every 12 weeks thereafter.

Figure 1. Study Design Schematic for ASCEND-D and ASCEND-ND



Source: CSR 20808 Figure 1.
Abbreviations: CSR, clinical study report; ESA, erythropoiesis-stimulating agent; EU, European Union; HD, hemodialysis; Hgb, hemoglobin; MACE major cardiovascular adverse event; PD, peritoneal dialysis; RoW, rest of world

During the 4-week placebo run-in period, subjects who were ESA naïve received placebo tablets and those who had received prior ESA therapy continued to receive an ESA during the screening and run-in periods.

In ASCEND-ND, subjects were randomized in a 1:1 ratio to either oral daprodustat or to darbepoetin alfa SC. In ASCEND-D, subjects were randomized in a 1:1 ratio to oral daprodustat or to IV epoetin alfa (HD) or SC darbepoetin alfa (PD). Throughout the remainder of this document, the subjects randomized to IV epoetin alfa or SC darbepoetin alfa in ASCEND-D are referred to as the ESA treatment arm.

In the ASCEND-ND study, daprodustat was dosed daily, while the control darbepoetin alfa was dosed weekly, every 2 weeks, or every 4 weeks, depending on the subject's prior ESA use. In the ASCEND-D study, daprodustat was also dosed daily while the control was dosed weekly, every 2 weeks, or every 4 weeks (darbepoetin alfa) or every 2 days or weekly (epoetin alfa), depending on the subject's prior ESA use. In both studies, the control arm was dosed less frequently, and the dosing frequency difference between daprodustat and the control arm was greater in the ASCEND-ND study.

An anemia rescue algorithm, which included a provision for the use of intravenous iron, an RBC transfusion, or both, was provided in the protocols (details are provided in the Appendix, Section 5.3.1). Additionally, the protocol required subjects to be iron replete throughout the study – and initiate iron therapy (investigator's choice) if ferritin was less than or equal to 100 ng/mL, transferrin saturation was less than or equal to 20%, or both.

Both ASCEND-D and ASCEND-ND had two coprimary noninferiority endpoints. The primary efficacy endpoint was mean change in the Hb level from baseline over weeks 28 to 52 and the primary safety endpoint was time to first occurrence of an adjudicated major adverse cardiac event (MACE; a composite of all-cause mortality, nonfatal MI, and nonfatal stroke). Cardiovascular events were adjudicated by an independent clinical adjudication committee.

The principal secondary endpoints, each tested for superiority and adjusted for multiplicity, were time to the first occurrence of MACE (tested for noninferiority as a coprimary endpoint; tested for superiority as a principal secondary endpoint), time to the first occurrence of MACE or a thromboembolic event, time to the first occurrence of MACE or hospitalization for heart failure, time to the first occurrence of CKD progression (ASCEND-ND only), and average monthly IV iron dose to week 52 (ASCEND-D only).

The sample size of both ASCEND-D and ASCEND-ND was determined by a fixed target of 664 adjudicated first occurrences of MACE, which corresponded to 90% power and a 2.5% one-sided Type I error rate to rule out a risk margin of 1.25 assuming an underlying hazard ratio of 0.97. Agreement on both the risk margin and the estimated number of events were reached between the Agency and the Applicant before closure of the trials.

In both trials, noninferiority to the active control on the coprimary efficacy endpoint could be claimed if the lower limit of the two-sided 95% confidence interval (CI) of the treatment difference was greater than the prespecified noninferiority margin of -0.75 g/dL. This is the standard noninferiority margin for active-controlled ESA trials.

Table 3. Key Study Design Elements of ASCEND-ND and ASCEND-D

	200808/ASCEND-ND	**200807/ASCEND-D**
Study design	Open-label, randomized, active-controlled, parallel-group	Open-label, randomized, active-controlled, parallel-group
Blinding	Open-label (Sponsor blind)	Open-label (Sponsor blind)
Control	Darbepoetin alfa (SC)	PD – Darbepoetin alfa (SC) HD – Epoetin alfa (IV)
Planned treatment duration (weeks)	Event driven Dependent upon the accumulation of 664 adjudicated first MACE	Event driven Dependent upon the accumulation of 664 adjudicated first MACE
Planned number of subjects	4500	3000
Population	Subjects with anemia and stage 3-5 CKD, not on dialysis or expected to start dialysis within 90 days Prior ESA treated or ESA naïve	Subjects with anemia associated with CKD on dialysis (HD or PD) for 90 days or longer, and ESA treated for 6 weeks.
Randomization	1:1	1:1
Stratification	Region* Current ESA use (yes/no) ABPM substudy	Dialysis type (HD or PD) Region ABPM substudy
Randomization (day 1) Hb range	ESA use: 8-11 g/dL No ESA use: 8-10 g/dL	8-11.0 g/dL and receiving at least minimum ESA Hb >11-11.5 and receiving greater than minimum ESA

	200808/ASCEND-ND	200807/ASCEND-D
Hb target range (g/dL)	10-11	10-11
Target US enrollment	30%	30%
Daprodustat starting dose (mg, once daily)		
Not using ESAs		
Baseline Hb (g/dL): 8 to <9 g/dL	4 mg	-
Baseline Hb (g/dL): 9 to 10 g/dL	2 mg	-
ESA Users		
Low dose[1]	1 mg	4 mg
Intermediate dose[2]	2 mg	4 mg
High dose	4 mg	4 mg

Source: Clinical Reviewer, curated from the ASCEND-D and ASCEND-ND Clinical Study Reports.
Abbreviations: ABPM, ambulatory blood pressure monitoring; CKD, chronic kidney disease; ESA, erythropoietin-stimulating agent; EU, European Union; Hb, hemoglobin; HD, hemodialysis; MACE major cardiovascular adverse event; PD, peritoneal dialysis; US, United States
[1] Epoetins: 1500 to 2000 U/week (IV equivalent); darbepoetin alfa: 20 to 30 µg/4 weeks; methoxy PEG-epoetin: 30 to 40 µg/month
[2] Epoetins: >2000 to <20,000 U/week (IV equivalent); darbepoetin alfa: >30 to 300 µg/4 weeks; methoxy PEG-epoetin: >40 to 360 µg/month

3.1.3 Demographics, Baseline Characteristics, and Exposure

3.1.3.1 ASCEND-ND

Demographic and baseline disease characteristics were generally well-balanced between the two treatment groups (Table 4). The median age of subjects was 67 years. Males constituted a slight minority of the population (44%). Slightly more than one-half of the subjects were Caucasian, 9.5% were Black, and 27% were Asian. Prior ESA users constituted a slight minority of the population (47%). Approximately one-quarter of subjects were from the US. More than one-third of subjects had a history of cardiovascular disease. About 6.9% of patients had a history of MI, 6.6% had a history of stroke, and 3.9% had a history of thromboembolic disease. Diabetes mellitus was reported as a baseline condition by 57% of subjects. A history of hypertension was reported by 94% of subjects. The baseline mean Hb was 9.9 g/dL and the median eGFR at baseline was approximately 17 to 18 mL/min/1.73 m^2.

Table 4. Baseline Demographics of ASCEND-ND, ITT Population

	Daprodustat N=1937	Darbepoetin N=1935
Age (median [IQR])	67 [57, 75]	67 [57, 74]
Sex, male (%)	835 (43.1)	864 (44.7)
Race (%)		
American Indian or Alaska Native (%)	88 (4.5)	100 (5.2)
Asian (%)	525 (27.1)	537 (27.8)
Black or African American	183 (9.4)	185 (9.6)
Multiple	36 (1.9)	51 (2.6)
Native Hawaiian or other Pacific Islander	7 (0.4)	7 (0.4)
White	1098 (56.7)	1055 (54.5)
Hispanic or Latino (%)	430 (22.2)	467 (24.1)

	Daprodustat N=1937	Darbepoetin N=1935
USA (%)	492 (25.4)	489 (25.3)
Weight (kg) (median [IQR])	71 [60, 85]	71 [60, 84]
eGFR (mL/min/1.73 m^2) (median [IQR])	17 [12, 26]	18 [12, 27]
Urine albumin creatinine ratio (mg/mmol) (median [IQR])	84.4 [15.4, 222.6]	75.0 [14.6, 212.6]
ESA use (%)	907 (46.8)	903 (46.7)
TSAT (median [IQR])	30 [24, 37]	29 [23, 36]
Ferritin (µg/L) (median [IQR])	267 [164, 456]	275 [171, 448]
History of diabetes (%)	1084 (56)	1134 (58.6)
History of cardiovascular disease (%)	716 (37)	716 (37)
History of MI (%)	133 (6.9)	136 (7)
History of stroke (%)	128 (6.6)	128 (6.6)
History of thromboembolic events (%)	80 (4.1)	70 (3.6)
History of stroke	128 (7)	128 (7)
hsCRP (mg/L) (median [IQR])	2.0 [0.8, 5.3]	2.0 [0.8, 5.5]
History of heart failure (%)	348 (18)	339 (17.5)
Vitamin K antagonist use (%)	71 (3.7)	55 (2.8)
Clopidogrel use (%)	174 (9)	172 (8.9)
Aspirin use (%)	589 (30.4)	570 (29.5)
Systolic blood pressure (mmHg) (median [IQR])	135 [125, 147]	135 [125, 147]
Hypertension	1828 (94)	1829 (95)
IV oral use	153 (8)	165 (9)
Oral iron use	893 (46)	879 (45)
Hemoglobin (%)		
<9 g/dL	305 (15.7)	338 (17.5)
9-<10 g/dL	742 (38.3)	717 (37.1)
10-11 g/dL	689 (35.6)	704 (36.4)
>11 g/dL	201 (10.4)	176 (9.1)

Source: Clinical Reviewer, R version 4.2, ADSL.xpt.
Abbreviations: eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; IV, intravenous; MI, myocardial infarction; TSAT, transferrin saturation; USA, United States of America

3.1.3.2 ASCEND-D

Demographic and baseline disease characteristics were generally well-balanced between the two treatment groups (Table 5). The median age of subjects was approximately 58 years. Males constituted a slight majority of the population (57%). Approximately two-thirds of the subjects were Caucasian, 15% were Black, and 12% were Asian. Approximately one-quarter of subjects were from the US. Slightly less than one-half (45%) of subjects had a history of cardiovascular disease. About 9.4% of patients had a history of MI, 7.0% had a history of stroke, and 17.4% had a history of thromboembolic disease. At baseline, diabetes mellitus was reported by 42% of subjects and hypertension was reported by 92% of subjects. The baseline mean Hb was 10.4 g/dL.

Table 5. Baseline Demographics of ASCEND-D, ITT Population

	Daprodustat N=1487	ESA N=1477
Age (median [IQR])	58 [48, 67]	59 [47, 68]
Sex, male (%)	851 (57.2)	847 (57.3)
Race		
American Indian or Alaska Native	19 (1.3)	32 (2.2)
Asian	176 (11.8)	181 (12.3)
Black or African American	228 (15.3)	233 (15.8)
Multiple	43 (2.9)	24 (1.6)
Native Hawaiian/Pacific Islander	26 (1.7)	25 (1.7)
White	995 (66.9)	982 (66.5)
Hispanic or Latino (%)	367 (24.7)	371 (25.1)
USA (%)	425 (28.6)	421 (28.5)
Predialysis weight (kg) (median [IQR])	76 [64, 91]	76 [65, 90]
TSAT (median [IQR])	33 [26, 41]	32 [26, 42]
Ferritin (µg/L) (median [IQR])	589 [344, 975]	604 [341, 948]
History of diabetes (%)	615 (41.4)	617 (41.8)
History of cardiovascular disease (%)	666 (44.8)	665 (45)
History of MI present (%)	133 (8.9)	147 (10)
History of stroke (%)	96 (6.5)	110 (7.4)
History of thromboembolic events (%)	273 (18.4)	242 (16.4)
hsCRP (mg/L) (median [IQR])	4.0 [1.6, 10.9]	4.0 [1.5, 9.8]
History of heart failure (%)	399 (26.8)	389 (26.3)
Vitamin K antagonist use (%)	80 (5.4)	71 (4.8)
Clopidogrel use (%)	129 (8.7)	165 (11.2)
Aspirin use (%)	522 (35.1)	532 (36)
Dialysis type (%)		
HD - conventional	1265 (85.1)	1252 (84.8)
HDF/HF	51 (3.4)	56 (3.8)
PD	171 (11.5)	169 (11.4)
Vascular access (%)		
Arteriovenous fistula	1033 (69.5)	1022 (69.2)
Arteriovenous graft	129 (8.7)	127 (8.6)
Central venous catheter - tunneled	137 (9.2)	132 (8.9)
Peritoneal catheter	171 (11.5)	168 (11.4)
IV iron use	899 (60)	887 (60)
Hypertension	1366 (92)	1373 (93)
Hemoglobin (%)		
<9 g/dL	135 (9.1)	122 (8.3)
9-<10 g/dL	356 (23.9)	324 (21.9)
10-11 g/dL	614 (41.3)	644 (43.6)
>11 g/dL	382 (25.7)	387 (26.2)

Source: Clinical Reviewer, R v. 4.2, ADSL.xpt.
Abbreviations: eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; HD, hemodialysis; HDF/HF, hemodiafiltration/hemofiltration; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; ITT, intention-to-treat; IV, intravenous; MI, myocardial infarction; PD, peritoneal dialysis; TSAT, transferrin saturation; USA, United States of America

3.1.4 Disposition and Discontinuation

3.1.4.1 ASCEND-ND

Study completion was defined as subjects who had completed all five periods of the study through the End-of-Study visit with the following exception: subjects who died while on study were also considered as having completed the study. Nearly all subjects randomized to

daprodustat and the comparator treatment completed the study (96.7% and 96.6% of subjects in the daprodustat and darbepoetin alfa arms, respectively) (Table 6).

Adverse events (including death) and withdrawal by subject accounted for most treatment discontinuations and were balanced between the treatment arms. In the total population (N=3872), the most common reasons for meeting the protocol-specified stopping criteria (285/312) were renal transplantation (n=108), rescue therapy (n=103), and development of cancer (n=74). These events were balanced between the treatment arms.

Table 6. Subject Disposition of ASCEND-ND, ITT Population

	Daprodustat N=1937 N (%)	**Darbepoetin alfa N=1935 N (%)**
Randomized (ITT population)	1937	1935
Not treated	0	2 (0)
Safety population	1937 (100)	1933 (99.9)
Completed study	1837 (97)	1870 (97)
Withdrawn from the study	64 (3.3)	65 (3.4)
Treatment status		
Did not prematurely discontinue randomized treatment	1210 (62.5)	1207 (62.4)
Died while taking randomized treatment	156 (8.1)	166 (8.6)
Discontinued treatment early	571 (29.5)	560 (28.9)
Reason for discontinuation of treatment		
Adverse event (includes death)	254 (13.1)	222 (11.5)
Investigator site closed	6 (0.3)	12 (0.6)
Lost to follow-up	20 (1)	21 (1.1)
Missing	1 (0.1)	0 (0)
Protocol-specified withdrawal criterion met	151 (7.8)	161 (8.3)
Protocol deviation	14 (0.7)	20 (1)
Sponsor terminated study treatment	0 (0)	2 (0.1)
Withdrawal by subject	281 (14.5)	288 (14.9)

Source: Clinical Reviewer, R v. 4.2, ADSL.xpt.
Abbreviation: ITT, intention-to-treat
* Participants were considered to have completed the study if they completed the 52-week treatment period and the follow-up visit irrespective of whether they discontinued randomized treatment.

The duration of study drug exposure was similar in subjects treated with daprodustat (median 17.5 months per subject, total exposure 2982 PY) and subjects who received darbepoetin alfa (median 17.5 months per subject, total exposure 3056 PY) (Table 7). Approximately two-thirds of subjects were treated for at least 1 year. Similarly, overall subject follow-up (both in duration and total exposure) was balanced between the treatment arms.

Table 7. Drug Exposure of the ASCEND-ND, ITT Population

	Daprodustat N=1937	Darbepoetin alfa N=1935
Cumulative exposure (patient-years)	2982	3056
Months of exposure (months) (median [IQR])	17.5 [7.4, 28.0]	17.5 [8.3, 28.6]
Months of exposure, n (%)		
6 months or less	398 (20.5)	356 (18.4)
Greater than 6 months to 12 months	314 (16.2)	337 (17.4)
Greater than 12 months to 24 months	566 (29.2)	543 (28.1)
Greater than 24 months to 36 months	460 (23.7)	486 (25.1)
Greater than 36 months	199 (10.3)	211 (10.9)
Cumulative follow-up[1] (Patient-years)	3593	3592
Duration of overall follow up (months) (median [IQR])	22.3 [12.0, 32.2]	22.3 [12.0, 32.4]
Duration of post-treatment follow up (months) (median [IQR])[2]	1.0 [0.7, 1.6]	1.0 [0.5, 1.5]

Source: Clinical Reviewer, R v. 4.2, ADSL.xpt.
Abbreviations: IQR, interquartile range; ITT, intention-to-treat
[1] Defined as the time between treatment start date and end-of-study date.
[2] Defined as the time between the decision to stop treatment and end-of-study date.

3.1.4.2 ASCEND-D

Study completion was defined as subjects who had completed all periods of the study through the End-of-Study visit with the following exception: subjects who died while on study were also considered as having completed the study. Most subjects randomized to the daprodustat and ESA treatment arms completed the study (92.1% and 92.5%, respectively) (Table 8).

Adverse events (which includes deaths) and withdrawal by subject accounted for most treatment discontinuations and were balanced between treatment arms. In the total population (N=2864), the most common reasons for meeting protocol-specified stopping criteria were renal transplantation (n=267), rescue therapy (n=106), and development of cancer (n=65). These events were balanced between the treatment arms. All other reasons for meeting protocol-specified stopping criteria were infrequent (combined n=88).

Table 8. Subject Disposition of the ASCEND-D ITT Population

	Daprodustat N=1487 N (%)	ESA N=1477 N (%)
Randomized to Treatment (ITT)	**1487**	**1477**
Not treated	5	3
Safety population	1482 (99.7)	1474 (99.8)
Withdrawn from the study	117 (7.9)	111 (7.5)
Completed study	1370 (92)	1366 (92)
Treatment status		
Did not prematurely discontinue treatment	697 (46.9)	693 (46.9)
Discontinued treatment early	671 (45.1)	662 (44.8)
Died while taking randomized treatment	114 (7.7)	119 (8.1)

	Daprodustat N=1487 N (%)	ESA N=1477 N (%)
Randomized to Treatment (ITT)	**1487**	**1477**
Reason for discontinuation of treatment		
Adverse event (includes death)	233 (15.7)	236 (16)
Investigator site closed	39 (2.6)	35 (2.4)
Lost to follow-up	6 (0.4)	7 (0.5)
Missing	1 (0.1)	0 (0)
Protocol-specified withdrawal criterion met	237 (15.9)	222 (15)
Protocol deviation	9 (0.6)	5 (0.3)
Sponsor terminated study treatment	2 (0.1)	1 (0.1)
Withdrawal by subject	258 (17.4)	275 (18.6)

Source: Clinical Reviewer, R v. 4.2, ADDS.xpt.
Abbreviations: ESA, erythropoiesis-stimulating agent; ITT, intention-to-treat

The duration of study drug exposure was similar in subjects treated with daprodustat (median 25.8 months per subject, total exposure 2712 PY) and subjects who received ESA (median 25.8 months per subject, total exposure 2745 PY) (Table 9). Approximately three-quarters of subjects were treated for at least 1 year. Similarly, overall subject follow-up (both in duration and total exposure) was balanced between the treatment arms.

