22 June 2023
EMA/319166/2023
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Jesduvroq

International non-proprietary name: Daprodustat

Procedure No. EMEA/H/C/005746/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

APD	Automated peritoneal dialysis
AS	active substance
AUC	Area under the concentration-time curve
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-x)	Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-t)	Area under the concentration-time curve over the dosing interval
BCRP	Breast cancer resistance protein
BID	Twice daily
BL	Baseline
BP	Blood pressure
Bq	Becquerel
CAPD	Continuous ambulatory peritoneal dialysis
CFB	Change from baseline
CI	Confidence Interval
CKD	Chronic kidney disease
CL	Clearance
CLd	Dialysis clearance
CL/F	Apparent clearance
Cmax	Maximum observed concentration
CPP	critical process parameter
CQA	critical quality attributes
CV	Coefficient of variation
CVb	Between-subject coefficient of variation
CVw	Within-subject coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DRM	Drug-related material
DS	design space
DSC	differential scanning calorimetry
eGFR	Estimated glomerular filtration rate
EP	Evaluation period
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
F	Bioavailability
FOCE	First-order condition estimation method
FP	finished product
GC	gas chromatography
GFR	Glomerular filtration rate
GLS	Geometric least squares
GSK	GlaxoSmithKline
Hct	Hematocrit
HD	Hemodialysis
HDPE	high density polyethylene

Hgb	Hemoglobin
HIF	Hypoxia-inducible factor
HPLC	high performance liquid chromatography
HR	Heart rate
IC50	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IR	infrared spectrometry
IU	International units
IIV	Inter-individual variability
INN	International non-proprietary name
IV	Intravenous
KF	Karl Fischer titration
L	Liter
LDPE	low-density polyethylene
LSM	Least squares mean
MAP	Mean arterial blood pressure
MATE	Multidrug and toxin extrusion transporter
MDRD	Modification of Diet in Renal Disease
msec	Milliseconds
MO	major objection
ND	Non-dialysis, or pre-dialysis
ng	Nanogram
NMR	nuclear magnetic resonance
OAT	Organic anion transporter
OATP	Organic-anion-transporting polypeptide
OCT	Organic cation transporter
PACMP	post-approval change management protocol
PASP	Pulmonary artery systolic pressure
PHD	Prolyl-4-hydroxylase
Ph. Eur.	European Pharmacopoeia
PHI	Prolyl hydroxylase inhibitors
PD	Pharmacodynamic
P-gp	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetics
POPPK	Population pharmacokinetics
PP	process parameter
QbD	quality by design
QT	QT interval
QTc	Corrected QT interval
QTcF	QT duration corrected for heart rate by Fridericia's formula
QTPP	Quality Target Product Profile
RBC	Red blood cell
RH	relative humidity
rhEPO	Recombinant human erythropoietin
RSE	Relative standard error
SD	Standard deviation
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
τ	Dosing interval

TIBC	Total iron-binding capacity
TIR	Time in range
TIW	Three-times weekly
tmax	Time to reach Cmax
UIBC	Unsaturated iron-binding capacity
USAN	United States adopted name
UV	ultraviolet spectrometry
V	Volume of distribution
V/F	Apparent central volume of distribution
VEGF	Vascular endothelial growth factor
Vss	Volume of distribution at steady state
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxosmithkline Trading Services Limited submitted on 3 February 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Jesduvroq, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 September 2020.

The applicant applied for the following indication Jesduvroq is indicated for the treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 22 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0047/2021 on the acceptance of a modification of an agreed paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001452-PIP01-13-M03 was not yet completed.

A partial compliance check of the PIP EMEA-001452-PIP01-13-M03 was concluded positively by the PDCO on 15 October 2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance daprodustat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received Scientific advice on the development relevant for the indication subject to the present application.

The Scientific advice pertained to the following nonclinical, and clinical aspects:

- Sufficiency of the proposed nonclinical and clinical pharmacology studies to support a marketing authorisation application (MAA).
- The proposed modelling approach to inform the selection of starting doses and titration steps in the Phase 2B trials and subsequently for the Phase 3 registration studies. Haemoglobin targets proposed for treatment goals. Adequacy of the extent of patient exposure and safety monitoring proposed for the Phase 2 program to progress into Phase 3 trials.
- Design of the Phase 3 development program, including patient populations, haemoglobin targets proposed for treatment goals, dosing strategy, rescue therapy, assessment of efficacy vs rhEPO, including primary and secondary endpoints, statistical assessments, the estimand definition and handling of missing values, approach to assess safety, including cardiovascular outcomes and risk of hypertension vs rhEPO, and a proposed data integration strategy for safety reporting. Efficacy in treating anemia in patients with hyporesponsiveness to rhEPO. A proposed revision of the interim analysis strategy and a change in the MACE non-inferiority margin in the ongoing Phase 3 cardiovascular outcomes studies 200807 (ASCEND-D) and 200808 (ASCEND-ND) were discussed in separate advice.

The following relevant items were discussed with EMA (and FDA) and seemed to have been followed:

- In June/July 2020, the FDA agreed to alter the NI margin for the two ongoing studies, from 1.20 to 1.25, for MACE.
- The CHMP advised of the importance of demonstrating the adequacy of the Blinding Plan, given the open-label nature of the studies and that the issues identified within Points to Consider on implications of COVID-19 on methodological aspects of ongoing clinical trials (EMA/1588330/2020) should be addressed. At the same time, GSK modified the multiplicity adjustment strategy from Hommel to Holm-Bonferroni to address previous FDA feedback regarding assumption-free techniques to maintain family-wise error rates.
- The NI margin of -0.75 g/dL for the primary Hgb assessment in all the global Phase III studies was supported by EMA.
- The analysis of the haemoglobin co-primary endpoint was altered based on FDA feedback to use data from all randomized participants, imputing data for participants with missing Hgb values.
- The FDA and CHMP agreed that GSK's proposal to borrow MACE data from the control group in Study 200807/ASCEND-D with daprodustat QD administration using a Bayesian framework in Study 204837/ASCEND-TD to provide complementary information regarding the cardiovascular safety profile of the TIW daprodustat regimen was reasonable (FDA: September 2017, CHMP: June 2021).
- In September 2021, the FDA requested additional analyses be included in the planned NDA to explore definitions of on-treatment events and the relationship between safety endpoints and dose/Hgb levels. In October 2021, it was agreed with the Rapporteur to also include these analyses in the European Marketing Authorization Application.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Kristina Dunder

PRAC Rapporteur: Jan Neuhauser

The application was received by the EMA on	3 February 2022
The procedure started on	24 February 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 May 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	31 May 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 June 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 September 2022
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at the sponsor site in the United Kingdom and three clinical sites in Spain and Argentina between 19 April and 10 June 2022. The outcome of the inspection carried out was issued on:	02 August 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 November 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 February 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 March 2023
The CHMP agreed on a 2nd list of outstanding issues in writing to be	30 March 2023

sent to the applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 May 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	23 May 2023
The CHMP agreed on a 3rd list of outstanding issues in writing to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 June 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jesduvroq on	22 June 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	22 June 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant has applied for the following indication: "Jesduvroq is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis."

2.1.2. Epidemiology and risk factors

Chronic kidney disease (CKD) is a worldwide public health challenge that afflicts a substantial proportion of the population. For example, the overall prevalence of CKD (Stages 1-5) in the United States (US) adult general population was 14.8% in 2013-2016 [United States Renal Data System, 2018]. Worldwide prevalence for all CKD stages is estimated to be between 9% and 13% [Hill, 2016; Bikbov, 2020]. In Europe, the average prevalence of CKD regardless of age lies between 5% and 11% [Zoccali et al., 2010].

Renal anemia is a common and serious complication which often develops during the progression of CKD and is present in almost all patients with end-stage renal disease (ESRD) (Kovesdy 2006; Locatelli 2004; Astor 2002). Anemia is twice as prevalent in people with CKD (15.4%) as compared to the general population (7.6%) (Stauffer 2014). The increasing prevalence of anaemia in CKD is reported in the more advanced stages of the disease, rising from 8.4% in Stage 1 patients to 53.4% in Stage 5 patients in US populations [Stauffer, 2014]. Anaemia in CKD is present in >90% of dialysis (D) patients [Nakhoul, 2016].

2.1.3. Aetiology and pathogenesis

Chronic kidney disease (CKD) is defined by the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause. Anaemia associated with CKD is multifactorial, including insufficient EPO synthesis and EPO resistance (Babitt, 2012), reduced absorption of dietary iron and suboptimal mobilisation of iron stores due to insufficient biologically available iron due to a reduced ability to absorb iron through the gut and to mobilise it from internal stores (e.g., liver, macrophages), chronic inflammation or acute infection, surgical intervention for malfunctioning of the artery-venous fistula, and gastrointestinal blood loss. Anaemia is further exacerbated by shortened erythrocyte survival that is associated with the uremic milieu and haemodialysis (HD) procedure.

It is a common complication for patients with CKD and is associated with cardiovascular comorbidities, hospitalisations, mortality, cognitive impairment, and reduced quality of life (QoL) (Babitt, 2012; Akizawa, 2018). Quality of life may be significantly impacted by the anaemia of CKD. Feeling weak or lacking strength, tiredness, shortness of breath, difficulty remembering things, and interference with daily activities are the most frequently reported symptoms and impacts [Eriksson, 2016].

2.1.4. Clinical presentation, diagnosis

Anaemia contributes to excess morbidity and mortality in CKD patients [Foley, 1996]. Anaemia in patients with CKD is also associated with symptoms such as fatigue, reduced oxygen use, shortness of breath, increased cardiac output, left ventricular hypertrophy, insomnia, lethargy, headaches, dizziness, lack of concentration and reduced cognitive functioning, reduced libido and reduced immune responsiveness (National Institute for Health and Care Excellence, Chronic kidney disease: managing anaemia, Jun 2015) [Fishbane & Spinowitz, 2018; Eriksson, 2016; Hirakata, 2010]. Patients with the lowest Hb have worse outcomes [Unger, 2010]. In patients with CKD, the severity of anaemia correlates directly with the risk of hospitalisation, cardiovascular (CV) disease and death [Thorp, 2009]. The severity of anaemia in patients with CKD on dialysis is also strongly associated with increased CV disease, hospitalisation and mortality [Collins, 1998]. CKD patients on dialysis with Hct < 30% and Hb < 11.0 g/dL have an increased associated risk for death (18% to 40% higher), whereas patients with higher Hct (33% to 36%) had a lower associated risk of death (7% lower) [Collins, 1998]. Symptoms of anaemia in patients with CKD also reduce their quality of life (QoL) and increase the healthcare system burden [Akizawa, 2018; Fishbane & Spinowitz, 2018; Covic, 2017; Eriksson, 2016].

2.1.5. Management

Current treatments for aneamia in non-dialysis (ND) or hemodialysis-dependent (HD) patients with CKD of CKD include erythropoiesis-stimulating agents (ESAs) for subcutaneous or intravenous use (rhEPO and its analogues), supplemental iron therapy (intravenous or oral), and blood transfusions [Kidney Disease: Improving Global Outcomes (KDIGO), 2012].

Treatment guidelines, including target levels for hemoglobin and biomarkers of iron metabolism, have been developed. These guidelines slightly differ between USA and Europe.

While existing therapies are useful and effective in treating anaemia, they each have significant limitations:

- **rhEPO**: Approved rhEPOs include epoetin alfa, epoetin beta, biosimilars as well as the longer half-life analogs darbepoetin alfa and epoetin beta pegol. These rhEPOs require IV or subcutaneous administration and must be refrigerated during shipping and storage, thus requiring careful handling. In addition, treatment with rhEPOs has been associated with increased cancer-related morbidity and mortality and increased risk of major cardiovascular events (MACE), e.g., stroke, myocardial infarction (MI), and all-cause mortality when targeting physiologically normal levels of Hgb [Besarab, 1998; Drüeke, 2006; Singh, 2006; Pfeffer, 2009; Food and Drug Administration, 2011]. The mechanism(s) contributing to the risks are not clear, and factors beyond excessive erythropoietic effect could be relevant. As a result, treatment guidelines restrict the range of Hgb levels to be targeted by rhEPO use but differ across regions (US, Europe, Japan). Access to these agents, the logistical challenges of administering parenteral therapies, and the restrictive Hgb targets in the US contribute to significant undertreatment of anaemia in ND patients [Lopes, 2021]. In rare cases, rhEPOs can cause life-threatening pure red cell aplasia linked to the production of neutralising anti-erythropoietin antibodies [Pollock, 2008].
- **Iron**: Oral iron therapy may be poorly absorbed, has low compatibility with other agents, and causes gastrointestinal symptoms such as nausea and vomiting, leading to poor compliance. IV iron may, in rare cases, cause anaphylaxis and may have an increased risk of hospitalisation due to infection, MACE, and iron overload (which causes deposition of iron in organs such as the liver and induces organ dysfunction) [Agarwal, 2015; Rostoker, 2016].

- **Blood transfusions**: These are avoided when possible because of potential alloimmunization, which can add an additional risk of complications and hence reduce the probability of success of a subsequent kidney transplant and the risk of iron overload and induction of organ dysfunction. Patients with renal disease not on dialysis are at particular risk of cardiopulmonary complications of transfusion because they have limited capacity to excrete the volume load it represents without additional diuretic intervention. This difficulty in handling the volume load can be exacerbated by cardiomyopathy, which is not uncommon due to the high prevalence of hypertension in the population. Additionally, vascular access may be needed, which may be problematic in peritoneal dialysis and ND patients. Managing the transfusion supply from a sterility and temperature perspective is a technically complex procedure. Blood transfusions also carry a risk of severe hyperkalemia [Rizos, 2017].
- **One oral HIF inhibitor**, i.e. roxadustat (Envrenzo), has currently been authorised for the treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD) in Europe by the centralized procedure in 2021. The approved indication is "Evrenzo is indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)". Further, vadadustat (Vafseo) has currently been authorised for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis in Europe by the centralised procedure in 2023.

IV rhEPO can be administered during the HD session for in-center HD patients, but for ND and peritoneal dialysis patients, this dosage form is logistically inconvenient and can be associated with discomfort and local irritation. Treatment rates for both rhEPO and IV iron supplementation are commonly reported to be low in ND patients with anaemia of CKD [Stauffer, 2014; Lawler, 2010], and evidence from patient-reported outcomes (PRO) studies indicate a patient desire for less frequent injections or visits while maintaining effective treatment [Vigneau, 2019; Hauber, 2017].

Thus, there remains an unmet need for an alternative form of treatment for anaemia of CKD that is well-tolerated and allows safe and effective management of target Hgb levels with no increased iron supplementation or blood transfusion requirement compared with currently available treatment. Daprodustat is available in a tablet form once daily (QD), making it more convenient than rhEPOs, particularly in ND and peritoneal dialysis patients. For greater convenience of HD patients, who routinely attend dialysis centers three times a week, daprodustat is also available for three times weekly (TIW) oral administration.

2.2. About the product

Daprodustat is a member of a new class of drugs that inhibits these prolyl-4-hydroxylase enzymes leading to a stabilisation of HIF-alpha and a consequent increase in endogenous erythropoietin (EPO) production and erythropoiesis. HIF activation also results in hepatic hepcidin suppression and upregulation of iron metabolism and transport genes, including transferrin, the transferrin receptor, and ferroportin, leading to improvements in iron mobilisation and utilization.

Next to erythropoiesis, the HIF signalling cascade also plays a role in physiological and pathobiological processes, including angiogenesis, glycolysis, apoptosis, cellular proliferation, inflammation, embryonic development, ischemic cardiovascular disease, wound healing, and malignancy. Due to their influence on multiple biologic processes, HIF-PHI could potentially cause adverse on-target effects.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as an immediate release film-coated tablet containing 1 mg, 2 mg, 4 mg, 6 mg or 8 mg of daprodustat as the active substance.

Other ingredients are:
-Tablet core: mannitol (E421), microcrystalline cellulose (E460), hypromellose (E464), croscarmellose sodium (E468), silica colloidal anhydrous (E551), magnesium stearate (E470b);

-Film coat:

Jesduvroq 1 mg, 2 mg and 6 mg film-coated tablets: hypromellose (E464), titanium dioxide (E171), macrogol (E1521), oron oxide black (E172), iron oxide yellow (E172), iron oxide red (E172);

Jesduvroq 4 mg film-coated tablets: hypromellose (E464), titanium dioxide (E171), macrogol (E1521)

Jesduvroq 8 mg film-coated tablets: hypromellose (E464), titanium dioxide (E171), macrogol (E1521), iron oxide yellow (E172), iron oxide red (E172).

The product is available in opaque white high density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction heat seal liner containing 30 and 90 film-coated tablets, as described in section 6.5 of the SmPC.

2.3.2. Active Substance

2.3.2.1. General information

Daprodustat is the INN for N-[(1,3-Dicyclohexylhexahydro-2,4,6-trioxopyrimidin-5-yl)carbonyl]glycine, corresponding to the molecular formula $C_{19}H_{27}N_3O_6$. It has a relative molecular mass of 393.43 and the following structure shown in Figure 1:

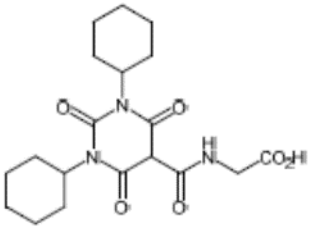


Figure 1. Active substance structure

The active substance (AS) was characterised by ^{1}H- and ^{13}C-NMR, IR, Mass Spectrometry, Infrared spectroscopy and elemental analysis; solid state properties were investigated by DSC and XRD Analysis.

Daprodustat appears as a white to almost white, non-hygroscopic crystalline powder. It is practically insoluble in water and exhibits very poor aqueous solubility in all media relevant to physiological pH, and is highly lipophilic (Log P = 5.28). It has two pKa's 3.24 (carboxylate) and 6.18 (hydroxyl).

Solid state form screening identified the crystalline form. The molecule possesses no chiral centres or potential to form optical or geometric isomers; however, it exhibits keto-/-enol tautomerism, and in the solid state, is present as the -enol tautomer.

2.3.2.1. Manufacture, characterisation and process controls

The manufacturing process consists of 3 main steps and involves well-defined acceptable starting materials (SM). Detailed justifications for SM designations in line with ICH Q11 were provided as well as a process flowchart and a narrative description. Following a MO raised, the description of the manufacturing process has been updated to include further information and details that were missing from the initial submission and the relevant parts of the dossier were updated as requested, thus resolving the MO. The process can be characterised as "semi-continuous", i.e., a hybrid continuous manufacturing process. A clear process narrative has been provided for each stage. Batch sizes are defined. The analysis of clinical batches demonstrated that the defined crystalline form is reproducibly formed.

A specification for the only isolated intermediate has been presented; the justification considers origin, fate and purge of impurities through spiking studies, as well as batch data. Controls of reagents, solvents, and auxiliary materials are acceptable. No materials of human or animal origin are used.

Two non-mutagenic impurities are discussed and are controlled in the active substance specification in line with ICH Q3A. A discussion on other potential and observed impurities, their carryover, and control strategy has been provided and is acceptable.

CPPs and their target values or ranges were identified. Target values or ranges for non-critical process parameters (PPs) were also included in the process description.

Design spaces (DS) have been defined for Stages 1, 2 and 3 of the proposed commercial manufacturing process, being multivariate combinations of ranges for critical process parameters (CPPs) and associated process parameters (PPs), as applicable. DS have been developed in conjunction with control of attributes in starting materials, intermediates, reagents, solvents and other raw materials in their respective specifications as part of the overall control strategy.