Table 9. Drug Exposure in ASCEND-D, ITT Population

	Daprodustat N=1487	ESA N=1477
Cumulative exposure (Patient-years)	2712	2745
Months of exposure (months) (median [IQR])	25.8 [10.8, 31.1]	25.8 [12.0, 31.3]
Months of exposure, n (%)		
6 months or less	218 (14.7)	204 (13.8)
Greater than 6 months to 12 months	178 (12.0)	167 (11.3)
Greater than 12 months to 24 months	254 (17.1)	271 (18.4)
Greater than 24 months to 36 months	714 (48.2)	696 (47.2)
Greater than 36 months	118 (8)	136 (9.2)
Cumulative follow-up (Patient-years)	3512	3483
Duration of overall follow up (months) (median [IQR])	29.9 [26.6, 34.6]	29.7 [26.0, 34.8]
Duration of post-treatment follow up (months) (median [IQR])	0.99 [0.8, 9.1]	0.99 [0.7, 6.7]

Source: Clinical Reviewer, R v. 4.2, ADDS.xpt.
Abbreviations: ESA, erythropoiesis-stimulating agent; IQR, interquartile range; ITT, intention-to-treat

Some differences in the study population and disposition between the ASCEND-D and ASCEND-ND are notable. A greater proportion of subjects discontinued treatment earlier in the ASCEND-D trial compared to the ASCEND-ND trial. This may be related to a difference in follow up between the two studies (median follow up in ASCEND-D was 29.7 to 29.9 months, median follow up in ASCEND-ND was 22.3 months). Additionally, more subjects received a renal transplant in the ASCEND-D study. Subjects in ASCEND-D tend to be younger (median age in ASCEND-ND was 67 years, median age in ASCEND-D was 58 to 59 years).

3.1.5 Efficacy Results

The primary endpoint for efficacy was the mean change in Hb from baseline to the evaluation period (mean values during weeks 28 to 52), regardless of rescue therapy, using the intention-to-treat analysis set. Both the ASCEND-ND and ASCEND-D demonstrated noninferiority of daprodustat to darbepoetin alfa with respect to change in Hb and FDA was able to corroborate the Applicant's findings (Table 10). Noninferiority was concluded because the lower limit of the two-sided 95% confidence interval for the treatment difference was greater than the prespecified noninferiority margin of -0.75 g/dL in both trials. We also noted that both lower bounds of the confidence intervals are greater than 0, however, the superiority test was not pre-planned. In both trials, the conclusion of noninferiority was robust to multiple sensitivity analyses which assessed the impact of important model assumptions, such as accounting for rescue therapy, and missingness mechanisms such as MAR (missing at random), and MNAR (missing not at random).

Table 10. Key Statistical Efficacy Results of ASCEND-ND and ASCEND-D

	ASCEND-ND		ASCEND-D	
Trial/Treatment Arm	**Daprodustat N=1937**	**Darbepoetin alfa N=1935**	**Daprodustat N=1487**	**Darbepoetin alfa N=1477**
Mean baseline Hb (SD)	9.9 (0.9)	9.9 (0.9)	10.4 (1.0)	10.4 (1.0)
Mean Hb weeks 28-52 (SD)	10.6 (0.6)	10.5 (0.7)	10.7 (0.8)	10.5 (0.8)
Adjusted mean change from baseline (SE)	0.7 (0.02)	0.7 (0.02)	0.3 (0.02)	0.1 (0.02)
Adjusted mean treatment difference (daprodustat-darbepoetin)	0.0		0.2	
Two-sided 95% CI for adjusted mean difference	(0.03, 0.13)		(0.12, 0.24)	

Source: Statistical Reviewer using R v. 3.61, adlbhgb.xpt; Table 23 and Table 27 of Clinical Efficacy Summary.
Abbreviations: CI, confidence interval; Hb, hemoglobin; SD, standard deviation; SE, standard error
For both ASCEND-ND and ASCEND-D, multiple imputation method was used to impute missing data.
For ASCEND-ND, the ANCOVA model was used while adjusting for baseline Hgb, current ESA, and region.
For ASCEND-D, the ANCOVA model was used while adjusting for baseline Hb, dialysis start manner, dialysis type, and region.
In ASCEND-ND the dropout rates were 361 (19%) in the daprodustat group and 357 (18%) in the darbepoetin group.
In ASCEND-D the dropout rates were 123 (8%) in the daprodustat group and 125 (8%) in the darbepoetin group.

The titration algorithm for daprodustat and comparators was prespecified. FDA reviewed the titration algorithms and determined they reflected reasonable clinical practice. Instances where the algorithm was not explicitly followed were recorded as protocol violations. The protocol violations were reviewed by the FDA and were balanced between arms. While Hb did not increase much, particularly in ASCEND-D, it is important to note that these patients were on ESA therapy pre-study and would have been expected to have a decline in Hb at Weeks 26 to 52 without continued treatment during the randomized period based on the known setting of ineffective erythropoiesis due to CKD.

The observed Hb versus time profile confirms that the titration algorithms resulted in similar Hb vs. time trajectories (Section 5.2.1). We are reassured that mean-level plots fell in the middle of the Hb target range for both arms during the EP. This provides assurance that the comparators were titrated and subsequently performed acceptably. In addition, the comparators performed reasonably similar to other programs on Hb vs. time. The within-subject variability in Hb data

was also similar between arms. The use of rescue therapy for anemia, i.e., intravenous iron, and transfusions was also evaluated and was balanced between arms (Table 11 and Table 12). The above results confirm the non-inferiority conclusion of the efficacy of daprodustat on Hb. We expect the similarity in Hb response between daprodustat and the ESA control arms to translate into similar reductions in the need for RBC transfusions, an accepted clinical benefit for treatments for anemia of CKD, because of avoiding the procedure and its attendant risks.

The Applicant did not demonstrate any other benefits of daprodustat on how patients feel, function, or survive (see the Appendix for a discussion of a patient-reported outcome instrument used in ASCEND-NHQ trial that did not show clinically meaningful improvement with daprodustat compared to placebo).

Table 11. ASCEND-ND—Time to First Occurrence of Rescue or Transfusion, ITT Population (On-Treatment Analysis)

	Daprodustat Incidence Rate N=1937	Darbepoetin alfa Incidence Rate N=1935	Hazard Ratio (95% CI)	Rate Difference per 100 Patient-Years (95% CI)
Transfusion (PRBC or whole blood)[1]	8.8 (7.8, 10.0)	9.2 (8.1, 10.4)	1.0 (0.8, 1.1)	-0.4 (-1.9, 1.2)
Anemia rescue[2]	1.3 (0.9, 1.8)	2.1 (1.6, 2.7)	0.6 (0.4, 0.9)	-0.8 (-1.4, -0.1)

Source: Adapted from 200808 CSR.
Abbreviations: CI, confidence interval; CSR, clinical study report; ITT, intention-to-treat; PRBC, packed red blood cells
[1] See Section 5.3.1 for criteria triggering RBC transfusion.
[2] See Section 5.3.1 for criteria triggering anemia rescue.

Table 12. ASCEND-D—Time to First Occurrence of Rescue or Transfusion, ITT Population (On-Treatment Analysis)

	Daprodustat Incidence Rate N=1487	ESA Incidence Rate N=1477	Hazard Ratio (95% CI)	Rate Difference per 100 Patient-Years (95% CI)
Transfusion (PRBC or whole blood)	9.3 (8.1, 10.6)	10.9 (9.6, 12.3)	0.9 (0.7, 1.0)	-1.6 (-3.3, 0.2)
Anemia rescue	2.0 (1.5, 2.6)	1.9 (1.5, 2.5)	1.0 (0.7, 1.5)	0.0 (-0.7, 0.8)

Source: Adapted from 200807 CSR.
Abbreviations: CI, confidence interval; CSR, clinical study report; ESA, erythropoiesis-stimulating agent; ITT, intention-to-treat; PRBC, packed red blood cells

3.2 Safety Issues

Safety issues that are discussed in further detail below include:

- Higher incidence of MACE with daprodustat compared to darbepoietin alfa on some analyses in the ASCEND-ND study (e.g., when using a supportive on-treatment analysis, when analyzed in the US subgroup of patients; and when analyzed using cardiovascular death instead of all-cause mortality in the MACE composite)
- Higher incidence of other CV endpoints with daprodustat compared to darbepoietin alfa in the ASCEND-ND study, including thromboembolic disease and vascular access thrombosis
- Higher incidence of CV endpoints with daprodustat compared to darbepoietin alfa in the USA subgroup in the ASCEND-ND study

- Higher incidence of hospitalization for heart failure with daprodustat compared to darbepoietin alfa in the ASCEND-ND and ASCEND-D studies

Additional adverse events that merit further discussion include (1) a higher incidence of gastrointestinal erosions and bleeds in ASCEND-ND and ASCEND-D, and (2) AKI. These adverse events are discussed in further detail below.

3.2.1 Analysis Methods—MACE and CV Endpoints, ASCEND-ND, ASCEND-D

The coprimary safety endpoint in both ASCEND-ND and ASCEND-D was the time to first occurrence of adjudicated MACE (composite of all-cause mortality, nonfatal MI, and nonfatal stroke). The primary safety analysis in both trials tested for noninferiority of daprodustat relative to the active control. Noninferiority to the active control on MACE would be claimed if the upper limit of the two-sided 95% confidence interval (CI) was less than the hazard ratio of 1.25, the prospectively defined risk margin.

Adjudicated secondary safety endpoints in both trials are listed below. These endpoints are time-to-event endpoints.

- All-cause mortality
- CV mortality
- Fatal or nonfatal MI
- Fatal or nonfatal stroke
- Fatal or nonfatal HHF
- Fatal or nonfatal TEE
- Composite of MACE and HHF[2]
- Composite of CV mortality and nonfatal MI
- Composite of MACE, HHF, and TEE

The FDA considered additional time-to-event endpoints of CV MACE (composite of CV mortality, nonfatal MI, and nonfatal stroke) and vascular access thrombosis (VAT)[3], a type of TEE, to be clinically meaningful; these are presented below. The secondary endpoints and these additional safety endpoints were not controlled for multiple comparisons.

Analysis

The primary population for the analyses of MACE and CV endpoints is the intention-to-treat (ITT) population, defined as all randomized subjects analyzed according to the treatment to which subjects were randomized.

[2] A recurrent event with data on multiple events for analysis

[3] For VAT, either as a standalone endpoint or as a component of TEE, the event of interest is vascular access that becomes thrombosed.

The primary estimand strategy[4] was the treatment policy strategy, referred to as the on-study analysis in the ASCEND-ND and ASCEND-D trials. The period for capturing CV safety endpoints began at randomization and ended at the date of study completion/subject withdrawal[5], with the exception that if a death was reported in the clinical database after this time, then the death was included in the analysis.[6] Intercurrent events[7] such as treatment discontinuation, use of rescue therapies, or changes in other treatments were considered as part of the treatments (daprodustat versus control) being compared. Rescue therapy use including intravenous iron and transfusion were similar between treatment arms for both trials.

Within-treatment-group incidence rates, expressed as numbers of events per 100 person-years (PY), and confidence intervals (CI) for primary and secondary endpoints adjusted for follow-up time were calculated using the exact Poisson method.

The primary analysis of time to first MACE and other time-to-event endpoints was a Cox proportional hazards model controlling for treatment and adjusting for the following baseline variables used in stratified randomization: region (Asia Pacific, Eastern Europe/South Africa, Western Europe/Canada/(Australia and New Zealand), Latin America, USA), current ESA use (ASCEND-ND only: User, Non-user), and dialysis type (ASCEND-D only: hemodialysis, peritoneal dialysis).

In addition to the hazard ratio estimate from the Cox model, the prespecified, unadjusted incidence rate difference (IRD) between treatments provided an interpretation (without hypothesis testing) on the absolute scale. IRD and CIs between treatments were calculated using Wald's method for normal approximation.

In a supportive analysis of MACE, the Applicant used another estimand strategy called the while-on-treatment strategy, referred to as the On-Treatment (OT) analysis, whereby response to treatment within a time window (ascertainment window) of the intercurrent event is of interest. Three variations of the OT analysis accounting for differing dosing intervals in the treatment arms (see Section 3.1.2) are considered here. These variations result in different ascertainment windows:

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[4] FDA Guidance for Industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*. https://www.fda.gov/media/148473/download.

[5] Withdrawal includes withdrawal of consent, lost to follow-up, and study site closure.

[6] We note that analyses including deaths after study completion/withdrawal is not customary of survival analysis with a study completion date. Furthermore, including these deaths assumed that patients did not have nonfatal MACE events after the CV follow-up period and allowed for differing follow-up periods that depended on the occurrence of death. The Sponsor was asked to conduct exploratory analyses of MACE for the entire population and for select subgroups excluding deaths after the date of study completion/withdrawal. Because these results did not materially change the interpretation of the MACE results that included deaths after study completion/withdrawal, we presented findings that included deaths after study completion/withdrawal.

[7] Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

- OT + 28 (prespecified): The period for capturing MACE began at the treatment start date and ended at the earlier of the date of study completion/withdrawal or last non-zero dose date + 28 days.
- OT + Dosing Frequency (exploratory): The period for capturing MACE began at the treatment start date and ended at the earlier of the date of study completion/withdrawal or last non-zero dose date + dosing interval, where the dosing interval was 1 day (daprodustat); 7, 14, or 28 days (darbepoetin alfa); 2 or 7 days (epoetin alfa).
- OT + Dosing Frequency + 28 (exploratory): The period for capturing MACE began at the treatment start date and ended at the earlier of the date of study completion/withdrawal or last non-zero dose date + dosing interval + 28 days.

Subgroup Analysis of MACE

Prespecified subgroup analyses of MACE (without multiplicity control) included the following characteristics at randomization:

- Age category (<65, 65 to <75, ≥75 years)
- Sex (female, male)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Mixed Race)[8]
- Regions combined (USA, non-USA)
- Current ESA use at randomization (ASCEND-ND only: ESA non-user, ESA user)
- Dialysis type (ASCEND-D only: hemodialysis, peritoneal dialysis)

Exploratory Analyses

Exploratory analyses conducted by FDA included:

- Time-to-event analysis of all adjudicated secondary CV endpoints by regions combined (USA, non-USA)
- Time-to-event analysis of all adjudicated secondary CV endpoints by ESA use at randomization (ASCEND-ND only: ESA non-user, ESA user)
- Time-to-event analysis of HHF by history of heart failure (Yes, No), defined as a having any of the following medical history conditions: heart failure, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, or pulmonary hypertension
- OT+28 analysis of CV endpoints

[8] Because of model convergence issues for the small race subgroup of Native Hawaiian or Other Pacific Islander, we combined Native Hawaiian or Other Pacific Islander with Mixed Race into a category called “Other” for analysis.

3.2.2 Summary Safety Results

3.2.2.1 All-Cause Mortality Summary—ASCEND-ND, ASCEND-D

Adjudicated causes of death in the On-Study analysis are summarized in Table 13 and Table 14. In the ASCEND-ND study, all-cause mortality, a prespecified secondary endpoint, was similar between arms (HR 1.03; CI 0.87, 1.20) (see Appendix Figure 9 for survival curves). There were 301/1937 deaths [8.3 deaths/100 PY] in the daprodustat arm and 298/1935 deaths [8.3 deaths/100 PY] in the darbepoetin alfa arm. The incidence of death from cardiovascular causes was higher in subjects who received daprodustat. Death from undetermined cause was lower with daprodustat (Table 13).

In the ASCEND-D study, all-cause mortality was also similar between arms (HR 0.96; CI 0.82, 1.13) (see Appendix Figure 10 for survival curves). There were 294/1487 deaths [8.3 deaths/100 PY] in the daprodustat arm and 300/1477 deaths [8.6 deaths/100 PY] in the ESA arm (Table 14). Death from undetermined cause was higher with daprodustat.

Table 13. Adjudicated Causes of Death—ASCEND-ND, (On-Study Analysis)

	Daprodustat N=1937	Darbepoetin alfa N=1935	Relative Risk	Risk Difference
CV Death	109 (5.6%)	92 (4.8%)	1.2 [0.9, 1.6]	0.9 [-0.5, 2.3]
Heart failure	20 (1%)	13 (0.7%)	1.5 [0.8, 3.1]	0.4 [-0.2 , 0.9]
Stroke	14 (0.7%)	11 (0.6%)	1.3 [0.6, 2.8]	0.2 [-0.4, 0.7]
Sudden cardiac death	34 (1.8%)	31 (1.6%)	1.1 [0.7, 1.8]	0.2 [-0.7, 1.0]
Acute myocardial infarction	9 (0.5%)	9 (0.5%)	1.0 [0.4, 2.5]	0.0 [-0.4, 0.4]
Presumed sudden death	11 (0.6%)	11 (0.6%)	1.0 [0.4, 2.3]	0.0 [-0.5, 0.5]
Presumed CV death	9 (0.5%)	11 (0.6%)	0.8 [0.3, 2.0]	-0.1 [-0.6, 0.4]
Non-CV Death	149 (7.7%)	148 (7.7%)	1.0 [0.8, 1.3]	0.0 [-1.6, 1.7]
Pulmonary	6 (0.3%)	5 (0.3%)	1.2 [0.4, 4.0]	0.0 [-0.3, 0.4]
Infection (includes sepsis)	90 (4.7%)	90 (4.7%)	1 [0.8, 1.3]	0.0 [-1.3, 1.3]
Renal	20 (1%)	22 (1.1%)	0.9 [0.5, 1.7]	-0.1 [-0.8, 0.6]
Malignancy	11 (0.6%)	14 (0.7%)	0.8 [0.4, 1.7]	-0.2 [-0.7, 0.4]
Undetermined	43 (2.2%)	58 (3%)	0.7 [0.5, 1.1]	-0.8 [-1.8, 0.2]

Source: Clinical Reviewer, R v. 4.2, ADSL.xpt; ADEVENT.xpt.
Abbreviations: CV, cardiovascular; ITT, intention-to-treat
ITT population, groups correspond to planned treatment assignment. Events occurring 10 times or more are included. Ordered by risk difference.

Table 14. Adjudicated Causes of Death—ASCEND-D, (On-Study Analysis)

	Daprodustat N=1487	ESA N=1477	Relative Risk	Risk Difference
CV Death	117 (7.9%)	121 (8.2%)	1.0 [0.8, 1.2]	-0.3 [-2.3, 1.6]
Sudden cardiac death	47 (3.2%)	39 (2.6%)	1.2 [0.8, 1.8]	0.5 [-0.7, 1.7]
Acute MI	12 (0.8%)	9 (0.6%)	1.3 [0.6, 3.1]	0.2 [-0.4, 0.8]
Heart failure	14 (0.9%)	11 (0.7%)	1.3 [0.6, 2.8]	0.2 [-0.5, 0.9]
Other cardiovascular causes	6 (0.4%)	4 (0.3%)	1.5 [0.4, 5.4]	0.1 [-0.3, 0.6]
Stroke	13 (0.9%)	15 (1%)	0.7 [0.4, 1.8]	-0.1 [-0.8, 0.6]
Presumed sudden death	11 (0.7%)	15 (1%)	0.7 [0.3, 1.6]	-0.3 [-1.0, 0.4]
Presumed cardiovascular death	10 (0.7%)	15 (1%)	0.7 [0.3, 1.5]	-0.3 [-1.0, 0.3]

	Daprodustat N=1487	ESA N=1477	Relative Risk	Risk Difference
Non-CV Death	132 (8.9%)	155 (10.5%)	0.9 [0.7, 1.1]	-1.6 [-3.8, 0.5]
Accidental	5 (0.3%)	5 (0.3%)	1.0 [0.3, 3.4]	0.0 [-0.4, 0.4]
Gastrointestinal	7 (0.5%)	7 (0.5%)	1.0 [0.4, 2.8]	0.0 [-0.5, 0.5]
Renal	15 (1%)	15 (1%)	1.0 [0.5, 2.0]	-0.0 [-0.7, 0.7]
Hemorrhage (ex. stroke)	5 (0.3%)	6 (0.4%)	0.8 [0.3, 2.7]	-0.1 [-0.5, 0.4]
Malignancy	15 (1%)	19 (1.3%)	0.8 [0.4, 1.5]	-0.3 [-1.0, 0.5]
Infection (includes sepsis)	77 (5.2%)	90 (6.1%)	0.9 [0.6, 1.1]	-1.0 [-2.6, 0.8]
Undetermined	45 (3%)	24 (1.6%)	1.9 [1.1, 3.0]	1.4 [0.3, 2.5]

Source: Clinical Reviewer, R v. 4.2, ADSL.xpt, ADEVENT.xpt.
Abbreviations: CV, cardiovascular; ITT, intention-to-treat; MI, myocardial infarction
ITT population, groups correspond to planned treatment assignment. Events occurring 10 times or more are included. Ordered by risk difference.

3.2.2.2 MACE Summary

3.2.2.2.1 ASCEND-ND

Results for the prespecified primary analysis of time to first MACE are shown in Table 15. The HR (95% CI) from the primary analysis (on-study analysis) for time to first MACE was 1.03 (0.89, 1.19) comparing daprodustat to darbepoetin alfa. The upper bound of the 95% CI was lower than the prespecified risk margin of 1.25, i.e., the study ruled out a relative risk for MACE greater than 1.25. Kaplan-Meier survival curves for MACE overlapped throughout the follow-up period (Appendix Figure 11). The incidence rate difference (IRD) is 0.2 events/100 PY (95% CI -1.3, 1.8) between daprodustat and darbepoetin alfa. MACE (daprodustat 378/1937 [10.9 events/100 PY], darbepoetin alfa 371/1935 [10.6 events/100 PY]) comprised mostly all-cause mortality (daprodustat 252/378, darbepoetin alfa 259/371), followed by nonfatal MI (daprodustat 96/378, darbepoetin alfa 91/371), and nonfatal stroke (daprodustat 30/378, darbepoetin alfa 21/371).

Table 15. Summary of Results for MACE, ASCEND-ND (On-Study Analysis)

	Daprodustat N=1937 PY=3480	Darbepoetin alfa N=1935 PY=3489	Rate Diff per 100 PY (95% CI)	Hazard Ratio (95% CI)
MACE, n [IR]	378 [10.9]	371 [10.6]	0.2 (-1.3, 1.8)	1.03 (0.89, 1.19)
All-cause mortality, n (%[1])	252 (66.7)	259 (69.8)	-	-
Nonfatal myocardial infarction, n (%[1])	96 (25.4)	91 (24.5)	-	-
Nonfatal stroke, n (%[1])	30 (7.9)	21 (5.7)	-	-

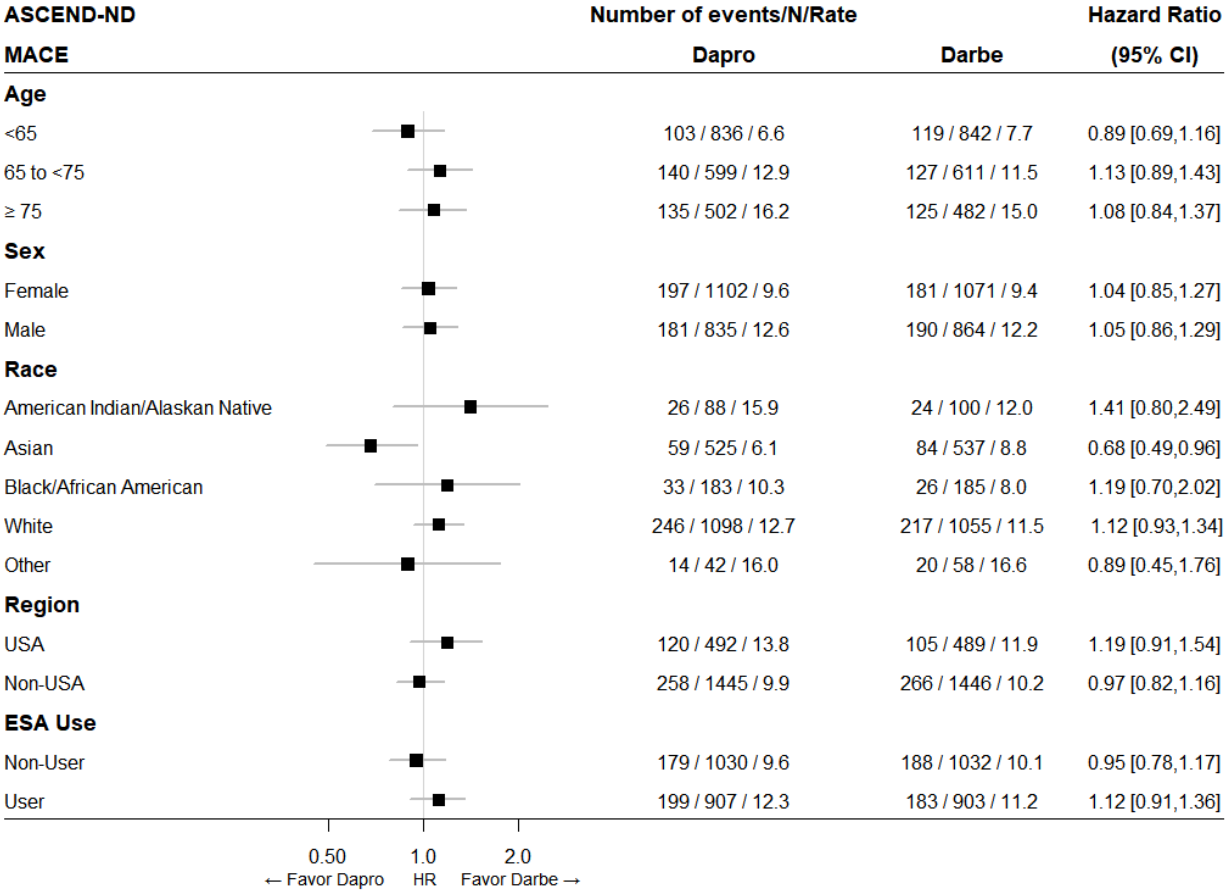
Source: FDA analysis.
[1] Percentage of MACE.
Abbreviations: CI, confidence interval; CV, cardiovascular; Diff, difference; IR, incidence rate per 100 PY, MACE, major adverse cardiovascular event; N, number of subjects; n, number of subjects with event; PY, person-year
Comparative estimates not calculated for MACE components.

Results of the prespecified subgroup analyses of MACE are shown in Figure 2. Estimated HRs for MACE were greater than 1.0 comparing daprodustat to darbepoetin alfa in the older age categories, among American Indian or Alaskan Native (HR 1.41; 95% CI 0.80, 2.49), among Black or African American (1.19; 95% CI 0.70, 2.02), among White (1.12; 95% CI 0.93, 1.34), in the USA

region (HR 1.19; 95% CI 0.91, 1.54), and among ESA users at randomization (HR 1.12; 95% CI 0.91, 1.36). Key considerations with the subgroup analyses include:

- In general, a limitation when looking at many subgroups in an exploratory manner is that the chance of observing a signal that is incongruous with the overall study population is non-negligible, i.e., the signal could be an overestimation of the truth.
- The low event rates and small samples sizes for the non-White race subgroups limit the interpretability of those analyses.
- The higher incidence of MACE in the daprodustat arm for the prespecified USA subgroup and ESA user subgroup is of particular interest because it represents the FDA's jurisdiction and standard of care, respectively. These subgroup sample sizes were moderate, approximately 500 to 900 subjects per treatment arm, and the treatment effect estimates were relatively precise compared to the other subgroups.
    - Exploratory analyses across the secondary CV endpoints also showed higher risk estimates in the USA subgroup compared to the non-USA subgroup in the NDD population. This is discussed further in Section 3.2.3.3.
    - Exploratory analyses of ESA subgroups for the secondary CV endpoints did not indicate a consistently higher risk among ESA users compared to non-users. See Section 5.1.1.2.3.

Figure 2. Subgroup Analyses of MACE, ASCEND-ND (On-Study Analysis)



Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; Darbe, darbepoetin alfa; ESA, erythropoietin-stimulating agent; MACE, major adverse cardiovascular event; N, number of subjects
MACE: Composite of all-cause mortality, nonfatal MI, and nonfatal stroke.
Rate: Incidence rate per 100 PY.

Two other considerations related to the MACE findings are discussed in further detail in Section 3.2.3:

- The supportive OT+28 days analysis of MACE provided HR estimates (HR 1.40; 95% CI 1.17, 1.68) inconsistent with the primary analysis (on-study analysis). See the discussion in Section 3.2.3.1.
- A limitation to the use of MACE to assess CV risk is that MACE was a composite endpoint prespecified to contain all-cause mortality, i.e., non-CV deaths were included. To better understand CV risk, secondary CV endpoints and CV MACE (a composite of CV mortality, nonfatal MI, and nonfatal stroke) were analyzed and are presented in Section 3.2.3.2.

3.2.2.2.2 ASCEND-D

Results for the prespecified primary analysis of time to first MACE are shown in Table 16. The HR (95% CI) from the primary analysis (on-study analysis) for time to first MACE was 0.93 (0.81, 1.07) comparing daprodustat to ESA. The upper bound of the 95% CI was lower than the prespecified risk margin of 1.25, i.e., the study ruled out the risk for MACE. Kaplan-Meier

survival curves for MACE overlapped during the follow-up period (Appendix Figure 12). The IRD was -0.8 events/100 PY (95% CI -2.4, 0.8) between daprodustat and ESA. MACE (daprodustat 374/1487 [11.1 events/100 PY], ESA 394/1477 [11.9 events/100 PY]) comprised mostly all-cause mortality (daprodustat 244/374, ESA 233/394), followed by nonfatal MI (daprodustat 101/374, ESA 126/394) and nonfatal stroke (daprodustat 29/374, ESA 35/394).

In summary, the analysis of MACE (HR 0.93; CI 0.81, 1.07) ruled out the risk margin of 1.25, with the risk estimate being less than the null of 1.0.

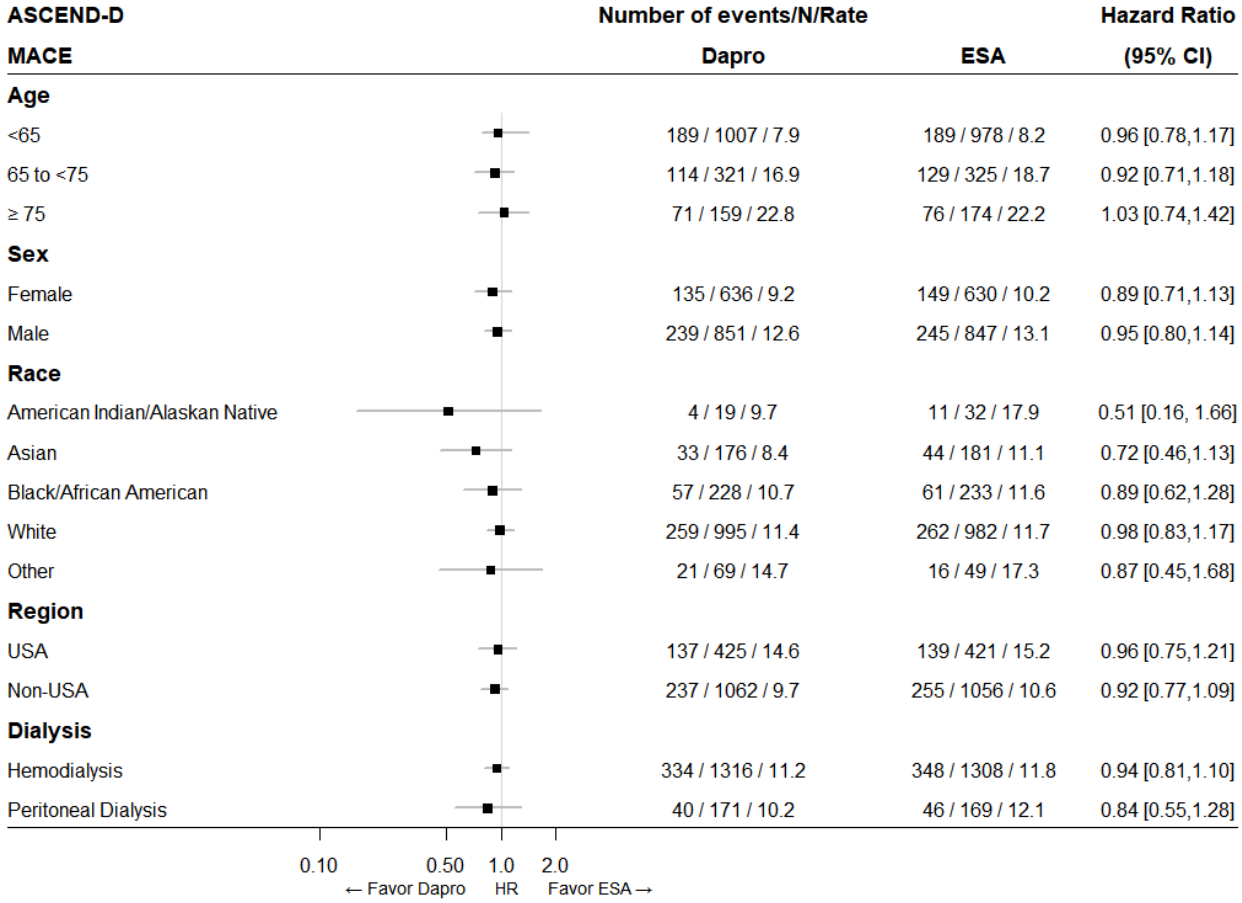
Table 16. Summary of Results for MACE, ASCEND-D (On-Study Analysis)

	Daprodustat N=1487 PY=3377	ESA N=1477 PY=3323	Rate Diff per 100 PY (95% CI)	Hazard Ratio (95% CI)
MACE, n [IR]	374 [11.1]	394 [11.9]	-0.8 (-2.4, 0.8)	0.93 (0.81, 1.07)
All-cause mortality, n (%[1])	244 (65.2)	233 (59.1)	-	-
Nonfatal myocardial infarction, n (%[1])	101 (27.0)	126 (32.0)	-	-
Nonfatal stroke, n (%[1])	29 (7.8)	35 (8.9)	-	-

Source: FDA analysis.
[1] Percentage of MACE.
Abbreviations: CV, cardiovascular; CI, confidence interval; Diff, difference; ESA, erythropoietin-stimulating agents; IR, incidence rate per 100 PY, MACE, major adverse cardiovascular event; N, number of subjects; n, number of subjects with event; PY, person-year

Results for prespecified subgroup analyses of MACE are shown in Figure 3. Subgroup HR estimates were less than or equal to 1.03 and generally consistent with the overall study population MACE estimate.

Figure 3. Subgroup Analyses of MACE, ASCEND-D (On-Study Analysis)



Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; ESA, erythropoiesis-stimulating agent; MACE, major adverse cardiovascular event; N, number of subjects
MACE: Composite of all-cause mortality, nonfatal MI, and nonfatal stroke.
Rate: incidence rate per 100 PY.

3.2.3 Safety Issues in Detail

3.2.3.1 Difference Between On-Study Versus On-Treatment Analyses Results—ASCEND-ND

In the assessment of risks, two common approaches to analysis are on-study analysis and OT analysis. An on-study analysis considers a subject at risk of experiencing an event from the time of randomization until trial discontinuation, which includes events that occur while a subject is OT and off-treatment (for those subjects who prematurely discontinued treatment but remained in the trial). An OT analysis considers a subject at risk of experiencing an event from the time of randomization to the time of treatment discontinuation plus some period of time thereafter (e.g., 28 days).

An on-study analysis approach is valuable in the assessment of risks that have a long latency period. In addition, such analyses preserve the integrity of randomization. A limitation of an on-study analysis approach is that it may be less sensitive than the OT analysis to detecting true adverse effects of the study drug, especially in cases of high rates or between-group imbalances of premature treatment discontinuation (these subjects who remain in the trial are still

considered at risk for adverse reactions in the analysis but are no longer taking study drug) or use of rescue medication (that carry their own risks).

An OT analysis approach is sensitive to risks thought to be pharmacodynamic responses to the drug, and as such, the risk would be expected to occur while exposed to treatment or shortly thereafter. The OT analysis approach has the potential to break the integrity of randomization and introduce bias as there may be differences between treatment arms in the types of subjects who adhere to treatment. Such differences cannot easily be adjusted for in analysis.

In the development program for daprodustat, an on-study analysis approach was the prespecified primary analysis approach and an OT analysis approach was considered supportive. Three variations of the OT analysis accounting for differing treatment dosing intervals, resulting in different ascertainment windows, were considered (see Section 3.2.1 and Table 17).

In ASCEND-ND, the prespecified primary on-study analysis approach captured events from randomization to study completion/withdrawal (mean follow-up duration 1.9 years; standard deviation 1.0 year). Treatment discontinuation was similar between treatment arms (daprodustat 38%, darbepoietin alfa 38%), as was study withdrawal (daprodustat 3%, darbepoietin alfa 3%) and use of rescue therapies (daprodustat 2%, darbepoietin alfa 3%).