The manufacturing process development of daprodustat synthesis has been performed using an enhanced (Quality by Design, QbD) approach aligned with ICH Q8, Q9, Q10, and Q11 guidelines, including knowledge and risk management. The quality of the AS has been determined through knowledge and understanding of the physical, chemical, biological, and microbiological properties or characteristics that can influence the quality and performance of the finished product. The proposed DSs defined for each stage are supported by extensive multivariate experimentation and are part of the control strategy. The DSs were verified at the intended commercial scale.

An overview of the manufacturing process has been presented, confirming that three routes have been used during development. Suitably detailed summaries of the different routes of synthesis were presented. Based on justifications and provided data, it is evident that the latest development route and the commercial route produce material of comparable quality.

The AS is packaged in low-density polyethylene (LDPE) liners inside an outer container. The materials comply with Commission Regulation (EU) No 10/2011 for food contact use. The polyethylene used in the manufacture of the bags meets the compositional requirements of Ph. Eur. 3.1.3.

2.3.2.2. Specification

The active substance specification includes tests and limits for: description, identification (IR), solid state form (XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.) and particle size (laser diffraction).

The proposed AS specification is acceptable and in line with ICH Q6A. The justifications for specification tests/limits are acceptable. The proposed limits for specified and unspecified impurities and residual solvents are in line with ICH Q3A and ICH Q3C respectively. The provided justification for the parameters included in the specification and those parameters not included in the specification is acceptable.

The analytical methods are adequately described and validated. An acceptable discussion regarding the use of QbD in the development of content and drug-related impurities methods was presented, but no method operable design ranges are proposed. Sufficient information has been presented regarding reference standards.

Batch data for nine production-scale batches, manufactured according to the proposed commercial process were presented. The results are within the specifications and consistent from batch to batch. Supporting batch data were provided for three production-scale batches of daprodustat used in primary stability studies, which were manufactured at the commercial site according to the previous process and tested by the proposed commercial methods.

Overall the batch results demonstrate that the AS is being manufactured to a consistent quality and that the process is under control.

2.3.2.3. Stability

Stability data from three commercial scale batches of active substance manufactured by the commercial route stored in the intended commercial package for up to 36 months under long term conditions (30 °C / 75% RH) and for up to six months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. In addition, supportive stability data from another three commercial scale batches stored in the intended commercial package for up to 48 months under the same long term conditions and for up to six months under accelerated conditions according to the ICH guidelines were also provided.

The following parameters were tested*:* description, solid state form, assay, impurities, water content and particle size. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specification limits.

Stress studies under elevated temperature, freeze/thaw cycle and photostability study (per ICH Q1B) were performed and all results complied with the proposed specification.

Furthermore, forced degradation studies have been performed and confirm that the AS is chemically stable in the solid phase. It is confirmed that the assay and impurities methods are stability indicating.

Overall the stability results indicate that the active substance manufactured by the proposed process is sufficiently stable. The proposed retest period in the proposed container is accepted.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Jesduvroq finished product (FP) is an immediate release film-coated tablet. The 1 mg, 2 mg, 4 mg, 6 mg and 8 mg tablets are round, biconvex tablets. Each strength has strength-specific text debossed on one face and is coated with a strength-specific colour, and thus is sufficiently differentiated. A science and risk–based approach, applying QbD and quality risk management principles in accordance

with ICH Q8, Q9 and Q10 has been used to develop daprodustat tablets. A Quality Target Product Profile (QTPP) has been established, Table 1, and critical quality attributes (CQA) have been identified.

Table 1. Quality Target Product Profile

Dosage Form and Strength	Film-coated, immediate release tablets containing 1 mg, 2 mg, 4 mg, 6 mg or 8 mg drug substance as the free acid for once daily (QD) or three times weekly (TIW) dosing will be developed.
Drug Product Quality Criteria	The product components (active and inactive ingredients) must have the requisite functional characteristics. The dosage form must meet compendial and any other relevant quality standards at manufacture and over the proposed commercial shelf-life. This includes meeting the drug product CQA, which are considered critical to ensure quality and safety of the medicine. The manufacturing process needs to be robust, reproducible and suitable for the use of drug substance.
Drug Delivery and Release Considerations	Immediate release tablet will be developed.
Container Closure System	A container closure system will be targeted which will provide adequate protection for the product.
Stability Criteria	Components of the drug product (active and inactive ingredients) must be physically and chemically compatible with the requisite functional characteristics to ensure appropriate stability of the drug product over the proposed shelf life.

Several physicochemical and biopharmaceutical properties have been evaluated. The applicant has confirmed that only one stable polymorphic form is manufactured. The AS is a weak acid, is highly lipophilic (log P 5.34), and exhibits very poor solubility at physiologically relevant pH's. The dissolution of each of the tablet strengths in biologically relevant media is considered adequately characterised, and a bioavailability study performed using tablets with different dissolution profiles demonstrates that the proposed QC dissolution method is discriminatory.

Commonly used excipients are employed, and AS compatibility is verified through long-term and accelerated stability studies. All excipients, except for colourants in film coats, are controlled as per the Ph. Eur.; colourants are listed in EC Regulation 1333/2008, as amended, and comply with EC Regulation 231/2012.

The applicant has developed two manufacturing processes – one continuous mode and one batch mode. Both processes are proposed to be used for commercial manufacture and this strategy has been considered to be acceptable.

An extensive description of the development of the manufacturing process has been provided.

DOE studies identified a number of process parameters with statistically significant impact on the FP CQAs.

The manufacturing process development has been adequately described and includes PP, CPPs, and PARs.

The finished product is packaged into opaque, white HDPE bottles. The material complies with Ph. Eur. and EC requirements. The container closure system child-resistant packaging has been tested and complies with the current version of ISO 8317.

The container closure system is considered standard for the dosage form. Acceptable specifications were provided for each of the packaging components. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The manufacturers and their operations are defined, and it is confirmed that all manufacturers operate to GMP.

The applicant has provided a flow diagram and a narrative description of the batch and the continuous process mode, including the CPP, PP, and in-process material attribute ranges or target values. A MO was raised about the level of details included initially about the manufacturing process. The applicant in their response provided additional information and details that were missing from the initial submission and updated the relevant parts of the dossier as requested, thus resolving the MO.

The main steps of the process are preparation of the premix blendings followed by powder feeding *(design space),* wet granulation (*design space*), drying, dry milling, extragranular feeding and blending (*design space*), lubricant blending (*design space*), compression, film-coating and packaging.

Design spaces (DS) for the certain unit operations have been described and are acceptable.

The main steps of the batch process are dry mixing, wet granulation, drying, milling, extragranular blending, lubrication, compression, film-coating and packaging. The applicant has provided a flow diagram and a narrative description of the batch process, which includes the CPP, PP, and in-process material attribute ranges or target values.

Regarding control of critical steps and intermediate, the critical steps of both processes have been identified and IPCs (including their acceptance criteria) have been summarised. Bulk stability data support the bulk tablet storage times. A design space has been defined for a unit operation.

Process validation
Continuous manufacturing processes are considered non-standard manufacturing processes; furthermore, the 1 mg, 2 mg, and 6 mg strengths are also considered non-standard due to the low content of the AS. Sufficient process validation data has been submitted for all strengths manufactured by either the batch mode or the continuous mode in response to a MO raised in this regard.

The information and data presented confirm that the CTL manufacturing process is well-controlled, validated and capable of routinely achieving product of consistent quality.

The packaging material for bulk tablets of either process has been described and complies with the requirements of Commission Regulation (EU) No.10/2011 on plastic materials and articles intended to come into contact with food. Bulk holding times have been justified by appropriate stability studies.

2.3.3.3. Product specification

The finished product release and shelf life specifications shown in include appropriate tests for this kind of dosage form: description (visual), identification (HPLC-UV), assay (HPLC), impurities (HPLC), uniformity of dosage units (HPLC), dissolution (Ph. Eur.), and microbiological quality (Ph. Eur.). The proposed specification is acceptable and is in line with ICH Q6A and the Ph. Eur. Requirements for the dosage form. During stability, only description, assay, impurities, dissolution and microbial limits are performed.

Generally, acceptable justifications for the proposed specification have been provided, referencing ICH and EMA guidance and batch/stability data as appropriate.

An elemental impurities (Eis) risk assessment was performed on the FP. In line with the guidance all Class 1, 2A and any intentionally added Class 2B and 3 elemental impurities were included in the risk assessment considering all possible sources. The applicant provided a summary showing that the total amount for all Class 1 and 2A elemental impurities, calculated by summing the maximum amounts present in each of the components of the formulation for the maximum daily dose (48 mg daprodustat), were all less than 30% of the PDE as per option 2b of ICH Q3D. Therefore, no elemental impurities test is included on the finished product specification.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product was missing from the initial submission and a MO was raised in this respect. In the provided responses a risk evaluation has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The descriptions of the analytical procedures and their validations as provided were acceptable. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. The applicant has confirmed that the FP will be subject to full release testing at the batch release site located within the EU, in line with the requirements of Directive 2001/83/EC Article 51.

Batch analysis data for multiple batches of each tablet strength covering both the continuous and the batch mode were presented; all results comply with the proposed specification. The data is comparable across batches manufactured using the continuous manufacturing, and across batches manufactured using continuous and batch modes.

2.3.3.4. Stability of the product

Stability data from three production-scale batches of each strength of daprodustat tablets, 1 mg, 2 mg, 4 mg and 6 mg, manufactured by the continuous mode process stored for up to 36 months under long term conditions (30 °C / 75% RH) and for six months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. In addition, 24 months stability data were presented for four production-scale batches of daprodustat tablets 8 mg. An acceptable bracketing approach was applied.

All the above-mentioned stability batches are identical to those proposed for marketing (bar the debossing) and were packed in the primary packaging proposed for marketing. Minor differences in the container closure liner have been discussed and are considered acceptable, not affecting the stability conclusions.

In addition, stability data from three production-scale of each strength of finished product 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablets manufactured by the batch mode and stored for up to 12 months under long term conditions (30 °C / 75% RH) and for 6 months under accelerated conditions were also presented. An acceptable matrix and bracketing approach has also been applied.

Samples were tested for description, assay, impurities, dissolution and microbial growth. No significant changes were observed and results remained within the specifications. The analytical procedures used were the same as for release and are stability indicating.

In addition, stability data has been generated following short-term storage of one batches of each strength of daprodustat tablets under stress conditions of 50°C/Ambient for 3 months, after a freeze/thaw cycle (-20°C/30°C) for 1 month or after exposed photostability testing in accordance with ICH Q1B (Option 2). The results demonstrate the chemical and physical stability of daprodustat tablets at all the stressed storage conditions. Photostability studies performed in line with ICH Q1B confirm the product does not demonstrate any sensitivity to light.

Forced degradation studies have also been performed to identify the main degradants formed under elevated temperature and humidity. Results showed little to no degradation in the drug product after exposure.
Finally in-use stability studies were presented for one batch of each strength of daprodustat tablets at the initial timepoint and after storage at the long term storage condition for up to 12 months. No significant changes were observed in description, daprodustat content, drug related-impurities content and dissolution, and all results comply with the proposed specification.
In-use shelf-life data shows no deterioration in the product after opening; therefore, an in-use shelf life for the finished product is not required.

Based on available stability data, the proposed shelf-life of 4 years without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.3.3.5. Post approval change management protocol

A post-approval change management protocol (PACMP) to change the manufacturers of the starting materials with or without concurrent changes to the starting material synthetic route/process, and where there are no changes to the specification and/or analytical procedures, has been submitted. A second PACMP has been submitted, for deletion of the release test for impurities content by HPLC from the FP specification. Both PACMPs are acceptable.

2.3.3.6. Adventitious agents

No excipients derived from animal or human origin are used in Jesduvroq film coated tablets. A supplier TSE declaration for magnesium stearate confirms it is of vegetable origin.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The MOs raised during the procedure regarding the active substance and finished product manufacturing processes development, description and control and the finished product process validation have been resolved by provision of appropriate additional information. The MO regarding the nitrosamine impurities risk evaluation was also resolved by additional data and information in line with current requirements.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance and finished product. The design spaces have been adequately verified.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

None.

2.4. Non-clinical aspects

2.4.1. Introduction

Daprodustat is an inhibitor of human PHD1, PHD2 and PHD3, which are Hypoxia-inducible factor prolyl hydroxylases 1, 2 and 3. Inhibition of these hydroxylases aims to stabilize HIF1α and HIF2α and results in accumulation. A secondary effect thereof is the increase in EPO secretion, which ultimately leads to increased erythropoiesis.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In vitro

The *in vitro* effect of daprodustat on the enzymatic activity of human PHD1, PHD2 and PHD3, rat PHD2 and PHD3, and dog PHD3 was determined in a fluorescence based LANCE™ assay. Daprodustat was approximately equipotent against human PHD1, PHD2 and PHD3 with apparent inhibitory constant ($K_{i\ app}$) values of 1.8, 1.7-7.3, and 1.8-4.4 nM, respectively. Similar $K_{i\ app}$ values were observed for rat PHD2 and PHD3 and dog PHD3. Daprodustat IC_{50} values for human PHD2 and PHD3 increased linearly with increasing α KG concentrations, indicating α KG competitive inhibition of PHDs by daprodustat. In addition, IC_{50} values of daprodustat were at least 20-fold lower with a 30-min enzyme-inhibitor preincubation compared to a 1-min preincubation, suggesting that daprodustat inhibits human PHD2 and PHD3 in a time-dependent manner. Furthermore, this inhibition was reversible, with dissociative $t_{1/2}$ values of >90 minutes for human PHD2 and PHD3. Finally, the selectivity of daprodustat over other members of the α KG-dependent iron di-oxygenase superfamily, CP4H and FIH, was shown to be >6800-fold for CP4H and >90-fold for FIH based on $K_{i\ app}$ values.

The stabilisation of HIF1α and HIF2α as a result of inhibition of PHDs was investigated by Western blot analysis following a 6-hour treatment of Hep3B cells with 25 or 50 µM daprodustat. However, these concentrations were significantly higher than the free concentration daprodustat at MRHD (calculated at 0.014 µM). At both concentrations, treatment with daprodustat resulted in the accumulation of HIF1α and HIF2α subunits. Hep3B cells were also used to investigate the effect of daprodustat on EPO and VEGF-A production: ELISA analysis showed that incubation of Hep3B cells with daprodustat for 48 hours resulted in a 5.8- and 2.2-fold increase of secretion (above the vehicle control) for EPO and VEGF-A, respectively. The EC_{50} values of daprodustat for EPO and VEGF-A secretion were 3.3 and 2.2 µM, respectively.

Another study investigated the changes in mRNA (using RT PCR) and/or protein levels (using MSD ELISA) of specific HIF-responsive genes, including PGK-1, EPO, and VEGF-A, were investigated in Hep3B cells after treatment with daprodustat at 2.5-25 µM. There was a concentration-dependent increase in EPO mRNA from 1.7- to 7.4-fold. Additionally, the expression of HIF1α specific PGK-1 mRNA increased from 1.7- to 2.9-fold. Furthermore, there was a concentration-dependent increase in secreted EPO protein concentrations from 1.4- to 4.2-fold, whereas secretion of VEGF-A protein

increased from 1.6- to 2.1-fold. These results indicated that treatment of Hep3B cells with daprodustat results in concentration-dependent increases in EPO mRNA and protein, whereas there was minimal PGK-1 mRNA and VEGF-A protein induction.

Finally, the effects of daprodustat on the iron regulatory protein hepcidin were examined in Hep3B cells treated with bone morphogenic protein 6 (BMP-6) for 6 hours to induce hepcidin mRNA to detectable levels. Treatment with daprodustat for 48 hours decreased BMP-6-induced hepcidin mRNA expression ~55% at 12.5 µM, suggesting a potential for daprodustat to increase iron mobilization and utilization.

Daprodustat is extensively metabolised in humans by oxidative pathways. A preliminary quantitative assessment of circulating human metabolites warranted further investigation of the pharmacologic activity of six predominant human plasma metabolites (including relevant stereoisomers). All of the metabolites tested were approximately equipotent against human PHD1, human PHD2, human PHD3, rat PHD2, rat PHD3, and dog PHD3, with values comparable to daprodustat in a fluorescence-based LANCE assay. Finally, the selectivity of the metabolites over other members of the α KG-dependent iron di-oxygenase superfamily, CP4H and FIH, was shown to be >6800-fold for CP4H and >800-fold for FIH based on Ki app values.

Hep3B cells were treated individually with daprodustat or each of the human metabolites of daprodustat at 3 or 30 µM for 24 hours. Media samples were collected to determine levels of secreted EPO using an MSD EPO assay. EPO levels did not increase after treatment with the human metabolites of daprodustat at 3 or 30 µM. This is likely because these metabolites are the product of di- or tri-oxygenation, which increases their hydrophilicity, possibly resulting in reduced cellular permeability.

In vivo

In vivo studies in female B6D2F1 mice were performed by administering a single oral (gavage) dose of daprodustat at 60 mg/kg. In the first study, platelet-poor plasma samples were analyzed for EPO using MSD ELISA, and livers and kidneys were collected from each mouse for gene expression analysis using qRT-PCR. Liver EPO mRNA levels were increased at 6 hours post-dose, prior to increases in kidney EPO mRNA observed at 8 hours, followed by plasma EPO protein levels which were maximal at 8 to 12 hours. A second study (with up to 30 hours post-dosing) showed that daprodustat increased plasma EPO protein levels 11-fold relative to vehicle control after 12 hours, and EPO values at all other timepoints were elevated 1.9- to 2.9-fold relative to vehicle-treated mice. VEGF levels were shown to increase only modestly, with a 1.2- to 1.8-fold increase in plasma concentration over time.

In vivo studies in male SD rats given up to 30 mg/kg daprodustat as a single dose or once daily for 3 consecutive days by oral gavage showed no increase in plasma erythropoietin (EPO). However, dose-dependent increases in EPO mRNA expression were observed in the liver of rats given single oral doses of 10 or 30 mg/kg 6 hours post-dose. Liver expression of heme oxygenase 1 (HO-1) was also increased 6 hours following a single dose of 30 mg/kg daprodustat. There were no increases in liver mRNA expression of other HIF-related genes (VEGF-A, PDK1, and Glut-1).

The effects of daprodustat on erythropoiesis were investigated in female B6D2F1 mice and in male SD rats. After daily dosing of 3, 10, and 30 mg/kg daprodustat for 8 days in B6D2F1 mice, blood parameters including Hb, Hct, RBCs, reticulocytes, platelets and WBCs were analysed. Statistically significant increases in Hb (12-17%) and Hct (15-25%), as well as RBCs (15-17%) and reticulocytes (210-673%), were observed for all three doses. Statistically significant decreases in platelets (up to -51%) and in WBCs (up to -34%) were observed for all three dose levels. Importantly, two clinical studies (a placebo-controlled clinical study and a comparative study versus ESA therapy) showed no evidence for decreases in platelets and WBCs in humans, revealing that the mouse study findings are not translated to clinical trials.

After daily dosing of male Sprague Dawley rats with daprodustat at 0.3, 1, 3 or 10 mg/kg for 21 days, blood samples were collected after 8, 15, and 22 days and subsequently analyzed for Hb, Hct, RBCs, and WBCs. Statistically significant increases in Hb were observed for 3 and 10 mg/kg on Day 15 (increases up to 19%) and Day 22 (increases up to 22%). Statistically significant increases in Hct were observed for 3 and 10 mg/kg on Day 15 (increases up to 21%), and for all dose levels on Day 22 (increases up to 26%). Statistically significant increases in RBCs were observed for all dose levels (except 1 mg/kg) on Day 15 (increases up to 13%) and for all dose levels on Day 22 (increases up to 18%). No statistically significant effects were observed for WBCs at any dose.