The prespecified primary analysis of MACE was on-study (HR 1.03; 95% CI 0.89, 1.19; see Section 3.2.2.2). The prespecified supportive OT analysis (OT+28) resulted in a higher incidence of MACE in the daprodustat arm compared to the control arm and an HR estimate (HR 1.40; 95% CI 1.17, 1.68) that was greater than the on-study analysis estimate (Table 17). Exploratory OT analyses adjusted by the dosing frequencies of the different treatments attenuated the effect estimate; the extent of attenuation depended on the ascertainment window chosen (OT+Dosing Frequency+28: HR 1.18 (95% CI 0.99, 1.40) versus OT+Dosing Frequency: HR 1.09 (95% CI 0.89, 1.33)).

In summary, OT analyses produced HR estimates for MACE that were greater than the on-study analysis estimate, and the OT estimates differed depending on the ascertainment window used. However, as noted above, comparisons based on the OT analyses are likely subject to bias, which cannot easily be corrected through analysis. The design and conduct of ASCEND-ND appears sufficient to evaluate and estimate risks based on an on-study analysis approach.

Table 17. MACE On-Study and On-Treatment Analyses, ASCEND-ND

	Dapro N=1937[a] PY=3480[a]	Darbe N=1935[a] PY=3489[a]	Hazard Ratio (95% CI)
	n [IR]		
On-study (primary)	378 [10.9]	371 [10.6]	1.03 (0.89, 1.19)
On-treatment + 28 days (supportive)	274 [9.9]	202 [7.2]	1.40 (1.17, 1.68)
On-treatment + dosing frequency + 28 days (exploratory)	275 [10.0]	248 [8.6]	1.18 (0.99, 1.40)
On-treatment + dosing frequency (exploratory)	192 [7.3]	189 [6.8]	1.09 (0.89, 1.33)

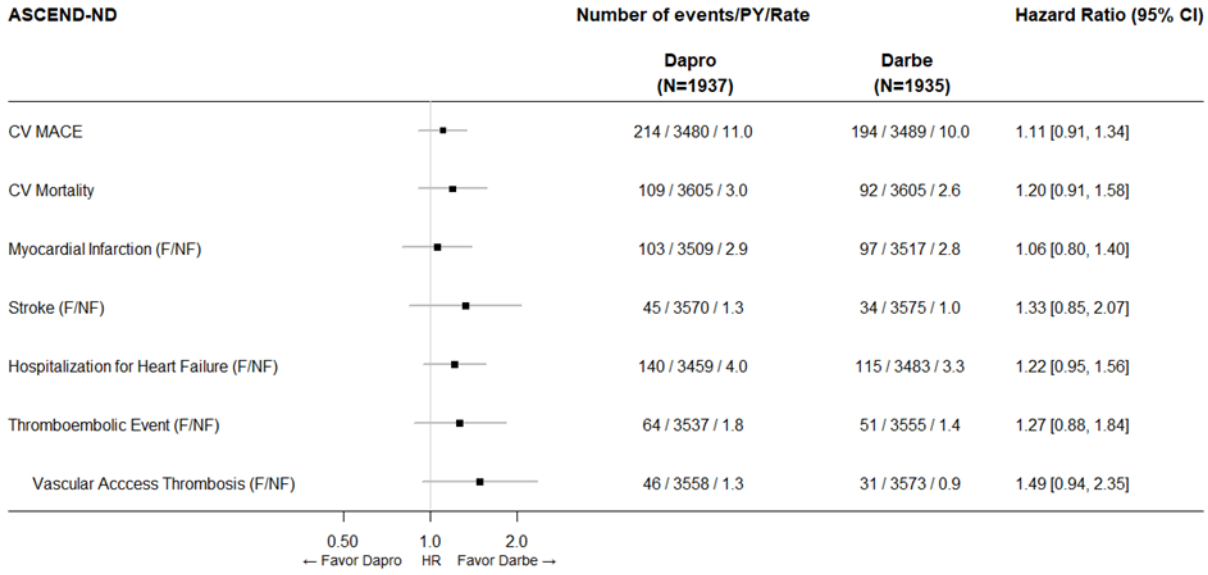
Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; Darbe, darbepoetin alfa; IR, incidence rate per 100 PY, MACE, major adverse cardiovascular event; N, number of subjects; n, number of subjects with event; PY, person-year
MACE: Composite of all-cause mortality, nonfatal MI, and nonfatal stroke.
Dosing frequency: Dapro: daily; Darbe: weekly, every 2 weeks, or every 4 weeks.
[a] Number of subjects (N) and person-years (PY) correspond to the on-study (primary) analysis only.

3.2.3.2 Higher Incidence of Cardiovascular Endpoints—ASCEND-ND

To better understand CV risk, only adjudicated CV endpoints, not including all-cause mortality, were assessed. Results of the primary (on-study) time-to-event analysis of CV endpoints in ASCEND-ND are shown in Figure 4. As shown in the figure, the estimated HRs for CV MACE, CV mortality, MI, stroke, HHF, TEE, and VAT are all increased for the comparison of daprodustat to darbepoietin alfa, ranging from 1.06 to 1.49. The corresponding IRDs (per 100-person years) ranged from 0.2 to 0.7 (Appendix Table 19).

Limitations of these analyses include lower precision (compared to MACE) because of lower event rates (and hence wider 95% CIs) and no Type I error control for treatment arm comparisons of the CV endpoints. However, in ASCEND-ND, the consistently increased risk estimates across different CV endpoints measuring related aspects of CV risk in a CV outcomes trial raises concerns as to whether daprodustat is safe relative to darbepoetin alfa, which itself carries an increased CV risk. In ASCEND-D, there was not a consistent pattern of increased risk estimates in the CV endpoints (Appendix Table 20). The reasons for discrepant trials results for CV safety are not clear.

Figure 4. Adjudicated Cardiovascular Safety Endpoints, ASCEND-ND (On-Study Analysis)



Source: FDA analysis.
Abbreviations: CI, confidence interval; CV, cardiovascular; Dapro, daprodustat; Darbe, darbepoetin alfa; F/NF, fatal or nonfatal; PY, person-year
CV MACE: Composite of CV mortality, nonfatal MI, nonfatal stroke.
Rate: Number of events per 100 PY.

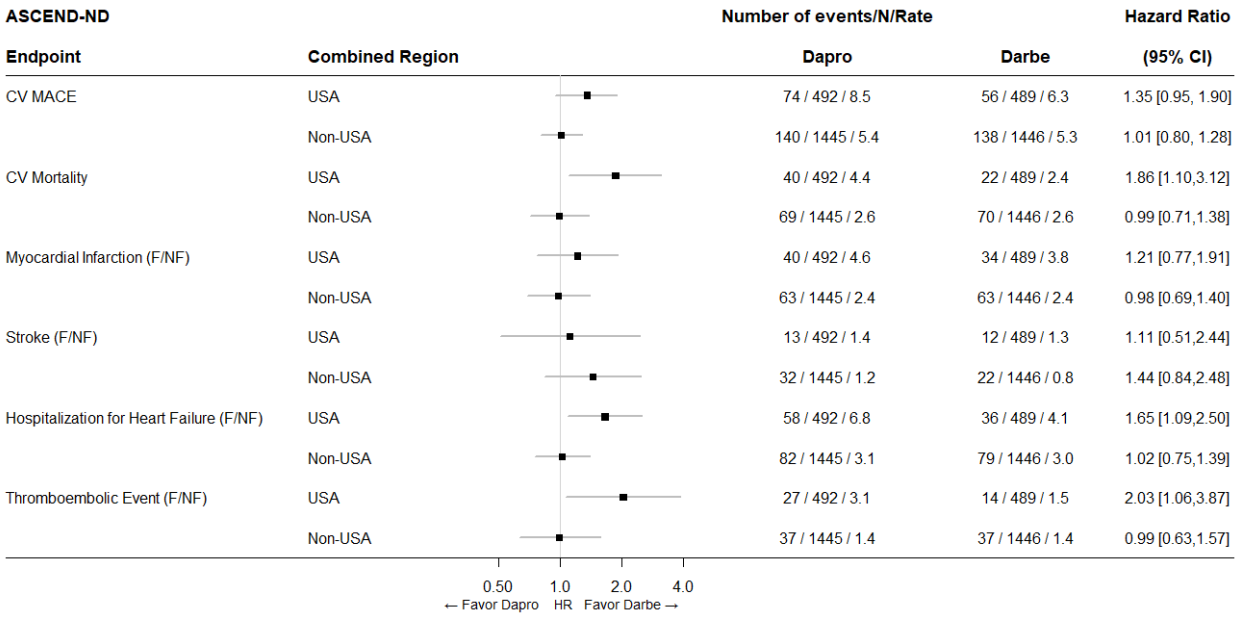
3.2.3.3 Higher Incidence of Cardiovascular Endpoints in the USA Subgroup—ASCEND-ND

To further explore CV endpoints in the regional subgroups, exploratory analyses were conducted for each adjudicated CV endpoint in the USA and non-USA subgroups. A higher incidence of each CV endpoint was observed in the daprodustat arm compared to the darbepoetin alfa arm in the USA region (Figure 5). Except for stroke, non-USA subgroup analyses had HRs of about 1.0, and USA subgroup analyses had elevated HRs (ranging from 1.21 to 2.03). The variability of HR estimates, i.e., 95% CI widths, depended on the number of events and sample sizes, with lower precision for the USA subgroup compared to the non-USA subgroup and for endpoints like stroke and TEE.

There were differences in baseline demographics for the USA compared to the non-USA subgroup. USA subjects used less ESAs at baseline, which was also reflected in baseline Hb category, and generally had more comorbid conditions at baseline (history of diabetes, heart failure, cardiovascular disease). In addition, there were differences in enrollment by race between non-USA and USA subgroups (Appendix Table 21). We are unclear if these differences contributed to the discrepant results between the USA and non-USA subgroups.

Although exploratory analyses could introduce bias and produce unreliable results, the higher risk estimates in the USA subgroup compared to the non-USA subgroup in the NDD population were seen across multiple CV endpoints and were consistent with the unfavorable MACE prespecified region subgroup results (Section 3.2.2.2.1). In summary, these higher incidences of CV endpoints in the daprodustat arm in the USA subgroup raise concerns as to whether daprodustat is safe relative to darbepoetin alfa, which itself carries an increased CV risk.

Figure 5. Combined Region (USA, non-USA) Subgroup Analyses for All Adjudicated CV Endpoints, ASCEND-ND (On-Study Analysis)



Source: FDA analysis.
Abbreviations: CI, confidence interval; CV, cardiovascular; Dapro, daprodustat; Darbe, darbepoetin alfa; F/NF, fatal or nonfatal; USA, United States of America
CV MACE: Composite of CV mortality, nonfatal MI, and nonfatal stroke.
Rate: Incidence rate per 100 person-years.

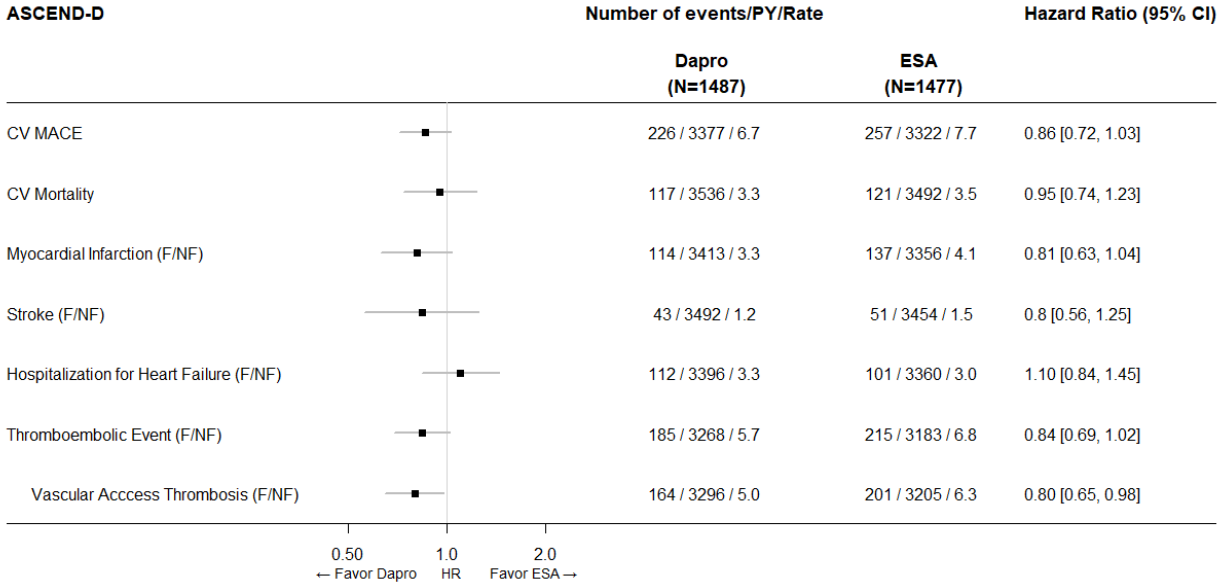
3.2.3.4 Higher Incidence of Hospitalization for Heart Failure—ASCEND-ND, ASCEND-D

For ASCEND-ND, results for the primary (on-study) time-to-event analysis of CV endpoints are shown in Section 3.2.3.2, Figure 4. A higher incidence of HHF was observed in the daprodustat arm (140/1937 [4.0 events/100 PY]) compared to the darbepoetin alfa arm (115/1935 [3.3 events/100 PY]), corresponding to a HR of 1.22 (95% CI 0.95, 1.56). As discussed previously, a higher incidence was also observed for other adjudicated CV endpoints in the daprodustat arm in ASCEND-ND (see Section 3.2.3.2).

For ASCEND-D, results for the time-to-event analysis of CV endpoints are shown in Figure 6. A higher incidence of HHF was observed in the daprodustat arm (112/1487 [3.3 events/100 PY]) compared to the ESA arm (101/1477 [3.0 events/100 PY]) corresponding to a HR of 1.10 (CI 0.84, 1.45). A higher incidence was not observed for other adjudicated CV endpoints in the daprodustat arm.

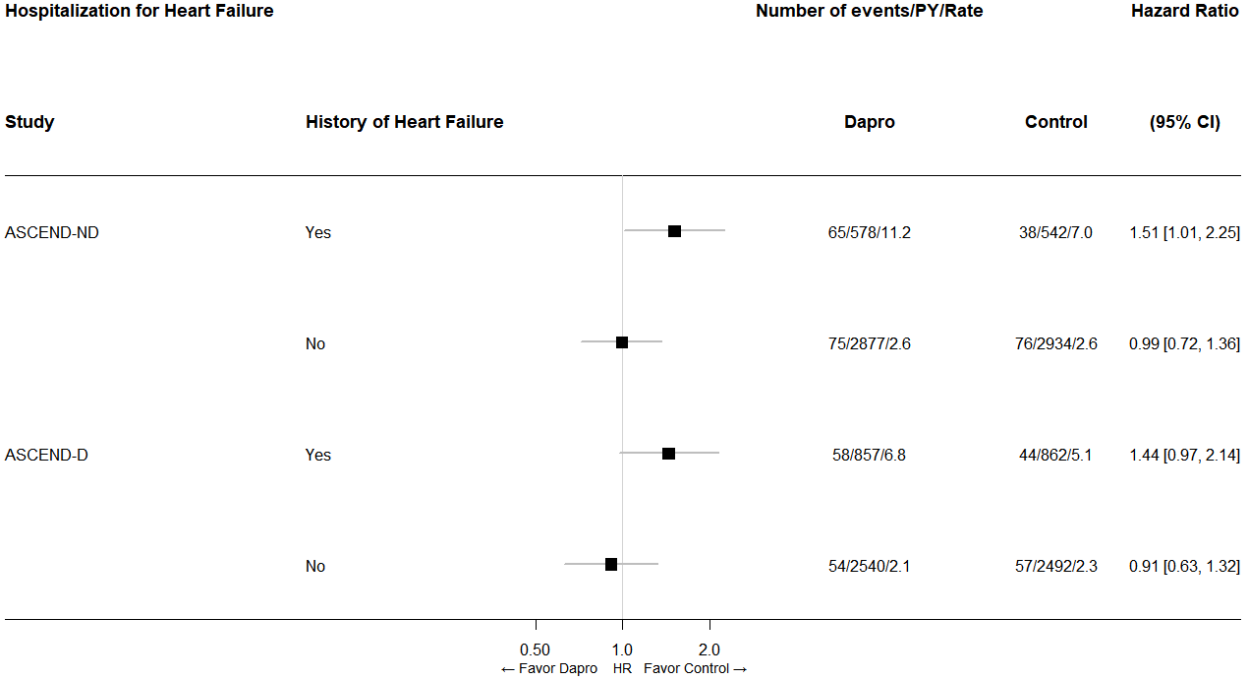
In both ASCEND-ND and ASCEND-D, exploratory subgroup analyses by history of heart failure (Yes, No) showed a higher incidence of HHF in the daprodustat arm compared to the control arm in the subgroup with a history of heart failure (Figure 7). The HR for the subgroup with history of heart failure was 1.51 (95% CI 1.01, 2.25) in ASCEND-ND and 1.44 (95% CI 0.97, 2.14) in ASCEND-D. In contrast, the HR for the subgroup without a history of heart failure was 0.99 (95% CI 0.72, 1.36) in ASCEND-ND and 0.91 (95% CI 0.63, 1.32) in ASCEND-D.

Figure 6. Adjudicated Cardiovascular Safety Endpoints, ASCEND-D (On-Study Analysis)



Source: FDA analysis.
Abbreviations: CI, confidence interval; CV, cardiovascular; Dapro, daprodustat; ESA, erythropoietin-stimulating agents; F/NF, fatal or nonfatal; PY, person-year
CV MACE: Composite of CV mortality, nonfatal MI, and nonfatal stroke.
Rate: number of events per 100 PY.

Figure 7. History of Heart Failure (Yes, No) Subgroup Analysis[1] for Hospitalization for Heart Failure, ASCEND-ND, ASCEND-D (On-Study Analysis)



Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; PY, person-year
Rate: Number of events per 100 PY.
History of heart failure defined as having the medical history conditions: heart failure, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, or pulmonary hypertension.
[1] Analyses did not include six subjects (ASCEND-ND) and three subjects (ASCEND-D) missing history of hemofiltration.

3.2.3.5 Treatment-Emergent Adverse Events and Adverse Events of Special Interest (AESI)

The Applicant identified several AESIs related to nonclinical findings, known safety issues with ESA products, and based on the mechanism of action of daprodustat.

The AESI of esophageal and gastric erosions are discussed in further detail in this section. We also discuss a signal for AKI which emerged during our review and analysis of the safety data.

The AESI of malignancy is discussed in the Appendix. We did not identify a noteworthy increase in malignancy compared to the ESA control, but recognize that the duration of the trials limits interpretability on long-term cancer risk.

3.2.3.5.1 Higher Incidence of Gastrointestinal Erosions—ASCEND-ND, ASCEND-D

The Applicant's nonclinical data demonstrated gastric erosions/ulcerations in mice, rats, dogs and monkeys with a possible basis for erosions and ulcers being compromised vascular perfusion associated with marked increases in hematocrit. Potential upper gastrointestinal erosive events were identified and collected prospectively in the ASCEND-D and ASCEND-ND trials as an AESI.