In vivo evaluation of a major metabolite (M13) was performed after a single intravenous (IV) bolus administration to male CD-1 mice at 40 or 100 mg/kg. Administration of M13 at 40 and 100 mg/kg did not significantly increase plasma EPO and VEGF levels, although small elevations of plasma levels for EPO were observed at 4 hours post-dose. VEGF levels in plasma were near the lower limit of detection. Additionally, the pharmacological activity of three major circulating human metabolites of daprodustat was evaluated in female CD1 mice subcutaneously co-administered with a cocktail of M2, M3 (GSK2506104) and M13 (GSK2531401) at 2.0, 2.5 and 1.3 mg/kg, respectively. After 28 days of daily dosing, mean Hb, Hct, and total RBC count increased by 10%, 10%, and 9%, respectively, indicating that this combination of metabolites results in pharmacologic activity in mice, although the concentrations observed for these metabolites appear to be significantly higher than that observed in humans.

Studies supporting other indications and routes of administration were not assessed.

2.4.2.2. Secondary pharmacodynamic studies

The selectivity of daprodustat was assessed in a variety of *in vitro* assays unrelated to Prolyl Hydroxylase inhibitory activity. The assays included 50 receptor binding, enzymatic, and ion channel assays using the free acid form of daprodustat at 10 µM. Daprodustat demonstrated no significant (<20%) inhibitory activity versus all 50 of the tested targets. Importantly, daprodustats estimated human free plasma C_{max} at the MRHD was calculated at ~0.014 µM, indicating that the concentration tested (10 µM) was well in excess of that obtained by MRHD.

In addition, daprodustat and its 9 metabolites did not show any significant activity on any liability target, including the surrogate measures of cellular toxicity, genotoxicity, and phospholipidosis assays. However, for one of the isomers of M3 (GSK2506104A), the results showed that this compound might cause partial inhibition of the KCNQ channel, although the pIC_{50} value was determined at an average of 5.8 (corresponding to ~1.5 µM), which is significantly higher than the C_{max} (total concentration of ~0.02 µM) for this metabolite in human studies.

When daprodustat was tested against seven in house protein kinases (human-cell division kinase-2 (CDK 2)/Cyclin A, polo-like kinase 1 (PLK1), 70 kDa ribosomal protein S6 kinase I (p70S6K), steroid receptor coactivator 1 (SRC1), dual specificity tyrosine phosphorylation-regulated kinase 3 (DYRK3, also known as YAK3), vascular endothelial growth factor receptor-2 (VEGFR-2) and rat ribosomal s6 kinase-1 (RSK1)), the IC_{50} values were >10 µM in all tests, suggesting that daprodustat selectively inhibits PHDs versus these protein kinases. Again, the MRHD resulted in a free C_{max} concentration of ~0.014 µM, thus indicating that the concentrations tested were well in excess of MRHD.

Daprodustat inhibited COX1 in a concentration-dependent manner in rat whole blood with an IC_{50} value of ~66 µM, whereas no effect on COX2 in rat whole blood was observed up to a concentration of 100 µM. In comparison, indomethacin showed an IC_{50} of ~2 µM for rat COX1, indicating significantly lower inhibition for daprodustat. Since the MRHD free fraction, C_{max} was calculated at ~0.014 µM, the IC_{50} value of ~66 µM appears to not be within the range of clinical use.

Two studies were conducted to examine changes after treatment with daprodustat to γ-hemoglobin levels in erythroid progenitors or cell viability of human leukaemia (KU812) cells. There was no change to the level of human γ-hemoglobin protein from CD34+ derived erythroid progenitor cells after treatment with 0.5 nM-33 µM daprodustat. Additionally, there was no change in KU812 cellular viability after treatment with the identical dose range of daprodustat.

2.4.2.3. Safety pharmacology programme

Daprodustat was administered in a number of safety pharmacology studies designed to assess its effects on major organ systems and to detect any potential adverse pharmacodynamic effects.

Sprague Dawley rats were given a single oral (gavage) administration of daprodustat at 2, 7 and 20 mg/kg. No behavioural or overt pharmacological effects considered related to daprodustat administration were noted for any dose level. The C_{max} values observed in a repeat-dose study with identical dosing levels revealed C_{max} values of ~25 µM after the first dose of 2 mg/kg, indicating that the dose levels in this study exceeded those of MRHD (human free plasma C_{max} ~0.014 µM) excessively.

In another study, Sprague Dawley rats were given a single oral (gavage) administration of daprodustat at 2, 7 and 20 mg/kg/group. There were no effects on ventilatory function, airway resistance or body temperature for any dose level for 168 hours. As mentioned above, the dose levels tested (observed C_{max} in similar dosing study of ~25 µM after the first dose of 2 mg/kg) will have resulted in more than sufficient exposure when compared to MRHD (human free plasma C_{max} ~0.014 µM).

Daprodustat's potential to inhibit hERG tail current was measured by whole-cell patch clamping in HEK-293 cells stably transfected with hERG. Compared to vehicle-treated cells, daprodustat produced no statistically significant inhibition of hERG tail current when tested at the maximum soluble concentration, which exceeds daprodustats estimated human free plasma C_{max} at the MRHD (calculated at free concentration ~0.014 µM) >3300-fold. The six predominant human metabolites (including relevant stereoisomers) of daprodustat were all inactive against hERG tail current. Daprodustat was weakly active in the Nav1.5 assay with an IC_{50} value exceeding daprodustats free plasma C_{max} at the MRHD by >11000-fold, limiting its relevance.

Daprodustat was examined in the isolated rabbit left ventricular wedge preparation for effects on QT interval, Tpeak-end (Tp-e), and QRS interval. Daprodustat at 3 to 30 µM produced mild, concentration-dependent QT and Tp-e prolongation, a small increase in QRS interval at 100 µM and an increase in isometric contractile force at ≤30 µM, but exerted no torsadogenic potential up to 100 µM. In addition, since the estimated human free plasma C_{max} at MRHD was calculated at ~0.014 µM, these findings were observed at very high concentrations, thus making its relevance unclear.

A study to evaluate the effects of treatment with daprodustat on cardiovascular parameters in response to acute hypoxia (10% O_2, 90% N_2) was conducted in Sprague Dawley rats given vehicle or daprodustat at 10 or 30 mg/kg/day for 5 days. Following the last dose, peak right ventricular pressure (PRVP), aortic pressure and heart rate were obtained for ~15 to 20 minutes prior to, during and after acute exposure to hypoxia. Daprodustat did not alter the expected effects of acute hypoxia on heart rate or mean arterial pressure. There were increases in peripheral RBC parameters at 30 mg/kg, although increases in RBC parameters at 10 mg/kg/day were less pronounced. Doses of 10 and 30 mg/kg/day produced increases in PRVP during acute hypoxia that were slightly higher than controls. However, based on the primary statistical analysis (ANOVA), the increases in PRVP in daprodustat-treated rats, relative to the vehicle control group were not statistically significant.

Beagle dogs were given single oral (capsule) doses of vehicle and daprodustat at 3, 30 and 90 mg/kg. Arterial blood pressure, heart rate, ECG intervals, and body temperature were monitored continuously for up to approximately 76 hours after dosing. Single oral doses of 30 and 90 mg/kg produced mild, consistent increases in heart rate of up to approximately 28% and 33% (up to 20 and 21 beats/minute), respectively, from approximately 14-24 and 10-24 hours following the respective doses. This effect occurred in the absence of changes in arterial pressure and was not evident at 72-76 hours post-dose or following the 3 mg/kg dose. There were no effects on QTc and no evidence of daprodustat-induced ECG waveform abnormalities or arrhythmias up to 72 hours following a single oral dose of 90 mg/kg. The C_{max} values observed in a repeat-dose study with identical dosing revealed C_{max} values of ~30 µM after the first dose of 90 mg/kg in male dogs, indicating that the dose levels in this study exceeded those of MRHD (human free plasma C_{max} ~0.014 µM) excessively. As mentioned in below, no metabolites were detected in dog plasma after daprodustat administration. This might potentially have decreased the value of the present study since the effects of metabolites were not included as a result. However, clinical studies have investigated cardiovascular effects extensively (including ECG abnormalities), thus preventing the need for an alternative study with a different species.

There were no effects on ECG tracings during repeat dose oral toxicity studies of up to 13 weeks in dogs (up to 15 mg/kg/day) or up to 13 or 39 weeks in monkeys (up to 100 or 50 mg/kg/day, respectively).

2.4.2.4. Pharmacodynamic drug interactions

The applicant has not performed any studies regarding PD drug interactions.

2.4.3. Pharmacokinetics

Daprodustat pharmacokinetic profile was characterised following intravenous (iv) and oral administration to mice, rats, dogs and *Cynomolgus* monkeys. Toxicokinetic profiles were characterised in mice, rat, dog and monkey following daily oral dosing for up to 104 weeks in mice, 99 weeks in rats, 13 weeks in dogs and 39 weeks in monkeys. Exposure in juvenile rats and pregnant rats and rabbits was assessed in the juvenile toxicity studies in rats and as part of the Embryo-Fetal Development Study in Rabbits and in the pre- and post-natal development study (PPND) in rats. In addition, pharmacokinetic and toxicokinetic profiles of the three major human metabolites (M2, M3 and M13) were characterised in monkeys and pregnant rabbits, and following subcutaneous administration in mice and rats.

Methods of analysis

Daprodustat levels in plasma from mouse, rat, rabbit, dog, mini pig, and monkey were determined using protein precipitation followed by high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) analysis. The assays were sufficiently validated for intra- and inter-assay accuracy, precision, linearity, range (50 to 50000 ng/mL) and limit of quantification (50 ng/ml) as well as storage stability.

Also for the determination of the six predominant metabolites of daprodustat in plasma: M2, M3, M4, M5, M6 and M13 HPLC/MS/MS assays were developed and validated for mouse and monkey plasma. The lower and upper limits of quantitation in these assays were 1 and 1000 ng/mL. It is noted that these assays are achiral and can therefore not distinguish among the different stereoisomeric forms.

For the detection of daprodustat-related material in the whole body or in biological samples, [^{14}C]daprodustat was used and measured by liquid scintillation counting or in the whole body using

autoradiographic techniques with quantitative imaging. In addition, for profiling and identification of metabolites of daprodustat HPLC with radiochemical and UV detection, liquid chromatography-mass spectrometry (LC-MS) with in-line radiochemical detection, atmospheric pressure chemical isolation liquid chromatography-mass spectrometry (APCI/LC-MS), liquid chromatography with tandem mass spectrometry (LC-MSMS) and nuclear magnetic resonance (NMR) analysis were used.

Absorption

The plasma PK of daprodustat was investigated after single IV or oral administration in mice, rats, dogs and Cynomolgus monkeys. In dogs, exposure (Cmax and AUC) in females tended to be higher than in males (2.1 and 3.2 fold, respectively), although this might be affected by emesis in the males. In monkeys, no relevant gender effects on exposure were observed.

Daprodustat is readily absorbed following oral administration, with Tmax 1-2h in mice, 2-4h in rat, 8h in female dog and 1.5-6h in monkey, compared to 1-4h in humans. Oral bioavailability in solution was high in mouse (88%) and rat (78%) but lower in dog (45%) and monkey (34%) and even lower in dogs following capsule dosing of the crystalline parent (25%). Bioavailability in human was 65%.

Daprodustat is rapidly and widely distributed, but tissue concentrations were generally lower than blood concentrations. Distribution volume (Vss) was 0.3-0.8 L/kg in the mouse, rat, dog and monkey, approximately equal to total body water. In humans, Vss was 0.29 L/kg (for a 50 kg weighing adult).

Plasma clearance was low following intravenous administration to mice, rats, dogs and monkeys (0.7, 0.2, 0.9 and 8.4 ml/min/kg, respectively). Also in humans, plasma clearance was low: 6.3 ml/min/kg for a 50 kg weighing adult.

Terminal elimination half-life (t½) was 1.9h in monkeys, 6.6h in dogs, 33.5h in rats and 1-4h in humans.

In addition, the PK parameters of M8 were determined in the rat following IV or oral administration. Cmax was reached after 0.5 h, but the oral availability was minimal (1.5%). Also clearance (12.2 = ml/min/kg, i.e. higher than parent) and Vss (0.49 L/kg) were low, whereas the t1/2 was 5.4h. Following administration of M8, quantifiable amounts of M2, M3 and M4 were measured for up to 1-3h, but M5, M6 and M13 could not be detected.

Also, the PK parameters of M13 were assessed in mice and rat. As for M8, oral availability in rat was very low (0.85%) as were clearance (15-20 ml/min/kg in rats, 18-20 ml/min/kg in mice, i.e. higher than parent), Vss (0.4 L/kg in mice and 0.83 L/kg in rats) and T1/2 (0.083h in mice and 0.93h in rats).

Repeated dose toxicokinetic studies with daprodustat were performed in mice (14 days – 13 weeks), rats (5 days – 99 weeks), dogs (3 days – 13 weeks), and Cynomolgus monkeys (14 days – 39 weeks).

In all species, exposure parameters (Cmax and AUC) were comparable between males and females. Generally, gender averaged AUC and Cmax values increased in a dose-proportional to less than dose-proportional manner. According to the applicant, this might be explained by solubility limited absorption at the higher doses. Daily dosing did not result in accumulation.

In mice (30 mg/kg), only M2 was quantifiable at 1h (in 1 mouse only). In rats (30 mg/kg daprodustat), M2, M8, M9/M22, and M10 were quantifiable, with Tmax of 1h. In monkeys (3-100 mg/kg), M2, M3, M4, M5, M6, and M13 were all quantifiable, with Tmax between 0.5 and 8h. Metabolites increased in a less than dose-proportional manner and without gender differences. At week 39, the ratio of AUC0-t was <0.09 (metabolite: daprodustat) for all metabolites.

In juvenile rats, systemic exposure (AUC and Cmax) was lower at postnatal days (PND) 4 than at PND 10 or higher.

In pregnant rabbits, Tmax of oral administered daprodustat (4-250 mg/kg) was 4-8h, and as observed in the non-pregnant other species, exposure parameters increased less than dose-proportional. Maximal concentrations of the metabolites M2, M3, M4, M5, and M13 were analysed after administration of 60 mg daprodustat. The metabolites were quantifiable up to 24 hours (except for M6, which was only quantifiable up to 8h). The exposure of daprodustat was at least 16-fold higher than its metabolites.

Due to the absent formation of major human metabolites in mice and rats, studies were performed in which M2, M3 and M13 were subcutaneously injected together (or alone in one 14 day study in mice) with oral administered daprodustat. Tmax of the metabolites was ≤0.5h. Systemic exposures of the human metabolites increased proportionally in pregnant rat (from 2.5-7.5 mg/kg for M2, 3.2-9.6 mg/kg for M3 and 1.8-5.4 mg/kg for M13).

Overall, it can be concluded that the PK profile of daprodustat in humans is most similar to that of the rabbit and monkey.

Distribution

The extent of plasma protein binding of daprodustat was evaluated in plasma from mouse, rat, dog, monkey and human using equilibrium dialysis. Plasma binding was high in all species 97.8-99.8% in mice, 97.7-100% in rats, 99.5-99.9% in rabbits, 97.9-98.3% in dogs, 93.6-98.8% in monkeys and 98.3-99.5% in humans) and there was no clear evidence of concentration-dependent protein binding over the concentration range evaluated (0.2-50 µg/mL). In human plasma, daprodustat was mainly bound to serum albumin (>99%), while binding to AAG was low (<20%). It is noted that CV% is relatively high in the plasma binding studies. Nevertheless, the data indicate that plasma binding in mouse and rat is comparable to human and plasma binding in monkey is slightly lower.

For the main circulating human metabolites of daprodustat, (human) plasma protein binding was low for M2 (2.2-13.9%), M3 (13.2-23.5, main stereoisomer), M6 and M13 (0-3.9%) (and without evidence of concentration-dependent protein binding). Data for M4 and M5 did suggest concentration-dependent protein binding, with plasma binding increasing from 68 and 74%, respectively, at the lowest test concentration to ~98% at the highest test concentration. For metabolites, plasma protein binding is only analysed in human plasma, but not in animal plasma. Nevertheless, considering that the metabolites are structurally very similar to daprudostat, no dramatic difference in protein binding between humans and animals is expected and there is little concern that the unknown protein binding of major metabolites in the preclinical animal species would have a significant impact on the safety assessment.

Blood:plasma ratio measured *in vitro* by LC/MS/MS at concentrations of 1 and 10 µg/mL ranged from 0.45-0.71 in mice to 1.15-1.64 in rat (humans: 0.75-1.23).

Studies in Madin Darby canine kidney (MCDK) cells transfected with the human multi-drug resistant 1 gene (hMDR1) showed that daprodustat had moderate passive membrane permeability but was not a substrate of human P-gp.

Blood: plasma ratio determined in *in vivo* studies ranged from ranged from 0.505 to 0.560 in rat, was 0.84 in dog and ranged from 0.615 to 0.839 in the monkey.

Tissue distribution of daprodustat was investigated in fasted male partially pigmented Long Evans rats using quantitative whole-body autoradiography (QWBA) following a single oral administration of 10 mg/kg [^{14}C]daprodustat, 1% methylcellulose. Daprodustat was widely distributed. Most tissue concentrations were lower than those observed in blood. For most tissues, maximal concentrations were reached at 1h post-administration, except for mandibular lymph node, thymus, epididymis, testes, skin and skeletal muscle (4h), and several parts of the alimentary canal and uveal tract and

prostate gland (8h). In general, tissue radioactivity concentrations were not quantifiable by 7 days post-dose (exception for large intestine contents: BLQ at 35 days, and in the peripheral nerve: BLQ at 35 days). There was no indication of accumulation and/or retention in melanin-containing tissues.

After administration of a single IV (bolus) administration of either M13 at 40 or 100 mg/kg (saline), or daprodustat at 20 mg/kg (saline) to non-fasted male CD-1 mice, concentrations of M13 and daprodustat were determined in kidney samples at several time points varying from 0.083-24h. Kidney concentrations of daprodustat were 15- to 500-fold higher than kidney concentrations of M13 at all time points.

In the rat PPND study, in which oral administration of daprodustat (0.8-40 mg/kg) was combined with subcutaneous administration of the three major metabolites (2.5, 3.2 and 1.8 mg/kg/day for M2, M3 and M13), plasma exposure to daprodustat and its three major metabolites was demonstrated in pups on PND 10, presumably indicating exposure via lactation (considering the T1/2 of 33.5h for daprodustat in adult rats). However, placental transfer cannot be excluded.

Metabolism

Studies in liver microsomes and hepatocytes from mouse, rat, dog, monkey and human indicate that the intrinsic clearance of daprodustat is low ($\leq$ 0.5 ml/min/g liver, and 1.1 ml/min/g liver for human hepatocytes).

After incubation of [^{14}C]daprodustat with S9 fractions from livers of Aroclor 1254 induced male Sprague Dawley rats, only unchanged daprodustat was detected, but no metabolites were observed in the radio-chromatograms. Also in isolated perfused liver from bile duct cannulated rats, no metabolites were observed in plasma extracts. However, although the main peak observed in bile extract was for unchanged daprodustat, also four oxidative metabolites were also observed (M2, M8, M9 and M10).