The Applicant prespecified a list of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) (provided in Section 5.1.2.2) pertaining to the AESI of gastric erosions. The FDA review of the individual PTs used in the query determined that the breadth of the queries was reasonable for a risk specific to gastric erosion. The adverse events were not adjudicated and diagnostic confirmation with upper endoscopy was not required in the protocols.

There was a higher number of AESIs for serious gastric/esophageal erosions reported in the daprodustat arm compared to ESA with a more notable difference in the ASCEND-ND population (HR [95% CI]: 1.63 [1.17,2.27]) than in ASCEND-D (HR [95% CI]: 1.16 [0.78, 1.73]) (Table 18). The risk appears to accumulate constantly over time (i.e., there is not an apparent delay), and is driven by treatment differences in serious hemorrhages, rather than ulcerations (supportive data provided in Section 5.1.2.2). Importantly, the treatment arms in ASCEND-D and ASCEND-ND were balanced with respect to anti-platelet, anti-coagulant use, and prophylactic drugs (e.g., antiacids).

The Applicant provided an external, blinded, review of serious AESIs of gastric or esophageal erosions from ASCEND-D and ASCEND-ND suggesting that most included events were overt gastrointestinal bleeding, with over half requiring transfusion. However, the external blinded review also noted several limitations related to the fact that the AE reports did not trigger confirmatory testing (e.g., *Helicobacter pylori* testing and confirmatory endoscopy). Despite these limitations, this signal was seen in both the applicant's OT assessment of the AESI and FDA's on-study analysis.

Table 18. Summary of Results for the Prespecified Queries* Related to Serious Gastric Erosion Events—ASCEND-D and ASCEND-ND and Pooled, (On-Study Analysis)

ASCEND-D	Daprodustat N=1487 n [IR]	ESA N=1477 n [IR]	Rate Diff per 100 PY (95% CI)	Hazard Ratio (95% CI)
Erosions AESI* (all AEs)	84 [2.3]	98 [2.8]	-0.4 (-1.2, 0.3)	0.84 (0.63, 1.13)
Erosions AESI* (SAEs)	53 [1.5]	45 [1.3]	0.2 (-0.3, 0.7)	1.16 (0.78, 1.73)
ASCEND-ND	**Daprodustat N=1937 n [IR]**	**Darbepoetin alfa N=1935 n [IR]**	**Rate Diff per 100 PY (95% CI)**	**Hazard Ratio (95% CI)**
Erosions AESI* (all AEs)	91 [2.5]	56 [1.5]	1.0 (0.3, 1.6)	1.63 (1.17, 2.27)
Erosions AESI* (SAEs)	55 [1.5]	28 [0.8]	0.7 (0.3, 1.2)	1.96 (1.24, 3.09)
Pooled	**Daprodustat N=3424**	**ESA N=3412**	**Rate Diff per 100 PY (95% CI)**	**Hazard Ratio (95% CI)**
Erosions* AESI (all AEs)	175 [2.4]	154 [2.2]	0.3 (-0.2, 0.8)	1.13 (0.91, 1.40)
Erosions* AESI (SAEs)	108 [1.5]	73 [1.0]	0.5 (0.1, 0.8)	1.47 (1.09, 1.98)

Source: Clinical Reviewer, ADAE.xpt, ADSL.xpt, R v. 4.2, ITT population.
This analysis treats deaths and administrative censoring the same.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; Dapro, daprodustat; Diff, difference; GI, gastrointestinal; hem, hemorrhage; IR, incidence rate per 100 PY, MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects with event; PY, person-year; ESA, erythropoiesis-stimulating agent; SAE, serious adverse event

In summary, there was a treatment difference in serious esophageal and gastric erosions disfavoring daprodustat in both ASCEND-D and ASCEND-ND. Most of these reported serious events were related to gastrointestinal bleeding and had important clinical consequences such as transfusions.

3.2.3.6 Higher Incidence of Acute Kidney Injury—ASCEND-ND

We performed exploratory analyses to understand if there was a deleterious effect of daprodustat on renal function. Inspection of routine safety laboratory assessments (collected at least every 12 weeks) in ASCEND-ND (e.g., aggregate longitudinal plots and shift tables) for serum creatinine and BUN did not show a notable treatment difference. Time to progression of CKD[9] also indicated no harm (IRD [95% CI] -0.2 [-2.8, 2.4] events per 100 PY). In contrast, the FDA analyses using treatment-emergent serious adverse events (TESAEs) of AKI shows a potential increased risk for AKI for daprodustat compared to the ESA treatment arm in the ND population.

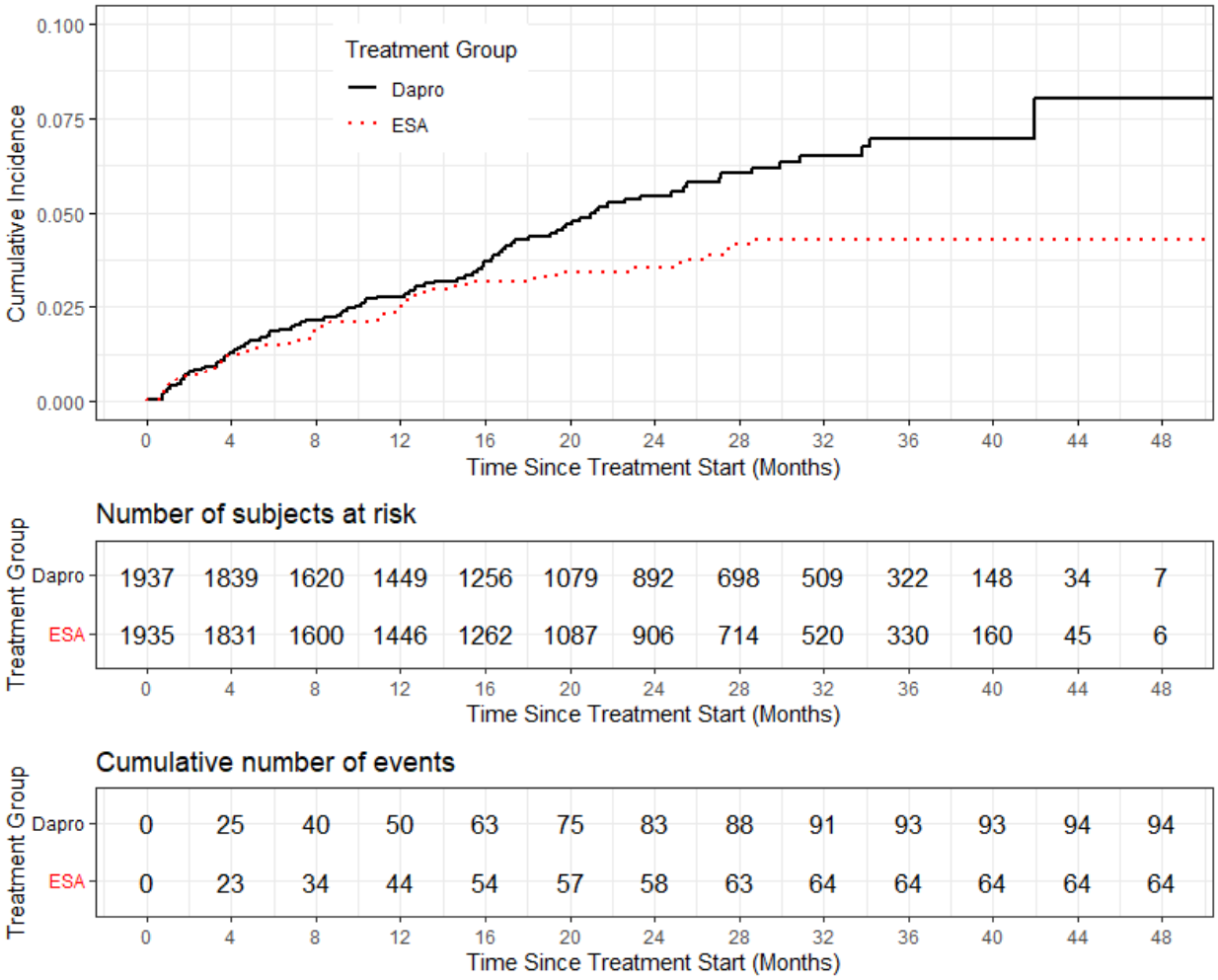
Our TESAE analyses of AKI showed a relative risk of 1.47 (95% CI 1.07, 2.00) and risk difference of 1.54% [0.30, 2.79]) (Table 22 in Section 5.1.2.1).[10] The risks were attenuated when considering all AKI TEAEs regardless of seriousness (relative risk of 1.2, 95% CI [-0.4, 2.7])(data not shown). We note that the treatment difference appears after 1 year on study so we preferred cumulative incidence differences to quantify risk. A Kaplan-Meier curve for time to

[9] Time to progression of CKD was a principal secondary endpoint in ASCEND-ND, assessed in all randomized participants with eGFR ≥15 mL/min/1.73 m^2. This endpoint was an adjudicated composite outcome, defined as meeting one of the following criteria: (i) 40% decline in eGFR (confirmed 4 to 13 weeks later), (ii) chronic dialysis, or (iii) kidney transplant.

[10] Using FDA Medical Query v. 2.0. Preferred Terms included in this query are provided in Section 5.1.2.4.

first TESAE of AKI for the ASCEND-ND study is presented in Figure 8. At 2 and 3 years, there was a cumulative incidence difference of 2.1% (95% CI: 0.5, 3.5) and 2.7% (95% CI 0.8, 4.6), respectively. See Section 5.1.2.4 for additional information, including the FDA query used.

Figure 8. Time to First TESAE of Acute Kidney Injury (Narrow FMQ), (On-Study Analysis)



Source: Clinical Reviewer, ADAE.xpt, ADSL.xpt, R v. 4.2, ITT population; TESAEs of acute kidney injury (narrow) per FMQ v. 2.0. This analysis treats deaths and administrative censoring the same.
Abbreviations: Dapro, Daprodustat; ESA, erythropoietin-stimulating agent; FMQ, FDA medical query; ITT, intention-to-treat; TESAE, treatment-emergent serious adverse event

We considered whether the AKI TESAE imbalance could be related to the increased risk for HHF with daprodustat compared to darbepoietin alfa. However, the AKI risk was still evident in subjects without a history of heart failure at baseline (data not shown); a population that did not appear to have an increased risk of HHF with daprodustat compared to darbepoietin alfa.

In summary, there are discrepant lines of evidence regarding kidney injury with daprodustat in the ND population. There were no differences detected for all-cause mortality or CKD progression, which are important sequelae of AKI.

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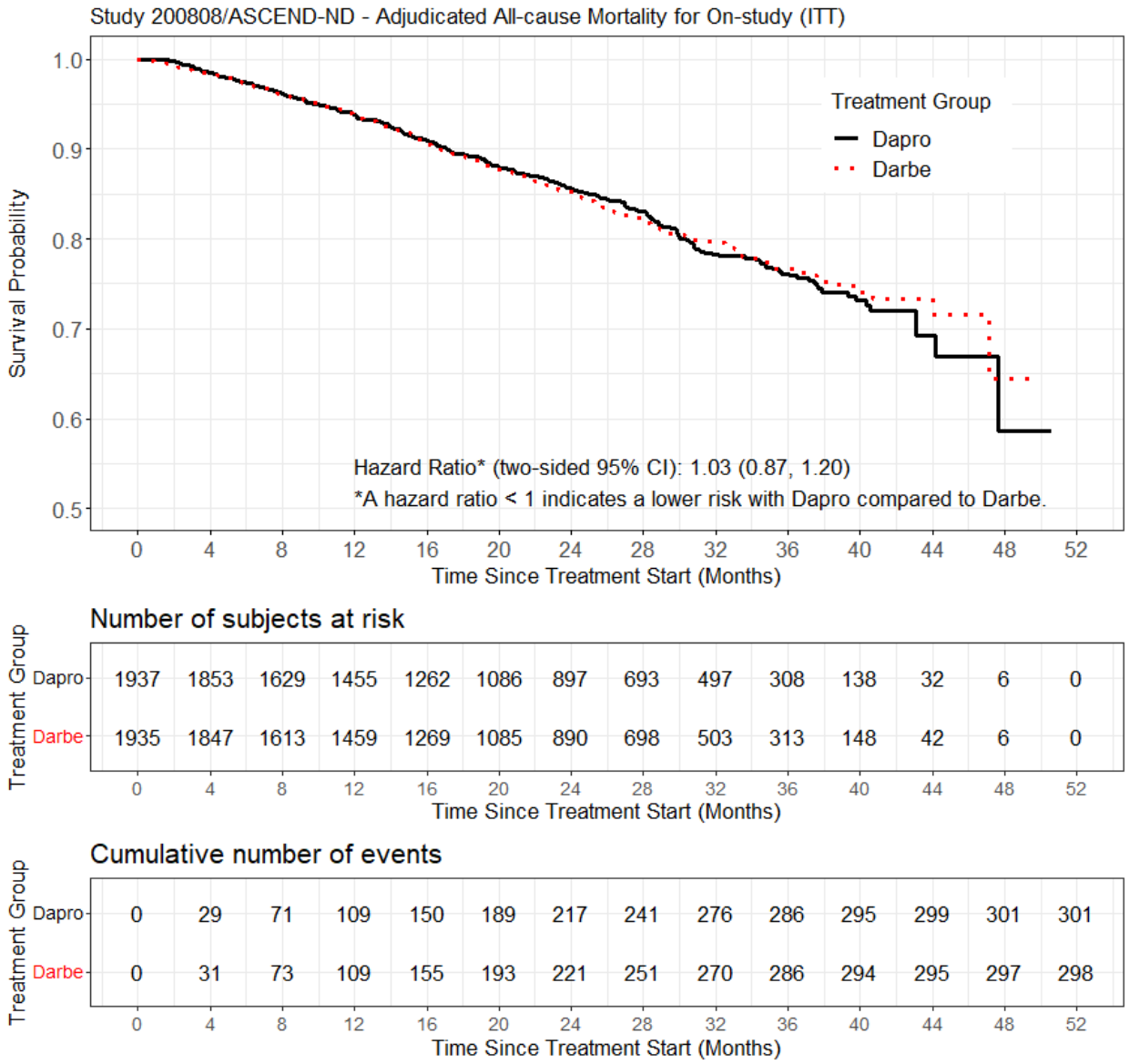
5 Appendix

5.1 Additional Safety Data

5.1.1 Additional MACE and CV Safety Data

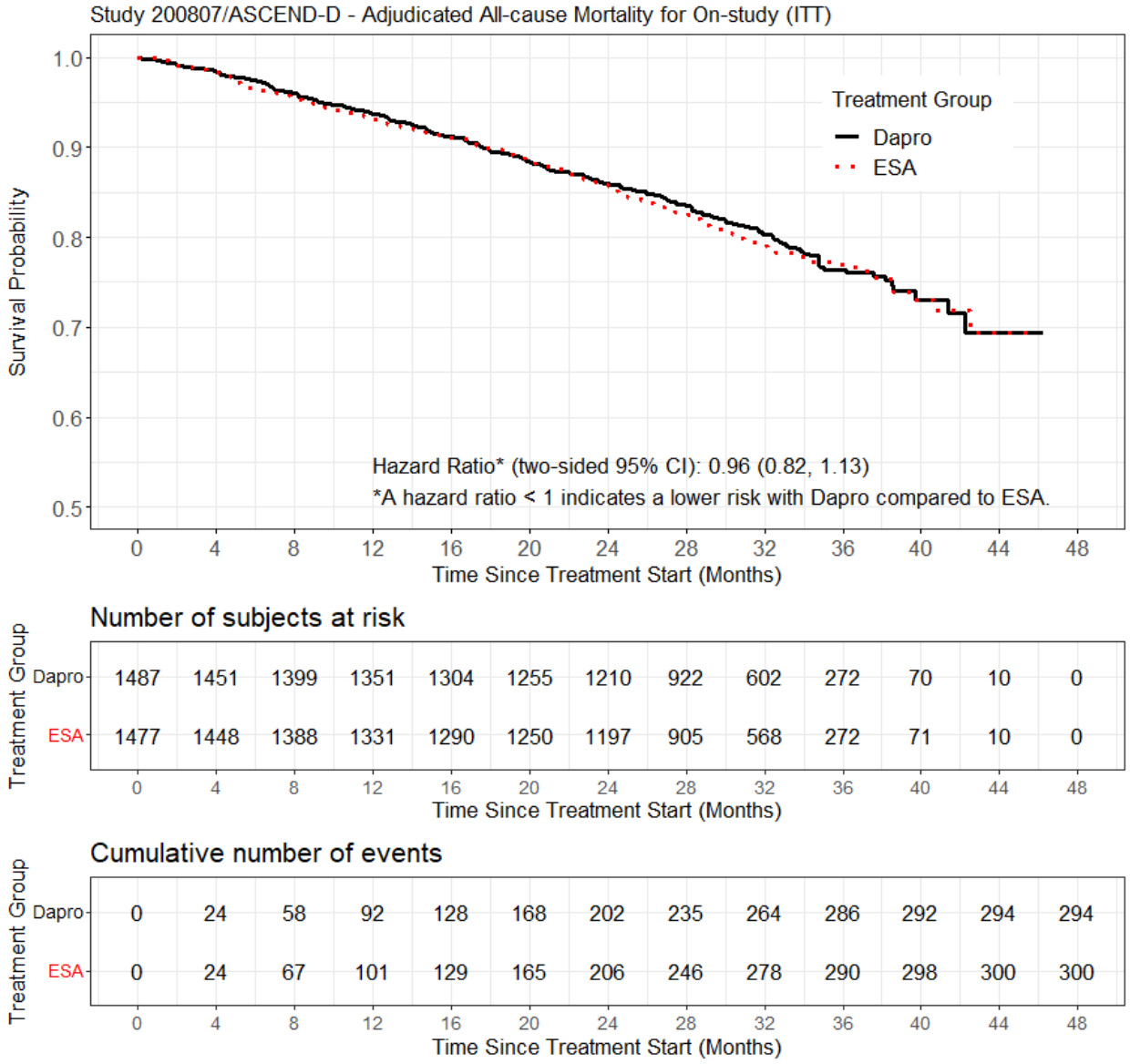
5.1.1.1 Time to All-Cause Mortality K-M Curves

Figure 9. Time to All-Cause Mortality, ASCEND-ND



Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, Daprodustat; Darbe, darbepoetin alfa; ITT, intention-to-treat

Figure 10. Time to All-Cause Mortality, ASCEND-D



Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, Daprodustat; Darbe, darbepoetin alfa; ESA, erythryopoeisis-stimulating agent; ITT, intention-to-treat

5.1.1.2 MACE and Cardiovascular Endpoint Analyses

5.1.1.2.1 Cardiovascular Endpoints Analyses

Table 19. Summary of Results for Adjudicated Cardiovascular Safety Endpoints, ASCEND-ND

	Daprodustat N=1937	Darbepoetin alfa N=1935	Rate Diff per 100 PY (95% CI)	Hazard Ratio (95% CI)
	n [IR]			
CV MACE	214 [6.1]	194 [5.6]	0.6 (-0.5, 1.7)	1.11 (0.91, 1.34)
CV mortality	109 [3.0]	92 [2.6]	0.5 (-0.3, 1.2)	1.20 (0.91, 1.58)
Fatal or nonfatal myocardial infarction	103 [2.9]	97 [2.8]	0.2 (-0.6, 1.0)	1.06 (0.80, 1.40)
Fatal or nonfatal stroke	45 [1.3]	34 [1.0]	0.3 (-0.2, 0.8)	1.33 (0.85, 2.07)
Hospitalization for heart failure	140 [4.0]	115 [3.3]	0.7 (-0.2, 1.6)	1.22 (0.95, 1.56)
Thromboembolic event	64 [1.8]	51 [1.4]	0.4 (-0.2, 1.0)	1.27 (0.88, 1.84)
Vascular access thrombosis	46 [1.3]	31 [0.9]	0.4 (-0.1, 0.9)	1.49 (0.94, 2.35)

Source: FDA analysis.
Abbreviations: CI, confidence interval; CV, cardiovascular; Diff, difference; IR, incidence rate per 100 PY, MACE, major adverse cardiovascular event; N, number of subjects; n, number of subjects with event; PY, person-year
CV MACE: Composite of CV mortality, nonfatal MI, and nonfatal stroke.