Metabolisation of daprodustat was investigated using incubation in hepatocytes from different species. No metabolites were observed in dog hepatocytes and only one (M8), two (M8 and M9), or four (M8, M9, M10 and M22) metabolites (all mono-oxygenated) were detected in mouse, rat and hamster hepatocytes. In rabbit, monkey and human hepatocytes, daprodustat was extensively metabolised. Besides the three mono-oxygenated metabolites (M8-M10), also several di-oxygenated metabolites (M1-M7 and in minipigs also M21, M23 and M24) were also detected. A glucuronide metabolite (M12) was only detected in the monkey. All of the metabolites detected in human hepatocyte incubates were also detected in monkey hepatocyte incubations and, except for M5, M6 and M7, also in the rabbit.

After incubation of daprodustat in hepatocytes from different species with the addition of human recombinant CYPs, nineteen metabolites were detected, of which fourteen in human hepatocytes. Three of the mono-oxidation metabolites were formed in rh-CYP2C9, 2D6 and 3A4 while no metabolites were detected in rh-CYP1A2 and 2C19 incubations. Further studies in human liver microsomes in the presence and absence of the selective CYP inhibitors or NADPH indicated that CYP2C8 is the primary CYP enzyme involved in the oxidative metabolism of daprodustat *in vitro* with a minor contribution by CYP3A4 and that potential for oxidative bioactivation is low.

Results from an *ex vivo* study in both human and mouse plasma indicate that the major circulating stereoisomeric forms of M3 and M13 metabolites are GSK2506104 and GSK2531401 and that interconversion of stereoisomers does not occur.

In *in vivo* mice studies, oral administered daprodustat was metabolised only to the three mono-oxidated metabolites M8, M9 and M22. In rat, only the parent compound was detected in plasma and liver. In bile however, several metabolites were found (20% of the dose), which were exclusively from the oxidative pathways and mainly mono-oxidation (hydroxylation) of the cyclohexane group at carbon 4. In another study in the rat, two mono-oxidation metabolites (M9 and M22) were detected in plasma.

No gender differences were observed.
In rabbit, more extensive metabolism of daprodustat was observed following oral administration: besides the parent compound, several products of mono- and di-oxidation (hydroxylation) (M2, M3, M4, M5, M8, M9, M10 and M22) were identified in plasma.
The only radiolabeled component detected in plasma in the dog was the parent compound.
As in rabbits, in monkey plasma, besides the parent compound (>47%), several products of oxidation, including mono-oxidation (M8, M9, M10 and M22), di-oxidation (M2, M3, M4, M5, M6, M7 and M21) and tri-oxidation (M13), were identified. Only the amounts of M9 and M22 increased slightly after repeated administration of daprodustat. Except for M18 at later timepoints (>20%), none of the metabolites were present at more than 5% of plasma radioactivity.

Extensive metabolism was also observed in humans: in plasma products of mono-oxidation (M8, M9, M10 and M22), di-oxidation (M2, M3, M4, M5, M6, M7 and M21) and tri-oxidation (M13) were identified. These metabolites were also detected in urine. Predominant metabolites M2, M3, M4 and M13 represented 5.7% to 8.3% of the plasma radioactivity. Metabolites M5 (co-eluting with M14), M6, M15 and M33 were observed at notable levels, each representing 2.3% to 4.5% of the plasma radioactivity.

Steady-state clinical data in CKD patients indicated that three circulating human metabolites (M2, M3 and M13) are >10% of DRM, while three additional circulating human metabolites M4, M5 and M6) are slightly below 10% of DRM.

Although the majority of the metabolites contain multiple chiral centres and could, therefore, exist in multiple stereoisomeric forms (except for M2, which, similar as daprodustat, does not contain a chiral centre), M3, M4, M5, M6 and M13 were primarily present in human urine as single stereoisomers. M5 and M6 were detected as pairs of stereoisomers. Chiral analysis of mouse plasma samples following dosing with daprodustat and metabolites M2, M3 and M13 indicated stereochemical conversion does not occur in the mouse.

The metabolites of daprodustat were predominantly eliminated via the bile (20% of the dose), with 2% of the dose in urine accounting for metabolites. In BDC dogs, excretion was almost exclusively as unchanged parent: >80% in faeces, 6% in bile and <2% in urine. Small amounts of M8 and M9 (0.05% each) were detected in urine. In BDC monkeys, biliary excretion of unchanged daprodustat and glucuronides of daprodustat (M19, M20, M25-M29) accounted for ~17% and 11% of the dose, respectively. In addition, oxidative metabolites were secreted into the bile, accounting for at least 24% of the dose. Excretion via urine is almost exclusively as oxidated metabolites (<4% for each metabolite) and only less than 1% as parent compound or as glucuronides.

Excretion

Excretion following single oral administration of [^{14}C]daprodustat was evaluated in rat (10 mg/kg), dog (20 mg/kg) and monkey (10 mg/kg). In all species, the main elimination route was via faeces (86-88% in rats, 81-86% in dogs and 78% in monkeys). Urinary excretion was 9-11% in rats, ~2% in dogs and 13% in monkeys. Experiments with bile duct cannulated animals showed that biliary excretion accounted for 42%, 8% and 53% in rats, dogs and monkeys, respectively. Also in humans excretion occurs predominantly via the faecal route.

In BDC rats, daprodustat was predominantly eliminated as unchanged parent in faeces (33% of the dose), with an additional 18% and 0.3% of the dose as parent in bile and urine, respectively.

In humans, 21% of the orally administered dose (25 mg) was excreted via urine (exclusively as oxidative metabolites). Faecal excretion accounted for 74% of the oral dose, with 0.5% as unchanged daprodustat.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Single-dose oral administration to rats and mice was lethal at doses of ≥1500 mg/kg daprodustat. No mortality was observed in dog and *Cynomolgus* monkey, up to doses of 180 and 600 mg/kg, respectively. At lower doses, across all species, adverse effects were related to changes in feces, reduced body weight and/or emesis.

2.4.4.2. Repeat dose toxicity

Repeat-dose toxicity studies with daprodustat and/or metabolites were conducted in mouse, rat, rabbit, mini-pig, Beagle dog and Cynomolgus monkey. The administration was performed through oral gavage, IV, and the topical route for daprodustat and SC for major human metabolites (in mouse only). For the assessment of this product, only the relevant pivotal repeat-dose toxicity studies for the indication and route of administration have been assessed (e.g. GLP mouse (≤3 months), rat (≤6 months), Beagle dog (≤3 months), and *Cynomolgus* Monkey ((≤9 months) oral gavage studies for daprodustat and human major metabolite studies in mouse).

In the chronic rodent repeat-dose toxicity studies animals were exposed to daprodustat up to an exposure margin of 896 (mouse), 1480 (rat), ~80 (Beagle dog) and 46.6 (cynomolgus monkey) fold exposure at MRHD, and a NOAEL was established at an exposure margin of 195 (mouse, 3 month study) and 295 (rat, 2 year carcinogenicity study), 20.5 (Beagle dog, 3 month study) and 3.75 (cynomolgus monkey, 9 month study) fold exposure at MRHD. In some of the shorter repeat-dose toxicity studies, even higher exposure margins were tested.

The following major findings were observed in the repeat-dose toxicity studies.

<u>(Exaggerated) pharmacology effects</u>

Across species, at lower doses of daprodustat, mainly expected pharmacology-related effects were observed, including increased extramedullary haematopoiesis (spleen, liver) and erythroid hyperplasia in the bone marrow. These findings often correlated with elevated increases in red blood cell (RBC) count, haemoglobin and reticulocytes (erythroid parameters), and alterations in serum iron parameters. Additional exaggerated pharmacology-related adverse effects observed at the LOAEL and higher included decreased platelet counts and plasma glucose and increased bilirubin. At the highest doses, adverse events related to exaggerated pharmacology of sustained erythropoiesis included multi-organ toxicity related to tissue hypoxia and congestion, leading to moribund conditions and mortality at the highest doses tested. At higher exposure margins (rat 1480 EM, mouse 719 EM, dog highest dose tested (EM not available)) exaggerated pharmacology mediated generalised congestion and thrombosis due to compromised blood flow and vascular perfusion was observed across multiple organs, including the heart, kidney brain, liver, lung and/or vessel walls.

In the half year repeated dose toxicity study in rats, males appeared to be more sensitive than females. The dose of 10 mg/kg/day was not tolerated by male rats and all animals died or were sacrificed between day 42 and 135 due to poor survival. For female rats, no histopathological observations were done at 4 mg/kg/day and a NOAEL of 4 mg/kg/day can be agreed. In males however, haemorrhage was observed in heart (n=2) and in lung (n=1) at 4 mg/kg/day and the number of incidents were even higher in the 10 mg/kg group (haemorrhage in heart, n=4 and in lung, n=4), indicative of a dose response. In addition, increased liver and spleen weight relative to body

weight were observed in males from 4 mg/kg/day and in females at 10 mg/kg/day. Due to the haemorrhage observations, increased organ weights and on the background of higher sensitivity seen in male rats, a NOAEL of 4 mg/kg/day is not agreed. Conclusively, these findings suggested a NOAEL for male rats of 0.8 mg/kg/day (251 fold exposure margin compared to MRHD) in the half year repeated dose toxicity study.

In *Cynomolgus* monkey, in the 9-month study, dose-related increases in Hct were related to multi-organ congestion in the kidney, liver, eye, and focal haemorrhage brain at exposure margins of ≥10 fold. The NOAEL in monkey was 3 mg/kg/day. The systemic exposure margins in monkey to estimated human exposure at MRHD was x3.75 and 4.38, based on AUC at the dose levels 24 mg/day QD or 48 mtg/day TIW, respectively.

In the dog, clinical signs associated with morbidity were tremors, staggering, convulsions, prostration, and laboured respiration. In mouse and *Cynomolgus* monkey, retinal (vessel) congestion was observed, with hyperaemia optic disc in monkey and choroidal hyperaemia in the mouse.

Effects on nerves

In the mouse repeat-dose toxicity studies with/without metabolites (SC) and mouse 2-year carcinogenicity study (with SC metabolites), nerve fibre degeneration in the sciatic nerve, axonal degeneration in the lumbar spinal cord, and myofiber atrophy in hindlimb skeletal muscle were observed. Findings were observed at exposure margins of 256 fold exposure at MRHD, with a NOAEL for this effect of 73 fold MRHD. Axonal degeneration of the sciatic nerve was observed in a single dog in the three-month study at an exposure margin of ~100 fold MRHD and was considered likely an effect of trauma due to convulsions observed in this dog a few days earlier. In rats and cynomolgus monkeys, no effects on nerves have been observed.

The applicant hypothesised that a possible basis for adverse effects on nerves might be ischemia as a consequence of compromised perfusion due to the increased haematocrit and/or decreased mean serum glucose concentrations, potentially related to increased glucose consumption due to the increased number of red blood cells. The latter is because it has been shown earlier that rodent hindlimb peripheral nerves are known to be sensitive to damage from hypoglycaemia.

To further investigate the cause of hypoglycaemia, the applicant performed an investigative 2-week oral dose study with rats, in which *ex vivo* blood was exposed to the anti-glycolutic agent sodium fluoride. This showed that decreases in plasma glucose concentrations observed are an *in vivo* effect of daprodustat administration and not an *ex vivo* artifact of glucose consumption due to increased RBCs counts. The applicant hypothesizes that decreased serum glucose concentrations may be a consequence of increased glucose utilization by red blood cells due to daprodustat pharmacology, as young red blood cells metabolize 2.5-fold more glucose than old red blood cells.

The applicant found the nerve effects in mice were not considered a safety concern in humans as findings were observed in a setting of severely exaggerated pharmacology and as daprodustat will be titrated to a specific range of Hb levels in patients. In addition, hypoglycaemia was not identified as a risk in the clinical trials.

Gastrointestinal effects

Oral treatment with daprodustat resulted in effects on the gastrointestinal tract in mice, rat, dogs, and *Cynomolgus* monkeys. Effects included abnormal faeces in all four species, emesis in dogs and *Cynomolgus* monkeys, and gastric erosions/ulcers in all four species. Gastric erosions were also observed in a rat IV study with similar plasma exposure. The applicant discussed COX inhibition as a possible mechanism behind ulcer forming, but COX1 and COX2 IC50 values in rat whole blood assays were found to be >46-fold Cmax at MRHD. Therefore, this mechanism is not likely related to the

daprodustat-induced gastric effects. The applicant argues that the most likely mechanism behind these erosions and ulcers could be vascular perfusion associated with marked increases in haematocrit. Gastric erosions in rats have earlier been associated with repeated administration of a recombinant human EPO at doses that caused similar Hct increases as daprodustat did. In addition, the applicant cites publications describing the intrinsic sensitivity of gastric microcirculation to increased blood viscosity, which can result in stasis, congestion, arteriovenous shunting, and ischemic injury in the stomach. In *Cynomolgus* monkey, the adverse gastric effects were also associated with sustained increased haematocrit, but after 6 weeks of recovery, these effects were not apparent. In a review of clinical safety data, the applicant did not find gastric erosion or ulceration as a safety concern.

2.4.4.3. Genotoxicity

Daprodustat was not found to be genotoxic in the reverse mutation test, mouse lymphoma assay and the *in vivo* Comet assay.

In the rat bone marrow micronucleus assay, daprodustat showed a small (2-fold), but statistically significant, increase in micronuclei in rats given 2000 mg/kg/day, but not following 1000 mg/kg/day. At these dose levels, high exposures have been reached as concentrations of daprodustat were higher than the Cmax in the single-dose TK study at a dose of 31 mg/kg. The applicant argued that this was due to the pharmacologic activity (increased erythropoiesis) of daprodustat, as evidenced by increased circulating reticulocytes, and was not considered a direct genotoxic effect. In addition, an *in vivo* chromosome aberration test was performed to evaluate the clastogenic potential of daprodustat. At all dose levels tested (500 – 2000 mg/kg), daprodustat induced marked reductions in the mitotic index in bone marrow lymphocytes and caused chromosome condensation 16 hours post-dose. This led to poor morphology, and therefore chromosome aberrations were not analysed. These effects were not observed 42 hours post-dose, but no analysis was performed due to mortality in the 2000 mg/kg group.

Metabolites M2, M3 (both stereoisomers), M4, M5, M6, and M13 were not found to be genotoxic in the reverse mutation test. Metabolites M2 and M3 (both stereoisomers) were not genotoxic in the mouse lymphoma assay.

In the mouse lymphoma assay, M13 was slightly genotoxic (2.4-fold and 2.8-fold compared to the mean vehicle control mutant frequency, respectively) at the 3 hr treatment in the presence of S9 (small colonies) and the 24 hr treatment in the absence of S9 (small and large colonies), at the maximum tested concentrations (160 and 425 µg/mL, respectively). These maximum tested concentrations were also found to be cytotoxic, as evident from reductions in Relative Total Growth of 11.9% and 17.4%, respectively.

In the Comet assay, M13 was negative following two intravenous doses of 25 or 100 mg/kg/day, while the results for 200 mg/kg/day were considered equivocal since a weak effect was observed that was not reproducible across three studies. The dose levels were based on the maximum tolerated dose in a dose range-finding study. The liver was chosen as a test organ as an endpoint not confounded by haematopoietic effects and as the site of M13 formation in humans. Mice were dosed intravenously (bolus injection) to maximise exposure to the test article.

In addition, an *in vivo* chromosome aberration test was performed to evaluate the clastogenic potential of M13 following single IV doses of 25, 100 or 200 mg/kg. M13 did not induce chromosome aberrations at any dose, but at 200 mg/kg, the mitotic index was decreased (31%) at 16 hours post-dose but not at 42 hours post-dose.

Overall, there was no genotoxic potential for daprodustat and its metabolites.

2.4.4.4. Carcinogenicity

Daprodustat's potential for induction of carcinogenicity was assessed in rat and mouse in long-term 2-year studies.

Tumour incidences for which there was an observed increase were often not statistically significant, not observed in a dose-responsive manner, or were common tumours for the specific strain based on historical control values within the test facility. Tumour findings within this context included hepatocellular carcinomas in male mice, gallbladder adenomas and harderian gland adenomas in female mice, thyroid c-cell adenomas in male rats, and endometrial stromal polyp in female rats.

In the rat carcinogenicity study, the incidence of fibroadenomas in females (77.14%) was outside literature data (reported up to 72.2%) or historical control data from the test facility (reported up to 68.33%). However, a greater number of high dose aged females were euthanized at termination than control aged females. Together with the fact that aged female Sprague Dawley rats are prone to develop mammary gland tumours, it has be agreed with the applicant that these are likely to be spontaneous. In males, the incidence (12.70%) was also above historical control data (up to 3.33%), but it can be agreed that the tumours are most likely not caused by a pharmacological dependent mechanism despite the pharmacological activity of daprodustat that was observed at this dose (increased hemoglobin). Thus, it has been agreed that there is a sufficiently large safety margin for the carcinogenic effect.

Two high-dose male rats showed adenomas in the stomach and hemangiosarcoma's in the spleen above the historical control range incidence. These tumours could be related to toxicological or pharmacodynamic effects since stomach toxicity (ulcers/erosion), and pharmacodynamic related haematology effects were observed in daprodustat-treated rats. It should be noted that carcinogenicity is covered in the RMP as an unidentified risk.

2.4.4.5. Reproductive and developmental toxicity

FEED

Male and female fertility was assessed in the rat. In male rats, decreases in seminal vesicle weight and prostate weight were observed, without any impact on fertility parameters or observed morphological changes, at an exposure margin of approximately 1850 fold exposure at MRHD. At extremely high exposure margins (~3.500 fold MRHD), and under maternal toxicity, the number of corpora lutea, implantation sites, and intra-uterine survival were reduced. The NOAEL for female fertility was established at an exposure margin of 1.168 fold exposure at MRHD. Due to the supratherapeutic exposure margins and presence of maternal toxicity, the findings for female fertility were not considered clinically relevant.

EFD

At the highest dose tested in pregnant rats, maternal toxicity consisted of decreased body weight gain and food consumption accompanied by salivation. In addition, at this dose, post-implantation loss and an increase in skeletal variations, including reduced ossification, were observed. These fetal findings are considered to be secondary to maternal toxicity. At the developmental NOAEL, the exposure margin was 1.168-fold exposure at MRHD.

In pregnant rabbits, at all doses tested (lowest dose 4 mg/kg/day or 24.5-fold EM), daprodustat induced maternal toxicity, including decreased body weight gain and food consumption, with two abortions at high dose. The number of implantations was decreased at low and high doses, resulting in a reduced number of live fetuses. A similar finding was observed in the rat FEED study at the highest

dose tested. At the mid-dose in the rabbit EFD study, however, reduced implantations were not observed, but there was an increase in resorptions in six dams, resulting in 33-63% post-implantation loss across these six animals. As in rabbits, adverse effects surrounding implantation were observed in all daprodustat dose groups; a developmental NOAEL is not established in the rabbit EFD study. Upon request, the applicant provided a thorough discussion of findings surrounding implantation in the rat FEED and rabbit EFD study. In the rat FEED study, a strong association between body weight losses and the effect on ovulations resulting in reduced numbers of corpora lutea and secondary effects on implants at 100 mg/kg/day was observed. Dosing stopped at implantation, but maternal toxicity was still present after discontinuation of the product, which may have affected implantation resulting in early resorptions. These effects were unlikely related to the PD as at lower doses, in absence of maternal toxicity and in presence of PD, these findings did not occur. In addition, the findings were observed at a supratherapeutic exposure.

Regarding the findings in the rabbit EFD outcome, the finding of post-implantation loss at the mid dose was within historical control of the CRO (6.8-28.1%). In addition, the pre-implantation loss effect at low and high dose were not considered relevant as exposure was initiated after implantation. As the NOAEL was established at 60 mg/kg/day, sufficient exposure to metabolites M2 and M3 was reached in the rabbit EFD. At this NOAEL in rabbit, M13 exposure is not sufficient.

As M13 exposure margins in the rabbit EFD at the NOAEL of 60 mg/kg/day were not sufficient, a follow-up investigation was implemented into the rat PPND study. To further investigate the effect of human metabolites M2, M3, and M13 on embryo-fetal development, a modified rat PPND study was conducted with SC dosing of the three major human metabolites as a fixed-dose cocktail together with daprodustat in three different dose groups. The applicant provided a rationale for their study design, which included a gross evaluation of pups, a viability evaluation on PND1, and a macroscopic necropsy of visceral and skeletal tissues for malformations at PND91 and of pups that died before end of study. The metabolites in this modified PPND/EFD study were tested at a sufficient exposure margin compared to exposure at MRHD, the non-clinical package investigating embryo-fetal developmental toxicity has been considered sufficient.

PPND

Effects on pre-and postnatal development by daprodustat by oral gavage and its major human metabolites M2, M3 and M13 by sub-cutaneous injection were investigated in rat. Level of exposure to major metabolites was the same across all dose groups (EM M2: 2.63 fold, M3:2.05 fold, M13: 2.77 fold).

For F0 and F1, adverse findings were only observed at high dose daprodustat (approximately 2400 fold exposure at MRHD), with a NOAEL for both F0 and F1 at approximately 900 fold exposure in F0 animals compared to exposure at MRHD.

At the highest dose tested, for F0, maternal body weight gain were reduced during gestation interval GD6-21, with the greatest change at late gestation. During lactation, maternal body weight gain was lower from LD1-4. Also, mean food consumption was reduced from GD18 through LD8.

At high dose, postnatal survival was decreased in the F1 generation, with an increase of pup death from PND2-7, a decreased lactation index, a reduced number of surviving pups per litter, and mean litter size. In addition, the mean pup weight was decreased until PND14.

Post-lactation, body weight gains were decreased in males until PND 43 and in females until PND29. Pregnant F1 female body weight gain was generally slightly decreased during gestation and lactation. No effects on PND7 F2 generation were observed.

In 8 F1 animals, from PND53 onwards, swelling of the abdomen was observed, but no correlated findings were found during necropsy.

Due to the high exposure margins obtained in this study for daprodustat, the effects observed on F1 generation were considered of limited importance for humans.

Juvenile Toxicity

Juvenile toxicity was assessed in rats. In exploratory studies, it was observed that Cmax exposure to daprodustat at similar doses was increased from PND4 through PND13. Therefore, the dosing scheme was adjusted over time in the pivotal JAS based on investigative exposure data in juvenile rats.

In the pivotal JAS, juvenile SD rats were treated with daprodustat by oral gavage from PND4-70. Daprodustat was dosed once every other day at dose levels of 0, 2, 10, or 20 mg/kg from PND 4 through PND 10 (PND 4, 6, 8, 10), and then doses in the respective groups were decreased to 0, 0.8, 4 or 10 mg/kg and given once daily after PND 12 up to PND 70. A 3-month recovery phase was included for all dose levels. The major human metabolites M2, M3 and M13 were not taken into account in this study.

Main body weight gain was decreased during PND 4 through 28, at high dose and with a non-significant trend at the mid-dose. At the end of the dosing period, mid and high-dose body weight gains were similar to control. Right femur length was non-significantly decreased in high dose females, which was also observed at this dose after recovery. At mid and high doses in females, delayed vaginal patency and at high doses, increased oestrous cycle length was observed with some animals in continuous oestrus cycle (although this finding was within historical controls of the testing facility). The applicant considered the femur, vaginal patency and oestrus cycle effects are secondary to the effects on body weight.

Pharmacodynamic effects were observed at high dose only from PND35 onwards and included increases in red blood cell mass parameters (red blood cell count, haemoglobin, and haematocrit) and reticulocyte counts (at PND64).

Based on the daprodustat induced effects on body weight and subsequent effects on femur length and female reproductive parameters, the NOAEL in this study was considered the low dose of 2/0.8 mg/kg.

2.4.4.6. Toxicokinetic data

Toxicokinetics

Plasma concentrations of daprodustat increased approximately dose proportionally to less than dose proportionally in the repeated dose toxicity studies with daprodustat. Exposure margins were calculated based on total daprodustat levels in plasma instead of the more accurate free fractions. For daprodustat, protein binding in humans is slightly higher than in animal species. Calculation of EMs based on total daprodustat instead of free daprodustat will result in smaller EMs than the more accurate EMs when based on free fractions. This was considered a worst-case scenario and is therefore acceptable. Exposure was sufficient to evaluate safety in the toxicologic studies. Exposure multiples (based on AUC_{0-24} and the 24 mg/day QD dose regimen in humans) at the NOAEL varied from 3.75 in monkeys to 295 in rat for oral administration.

Plasma protein binding of major metabolites was only investigated in human plasma but not in animal plasma. Therefore, accurate exposure margins (based on free fractions of the metabolites in plasma) could not be calculated. Nevertheless, considering that the metabolites are structurally very similar to daprodustat, no significant differences in protein binding between humans and animals are expected and there is little concern that the unknown protein binding of major metabolites in the preclinical

animal species would have a significant impact on the exposure margins as calculated based on total metabolite exposure. In addition, when the free fraction is very high, as is the case for the major metabolites in humans, minor discrepancies in protein binding in the animals have little impact. Taken together, there was no concern that the lack of protein binding data in animals for the major metabolites would have a clinically relevant effect on the exposure margins.

Interspecies comparison

The pharmacokinetics of daprodustat were studied in mice, rats, dogs and monkeys. Daprodustat was readily absorbed following oral administration (T_{max} 1-8h upon single and multiple dosing), which is similar to humans (1-4h). It was noted that dose-normalised C_{max} and AUC is clearly lower in monkeys than in other animal species, presumably due to the more extensive metabolism. Plasma clearance in animals is low at 0.2-8.4 ml/min/kg, as well as in humans (6.3 ml/min/kg for a 50 kg weighing adult). Following single or multiple oral dosing (up to 104 weeks of daily administrations), an approximately dose-proportional to less than dose-proportional increase in exposure was observed in all species as well as in humans at doses from 1-500 mg. Plasma AUC accumulation was not observed, in line with the short terminal elimination half-life. Elimination of daprodustat was rapid, with terminal elimination half-life ranging from 2 h in monkeys up to 33.5 h in rats. Daprodustat is predominantly excreted via faeces in both animals and humans. No gender differences were observed in the pharmacokinetics of daprodustat. In humans, a plasma terminal half-life (1-4h) was found. The oral bioavailability of daprodustat in humans was estimated to be 65%, which is in between the values observed for animal species (88% in mice, 78% in rats, 25-45% in dogs, depending on the formulation and 34% in monkeys).

The metabolism of daprodustat differs greatly between species. The three major metabolites observed in humans were detected only in rabbits and monkeys, but not in mice, rats and dogs.

2.4.4.7. Local Tolerance

A range of local tolerance tests was performed, mainly for a different topical indication for daprodustat. In the *in vivo* mouse local lymph node assay, daprodustat was considered not a contact sensitiser.

2.4.4.8. Other toxicity studies

Phototoxicity

Daprodustat does not absorb within the UV-visible spectrum (290 to 700 nm) and thus does not present a concern for phototoxicity.

2.4.5. Ecotoxicity/environmental risk assessment

Table 2: Summary of main study results

Substance (INN/Invented Name): Daprodustat			
CAS-number (if available): 960539-70-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log D_{ow} at pH 5 = 3.7 Log D_{ow} at pH 7 = 1.42 Log D_{ow} at pH 9 = -0.661	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log K_{ow}	Log D_{ow} at pH 7 = 1.42			not B
Persistence	inherent biodegradability	Not inherently biodegradable (0% biodegradation observed in an OECD TG 302C (MITI) study			P
	DegT50	$DT_{50, water}$ = 73.2/17.09 d (l/l) $DT_{50, sediment}$ = >10,000 d (both systems) (l/l) $DT_{50, system}$ = >10,000 d (both systems) (l/l)			l=lake DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	1.1 mg/L 0.99 mg/L ≥ 11 mg/L			not T
	CMR	Not addressed			
PBT-statement :	daprodustat is considered not PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, default F_{pen}		0.12 µg/L			> 0.01 threshold: Y
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 65065.0 $K_{F\ sludge}$ = 31686.6 $K_{oc\ soil}$ = 16579, 423, 949 L/kg $K_{F\ soil}$, 447.6, 20.7, 14.2 L/kg			Sorption is not OC dependent.
Inherent Biodegradability Test	OECD 302C	Not inherently biodegradable (0% biodegradation)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 34.5 d/8.05 d (l/l, dissipation) $DT_{50, sediment}$ = >1000 d (both systems; l/l) $DT_{50, system}$ = 518 d and >1000 d (r/r) Sediment shifting 29-78%			l=lake DT_{50} values at 20°C. Significant shifting to sediment (and NER) observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidocelis subcapitata*	OECD 201	NOEC	1100	µg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	990	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	≥11000	µg/L	No effects observed up to tested concentration
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	16000	µg/L	Respiration
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	> 10 000 d 0.5 - 12.8 $\%CO_2$		for all 4 soils *TP > 10%: yes, 28.2%, 1,3-dicyclohexyl-2,4,6-trioxohexahydropyrimidine-5-carboxamide*
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	>1000	mg/ kg_{dw}	Nitrification
Terrestrial Plants, Growth Test/*Daucus carota*	OECD 208	NOEC EC10	4.12 1.20	mg/ kg_{dw}	Seedling weight

Earthworm, Acute Toxicity Tests/*Eisenia fetida*	OECD 222	NOEC	95.3	mg/ kg_{dw}	Reproduction
Collembola, Reproduction Test/*Folsomia candida*	OECD 232	NOEC	95.3	mg/ kg_{dw}	Reproduction
Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	342	mg/ kg_{dw}	Development rate not normalised to 10% o.c.

Conclusions on studies for Jesduvroq

Daprodustat is not PBT, nor vPvB.

Considering the above data, daprodustat is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

Pharmacodynamics

In an *in vivo* mouse study, blood parameters showed increases concerning Hb, Hct, and RBCs. However, unintended decreases in platelets and WBCs were observed as well. Importantly, two clinical studies (a placebo-controlled clinical study and a comparative study versus ESA therapy) showed no evidence for decreases in platelets and WBCs in both studies, which reveals that the findings in the mouse study are not translated to clinical trials.
As mentioned in the pharmacokinetics section, no metabolites were detected in dog plasma after daprodustat administration. This might have potentially decreased the value of dog cardiovascular study since the effects of metabolites are not included as a result of the absence of metabolites in this species. However, clinical studies have investigated cardiovascular effects extensively (including ECG abnormalities), thus preventing the need for an alternative study with a different species.

The Applicant justified the absence of the Thyroid hormone receptor (TR) in a receptor binding screen by convincingly showing no indications for TR binding by daprodustat. Daprodustat was shown to inhibit COX1 in a dose-dependent manner, with an approximately 30-fold weaker effect than indomethacin. Nevertheless, despite that the metabolites have a similar pharmacologic effect as daprodustat, the inhibitory activity of the metabolites on COX1 has not been investigated, whereas this has been tested for COX2 (with IC_{50} values >100 µM for daprodustat and its metabolites). The Applicant justified why the inhibitory activities of the COX 1 metabolites were not investigated, by taking into account the low degree of plasma protein binding of metabolites in humans.

Upon request, the applicant provided evidence for transferrin expression increases upon daprodustat administration.

Pharmacokinetics

Plasma protein binding of major metabolites is only investigated in human plasma but not animal plasma. Therefore, accurate exposure margins (based on free fractions of the metabolites in plasma) cannot be calculated. Nevertheless, considering that the metabolites are structurally very similar to daprodustat, no dramatic difference in protein binding between humans and animals is expected. Therefore, there is little concern that the unknown protein binding of major metabolites in the preclinical animal species would significantly impact the safety assessment. According to ICH M3 (R2) – questions and answers, characterisation of metabolite toxicity would generally only be considered adequate when animal exposure (1 species is sufficient) is at least 50% of the exposure seen in humans. Since no other toxicity except that associated with the expected exaggerated pharmacology was demonstrated in the 39-week study in monkeys, and exposure margins based on total metabolite

concentration are above 1 in the carcinogenicity study in mice as well as in the PPND study is rats, it can be concluded that the metabolites are sufficiently characterised for these endpoints.

Toxicology

The mouse and rat single-dose toxicity studies were set up to determine a lethal dose in these animals. According to ICH M3(R2) and within the framework of 3Rs, lethality should not be an intended endpoint in studies assessing acute toxicity. As of ICHM3(R2), the applicant should have used a dose-escalation study design for the rat and mouse to determine the MTD instead, as they did for the dog and *Cynomolgus* monkey.

At the mid and/or high doses in the chronic repeat-dose toxicity studies in rats, observed effects were severely adverse, leading to moribundity and mortality of the animals. It is recognised that relatively high exposure margins (250 fold) were needed to achieve pharmacological response in rodents; however, the highest doses tested had an exposure margin of up to 1700 fold in rats, resulting in an extremely severe adverse response, including exaggerated pharmacology-driven morbidity and mortality. In addition, a similar approach was taken for dose selection in the chronic dog and monkey repeat dose toxicity studies, where extreme adverse exaggerated pharmacology at high exposure levels was observed. Considering the high exposure margins with severely exaggerated pharmacology-related toxicity and the 3Rs principles, the findings observed at these high exposures are not considered scientifically and clinically relevant. In accordance with 3Rs and Directive 2010/63/eu, information on adverse exaggerated pharmacology findings in the shorter repeat dose toxicity studies should have led to a lower high dose selection in the pivotal chronic repeat dose toxicity studies across all tested species. The applicant should consider the 3Rs principles more closely for future non-clinical study protocols.

Expected pharmacodynamic effects in rodents and dogs, including increased Hb and Hct levels, were observed at exposure levels up to orders of magnitude higher than in humans. In this case, exposure margins may not provide a clear understanding of safety. Therefore, a comparison between expected pharmacodynamic response and the presence of adverse findings at similar or lower exposure levels, in general, may be more informative. Across the repeat-dose toxicity studies in mouse, rat, dog and monkey, at lower doses expected pharmacology was observed, which was considered not adverse, followed by adverse exaggerated pharmacology at higher doses. In the rat 2-year carcinogenicity study, the NOAEL was set to 0.8 mg/kg/day. However, progressive cardiomyopathy was observed at a dose preceding the expected pharmacological response on RBC parameters at the set NOAEL. Upon request, the applicant showed that progressive cardiomyopathy has a high spontaneous background in aged rats at the test site, with even a higher incidence observed in males, with a mean historical control of 82% (margin 55% to up to 100%). In addition, the applicant provided a discussion that this finding is rat specific and no clinical correlate for this finding is apparent. It is agreed that this finding can be considered of low clinical relevance and that clinical cardiovascular outcome is more relevant.

In the rat bone marrow micronucleus assay, daprodustat showed a small (2-fold), but statistically significant, increase in micronuclei in rats given 2000 mg/kg/day but not following 1000 mg/kg/day. In addition, an *in vivo* chromosome aberration test was performed to evaluate the clastogenic potential of daprodustat. At all dose levels tested (500 – 2000 mg/kg), daprodustat induced marked reductions in the mitotic index in bone marrow lymphocytes and caused chromosome condensation 16 hours post-dose. This led to poor morphology; therefore, chromosome aberrations were not analysed. These effects were not observed 42 hours post-dose, but no analysis was performed due to mortality in the 2000 mg/kg group. It would have been preferable if the lower doses (500 and 1000 mg/kg) were analysed. Nevertheless, the maximum dose where no chromosome condensation was observed (1000 mg/kg) corresponds to an extremely high exposure compared to exposure at the MRHD (estimated to

have an AUC-based EM of approximately 5800 based on a 14-day rat toxicity study). Hence, the clinical relevance of this finding was considered limited.

In the Comet assay, M13 was negative following two intravenous doses of 25 or 100 mg/kg/day, while the results for 200 mg/kg/day were considered equivocal since a weak effect was observed that was not reproducible across three studies. From a 3Rs perspective, it is not understood why three independent studies were performed for M13 with the Comet assay. Upon request, the Applicant indicated that the Comet Assay was repeated to investigate the reproducibility of the positive response until two negative outcomes were acquired, resulting in an overall equivocal conclusion. This was not considered acceptable, nor was it justified from a 3Rs perspective. Nevertheless, the exposure of M13 at 100 mg/kg, at which in neither of the three studies positive results were observed, corresponds to an exposure multiple of 132 (based on AUC) based on a single dose PK study. Therefore, at clinically relevant exposures, no risk for DNA damage has been anticipated.

In addition, an *in vivo* chromosome aberration test was performed to evaluate the clastogenic potential of M13 following single IV doses of 25, 100 or 200 mg/kg. M13 did not induce chromosome aberrations at any dose, but at 200 mg/kg, the mitotic index was decreased (31%) at 16 hours post-dose but not at 42 hours post-dose. This was also observed with daprodustat itself. Upon requesting to discuss these findings, the Applicant reasoned that the observed mitotic index reductions in lymphocytes with daprodustat and M13 are likely due to daprodustats effects on cell cycle delay. This was considered plausible, considering the HIF-stabilization effects on cell cycle arrest in G1 phase and the decreased circulating lymphocyte counts observed in repeated dose toxicity studies. It was acknowledged that both daprodustat and M13 did not cause aberrant cells, and the mitotic index reductions were reversible.

In the mice carcinogenicity study, no dose-dependent daprodustat-related neoplastic findings were observed in mice at doses up to 3 mg/kg (EM 256 or 299 (based on 24 mg/kg QD or 48 mg/kg TIW, respectively).

In the rat carcinogenicity study, the incidence of fibroadenomas in females (77.14%) was outside literature data (reported up to 72.2%) or historical control data from the test facility (reported up to 68.33%). Phosphoglycerate kinase 1 (PGK1) is a target gene for the transcription factor HIF, and has, similar to VEGF, been implicated in tumour progression. In the two-year carcinogenic study in the rat, mammary gland neoplasia was considered the cause of demise for several females; however, a clear dose-response was not observed. In addition, the Applicant has investigated VEGF and PGK-1 gene expression by daprodustat treatment, *in vitro* by using Hep-3B cells (at 25 uM) and *in vivo* (60 mg/kg) in liver and kidney from mice. As stated above, the result showed that EPO induction was considerably stronger induced in the HEP 3B cells, 7.4-fold compared to 2.9 fold and 2.0 fold for PGK and VEGF mRNA, respectively, and in the *in vivo* gene expression analysis in mice, EPO increased ≥35 fold compared to <2 fold for PGK. It is agreed that contribution by VEGF and/or PGK by daprodustat treatment on tumorigenesis is not likely, while the margins to satisfactory EPO induction are also acceptable. Based on the large difference in expression levels of EPO compared to PGK (and VEGF), together with the fact that aged female Sprague Dawley rats are prone to develop mammary gland tumours and that a greater number of high-dose aged females were euthanised at termination compared to control aged females.