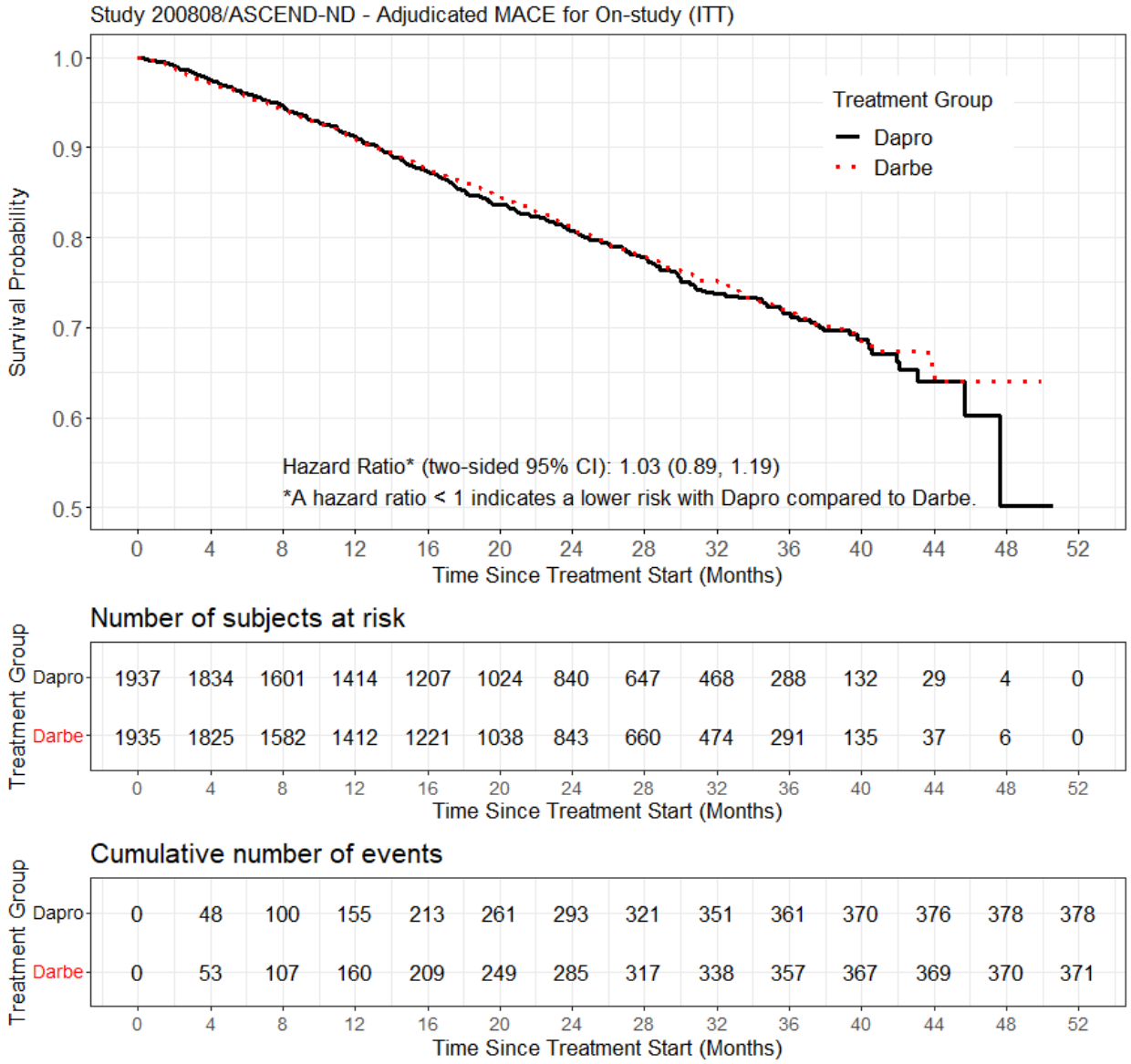
Table 20. Summary of Results for Adjudicated Cardiovascular Safety Endpoints, ASCEND-D

	Dapro N=1487	ESA N=1477	Rate Diff per 100 PY (95% CI)	Hazard Ratio (95% CI)
	n [IR]			
CV MACE	226 [6.7]	257 [7.7]	-1.0 (-2.3, 0.2)	0.86 (0.72, 1.03)
CV mortality	117 [3.3]	121 [3.5]	-0.2 (-1.0, 0.7)	0.95 (0.74, 1.23)
Fatal or nonfatal myocardial infarction	114 [3.3]	137 [4.1]	-0.7 (-1.7, 0.2)	0.81 (0.63, 1.04)
Fatal or nonfatal stroke	43 [1.2]	51 [1.9]	-0.2 (-0.8, 0.3)	0.84 (0.56, 1.25)
Hospitalization for heart failure	112 [3.3]	101 [3.0]	0.3 (-0.6, 1.1)	1.10 (0.84, 1.45)
Thromboembolic event	185 [5.7]	215 [6.75]	-1.1 (-2.3, 0.1)	0.84 (0.69, 1.02)
Vascular access thrombosis	164 [5.0]	201 [6.3]	-1.3 (-2.4, -0.1)	0.80 (0.65, 0.98)

Source: FDA analysis.
Abbreviations: CV, cardiovascular; CI, confidence interval; Dapro, daprodustat; Diff, difference; ESA, erythropoietin-stimulating agents; IR, incidence rate per 100 PY, MACE, major adverse cardiovascular event; N, number of subjects; n, number of subjects with event; PY, person-year
CV MACE: Composite of CV mortality, nonfatal MI, and nonfatal stroke.

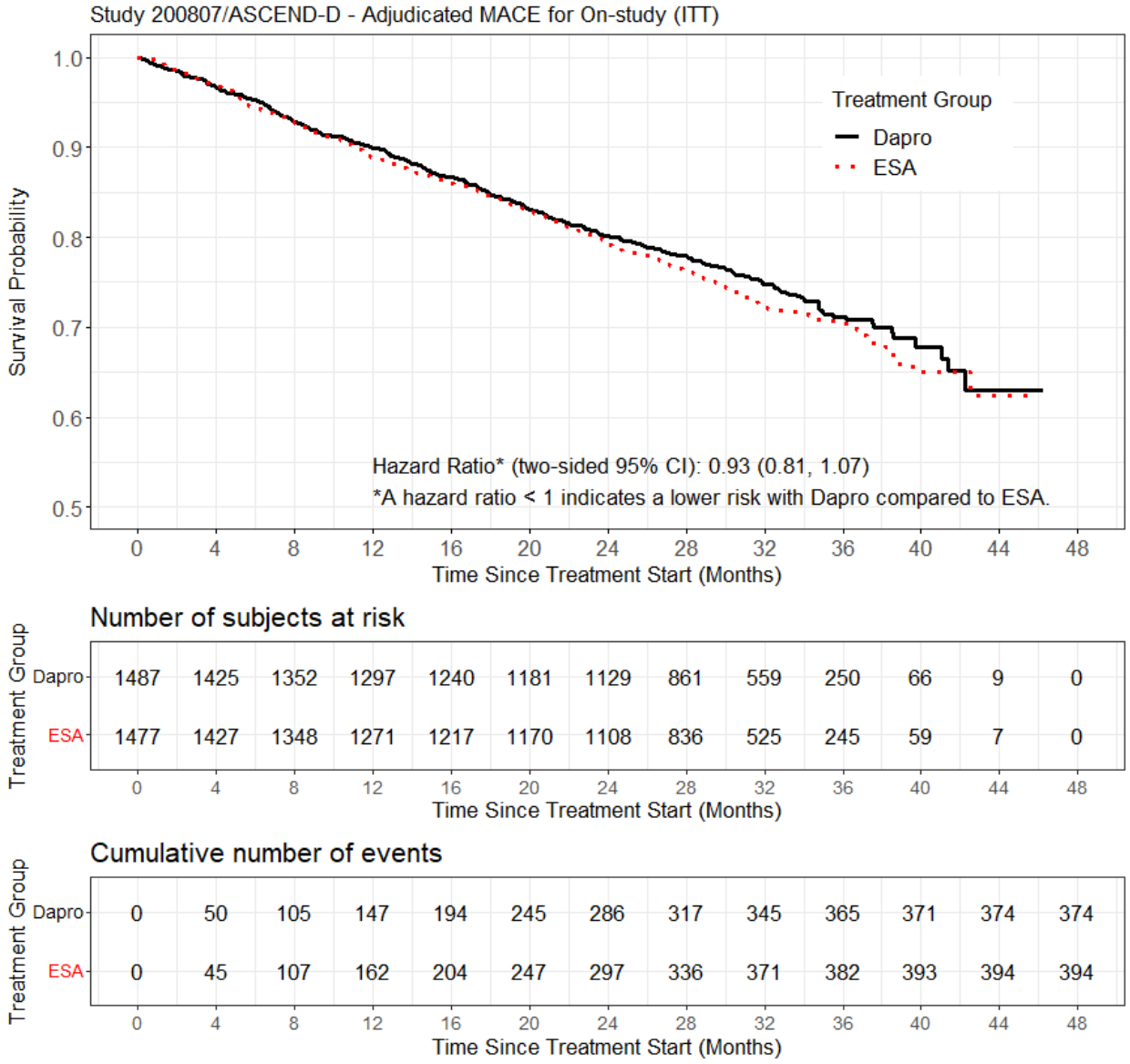
5.1.1.2.2 Kaplan-Meier Plots for MACE

Figure 11. Time to First MACE, ASCEND-ND



Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; Darbe, darbepoetin alfa; MACE, major adverse cardiovascular event
MACE: Composite of all-cause mortality, first nonfatal MI, and first nonfatal stroke.

Figure 12. Time to First MACE, ASCEND-D



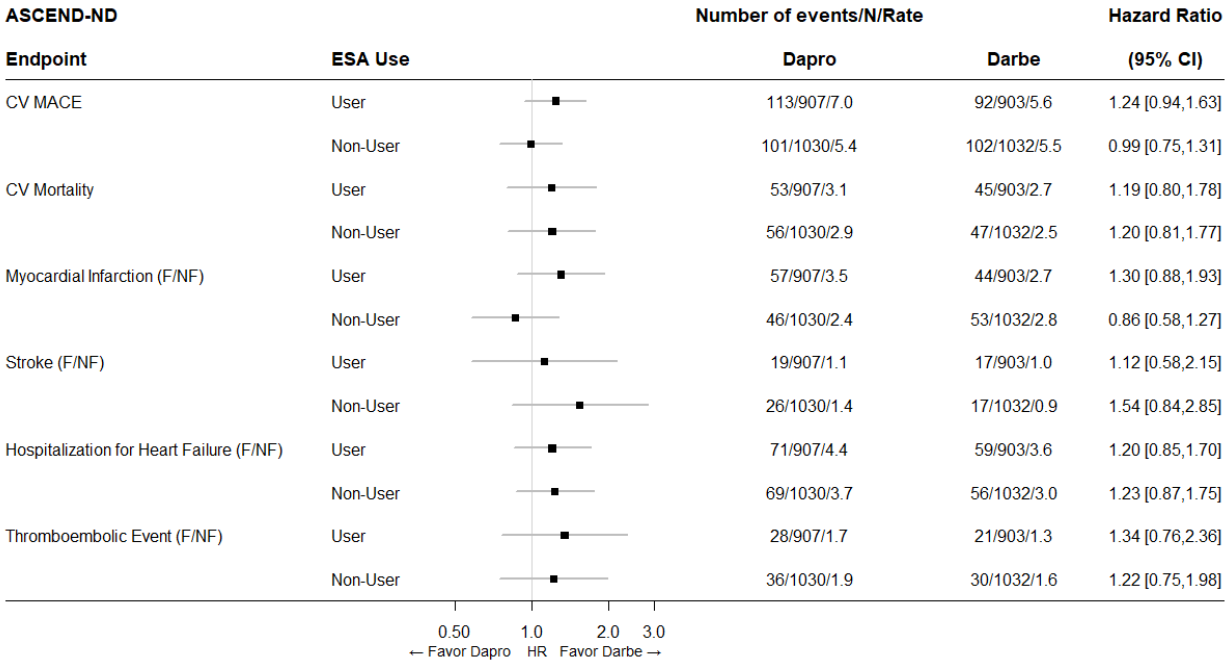
Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; ESA, erythropoietin-stimulating agents; ITT, intention-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction
MACE: Composite of all-cause mortality, nonfatal MI, and nonfatal stroke.

5.1.1.2.3 Subgroup Analyses by ESA Use – ASCEND-ND

To further explore CV endpoints among baseline ESA users vs. non-users in the ND population, exploratory subgroup analyses were conducted for each adjudicated CV endpoint. For all these CV endpoints, a higher incidence was observed with daprodustat compared to darbepoetin alfa among ESA users and non-users at randomization, except for CV MACE and MI among ESA non-users (Figure 13). The variability of HR estimates, i.e., CI widths, depended on the number of events and sample sizes, with lower precision for endpoints like stroke and TEE. In summary, analyses of ESA use subgroups did not indicate a consistently higher risk among ESA users

compared to non-users, but the elevated HR estimates in both subgroups across multiple CV endpoints corroborated the unfavorable results in the overall study population (Figure 4).

Figure 13. ESA Use at Randomization (User, Non-User) Subgroup Analyses for All Adjudicated CV Endpoints, ASCEND-ND



Source: FDA analysis.
Abbreviations: CI, confidence interval; CV, cardiovascular; Dapro, daprodustat; Darbe, darbepoetin alfa; ESA, erythropoietin-stimulating agent; F/NF, fatal or nonfatal; MACE, major cardiovascular adverse event
CV MACE: composite of CV mortality, nonfatal MI, and nonfatal stroke.
Rate: Incidence rate per 100 person-years.

5.1.1.2.4 CV Endpoints in the USA Subgroup

Table 21. Selected Baseline Demographics for the US and Non-US Populations of ASCEND-ND, ITT Population

	Non-USA	USA
	N=2891	N=981
Demographics		
Age (median [IQR])	66 [56, 74]	69 [60, 77]
Male (%)	1258 (43.5)	441 (45.0)
Race (%)		
American Indian or Alaskan Native	184 (6.4)	4 (0.4)
Asian	1034 (36)	28 (3)
Black or African American	47 (1.6)	321 (33)
White	1530 (53)	623 (64)
Bodyweight (kg) (median [IQR])	68 [58, 80]	81 [68, 97]

	Non-USA	USA
	N=2891	N=981
Medical History		
Baseline ESA user (%)	1515 (52)	295 (30)
Diabetes (%)	1542 (53)	676 (69)
History of stroke (%)	176 (6.1)	80 (8.2)
History of MI (%)	183 (6.3)	86 (8.8)
History of HF (%)	467 (16)	220 (22)
History of thrombosis (%)	92 (3.2)	58 (5.9)
History of CVD (%)	964 (33)	468 (48)
Hospitalization within 6 months	387 (13)	76 (7.7)
Concomitant Drugs		
Vitamin K anatgonist use (%)	85 (2.9)	41 (4.2)
Aspirin use (%)	705 (24)	454 (46)
Clopidogrel use (%)	232 (8.0)	114 (12)
CKD/Anemia Biomarkers		
eGFR (median [IQR])	17 [11, 25]	21 [15, 29]
Urine albumin/creatinine (median [IQR])	90 [18, 231]	51 [8.7, 175]
Systolic BP (mmHg) (median [IQR])	135 [125, 147]	135 [124, 147]
CRP (median [IQR])	1.9 [0.7, 5.1]	2.40 [1.0, 6.1]
Hemoglobin at baseline		
<9 g/dL	440 (15.2)	203 (21)
9-<10 g/dL	1029 (36)	430 (44)
10-11 g/dL	1088 (38)	305 (31)
>11 g/dL	334 (12)	43 (4.4)

Source: Clinical Reviewer; ADSL.xpt; R v. 3.4.
Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; HF, heart failure; IQR, interquartile range; ITT, intention-to-treat; MI, myocardial infarction; USA, United States of America

5.1.1.3 On-Study and On-Treatment Analyses

5.1.1.3.1 On-Study and On-Treatment Analyses of MACE—ASCEND-D

Table 22. MACE On-Study and On-Treatment Analyses, ASCEND-D

	Dapro N=1487[a] PY=3377[a]	ESA N=1477[a] PY=3323[a]	Hazard Ratio (95% CI)
	n [IR]		
On-study (primary)	374 [11.1]	394 [11.9]	0.93 (0.81, 1.07)
On-treatment + 28 days (supportive)	255 [9.9]	271 [10.4]	0.96 (0.81, 1.14)
On-treatment + dosing frequency + 28 days (exploratory)	255 [9.9]	278 [10.6]	0.94 (0.79, 1.11)
On-treatment + dosing frequency (exploratory)	177 [7.1]	207 [8.1]	0.88 (0.72, 1.07)

Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; ESA, erythropoietin stimulating agents; IR, incidence rate per 100 PY, MACE, major adverse cardiovascular event; N, number of subjects; n, number of subjects with event; PY, person-year
MACE: Composite of all-cause mortality, nonfatal MI, and nonfatal stroke
Dosing frequency: Dapro: daily; ESA: TIW, weekly, every 2 weeks, or every 4 weeks
[a] number of subjects (N) and person-years (PY) correspond to the on-study (primary) analysis only.