In males, however, the incidence (12.70%) was also above historical control data (up to 3.33%), but there were less aged males in the high-dose group at termination (15 vs 20 in control). Upon request, the Applicant provided a discussion on the clinical relevance and possible mechanism behind the tumours. It was concluded by the Applicant that the 12.7% incidence of male mammary fibroadenomas in the high dose group of the rat carcinogenicity study represents a spurious and spontaneous change. This was not agreed, as the incidence is still nearly 2-fold compared to the most

up to date historical control data of the test facility, which is more relevant than the provided literature on a variety of rat strains. In addition, a dose-response relationship could not be excluded. However, it was agreed that a pharmacologically based mechanism of these tumours by daprodustat-mediated HIF-PHI inhibition can most likely be excluded based on the following points: 1) increases of male mammary fibroadenomas were not reported in rat carcinogenicity studies with Roxadustat (Evrenzo), 2) there were no hormonal effects throughout the toxicity studies, while this would normally be a molecular driver for these tumours, 3) degradation of HIF1α would normally induce genes favouring neoplasia, and 4) the large difference in expression levels of EPO compared to PGK and VEGF, of which the last two are pro-carcinogenic HIF-pathway genes. Furthermore, there was no increase in male mammary fibroadenomas in the mouse carcinogenicity study and the male mammary fibroadenomas in rats did not develop further into malignant adenocarcinomas following life-long treatment.

Overall, it was agreed that the mammary fibroadenomas in high dosed male rats are most likely not caused by a pharmacologically dependent mechanism despite the pharmacological activity of daprodustat that was observed at this dose (increased hemoglobin). Thus, it was agreed that there was a sufficiently large safety margin for the carcinogenic effect, suggesting that the findings are not clinically relevant. However, a treatment-related effect at doses of 4 mg/kg and higher could not be excluded due to the high incidence. Upon request, the wording on carcinogenicity in section 5.3 of the SmPC reflects that daprodustat was not carcinogenic in the mid-dose male group in rats and the high dose group in mice, corresponding to EMs of ~300 times and 250 times those at the maximum recommended human dose (MRHD) based on AUC, respectively.

The applicant found the nerve effects in mice were not considered a safety concern in humans as findings were observed in a setting of severely exaggerated pharmacology and as daprodustat will be titrated to a specific range of Hb levels in patients. In addition, hypoglycaemia was not identified as a risk in the clinical trials.

Upon request, the applicant thoroughly discussed findings surrounding implantation in the rat FEED and rabbit EFD study. In the rat FEED study, a strong association between body weight losses and the effect on ovulations resulting in reduced numbers of corpora lutea and secondary effects on implants at 100 mg/kg/day, was observed. Dosing stopped at implantation, but maternal toxicity was still present after discontinuation of the product, which may have affected implantation resulting in early resorptions. The applicant argued these effects were unlikely related to the PD as at lower doses, in the absence of maternal toxicity and in the presence of PD, these findings did not occur. In addition, the findings were observed at a supratherapeutic exposure.

Regarding the findings in the rabbit EFD outcome, the finding of post-implantation loss at the mid-dose was within historical control of the CRO (6.8-28.1%). The applicant further argues that the pre-implantation loss effect at low and high dose were not relevant as the exposure was after implantation. As the NOAEL can be established at 60 mg/kg/day, sufficient exposure to metabolites M2 and M3 was reached in the rabbit EFD. At this NOAEL in rabbits, M13 exposure is not sufficient. However, as the approach to study embryo-fetal development in the rat PPND was considered adequate (see below), and the metabolites in this study were tested at a sufficient exposure margin compared to exposure at MRHD, the non-clinical package investigating embryo-fetal developmental toxicity was considered sufficient. According to the applicant, M13 exposure margins in the rabbit EFD at their proposed NOAEL of 60 mg/kg/day were insufficient, so a follow-up investigation was implemented into the rat PPND study. To further investigate the effect of human metabolites M2, M3 and M13 on embryo-fetal development, a modified rat PPND study was conducted with SC dosing of the three major human metabolites as a fixed-dose cocktail together with daprodustat in three different dose groups. Upon request, the applicant provided a thorough and clear overview and rationale for the combined rat EFD + PPND study. Specifically, the concern of not performing a necropsy at caesarean section for scoring of malformations was circumvented by providing an in-depth necropsy of the fetuses that died before

weaning in combination with necropsy performed before weaning. In conclusion, the study design was considered sufficient to investigate both EFD and PPND endpoints. In addition, the study design was considered sufficient to study the effects of major metabolites M2, M3 and M13, all of which had an exposure margin of ≥2.0 fold exposure at MRHD. These findings are reflected in section 5.3 of the SmpC. It has to be noted that these non-clinical data reveal no special hazard for humans at clinically relevant exposures based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In the Juvenile toxicity study, adverse effects are observed preceding expected pharmacodynamic effects, which were also only apparent at PND35 and PND64. In case of an indication extension procedure to the paediatric population, the clinical relevance of these findings should be taken into account.

Daprodustat is neither a PBT nor a vPvB substance. Daprodustat is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

Assessment of the non-clinical dossier of daprodustat revealed no major objections to marketing authorisation. All other concerns were addressed sufficiently. There were no objections to marketing authorisation from a non-clinical point-of-view.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 3 Summary of studies supporting the clinical pharmacokinetics of daprodustat

study	description	dosing regimen
Biopharmaceutical studies		
PHI114703	relative bioavailability - effect of particle size	single oral dose of 100 mg (13, 29, or 41 µm 90th percentile particle size)
207727	Part A: bioequivalence	single oral dose Part 1: 4 mg (2 x 2 mg tablet) or 4 mg (1 x 4 mg tablet) (final formulation)
213022	Part A: effect of dissolution Part B: bioequivalence	single oral dose Part A: 4 mg different dissolution profiles Part B: 1, 2, 4, 6, and 8 mg commercial Process 1 and Process 2 tablets
PK studies in healthy subjects		
PHX111427	PK (including urinary excretion), PD, safety and tolerability	single oral dose of 2, 5, 15, 50, 150, and 300 mg
PHI115385	PK (including metabolites), PD, safety and tolerability in	single oral dose Part 1 (Japanese): 10, 25, 50 and 100 mg Part 2 (Caucasian): 10, 25 and 100 mg

Table 3 Summary of studies supporting the clinical pharmacokinetics of daprodustat

	Caucasian and Japanese subjects	
PHI113635	PK, safety, and tolerability (including QTc)	single oral dose of 75 and 500 mg
PHI112842	PK, PD, safety and tolerability	multiple oral dose for 14 days 15, 50, 75 and 100 mg once daily and 25 mg twice daily
200232	mass balance and absolute bioavailability	single dose Period 1: 6 mg oral and 50 µg [^{14}C]-daprostat IV 1 h later Period 2: 25 mg [^{14}C]-daprostat oral solution
PHI113634[#]	Part A: food effect of high fat meal	Part A: single oral dose 100 mg daprostat
207727	food effect of CKD meal	Part 2: final formulation, single oral dose 4 mg fed or fasted
PK studies in patients with chronic kidney disease		
PHI112843	PK, PD, safety and tolerability in subjects with Stage 3 to 5 renal impairment -/+ dialysis	single oral dose of 50 and 150 mg daprostat
205665	compare effect of daprodustat to epoetin alfa	Part B: multiple oral dose of 24 mg once daily daprostat for 57 days
204836	PK, efficacy, safety and tolerability	multiple oral dose of 10, 15, 25 and 30 mg three-times per week for 29 days
PHI115573	PK (daprodustat and metabolites) in subjects with Stage 3 to 5 renal impairment -/+ dialysis	multiple oral dose of 5 mg once daily for 14 or 15 days
200942	PK (daprodustat and metabolites; including plasma protein binding), safety and tolerability in subjects with end stage renal disease undergoing peritoneal dialysis	multiple oral dose of 5 mg once daily for 14 days
PHI204716	PK, efficacy, safety and tolerability in Japanese patients	multiple oral dose of 4 mg once daily for 4 weeks followed by dose adjustment (1 to 24 mg) as needed for the following 20 weeks
201754	compare effect of daprodustat to epoetin alfa in Japanese patients	multiple oral dose of 4 mg once daily for 3 weeks followed by dose adjustment (1 to 24 mg) as needed for the following 49 weeks
PHI201753	PK, efficacy, safety and tolerability in Japanese patients -/+ dialysis	multiple oral dose of 2 or 4 mg once daily for 4 weeks followed by dose adjustment (1 to 24 mg) as needed
PHI116099	PK, efficacy, safety and tolerability in Japanese patients (sparse PK sampling)	multiple oral dose of 4, 6, 8, and 10 mg once daily for 4 weeks
PHI116581	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 0.5, 2 and 5 mg once daily for 4 weeks
PHI116582	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 0.5, 2 and 5 mg once daily for 4 weeks
PHI114837	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 12 mg once daily for 4 weeks followed by dose adjustment as needed for the following 12 weeks
PHI112844	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 10, 25, 50 and 100 mg once daily for 28 days

Table 3 Summary of studies supporting the clinical pharmacokinetics of daprodustat

PHI113633	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 4, 6, 8, 10 and 12 mg once daily for 4 weeks followed by dose adjustment (2-25 mg) as needed for the following 20 weeks
PHI113747	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 1, 2, and 4 mg once daily for 4 weeks followed by dose adjustment (0.5-10 mg) as needed for the following 20 weeks
PK studies in patients with chronic kidney disease		
204837	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 8, 12, 16 and 24 mg three-times a week for 28 weeks during which treatment was dose-titrated (2-48 mg three-times a week) to achieve target Hgb levels
210410	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 1, 2, 4, 6, 8 , 10, 12, 16 and 24 mg once daily for 4 weeks followed by dose adjustment as needed for the following 48 weeks
200807	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 1, 2, 4, 6, 8, 10, 12, 16 and 24 mg once daily for 4 weeks followed by dose adjustment as needed for the following year
200808	PK, efficacy, safety and tolerability (sparse PK sampling)	multiple oral dose of 1, 2, and 4 mg once daily for 4 weeks followed by dose adjustment (1-24 mg) as needed for the following year
PK studies in special populations		
PHI116008	PK and efficacy in healthy subjects with mild-moderate tricuspid regurgitation	multiple oral dose of 5 and 100 mg once daily for 5 days
PHI115573	PK (daprodustat and metabolites), safety and tolerability in subjects with renal impairment including subjects on dialysis	multiple oral dose of 5 mg once daily for 14 or 15 days
200231	PK (daprodustat and metabolites; including plasma protein binding), safety and tolerability in healthy subjects with mild and moderate hepatic impairment	single oral dose of 6 mg
DDI studies		
PHI113634[#]	DDI study to assess the effect of a strong CYP2C8 inhibitor (gemfibrozil) on daprostat	Part B: single oral dose 100 mg daprostat and steady-state gemfibrozil
200229	Part A: DDI study to assess the effect of daprostat on a CYP2C8 substrate (pioglitazone) and a OATP1B1/1B3 substrate (rosuvastatin) Part B: DDI study to assess the effect of a weak CYP2C8 inhibitor (trimethoprim) on daprostat	Part A Cohort 1: 15 mg pioglitazone, 10 mg rosuvastatin, 25 mg daprodustat on Day 1, 25 mg daprodustat on Day 2; or 15 mg pioglitazone, 10 mg rosuvastatin on Day 1 Cohort 2: 15 mg pioglitazone, 10 mg rosuvastatin, 100 mg daprodustat on Day 1, 100 mg daprodustat on Day 2; or 15 mg pioglitazone, 10 mg rosuvastatin on Day 1 Part B 25 mg daprodustat on Day 1, 200 mg trimethoprim twice daily for 5 days from Day 3, 25 mg daprodustat on Day 6

[#]*early formulation*

Pharmacodynamic parameters were evaluated in healthy subjects and in patients with CKD in several studies, including fifteen Phase I and II studies in both healthy volunteers and patients with renal impairment.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Daprodustat is a small molecule inhibitor of hypoxia-inducible factor prolyl-4-hydroxylases developed to treat anaemia associated with chronic kidney disease. The starting dose of daprodustat is based on the patient's dialysis status, Hgb level, and current use of erythropoiesis-stimulating agent therapy and ranges from 1 mg to 12 mg once daily or 2 mg to 24 mg three-times per week. The maintenance dose ranges from 1 mg to 24 mg once daily or 2 mg to 48 mg three-times per week. Daprodustat is for oral use and can be taken with or without food. Available strengths are 1 mg, 2 mg, 4 mg, 6 mg and 8 mg film-coated tablets.

Physicochemical properties

Daprostat has a molecular weight of 393.43 g/mol and no chiral centres. Daprodustat has a solubility of 0.074 mg/mL in water, of <0.001 mg/mL in simulated gastric fluid at pH 1.6 and of 0.049 - 0.59 mg/mL in Simulated intestinal fluid at pH 6.5.

In vitro, daprodustat had a moderate passive membrane permeability at pH 7.4, but permeability increased to high permeability in the presence of fasted state simulated intestinal fluid at pH 5.5 and pH 7.4.

Analytical methods

Bioanalytical methods were developed to quantify daprodustat and its metabolites in human plasma, urine, peritoneal fluid, and plasma/phosphate-buffered saline (PBS). Sample analysis involved protein precipitation, liquid-liquid extraction, solid-phase extraction sample clean-up, and HPLC-MS/MS. The analytical methods and assay validation were considered adequate to determine daprodustat and its metabolites in different biological matrixes. Several partial validation steps were performed, and methods were validated over time. Method performance was generally appropriate with accuracy and precision within the 15% limits for daprodustat and its metabolites. Adequate dilution linearity has been demonstrated for daprodustat in several matrixes has been demonstrated. Long term stability of daprodustat has been demonstrated for 249 and 424 days at -20°C and -70°C in human plasma, 716 days at -20°C and -70°C/pH 4.5 394 days at -20°C/pH 4.0 in human urine, 629 days at -20°C and -70°C in human peritoneal fluid. Also, the metabolites were stable in various matrixes for at least 1 year.

The bioanalyses were performed in three different laboratories: GlaxoSmithKline (GSK), King of Prussia, PA, and Lambda Therapeutic Research Ltd.; Pharmaceutical Product Development (PPD), Middleton, WI. The transfer between the different laboratories has been explained.

Population pharmacokinetic (PopPK) modelling

Overall, three PopPK models were developed sequentially, with Model 2 and Model 3 utilising model structural parameters and covariate effects from the initial Model 1. However, due to methodological limitations only the initial model 1 is acceptable. This model is shortly described below. The Phase III PopPK analysis using data of Japanese subjects (Model 2), and a Phase II/III PopPK analysis (model 3) are not presented in detail.

The initial PopPK Model 1 included dense sampling data of 12 Phase I studies in healthy subjects and 8 Phase II studies in CKD subjects. The dataset included 309 subjects (32.1%) with an age older than 65 years, and 655 subjects (67.9%) aged younger than or equal to 65 years. The daprodustat PK was best described by a 3-compartment PopPK model with first-order elimination from the central compartment and a delayed absorption modelled using serial transit absorption compartments.

Allometric scaling was applied to all clearance and volume terms using fixed exponents (0.75 and 1.00, respectively) to account for PK variability related to body weight. Apparent clearance and apparent central volume of distribution were estimated to be 24.6 L/h and 26.2 L (both relative to 70 kg), respectively.

The rejected Phase II/III PopPK Model 3 included daprodustat data of 707 patients from 1 Phase IIb study and 4 Phase III studies. In the Phase III studies, only sparse PK data were collected (pre-dose, and at 0.5, 1, 2, and 3 hours after dose). Hence, the Phase III data mainly contain information on absorption and not on distribution and elimination. There is no indication of any major differences in PK between populations, not between healthy volunteers and CKD patients, nor between non-dialysis and dialysis patients. Despite of this, in Model 3, two sub-populations with very different PK profiles were identified, and the estimates of the distribution parameters differed considerably between Model 3 and Model 1. This is an artefact of bad modelling practice, and therefore Model 3 cannot be used to support label claims for daprodustat.

Exploratory exposure-response analyses were done using the observed PK data from the PK population (n=664) in the global Phase III studies (studies 204837/ASCEND-TD,201410/ASCEND-ID, 200807/ASCEND-D and 200808/ASCEND-ND), each study analysed separately. The relationship between daprodustat extrapolated C_{max} and Hgb change versus baseline was explored. Further, exploratory exposure-safety analyses were undertaken with the observed PK data and safety endpoints, namely, Major Adverse Cardiovascular Events (MACE) and MACE^{++} (MACE or thromboembolic event or hospitalisation for heart failure events).

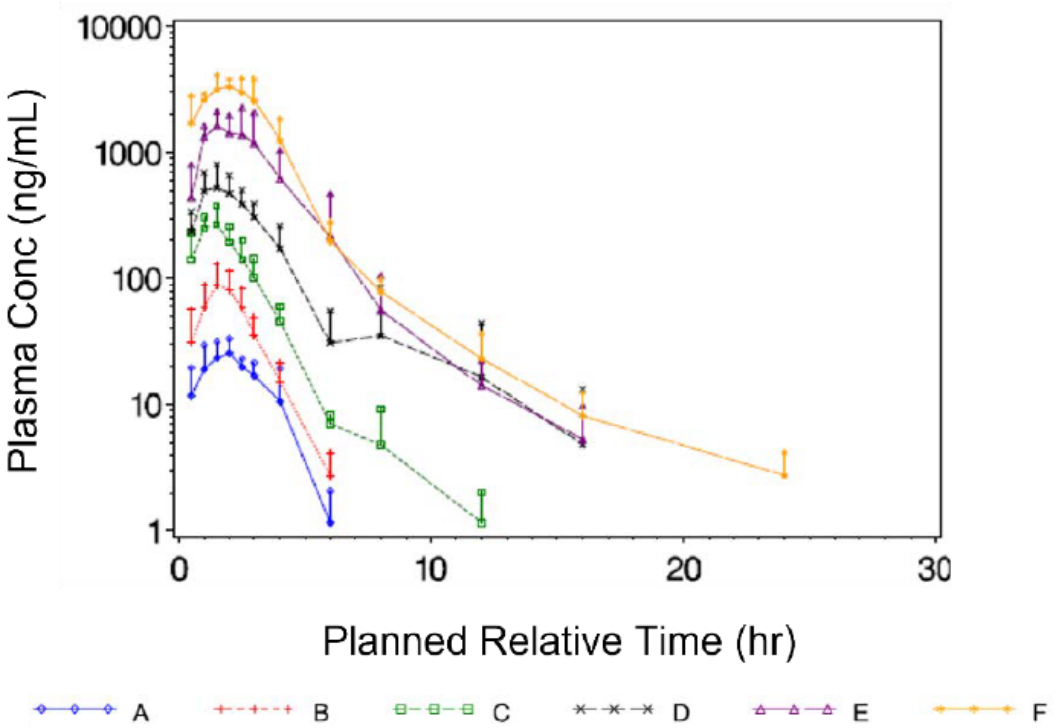
Pharmacokinetics in healthy volunteers

The pharmacokinetics of daprodustat in healthy volunteers were investigated following a single dose over a dosing range from 2 mg to 500 mg and following multiple dosing over a dose range of 5 mg to 100 mg once daily and 25 mg twice daily once daily for 5 to 15 days.