5.1.1.3.2 On-Study and On-Treatment Analyses of CV Endpoints—ASCEND-ND

Table 23. Endpoints On-Study and On-Treatment Analyses, ASCEND-ND

	Dapro N[a]=1937	Darbe N[a]=1935	HR (95% CI)
	n [IR]		
CV MACE			
On study	214 [6.1]	194 [5.6]	1.11 (0.91, 1.34)
OT+28	170 [6.2]	134 [4.8]	1.30 (1.04, 1.63)
CV mortality			
On study	109 [3.0]	92 [2.6]	1.20 (0.91, 1.58)
OT+28	66 [2.3]	51 [1.8]	1.34 (0.93, 1.93)
Fatal or nonfatal myocardial infarction			
On study	103 [2.9]	97 [2.8]	1.06 (0.80, 1.40)
OT+28	96 [3.5]	75 [2.7]	1.30 (0.96, 1.76)
Fatal or nonfatal stroke			
On study	45 [1.3]	34 [1.0]	1.33 (0.85, 2.07)
OT+28	35 [1.2]	22 [0.8]	1.64 (0.96, 2.80)
Hospitalization for heart failure			
On study	140 [4.0]	115 [3.3]	1.22 (0.95, 1.56)
OT+28	118 [4.3]	99 [3.5]	1.20 (0.92, 1.57)
Thromboembolic event			
On study	64 [1.8]	51 [1.4]	1.27 (0.88, 1.84)
OT+28	54 [1.9]	38 [1.3]	1.50 (0.99, 2.27)
Vascular access thrombosis			
On study	46 [1.3]	31 [0.9]	1.49 (0.94, 2.35)
OT+28	39 [1.4]	25 [0.9]	1.61 (0.97, 2.66)

Source: FDA analysis.
Abbreviations: CI, confidence interval; Dapro, daprodustat; Darbe, darbepoetin alfa; IR, incidence rate per 100 PY; N, number of subjects; n, number of subjects with event; PY, person-year
CV MACE: Composite of CV mortality, nonfatal MI, and nonfatal stroke
[a] Number of subjects (N) correspond to the on-study (primary) analysis only.

5.1.2 Additional Non CV Safety Issues

5.1.2.1 Serious Adverse Event Summary—ASCEND-ND, ASCEND-D

This section focuses on TESAEs which occur on study.

Our approach to presenting adverse event queries are as follows:

1. We show results for all AE and AE queries that have a nominal RR >1.3 and RD >0.5 (i.e., both must be co-occurring) for either study (i.e., if an AE or AE query was identified in ASCEND-D, but not ASCEND-ND, it is still included in ASCEND-ND – and vice versa).
2. We show results for all AE and AE queries that are related to the 50 prespecified AESIs for daprodustat.
3. We show results for AE and AE queries that are related to known risks for ESAs.

Table 24 shows the serious adverse events queries for ASCEND-ND for the on-study assessment and Table 25 shows the serious adverse events queries for ASCEND-D for the on-study assessment.

Hypertension, cardiomyopathy, and pulmonary hypertension were AESIs, and did not demonstrate concerning treatment differences for daprodustat compared to ESA, considering number of events. Serious adverse events for hypertension and worsening hypertension occurred at a similar incidence with daprodustat and the ESAs. There were no concerning findings based on mean-level plots of routine blood pressure assessments (collected at least every 12 weeks during the study).

In both studies, no clear safety signals seem apparent in arthritis and retinal disorders, although nominal imbalances are noted for retinal disorders. We did not identify a pattern in investigator reported TESAEs related to retinal disorders.

Neither study demonstrated an increased frequency for seizures or sepsis in the daprodustat arm compared to the comparator arms.

Table 24. Investigator-Reported Treatment-Emergent Serious Adverse Events—ASCEND-ND (On-Study Analysis)

	Daprodustat N=1937 n (%) [Events]	Darbepoetin N=1933 n (%) [Events]	Relative Risk	Risk Difference (%)
Renal				
Renal (SOC)	337 (17.4%) [387]	278 (14.4%) [327]	1.2 [1.1-1.4]	3.0 [0.7-5.3]
AKI (FDA)	94 (4.9%) [104]	64 (3.3%) [73]	1.5 [1.1-2]	1.5 [0.3-2.8]
Cardiac				
Cardiac disorders SOC	255 (13.2%) [386]	215 (11.1%) [309]	1.2 [1-1.4]	2.0 [-0.0-4.1]
Heart Failure (FDA)	123 (6.45%) [167]	97 (5.0%) [121]	1.3 [1.0-1.6]	1.3 [-0.1-2.8]
Pulmonary hypertension (SMQ)	23 (1.2%) [24]	18 (0.9%) [19]	1.3 [0.7-2.4]	0.3 [-0.4-0.9]
Peripheral edema (FDA)	44 (2.3%) [53]	41 (2.1%) [42]	1.1 [0.7-1.6]	0.2 [-0.8-1.1]
Dyspnea (FDA)	17 (0.9%) [18]	16 (0.8%) [16]	1.1 [0.5-2.1]	0.1 [-0.5-0.6]
Systemic hypertension (FDA)	37 (1.9%) [44]	36 (1.9%) [40]	1.0 [0.7-1.6]	0.1 [-0.8-0.9]
Cardiomyopathy (SMQ)	4 (0.2%) [4]	5 (0.3%) [5]	0.8 [0.2-3.0]	-0.1 [-0.4-0.3]
Embolic and thrombotic events				
Arterial (SMQ)	91 (4.7%) [104]	69 (3.6%) [76]	1.3 [1.0-1.8]	1.1 [-0.13-2.4]
Mixed/unspecified vessel (SMQ)	45 (2.3%) [48]	40 (2.1%) [46]	1.1 [0.7-1.7]	0.3 [-0.7-1.2]
Venous (SMQ)	17 (0.9%) [20]	19 (1.0%) [22]	0.9 [0.5-1.7]	-0.1 [-0.7-0.5]
Gastrointestinal perforation, ulceration, hemorrhage, or obstruction				
All (SMQ)	113 (5.8%) [141]	84 (4.4%) [98]	1.3 [1.0-1.8]	1.5 [0.1-2.9]
Perforation (SMQ)	42 (2.2%) [52]	28 (1.5%) [34]	1.5 [0.9-2.4]	0.7 [-0.1-1.6]
Hemorrhage (SMQ)	53 (2.7%) [61]	40 (2.1%) [42]	1.3 [0.9-2.0]	0.7 [-0.3-1.6]
Ulceration (SMQ)	19 (1.0%) [20]	15 (0.8%) [16]	1.3 [0.6-2.5]	0.2 [-0.4-0.8]
Obstruction (SMQ)	13 (0.7%) [16]	12 (0.6%) [14]	1.1 [0.5-2.4]	0.1 [-0.5-0.6]
Miscellaneous				
Hyperglycemia (FMQ)	35 (1.8%) [46]	33 (1.7%) [46]	1.1 [0.7-1.7]	0.1 [-0.7-0.9]
Skin and subcutaneous tissue disorders SOC	19 (1.0%) [23]	23 (1.2%) [30]	0.8 [0.5-1.5]	-0.2 [-0.9-0.4]
Arthritis (FDA)	22 (1.1%) [24]	15 (0.8%) [18]	1.5 [0.8-2.8]	0.4 [-0.3-1.0]
Retinal disorders (SMQ)	9 (0.5%) [9]	5 (0.3%) [6]	1.8 [0.6-5.4]	0.2 [-0.2-0.6]
Seizure (FDA-broad)	6 (0.3%) [6]	6 (0.3%) [7]	1 [0.3-3.1]	0 [-0.4-0.4]
Sepsis (SMQ)	78 (4.0%) [87]	81 (4.2%) [93]	1.0 [0.7-1.3]	-0.2 [-1.4-1.1]
Malignancy (FDA)	50 (2.6%) [58]	55 (2.9%) [62]	0.9 [0.6-1.3]	-0.3 [-1.3-0.8]

Source: Clinical Reviewer, R v. 4.2; ADAE.xpt and ADSL.xpt; ITT population (on-study); SMQ v. 24.1. FMQ v. 2.0. Script on-file (cSAE.R).
Abbreviations: ESA, erythropoiesis-stimulating agent; FMQ, FDA Medical Query; HLGT, high-level group term; ITT, intention-to-treat; SMQ, Standardized Medical Dictionary for Regulatory Activities query; SOC, system organ class

Table 25. Investigator-Reported Treatment-Emergent Serious Adverse Events—ASCEND-D, (On-Study Analysis)

	Daprodustat N=1487 n (%) [Events]	ESA N=1477 n (%) [Events]	Relative Risk	Risk Difference (%)
Cardiac				
Cardiac disorders SOC	254 (17.1%) [355]	281 (19.1%) [431]	0.9 [0.8-1.1]	-1.9 [-4.7-0.9]
Heart Failure (FDA)	87 (5.9%) [113]	91 (6.2%) [120]	1.0 [0.7-1.3]	-0.3 [-2.0-1.4]
Pulmonary hypertension (SMQ)	26 (1.8%) [29]	32 (2.2%) [37]	0.8 [0.5-1.4]	-0.4 [-1.4-0.6]
Peripheral edema (FDA)	66 (4.5%) [91]	65 (4.4%) [81]	1.0 [0.7-1.4]	0.0 [-1.4-1.5]
Dyspnea (FDA)	23 (1.6%) [26]	19 (1.3%) [20]	1.2 [0.7-2.2]	0.3 [-0.6-1.1]
Systemic hypertension (FDA)	38 (2.6%) [52]	36 (2.4%) [43]	1.1 [0.7-1.7]	0.1 [-0.1-1.3]
Cardiomyopathy (SMQ)	9 (0.6%) [9]	8 (0.5%) [8]	1.1 [0.4-2.9]	0.1 [-0.5-0.6]
Embolic and thrombotic events				
Arterial (SMQ)	89 (6.0%) [99]	100 (6.8%) [120]	0.9 [0.7-1.2]	-0.8 [-2.5-1.0]
Mixed/unspecified vessel (SMQ)	91 (6.1%) [122]	132 (9.0%) [178]	0.7 [0.5-0.9]	-2.8 [-4.7 - -0.9]
Venous (SMQ)	20 (1.4%) [20]	28 (1.9%) [32]	0.7 [0.4-1.3]	-0.6 [-1.5-0.4]
Gastrointestinal perforation, ulceration, hemorrhage, or obstruction				
All (SMQ)	137 (9.2%) [170]	127 (8.6%) [167]	1.1 [0.9-1.4]	0.6 [-1.4-2.7]
Perforation (SMQ)	55 (3.7%) [69]	57 (3.9%) [77]	1.0 [0.7-1.4]	-0.2 [-1.5-1.2]
Hemorrhage (SMQ)	50 (3.4%) [58]	46 (3.1%) [53]	1.1 [0.7-1.6]	0.3 [-1.0-1.5]
Ulceration (SMQ)	26 (1.8%) [28]	28 (1.9%) [31]	0.9 [0.5-1.6]	-0.2 [-1.1-0.8]
Obstruction (SMQ)	20 (1.4%) [23]	9 (0.6%) [10]	2.2 [1.0-4.8]	0.7 [0.1-1.5]
Miscellaneous				
Hyperglycemia (FMQ)	41 (2.8%) [57]	26 (1.8%) [29]	1.6 [1.0-2.6]	1 [-0.1-2.0]
Skin and subcutaneous tissue disorders SOC	29 (2.0%) [34]	14 (1.0%) [15]	2.1 [1.1-3.9]	1.0 [0.2-1.9]
Arthritis (FDA)	17 (1.2%) [18]	20 (1.4%) [21]	0.9 [0.4-1.6]	-0.2 [-1.0-0.6]
Retinal disorders (SMQ)	12 (0.8%) [14]	3 (0.2%) [3]	4.0 [1.1-14.1]	0.6 [0.1-1.1]
Seizure (FDA-broad)	10 (0.7%) [14]	15 (1.0%) [17]	0.7 [0.3-1.5]	-0.3 [-1-0.3]
Sepsis (SMQ)	101 (6.8%) [130]	117 (7.9%) [140]	0.9 [0.7-1.1]	-1.1 [-3.0-0.8]
Malignancy (FDA)	49 (3.3%) [56]	46 (3.1%) [53]	1.1 [0.7-1.6]	0.2 [-1.1-1.5]

Source: Clinical Reviewer, R v. 4.2; ADAE.xpt and ADSL.xpt; ITT population (on-study); SMQ v. 24.1. FMQ v. 2.0. Script on-file (cSAE.R).
Abbreviations: ESA, erythropoietin-stimulating agent; FMQ, FDA Medical Query; ITT, intention-to-treat; SMQ, Standardized Medical Dictionary for Regulatory Activities query; SOC, system organ class

5.1.2.2 Malignancy

Tumor progression, recurrence, and cancer-related mortality are theoretical risks based on the hypoxia-inducible factor biology. Hypoxia inducible factors are central transcription factors in hypoxia response and impact the expression of a number of survival genes in cancer cells and the tumor microenvironment. Daprodustat increases erythropoietin as part of its mechanism of action and drug labels for marketed erythropoiesis stimulating agents include an increased risk of tumor progression as a boxed warning. Whether daprodustat shares this risk of ESA products is uncertain.

Lifetime studies in rodents did not identify a carcinogenic effect of daprodustat. However, based on the findings with ESAs and the theoretical risk related to the mechanism of action of daprodustat, the applicant prespecified malignancy as an AESI. The prespecified analysis approach for non-CV events was OT, defined by the last dose given plus 1 day. As noted in Section 3.2.3.1, the ITT/on study analysis is more sensitive than the OT for long-latency events (such as malignancy), and less confounded by differences in dosing frequency (such as the darbepoetin alfa comparator in ASCEND-ND).

The ASCEND-D and ASCEND-ND protocols required treatment discontinuation following a diagnosis of cancer (new or recurrent), with the exception of squamous cell or basal cell carcinoma of the skin. Therefore, in the on-treatment assessment a malignancy diagnosis that was made two or more days after the last dose was not counted as an event, because per-protocol, subjects would not be dosed again. This scenario would exclude events occurring with a drug dosed less frequently, but that are still very proximal to randomized treatment.

For these reasons, we considered the OT analysis as prespecified in the protocol, but focused mainly on the on-study estimates for assessment of malignancy risk. We used a pooled analysis of ASCEND-ND and ASCEND-D and included treatment-emergent events regardless of reported seriousness. A summary of these results is presented in Table 26.

The on-study analysis did not suggest a treatment group difference in the incidence of malignancy (152 of 3419 [4.4% daprodustat and 161 of 3407 [4.7%] ESA control with RR of 0.9 (95% CI 0.8, 1.2). There did not appear to notable imbalances in any pattern type or location of cancer between treatment groups. Fatal outcomes due to malignancy in both arms were infrequent.

In summary, the risk for tumor progression does not appear to be further increased compared to currently labeled ESAs, however, the short latency period of the studies conducted to date and the low event rates for specific cancers do not allow for definite conclusions on the long-term risk of daprodustat on tumor progression or development of new malignancies.

Table 26. Pooled ASCEND-D and ASCEND-ND Adverse Events Related to Malignancy (SMQ and Prespecified Terms) – (On-Study Analysis)

	On-Study				On-Treatment			
AE	Daprodustat N=3424 n (%) [Events]	ESA N=3412 n (%) [Events]	Relative Risk % [95% CI]	Risk Difference [95% CI]	Daprodustat N=3424 n (%) [Events]	ESA N=3412 n (%) [Events]	Relative Risk	Risk Difference
Applicant AESI – malignancy	152 (4.4%) [187]	161 (4.7%) [211]	0.9 [0.8 - 1.2]	-0.3 [-1.3 - 0.7]	119 (3.5%) [133]	100 (2.9%) [125]	1.2	0.5
Reported as life-threatening	23 (0.7%) [27]	19 (0.6%) [21]	1.2 [0.7 - 2.2]	0.1 [-0.3 - 0.5]	14 (0.4%) [15]	7 (0.2%) [8]	2	0.2
Reported as contributing to death	17 (0.5%) [17]	26 (0.8%) [26]	0.7 [0.4 - 1.2]	-0.3 [-0.6 - 0.1]	9 (0.3%) [9]	12 (0.4%) [12]	0.7	-0.1
Malignancies[#]	136 (4%) [169]	149 (4.4%) [193]	0.9 [0.7 - 1.1]	-0.4 [-1.3 - 0.6]	105 (3.1%) [119]	95 (2.8%) [118]	1.1	0.3
Non-hematological malignant tumours[#]	115 (3.4%) [142]	116 (3.4%) [154]	1 [0.8 - 1.3]	0 [-0.9 - 0.8]	88 (2.6%) [100]	69 (2%) [89]	1.3	0.5
Hematological malignant tumours[#]	5 (0.1%) [5]	18 (0.5%) [18]	0.3 [0.1 - 0.7]	-0.4 [-0.7 - -0.1]	4 (0.1%) [4]	12 (0.4%) [12]	0.3	-0.2
Premalignant disorders[#]	75 (2.2%) [86]	73 (2.1%) [79]	1 [0.7 - 1.4]	0.1 [-0.6 - 0.7]	54 (1.6%) [63]	62 (1.8%) [68]	0.9	-0.2
Blood premalignant disorders[#]	8 (0.2%) [8]	8 (0.2%) [8]	1 [0.4 - 2.7]	0 [-0.2 - 0.2]	5 (0.1%) [5]	5 (0.1%) [5]	1	0
Gastrointestinal premalignant disorders[#]	46 (1.3%) [55]	55 (1.6%) [61]	0.8 [0.6 - 1.2]	-0.3 [-0.8 - 0.3]	34 (1%) [42]	48 (1.4%) [54]	0.7	-0.4
Skin premalignant disorders[#]	16 (0.5%) [16]	7 (0.2%) [7]	2.3 [0.9 - 5.5]	0.3 [0 - 0.5]	10 (0.3%) [10]	6 (0.2%) [6]	1.7	0.1
Hypoplastic anemias HLT	11 (0.3%) [12]	16 (0.5%) [16]	0.7 [0.3 - 1.5]	-0.1 [-0.4 - 0.1]	9 (0.3%) [9]	6 (0.2%) [6]	1.5	0.1
Skin neoplasms, malignant and unspecified[##]	40 (1.2%) [51]	36 (1.1%) [54]	1.1 [0.7 - 1.7]	0.1 [-0.4 - 0.6]	34 (1%) [42]	29 (0.8%) [44]	1.2	0.1
Skin malignant tumours[#]	32 (0.9%) [39]	30 (0.9%) [43]	1.1 [0.6 - 1.7]	0.1 [-0.4 - 0.5]	29 (0.8%) [33]	25 (0.7%) [36]	1.2	0.1
Breast malignant tumours[#]	11 (0.3%) [11]	9 (0.3%) [10]	1.2 [0.5 - 2.9]	0.1 [-0.2 - 0.3]	7 (0.2%) [7]	5 (0.1%) [5]	1.4	0.1
Colorectal neoplasms malignant HLT	9 (0.3%) [9]	8 (0.2%) [8]	1.1 [0.4 - 2.9]	0 [-0.2 - 0.3]	6 (0.2%) [6]	5 (0.1%) [5]	1.2	0
Renal neoplasms malignant HLT	13 (0.4%) [13]	10 (0.3%) [11]	1.3 [0.6 - 3]	0.1 [-0.2 - 0.4]	10 (0.3%) [10]	4 (0.1%) [4]	2.5	0.2
Prostate neoplasms, malignant and unspecified[#]	6 (0.2%) [7]	9 (0.3%) [9]	0.7 [0.2 - 1.9]	-0.1 [-0.3 - 0.1]	5 (0.1%) [6]	4 (0.1%) [4]	1.2	0