Absorption

The t_{max} of daprodustat was observed between 0.5 and 3 hours under fasted conditions. The inter-individual variability ranged from 15% to 57% for the C_{max} and from 14% to 55% for the $AUC_{0\text{-}inf}$. Daprodustat exhibited linear PK with approximately dose-proportional increases in plasma exposure (C_{max} and AUC) in doses between 1 and 500 mg (Figure 2). No accumulation was observed for the C_{max} and $AUC_{0\text{-}24}$ following once-daily dosing with daprodustat. It is unlikely that accumulation will occur following three-times per week dosing.

Figure 2 Mean (SD) plasma daprodustat PK concentration-time plot following single-dose administration (semi-Log scale; study PHX111427) with A is 2 mg, B = 5 mg, C = 15 mg, D = 50 mg, E = 150 mg and F = 300 mg



The absolute oral bioavailability of daprodustat is 65%, with ~80% absorption and ~18% first-pass metabolism.

The food effect was characterised in two studies with one investigating a high-fat meal and one a diet for chronic impaired disease patients. Concomitant administration with food did not have a large effect on the PK parameters of daprodustat after a single oral dose of daprodustat. When given with a CDK meal, daprodustat $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} were slightly lower in the fed state (9%, 9%, and 11%, respectively). Co-administration with a high-fat, high-calorie meal resulted in an 11% and 31% decrease in daprodustat $AUC_{0\text{-}inf}$ and C_{max}, respectively, and a 1 h mean delay of t_{max} relative to fasted administration. However, there was considerable overlap in the range of t_{max} values in the fed and fasted states. There were no food restrictions in the Phase III studies. Daprodustat can be given irrespective of food.

During clinical development, several different formulations and manufacturing processes were used. The Applicant conducted several PK studies to investigate the effect of particle size, differences in dissolution characteristics due to the granulation process. Tablet formulations with a different particle size have comparable bioavailability. Furthermore, dissolution differences do not appear to affect bioavailability. Bioequivalence was shown between Process 1 and Process 2, and an across study comparison of the PK shows similar PK characteristics between early formulations and the final commercial formulations. Further, a bioequivalence study was shown between the 2 mg and the 4 mg tablet strengths (study 207727 Part 1).

Distribution

The *in vitro* human plasma protein binding of daprodustat is high and ranges from 98.3% to 99.4% using equilibrium dialysis. *Ex vivo*, the plasma protein binding of daprodustat was 99.6%. Over the clinical concentration range, the plasma protein binding appears >99%. The binding to serum albumin is high, and the binding to α1-acid glycoprotein is low.

The *in vitro* blood-to-plasma ratio of daprodustat was 0.75-1.23, indicating some concentration dependency. Overall, daprodustat shows minimal association with human blood cells.

Following IV administration of daprodustat, the observed volume of distribution was 14.3 L, suggesting low tissue distribution of the compound outside the systemic circulation with likely low penetration into tissues.

Metabolism

In vitro, daprodustat is stable in human blood. Limited metabolism occurred following incubation of daprodustat with human liver microsomes for up to 60 minutes (after 30 minutes, only 5% was metabolised). Following incubation with human hepatocytes, 35% of the incubated daprodustat was metabolised after 4 hours. Overall, daprodustat is slowly metabolised *in vitro*.

In healthy volunteers, daprodustat is extensively metabolised *in vivo* to 18 identified mono, di- or tri-hydroxylated metabolites and some unidentified metabolites. Daprodustat was present for ~40% in plasma from 0-8 hours and not detected in plasma from 10-14 hours. In plasma from 0-8 hours, main metabolites (>5% of the total radioactivity) were M2, M3, M4, and M13. Most metabolites were not detected in plasma samples from 10-12 h; only M2 (14%), M3 (12%), and M13 (16%) were observed, indicating that these metabolites are most likely the main metabolites following once-daily dosing.

In vitro data showed that daprodustat is mainly metabolised by CYP2C8 and to a lesser extent by CYP3A4. CYP2C8 was able to form the main metabolites M2, M3, and M4, and CYP3A4 was not able to form one of these metabolites. *In vivo* data indicate that main human metabolite M13 is most likely formed by CYP2C8 from metabolite M4 and/or M2.

Metabolites M2, M3, and M4 were the main metabolites in faeces (>10% of the administered dose), and bile and M5/M14 were also present for >10% of the administered dose in bile. M5/M14 is most likely degraded or metabolised by the intestinal flora to some extent since it is present in faces to a lesser extent.

Metabolites M2, M3, M5/M14, and M13 were the main metabolites identified in urine. However, since urinary excretion is a minor route of excretion, all these metabolites were <4% of the administered dose.

In conclusion, daprodustat is extensively metabolised, with ~20% of the absorbed daprodustat metabolised prior to reaching the systemic circulation and extensive metabolism prior to excretion (no parent compound was detected in urine, only 0.5% of the dose in faeces as a parent).

Transporters

Daprodustat is a substrate of BCRP and OATP1B1, but not of P-glycoprotein, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K.

Only one concentration (5 µM) was used in the study evaluating if daprodustat is a substrate for P-gp. Although this experiment was not fully conducted according to the EMA DDI guideline (CPMP/EWP/560/95/Rev. 1 Corr. 2**) no additional studies investigating that daprodustat is a substrate of P-glycoprotein are warranted as the absorption was 80% and P-glycoprotein is not expected to be involved in the active elimination of daprodustat since the majority is eliminated as metabolite. Inhibitors of P glycoprotein are not expected to have a clinically relevant on the exposure.

Excretion

The majority of the orally administered daprodustat was eliminated via faeces. When correcting for the absorbed fraction (~80%), ~28% of the absorbed dose is excreted via urine (as metabolite) and the rest is eliminated via faeces. Daprodustat is mainly cleared via oxidative metabolism and primarily

eliminated via hepatobiliary excretion in faeces. Unchanged daprodustat accounted for <0.5% in faeces and <0.05% in urine.

Daprodustat has a short elimination half-life ranging from 0.8 to 4 hours and a clearance of 19 L/h.

PK of daprodustat metabolites

The pharmacokinetics of the metabolites M2, M3, M4, M5, M6, and M13 was investigated. M2, M3, M4, and M13 are main metabolites (see Table 4).

Table 4 Parent and metabolite exposure (based on mass balance study 200232)

	Plasma AUC_{inf}* (ng·h/mL)	Analyte exposure (% of total ^{14}C)	Metabolite exposure (% of parent)
Total ^{14}C	2279		
Parent	940	**41.2**	n/a
M2	140	**6.1**	14.9
M3	140	**6.1**	14.9
M4	92.1	**4.0**	9.8
M5	33.1	**1.5**	3.5
M6	61.8	**2.7**	6.6
M13	124	**5.4**	13.2

* Geometric mean values following an oral 25 mg single dose of [^{14}C]–Daprodustat

Data from the massbalance with Study No. 200232

The PK of daprodustat is dose-proportional over a dose range of 1 and 500 mg, but the PK of the major metabolites M2, M3, and M13 is less than dose-proportional over a dose range of 10 to 500 mg, indicating that the metabolism via CYP2C8 and an unidentified enzyme (formation of M13) may become saturated at higher exposure, but that other metabolism routes can take over.

The systemic exposure of the metabolites was 1.1 to 1.7-fold higher in Japanese than Caucasian subjects. Furthermore, the metabolite exposure increased with decreasing renal function. This is most likely because M2, M3, M4, and M13 are (partly) eliminated via renal clearance. In addition, mild and moderate hepatic impairment also led to an increase in metabolite exposure. This is most likely due to the fact that the metabolites are eliminated via bile into faeces.

The metabolites M2, M3, and M13 were no direct or time-dependent inhibitors of CYP1A2, 2C8, 2C9, 2C19, 2B6 (only investigated for M3) and 3A4. M4 was not a direct or time-dependent inhibitor of CYP1A2, 2B6, 2C9, and 2D6. M4 is not an inhibitor of CYP2C8, 2C19 and 3A4.

The metabolites M2, M3, M4 and M13 were not inhibitors of OATP1B1, OAT1, OAT3, OCT2, MATE1 and MATE2-K. The Applicant investigated the inhibition potential of the metabolites sufficiently, except for inhibition of CYP2B6, which has not been evaluated for M2 and M13.

<u>PK in the target population: patients with chronic kidney disease (CKD)</u>

The PK is similar in healthy volunteers and patients with chronic kidney disease. Following once-daily dosing with 24 mg daprodustat, the C_{max} was 164 ng/mL, and AUC_{0-24h} was 616 ng × h/mL based on study **205665**. This study included 68 HD subjects with anaemia due to CKD and subjects received 24mg once daily for 57 days.

Based on NCA analysis, the highest estimated C_{max} and AUC_{0-24h} were 706 ng/mL and 2045 ng*h/mL, respectively (after administration of 48 mg TIW).

There was no exposure-efficacy relationship between daprodustat extrapolated C_{max} and Hgb change versus baseline, based on Phase II data.

In addition, there was a high overlap with no marked difference in the median levels of daprodustat in subjects with MACE or MACE^{++} compared to those without MACE or MACE^{++}. There was a trend for higher median systemic exposure in subjects with MACE or MACE^{++} compared to those without MACE, indicating that there is some exposure-safety relationship. However, daprodustat is individually dosed based on efficacy and safety.

Special populations

Genetic polymorphism

CYP2C8 is the main enzyme responsible for the metabolism of daprodustat. CYP2C8 has genetic polymorphisms affecting the activity and may lead to decreased or increased activity of CYP2C8.

A post hoc study (report 2022N524768) was conducted to evaluate the effect of genetic polymorphisms in CYP2C8 on the pharmacokinetics of daprodustat and the Hgb response using 222 PGx subjects from the eight clinical studies. Only one subject (1 of 222 subjects) with poor metabolizer (PM) status had PK data available. 17% of the subjects (38 of 222) had only 1 copy of a *allele (*2, *3, or *4) associated with intermediate metabolizer (IM) function. No difference was observed in daprodustat PK exposure between those with predicted "extensive metaboliser" and "intermediate metaboliser" status; the effect of CYP2C8 poor metabolising status on the PK remains unclear.

Impaired renal function

In study PHI115573, the impact of various degrees of renal impairment was investigated. This study included subjects with normal renal function, non-haemodialysis (non-HD) subjects with renal impairment (Stages 3/4/5 CKD), and haemodialysis (HD) subjects with Stage 5 CKD. Consistent with the minimal renal elimination of daprodustat observed in the mass balance study, renal impairment had no clinically relevant impact on the PK of daprodustat (Table 5).

Table 5 Daprodustat exposure on Day 14/15 in subjects with varying degrees of renal impairment following administration of daprodustat (study PHI115573)

	ratio of GLS Means (90% CI)				
Parameter	**Stage 3/4 versus normal (Day 1)**	**Stage 3/4 versus normal (Day 14)**	**Stage 5 HD versus normal (Day 14)**	**Stage 5 HD Day 15 versus normal Day 14**	**Stage 5 HD Day 14 versus Stage 5 HD Day 15**
AUC	0.97 (0.66-1.42)	0.93 (0.62-1.40)	1.12 (0.77-1.64)	0.99 (0.68-1.45)	1.13 (0.99-1.29)
C_{max}	0.59 (0.38-0.91)	0.80 (0.52-1.24)	0.79 (0.53-1.19)	0.82 (0.54-1.22)	0.97 (0.76-1.23)

Further the effect of dialysis on the pharmacokinetics of daprodustat has been evaluated using PopPK analysis. In early Phase I PopPK analysis model 1, haemodialysis slightly reduced daprodustat clearance 22.4%), with the an estimated effect on exposure of 1.29-fold change in AUC_{inf}; 1.11-fold change in C_{max}. The final Phase II/III population model 3 is not considered acceptable due to methodological issues (see methodology).

Impaired hepatic function

PK/PD Study 200231 evaluated the pharmacokinetics of daprodustat and its metabolites in adults with mild (Child-Pugh 5-6) and moderate (Child-Pugh 7-9) hepatic impairment, and confirmed clinical evidence of chronic liver disease and/or cirrhosis. An approximate 1.5- to 2-fold higher exposure of

daprodustat in both AUC and C_{max} was observed in patients with mild to moderate hepatic impairment. Since there is no clinical evidence of a concentration/EPO relationship observed from this study and in view of the known large intra-individual variability in Hgb response, no adjustment of the starting dose is indicated; daprodustat should be titrated individually.

Current unstable liver or biliary disease at baseline was an exclusion criterion for the ASCEND phase 3 program. No information regarding baseline hepatic status was collected in the phase 3 studies, thus patients with mild or moderate hepatic impairment were not identified and the potential impact of hepatic impairment cannot be assessed based on phase 3 data.

Daprodustat has not been studied in patients with severe hepatic impairment.

Age

More than 4000 patients were exposed to daprodustat during the global Phase III program. The age range was 18-95 years, and almost 20% were ⩾75 years old. The effect of age on the pharmacokinetics of daprodustat has been evaluated using PopPK analysis, however the submitted population model 3 is not considered acceptable. Overall, there is no indication that age would be a clinically relevant factor.

The PK of daprodustat has been investigated in a total number of 1400 subjects, the age breakdown for these subjects can be found in the table below.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	343/1400 (24.5%)	195/1400 (13.9%	36/1400 (2.6%)

Daprodustat is intended for subjects 18 years and older. Therefore, no clinical PK studies were conducted in paediatric subjects.

Body weight

Among patients exposed to daprodustat during the global Phase III program, the body weight range was 35-194 kg. Body weight was included as a covariate in Pop PK modelling, where allometric scaling was applied to all clearance and volume terms using fixed exponents (0.75 and 1.00, respectively) to account for PK variability related to body weight. Further, body weight was included as a covariate on dose in the Dose-Response analysis (2019), indicating that a patient weighing 110 kg would require an almost doubled dose compared to a patient weighing 45 kg, to achieve the same Hb response. Patients' Hb levels are monitored, and the dose is titrated to achieve and maintain Hb within the target range. Some patients receive a lower dose (or no dose at all) after the first dose adjustment compared with their starting dose. This raised some concerns that patients with a low body weight may receive a too high starting dose The Applicant has provided ad-hoc analyses of changes in dosing from the starting dose in non-ESA-user dialysis and non-dialysis subjects at Week 4, stratified on body weight quartiles. The proportion of subjects with dose decreases or increases at Week 4 did not correlate to body weight in a clear way, although a weak trend was seen.

Gender

More than 4000 patients were exposed to daprodustat during the global Phase III program. About 50% of the patients were females. The effect of sex on the pharmacokinetics of daprodustat has been

evaluated using PopPK analysis, however the submitted population model 3 is not considered acceptable. Overall, there is no indication that sex would be a clinically relevant factor.

Race

In study PHI115385, the systemic exposure of daprodustat was 1.2- to 1.4-fold higher in Japanese than Caucasian subjects at a given oral dose of daprodustat. The difference in body weight appears to explain the difference between groups.

It cannot be excluded that race differences in CYP2C8 genetic polymorphisms/phenotypes may also play a role.

Pharmacokinetic interaction studies

Daprodustat as victim

In vitro data showed that daprodustat is mainly metabolised by CYP2C8 and, to a lesser extent, by CYP3A4. Furthermore, daprodustat is a substrate of BCRP and OATP1B1. Clinical DDI studies were conducted to investigate the effect of strong and weak CYP2C8 inhibitors on the PK of daprodustat.

Co-administration with a strong CYP2C8 inhibitor (gemfibrozil) with a single oral dose of 100 mg daprodustat resulted in a 3.9-fold increase in C_{max} and a 19-fold increase in AUC of daprodustat. The concomitant administration with gemfibrozil (CYP2C8 and OATP1B1 inhibitor) is contraindicated.

Co-administration with a weak CYP2C8 inhibitor (trimethoprim) with a single dose of daprodustat resulted in a 1.3-fold increase in C_{max} and a 1.5-fold increase in AUC of daprodustat. No dose adjustment is necessary in patients treated with daprodustat and concomitantly taking moderate and weak CYP2C8 inhibitors.

The use of moderate CYP2C8 inhibitors such as clopidogrel was not an exclusion criteria in the Phase II and III studies. About 15% of the total population used clopidogrel as co-medication. The potential effect of clopidogrel on the PK of daprodustat was evaluated in PopPK analysis. However, due to methodological issues these PopPK results cannot be used to support the absence of an interaction. The Applicant provided information on observed C_{max} and C_{tau} in the PK studies when daprodustat was given concomitantly with clopidogrel as compared to daprodustat alone. In addition, information on the incidence of AEs and dose adjustments were provided from the pivotal clinical studies. Overall, the data indicate that there is potentially no need for dose adjustment for daprodustat when used in combination with clopidogrel. However, it is worth emphasising that the classification of CYP2C8 inhibitors based on their potency (i.e., classifying them as mild, moderate and strong CYP2C8 inhibitors) is not so well-established as for CYP3A4 inhibitors which are more common/broad and have much more clinical DDI data available. Daprodustat appears to be a highly sensitive CYP2C8 substrate (i.e. up to 19-fold increase in its exposure was observed with gemfibrozil as a strong CYP2C8 inhibitor), and therefore a significant DDI impact can be expected even with moderate CYP2C8 inhibitors. Therefore, as a precautionary measure, a more intense monitoring of Hgb levels should be performed when a concomitant treatment with a moderate CYP2C8 inhibitor is initiated during daprodustat treatment or when the dose of the moderate CYP2C8 inhibitor is changed.

A large decrease in exposure is expected when daprodustat is co-administered with a moderate/strong CYP2C8 inducer. No clinical DDI studies were conducted investigating the effect of CYP induction on the exposure of daprodustat. Rifampicin induces both CYP2C8 and 3A4, but cannot be used in clinical DDI studies, due to nitrosamine impurities. A reduction of 81 to 93% in daprodustat exposure was predicted when given in the presence of a strong CYP2C8 and 3A4 inducer using a mechanistic static model as described in EMA guidance. Co-administration with CYP2C8 inducers should be avoided. If co-administration cannot be avoided, haemoglobin monitoring is required (and daprodustat doses should be adjusted as appropriate) when initiating or stopping therapy with CYP2C8 inducers.

No clinical study was conducted with an OATP1B1 inhibitor. Although CYP metabolism is most likely the rate limiting step and it cannot be excluded that hepatic uptake via OATP1B1 plays a role. As a precautionary measure, Hgb monitoring should be performed when concomitant treatment with an OATP1B1 inhibitor.

The solubility of daprodustat is pH-dependent. A higher solubility is observed at higher pH. A large fraction of daprodustat (fa=80%) is absorbed from the gastrointestinal tract into blood. Consequently, an increase in pH is expected to have a limited effect on the systemic exposure. Thus, concomitant treatment with acid reducing agents is not expected to have any clinically relevant impact on the pharmacokinetics of daprodustat.

No interaction studies of daprodustat with oral iron or phosphate binders taken concurrently have been conducted. The Applicant provided information on the observed C_{max}, incidence of AEs and dose-adjustments in patients treated with or without phosphate binders and oral iron in the Phase IIII studies to support that there is no interaction between daprodustat and phosphate binders and oral iron. However, it is unclear whether these substances were taken at the same time as daprodustat. As an interaction cannot be ruled out, the patient should be advised to take daprodustat at a consistent time relative to these other medicinals product.

No clinical DDI study was performed with a BCRP inhibitor since oral daprodustat is well-absorbed (calculated absorption fraction of 80%) and the limited hepatobiliary clearance (cleared almost exclusively by metabolism). It is agreed that no clinical DDI study is warranted to investigate the effect of co-administration with a BCRP inhibitor.