Source: Clinical Reviewer, ADAE.xpt, ADSL.xpt, R v. 4.2, ITT population. Includes SMQ queries or MedDRA HLTs with 15 or more occurrences.
[#] MedDRA SMQ narrow query.
[##] MedDRA SMQ broad query.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; ESA, erythropoiesis-stimulating agent; HLT, high-level term; ITT, intention-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects; n, number of subjects reporting at least one event; %, percentage of subjects reporting at least one event; SMQ, standardized medical query

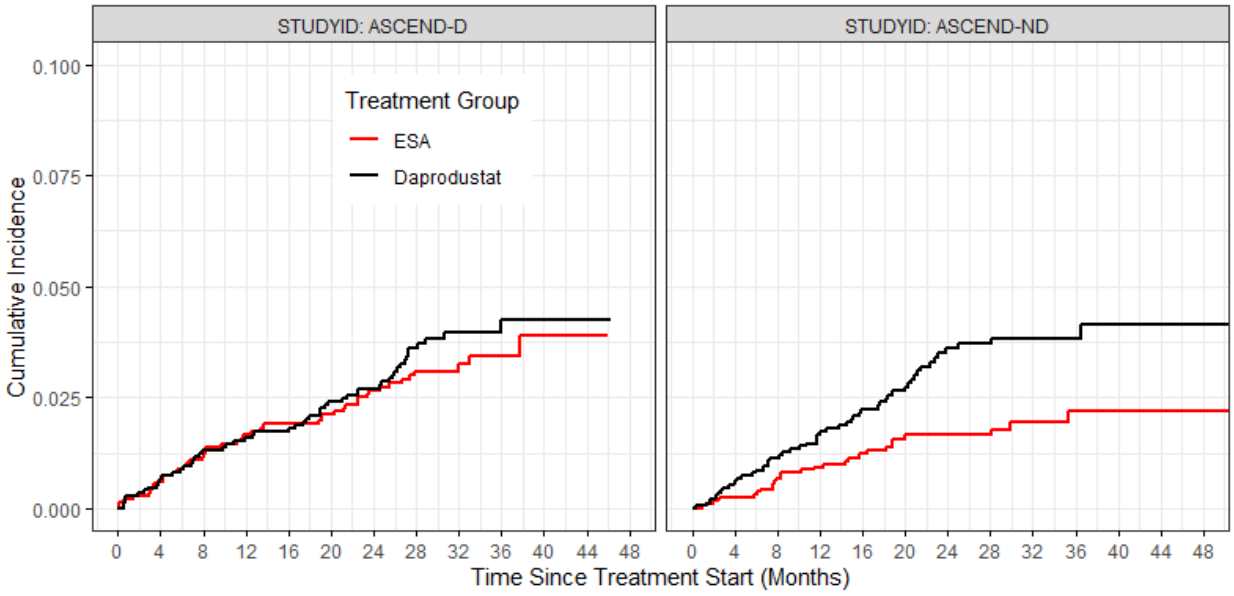
5.1.2.3 Additional information Pertaining to the AESI—Gastric Erosions

The list of high level terms and preferred terms for the Gastric Erosions query (Prespecified AESI) is described below.

- High-Level Terms: 'Duodenal ulcers and perforation', 'Gastric ulcers and perforation', 'Gastrointestinal ulcers and perforation, site unspecified', 'Oesophageal ulcers and perforation', 'Peptic ulcers and perforation'
- Preferred Terms: 'Haematemesis', 'Gastrointestinal haemorrhage', 'Upper gastrointestinal haemorrhage', *'Helicobacter* duodenitis', *'Helicobacter* gastritis', 'Melaena'

A Kaplan-Meier curve for time to first TESAE of gastrointestinal bleed using the Applicant's prespecified AESI query is presented for the ASCEND-D and ASCEND-ND trials in Figure 14. Table 27 presents a summary of all serious gastric erosion events identified by the prespecified query for the ASCEND-D and ASCEND-ND populations (i.e., events occurring more than once in a single subject were included).

Figure 14. Time to First TESAE for Gastrointestinal Bleed, ASCEND-ND and ASCEND-D, ITT



Source: Clinical Reviewer, ADAE.xpt, ADSL.xpt, R Version 4.2, ITT population.
Abbreviations: Dapro, Daprodustat; ESA, erythropoiesis-stimulating agent; ITT, intention-to-treat; TESAE, treatment-emergent serious adverse event
This analysis treats deaths and administrative censoring the same.

Table 27. Summary of Clinical Outcomes for Serious Gastric Erosions (Prespecified MedDRA Terms*)—Pooled ASCEND-D and ASCEND-ND (On-Study Analysis)

	Daprodustat N=118	ESA N=82
Outcome n (%)		
Fatal	8 (6.8)	3 (3.7)
Not recovered/not resolved	14 (11.9)	10 (12.2)
Recovered/resolved	92 (78.0)	66 (80.5)
Recovered/resolved with sequelae	4 (3.4)	2 (2.4)
Recovering/resolving	0 (0.0)	1 (1.2)
Severity n (%)		
Mild	6 (5.1)	3 (3.7)
Moderate	42 (35.6)	40 (48.8)
Severe	70 (59.3)	39 (47.6)
Duration (days) (median [IQR])	8.00 [5.00, 12.50]	8.00 [6.00, 16.50]
Action taken n (%)		
Dose increased	2 (1.7)	1 (1.2)
Dose not changed	67 (56.8)	56 (68.3)
Drug interrupted	9 (7.6)	2 (2.4)
Drug withdrawn	7 (5.9)	1 (1.2)
Not applicable	33 (28)	22 (26.8)
Life threatening n (%)	16 (13.6)	10 (12.2)
MedDRA PTs selected by query (only events occurring >4 times shown overall) n (%)		
Duodenal ulcer	6 (5.1)	4 (4.9)
Duodenal ulcer hemorrhage	7 (5.9)	2 (2.4)
Gastric ulcer	6 (5.1)	9 (11)
Gastric ulcer hemorrhage	7 (5.9)	6 (7.3)
Gastritis erosive	11 (9.3)	5 (6.1)
Gastrointestinal hemorrhage	41 (34.7)	24 (29.3)
Upper gastrointestinal hemorrhage	23 (19.5)	15 (18.3)

Source: Clinical Reviewer, ADAE.xpt, ADSL.xpt, R v. 4.2, ITT population.
Abbreviations: Erythropoiesis-stimulating agent; IQR, interquartile range; ITT, intention-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; N, number of events; n, number of events with characteristic; %, percentage of events with characteristic; PT, preferred term
Includes all reported events.
* List of preferred terms provided in Appendix 5.1.2.3)

5.1.2.4 Additional Information Pertaining to Acute Kidney Injury

Acute Kidney Injury (Narrow–FDA)

Preferred Terms**: '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', and 'Urine output decreased.'**

Most patients with TESAE AKI events recovered, with most events lasting 14 to 16 days. A majority of events occurred while receiving study drug (16 to 19% occurred off treatment). See Table 28.

Table 28. Severity and Outcome of TESAEs of AKI (FMQ-FDA Query) in ASCEND-ND, (On-Study Analysis)

	Daprodustat N=104	Darbepoetin N=73
Outcome		
Fatal	4 (3.8)	3 (4.1)
Not recovered	9 (8.7)	6 (8.2)
Recovered	78 (75.0)	59 (80.8)
Recovered with sequelae	13 (12.5)	5 (6.8)
Severity		
Mild	5 (4.8)	5 (6.8)
Moderate	34 (32.7)	35 (47.9)
Severe	65 (62.5)	33 (45.2)
AE duration, days (mean, SD)	14.4 (20.5)	16.1 (29.8)
AE action		
Dose not changed	70 (67.3)	57 (78.1)
Drug interrupted	11 (10.6)	1 (1.4)
Drug withdrawn	3 (2.9)	3 (4.1)
Off treatment	20 (19.2)	12 (16.4)

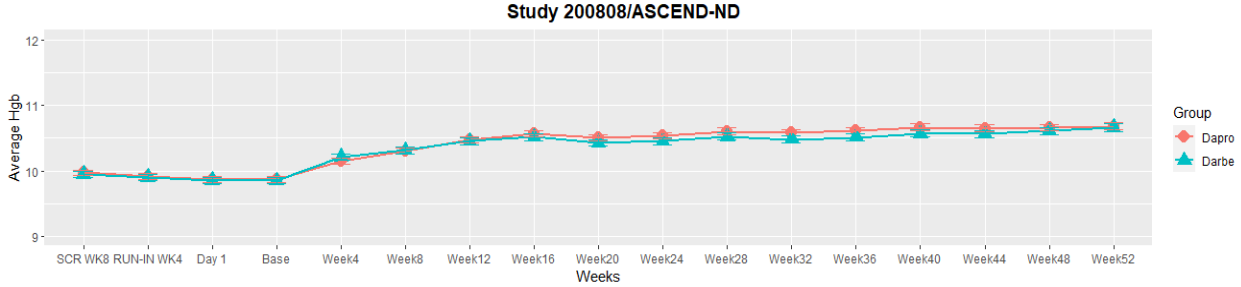
Source: Clinical Reviewer, ADAE.xpt, ADSL.xpt, R v. 4.2, On study (ITT population), TESAEs of AKI (narrow) per FMQ v. 2.0
Abbreviations: AE, adverse event; AKI, acute kidney injury; FMQ, FDA Medical Dictionary for Regulatory Activities query; ITT, intention-to-treat; SD, standard deviation; TESAE, treatment-emergent serious adverse event
Includes all reported events.
* Associated (i.e., co-occurring within -14 to +7 days) with another potentially causal SAE.

5.2 Additional Efficacy Analyses

5.2.1 Hemoglobin Level Versus Time Profiles

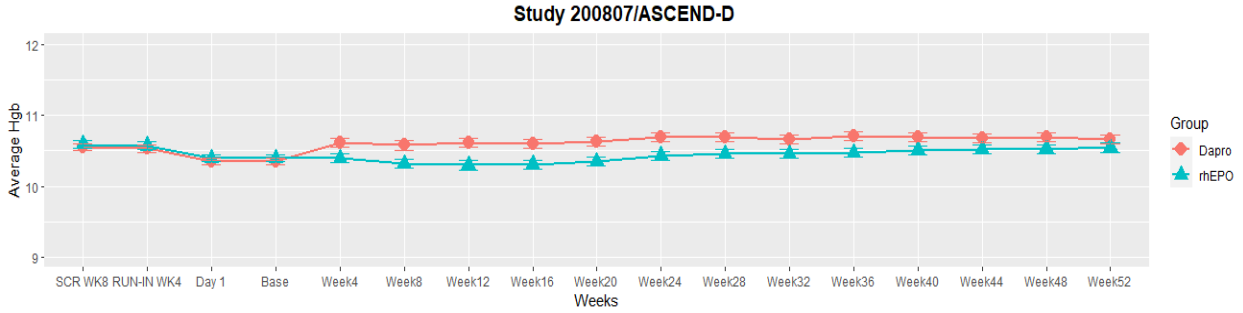
The observed Hb vs. time plots confirm that the titration algorithms resulted in similar Hb vs. time trajectories (Figure 15 and Figure 16).

Figure 15. Hemoglobin (Hbg) Versus Time Profiles for ASCEND-ND



Source: Statistical Reviewer, R v. 4.2.
Abbreviation: CI, confidence interval
Observed data only. Error bars represent 95% CI around the average Hbg.

Figure 16. Hemoglobin (Hbg) Versus Time Profiles for ASCEND-D



Source: Statistical Reviewer, R v. 4.2
Abbreviation: CI, confidence interval
Observed data only. Error bars represent 95% CI around the average Hbg.

5.2.2 Patient-Reported Outcomes in ASCEND-NHQ

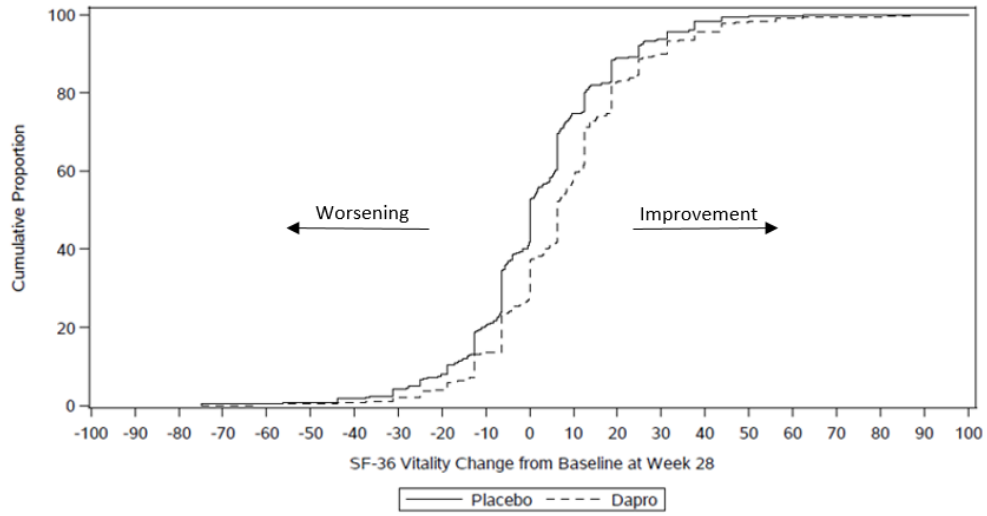
Patient-reported outcomes (PROs) were collected in the principal studies (ASCEND-ND and ASCEND-NHQ) to evaluate clinical benefit. The FDA review team focused on the PRO results from ASCEND-NHQ (a randomized, double-blinded, placebo-controlled, 28-week trial) as the open-label trial design of ASCEND-ND was a limitation in interpreting the PRO data.

The key secondary PRO-based efficacy endpoint in ASCEND-NHQ was the mean change in the Vitality domain score from the 36-item Short Form Health Survey version 2.0 (SF-36 v. 2.0) between baseline and end of treatment at week 28. This Vitality domain measures several important aspects of fatigue.

The data from ASCEND-NHQ demonstrated that daprodustat had a statistically significant improvement in the key secondary PRO-based endpoint compared with placebo. Despite achievement of statistical significance, there were minimal observed changes in the SF-36 v. 2.0 Vitality domain score, if any, when looking at the item- and domain-level data using the non-normalized and non-transformed raw score scale (e.g., change in the 4 to 20 raw domain scores reflects less than one response category change on each item). The change observed on the 0 to 100 transformed domain scores was also minimal as evidenced by the minimal separation observed between the treatment arms in the empirical cumulative distribution function curves (Figure 17), where a positive change (>0) to the right represents an improvement in the SF-36 v. 2.0 Vitality domain score.

In summary, we have determined that ASCEND-NHQ did not substantiate a clinically meaningful improvement of daprodustat against placebo on the Vitality domain score of the SF-36. Additionally, as a placebo-controlled study, these results are challenging to interpret under the context of already available therapies.

Figure 17. Cumulative Distribution Function Plot of On-Treatment Observed and Imputed SF-36 v. 2.0 Vitality Domain Change from Baseline at Week 28, 0 to 100 Transformed Scoring



Source: Figure 2.31 in the Applicant's Study 205270 Clinical Study Report (p. 909), with arrows added by the Patient-Focused Statistical Support reviewer to indicate the direction of improvement and worsening in the SF-36 v. 2.0 Vitality domain score.

5.3 Additional Study Design Details

5.3.1 Anemia and Iron Rescue Algorithms

Table 29. Rescue Algorithm for Anemia Management

Evaluate Participant for Rescue if: HemoCue Hb remains <9 g/dL (at a scheduled study visit, Week 4 onwards) despite three[a] consecutive dose increases above the starting[b] or post-rescue[c] dose (where HemoCue Hgb is <9 g/dL prior to each dose increase) OR HemoCue Hb is <7.5 g/dL despite a dose increase at the prior study visit.	
Step 1: Initial Intervention	While continuing randomized treatment (increase dose if HemoCue Hgb <7.5 g/dL; otherwise maintain current dose), intervene with one or more of the following as dictated by clinical comorbidities • Single course of IV iron up to 1000 mg (in addition to the iron management criteria) • Transfusion of up to two units of PRBC if clinically indicated • Allow additional 4 weeks on randomized treatment (NOTE: this is a required choice; can be combined with either or both of the above).
Step 2: Rescue	Check HemoCue Hgb 4 weeks ±1 week from last study visit; earlier checks of Hgb may be obtained to advise further intervention as clinically indicated. **Randomized treatment should be permanently discontinued, and the participant should be rescued according to local clinical practice if either,** • If HemoCue Hgb remains <9 g/dL despite initial intervention based on the average of two HemoCue Hgb values[d] OR • More than two units of PRBC were needed for transfusion (and was not related to acute bleeding).

Source: Adapted from Table 10 of the ASCEND-ND CSR and Table 10 of the ASCEND-D CSR.
Abbreviations: CSR, clinical study report; Hb, hemoglobin; PRBC, packed red blood cells
[a] Two consecutive dose increases if starting/post-rescue dose is daprodustat 12 mg or darbepoetin alfa 200 µg over 4 weeks or epoetin alfa 42,000 U per week; one dose increase if starting/post-rescue dose is daprodustat 16 mg or darbepoetin alfa 300 µg over 4 weeks or epoetin alfa 48,000 U per week; and no prior dose increase if starting/post-rescue dose is daprodustat 24 mg or darbepoetin alfa 400 µg over 4 weeks or epoetin alfa 60,000 U per week (top dose)
[b] For participants who switched from HD to peritoneal dialysis who were randomized to rhEPO, the baseline dose for the purposes of the rescue algorithm was the new darbepoetin alfa dose.
[c] For participants who previously were evaluated for rescue and who are able to continue in the trial, "post-rescue" dose is the dose of randomized treatment that a participant is receiving at the study visit after initial intervention.
[d] Repeat HemoCue Hgb at the same study visit to confirm Hgb (using the same sample); take the average of two values.

5.3.2 Key Regulatory Interactions

Table 30. Key Regulatory Interactions

Date	Meeting Topic
May 22, 2008	Pre-IND meeting to discuss proposed first clinical study and early development plan for treatment of anemia of chronic renal disease
July 15, 2014	Type C meeting to obtain advice for the global Phase 3 program to support registration of daprodustat for the treatment anemia associated with chronic kidney disease (CKD) in both dialysis and non-dialysis patients. The NI margin of -0.75 g/dL for the primary Hb assessment in all the global Phase 3 studies was discussed and agreed upon with FDA
July 27, 2020	Type C meeting to discuss a change in the noninferiority margin from 1.2 to 1.25 for the coprimary safety endpoint of MACE in ASCEND-D and ASCEND-ND.
September 7, 2021	Type B Pre-NDA Meeting: Discussion of prespecified treatment-emergent and on-treatment analysis

Source: Clincal Reviewer