Daprodustat as perpetrator

Several *in vitro* tests were conducted to investigate the daprodustat potential for interactions.

In vitro experiments showed that daprodustat is not an inhibitor of CYP3A4 at maximal intestinal concentrations. It should be noted that only midazolam was investigated as marker substrate (and not testosterone).

In the CYP induction study, a decrease in the mRNA levels has been observed, at higher concentrations of daprodustat, possibly due to cytotoxicity of daprodustat. As *in vitro* experiment was performed correctly and the positive control showed significant increase in mRNA, no additional induction study is warranted.

In vitro experiments showed that daprodustat is not an inhibitor of P-glycoprotein and BCRP at maximal intestinal concentrations. Furthermore, daprodustat is not an inhibitor of OATP1B1 and 1B3 at maximal portal vein concentrations. In addition, daprodustat is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 and of the transporters P-glycoprotein, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2-K at maximal systemic concentrations. Furthermore, daprodustat is not a time-dependent CYP inhibitor or an inducer of AhR, CAR, and PXR at maximal systemic concentrations and maximal intestinal concentrations. Therefore, no clinical DDI studies are warranted with daprodustat as a perpetrator.

A clinical DDI study was conducted in which the effect of daprodustat on the exposure of sensitive CYP2C8 and OATP1B1 substrates was investigated. At a dose of 25 mg or 100 mg daprodustat, no effect was observed on the exposure to a sensitive CYP2C8 substrate (pioglitazone) and a sensitive OATP1B1 substrate (rosuvastatin). Therefore, no DDI is expected when daprodustat is co-administered with substrates of CYP2C8 and OATP1B1.

A commitment was made to investigate the potential of metabolites M2 and M13 to be inhibitors of CYP2B6 *in vitro*.

2.5.2.2. Pharmacodynamics

Mechanism of action

Hypoxia-inducible factor (HIF) is a transcription factor that regulates the expression of genes involved in erythropoiesis (including erythropoietin) and genes involved in iron metabolism. Activation of the HIF pathway is important in the adaptative response to hypoxia and increases red blood cell production. Hypoxia-inducible factor (HIF) is degraded by prolyl-4-hydroxylase enzymes. Daprodustat is claimed to inhibit prolyl-4-hydroxylase enzymes, thereby slowing the degradation of HIF and thus enhancing the production of erythropoietin. Also, hepatic hepcidin production is claimed to be suppressed, and transcription of genes involved in iron absorption and mobilization (including transferrin, the transferrin receptor, and ferroportin) is stimulated.

Pharmacodynamic studies

Fifteen Phase I and II studies investigated the pharmacodynamics of daprodustat in both healthy volunteers and patients with renal impairment. These included single and repeat-dose studies and evaluated the primary pharmacology related to effects on EPO, red blood cells, and hemoglobin as well as biomarkers for iron metabolism, and secondary (off-target) effects of possible revascularisation (VEGF), glucosylation gene expression (glucose), lipid metabolism, inflammation (hsCRP), bone metabolism (FGF23), and vital signs of blood pressure, pulmonary hypertension and cardiac repolarisation (QT prolongation potential) based on possible identified (theoretical) mechanism and regulatory requirement. Studies included doses (up to 300 mg) well beyond the clinically effective dose of 1 mg to 24 mg once daily and 2 mg to 48 mg TIW.

Table 6 Summary of pharmacodynamic endpoints by study

Study	Description	EPO	Reticulocytes	Hgb, Hct, RBC	Hepcidin	Serum Iron	Ferritin	TIBC, UIBC	VEGF	ABPM	Lipids
PHX111427	HV, SD	x	x	x	x[1]	x	x	x	x	NS	NS
PHI115385	HV, SD	x	x	x	NS	x	x	x	x	NS	NS
PHI112842	HV, 14d RD	x	x	x	x	x	x	x	x	NS	NS
200232	HV, SD (mass balance)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
PHI113634	HV, SD (DDI)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
200229	HV, SD (DDI)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
PHI113635	HV, SD (TQT)	x	NS	NS	NS	NS	NS	NS	x	NS	NS
PHI116008	HV, 5d RD (PASP)	x	NS	NS	x	NS	x	NS	NS	NS	NS
PHI112843	Renal impairment and HV, SD	x	x	x	x	x	x	x	x	NS	NS
PHI115573	Renal impairment, 14d RD	x	NS	NS	x	NS	NS	NS	NS	NS	NS
200942	ESRD, 14d RD	x	NS	NS	x	NS	NS	NS	NS	NS	NS
205665	CKD HD, 57d RD	x	NS	NS	NS	NS	NS	NS	NS	x	NS
204836	CKD HD, 29d RD	x	x	x	x	x	x	x	x	NS	NS
PHI116099	CKD HD, 4wk RD	x	x	x	x	x	x	x	x	NS	x
PHI116581	CKD ND, 4wk RD	x	x	x	x	x	x	x	x	NS	x
PHI116582	CKD HD, 4wk RD	x	x	x	x	x	x	x	x	NS	x
PHI114837	CKD HD, 16wk RD	x	x	x	x	x	x	x	x	NS	NS

Study	Description	EPO	Reticulocytes	Hgb, Hct, RBC	Hepcidin	Serum Iron	Ferritin	TIBC, UIBC	VEGF	ABPM	Lipids
PHI112844	CKD HD, 28d RD	x	x	x	x	x	x	x	x	NS	NS
PHI113633	CKD HD, 24wk RD	x	x	x	x	x	x	x	x	NS	x
PHI113747	CKD ND, 24wk RD	x	x	x	x	x	x	x	x	NS	x
204837/ASCEND-TD	CKD HD, 52wk RD	x	x	x	x	x	x	x	x	NS	NS
200231	Hepatic impairment and HV, SD	x	NS	NS	x	NS	NS	NS	NS	NS	NS

† Pro-hepcidin

EPO = erythropoietin; ESRD = End-stage renal disease; Hct = hematocrit; HD = hemodialysis; Hgb = hemoglobin; HV = healthy volunteer, ND = non-dialysis; NS = not sampled; PASP = pulmonary artery systolic pressure; SD = single dose; RBC = red blood cell; RD = repeat dose; TIBC = total iron binding capacity; UIBC = unsaturated iron binding capacity; TQT = thorough QT; VEGF = vascular endothelial growth factor

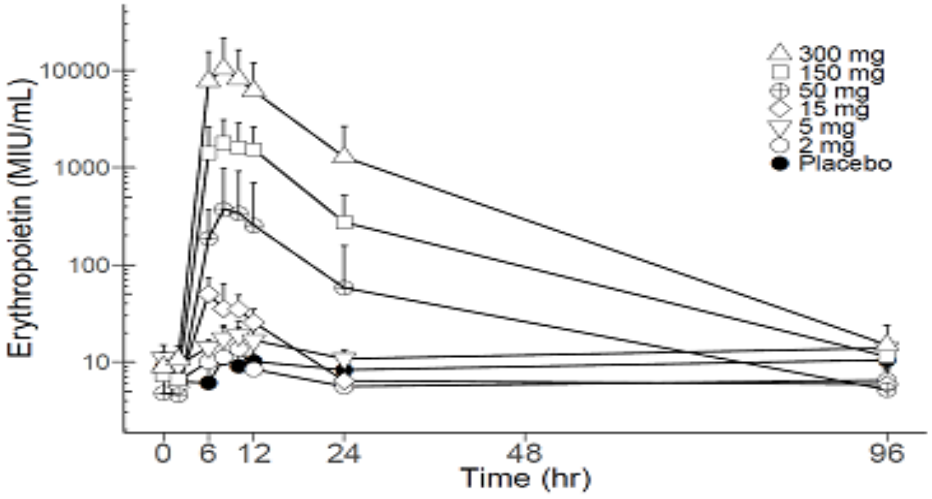
In addition, separate studies have been performed on the effect on blood pressure, pulmonary artery systolic blood pressure, and cardiac repolarisation (QTc) safety study

Primary pharmacology

Erythropoietin

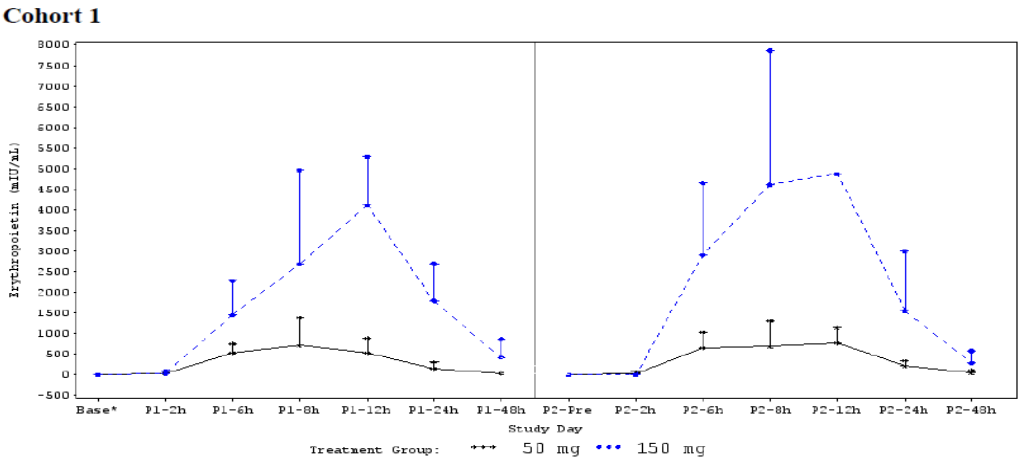
In healthy subjects, daprodustat causes an increase in EPO-level post-dose in a dose-dependent way after a single dose of 10 to 300 mg (Figure 2). Repeat administration of daprodustat over 14 days ranging from 15 to 100 mg OD resulted in dose-dependent peak levels of 28.8-9.7 IU/L (day 1-14), and 718.1-406.6 IU/L (day 1-14) at 15 and 100 mg, respectively. EPO peak level was reached at 4-11 hours post-dose and returned towards baseline after 24 hours without accumulation. At a dose of 300 mg, the plateau phase of EPO was not reached.

Figure 3 Mean (+SD) EPO Concentration-Time Profile in healthy volunteers



In CKD3,4 non-dialysis (ND) patients, a single dose of 50 and 150 mg increased the EPO-peak level 3 to 10-fold compared to healthy controls. In CKD3,4 ND daprodustat, a dose-range of 0.5 to 100 mg OD caused a dose-dependent peak in EPO-level without accumulation. At a higher dosage of daprodustat, EPO peak levels rise disproportionally and exceed physiological levels, e.g. at once-daily dosing for 4 weeks, daprodustat 25 mg OD results in a mean peak EPO level of 490.9 IU/L, as compared to a peak EPO level of 73.0 IU/L on 10 mg (PHI112844).

Figure 4 Mean (±SD) of the change from Baseline in erythropoietin values (mIU/mL) versus study time by study cohort and treatment group (Study PHI112843; Cohort 1=CKD3,4 ND)



In CKD5 HD a dose-dependent rise in EPO-level was observed at a dose-range of 0.5 to 25 mg OD and 10-48 mg TIW. No clear increase in EPO was demonstrated in CKD5 HD patients as compared to CKD3/4 ND patients with multiple doses of daprodustat 10 and 25 mg OD for 4 weeks (PHI112844). At a single dose of 150 mg, EPO concentrations tended to be higher on dialysis days than non-dialysis days (~1.5-fold), with maximum levels achieved within 6 to 12 h post-dose. Upon repeat administration, no accumulation is seen. Compared to patients treated with rhEPO, EPO peak levels are less in patients treated with daprodustat. In patients with CKD 5HD, previously treated with ESAs, the median maximum observed circulating EPO concentration for the combined daprodustat group (36.50 IU/L), treated at a mean dose of 4.6 mg OD (range 2.5-6 mg) for 24 weeks to maintain a stable Hgb, was approximately 14 times less than noted for the control group (rhEPO) of 522.85 IU/L, which was assessed 5-15 minutes after rhEPO administration (PHI113633).

Reticulocytes

Increases in reticulocytes were already seen after 24 h post-dose in healthy subjects and diminished 7 days after treatment discontinuation. In patients with CKD3,4,5 ND, daprodustat increased reticulocytes in a dose range of 0.5 to 100 mg OD, without clear dose-dependency at a dosage exceeding 50 mg OD. In patients with CKD5 HD, with prior treatment with ESA, daprodustat in a dose-range of 10 to 30 mg TIW or 4 to 25 mg OD (study PHI116581, PHI116099, PHI112844) resulted in a dose-dependent change of reticulocytes. At a dose of 0.5 to 2 mg OD the reticulocytes remained stable compared to ESA (PHI116582).

Haemoglobin, hematocrit, RBC count

Daprodustat resulted in a dose-dependent increase of haemoglobin in healthy volunteers (15-100 mg OD, study PHI112842) and in CKD3,4 ND patients (0.5 to 100 mg OD, study PHI116581 and PHI112844)) as well as CKD5 HD (4-25 mg OD, 10-30 mg TIW, study PHI116582, PHI116099 and 204837), with substantial study-withdrawal at the highest dose due to high haemoglobin levels. Haemoglobin levels returned to baseline values at 14 days after discontinuation of daprodustat (study PHI112842) in healthy volunteers.

In patients with CKD5 HD previously treated with ESA, Hgb level remained stable at a mean dose of 4.6 mg OD (study PHI116582, PHI113633) or 10-15 mg TIW (study204836). See also the Figure 5*,* Figure 6*, and* Figure 7 below for the dose-response model.

Figure 5 Observed mean Hgb (g/dL) Change from baseline and 95% confidence intervals over time by treatment (CKD3,4 ND, Study 116581)

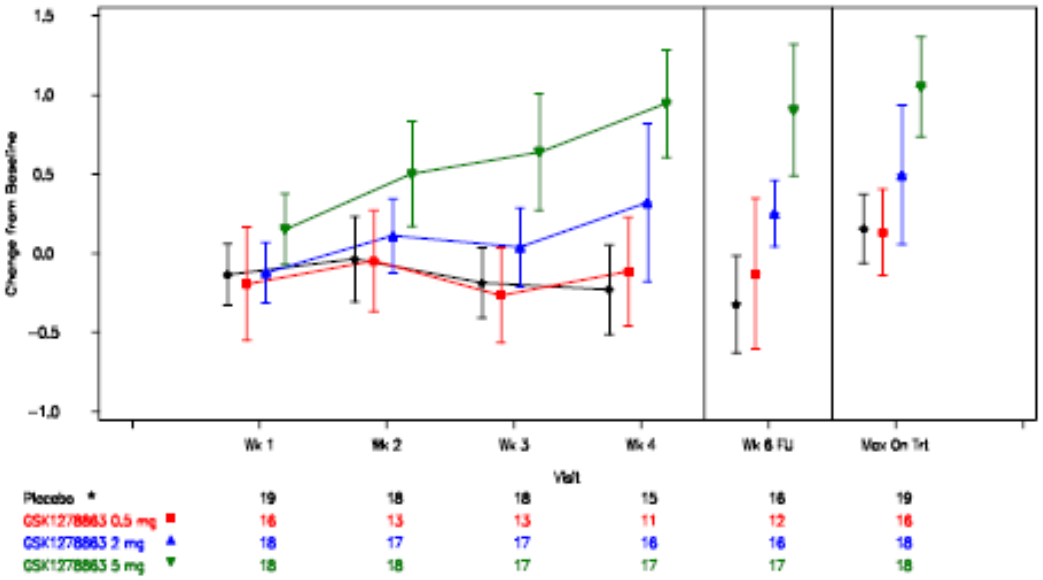


Figure 6 Mean Change form baseline in hemoglobin values (g/l) versus study time in CKD3,4 ND (PHI112844)

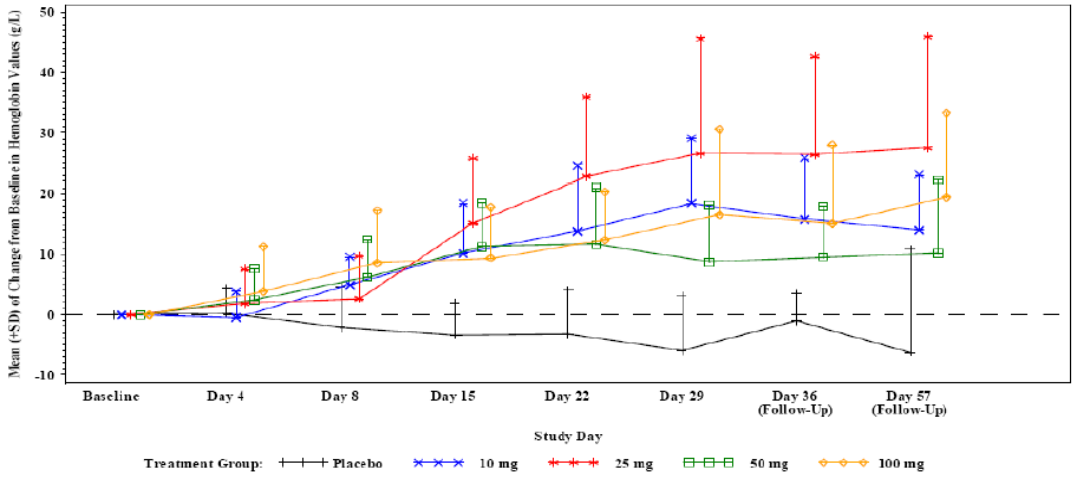
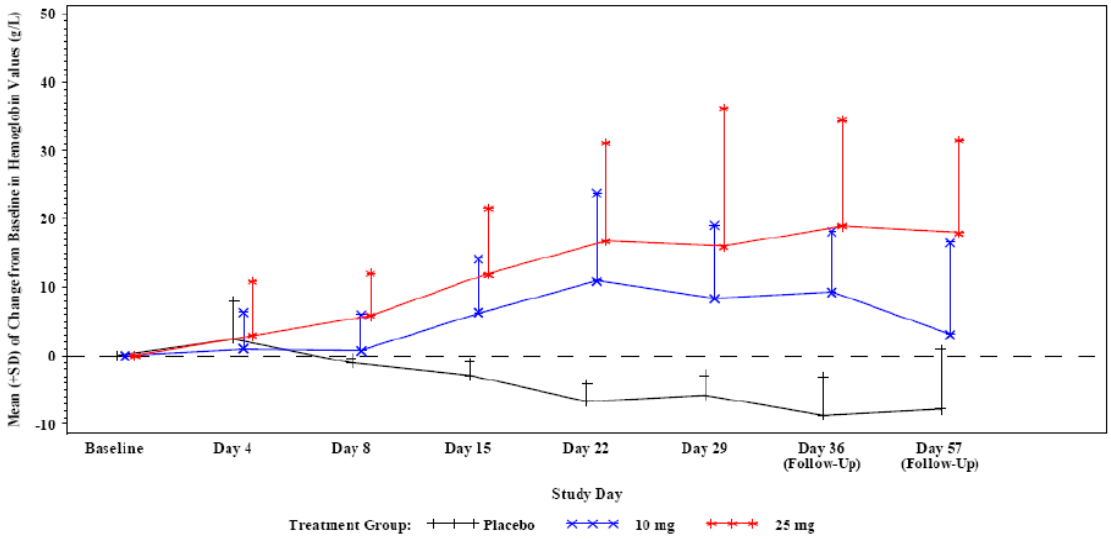


Figure 7 Mean (+SD) change form baseline in hemoglobin values (g/l) versus study time in CKD5 HD (Study PHI112844)previously been treated with ESA



Hepcidin and markers of Iron metabolism and utilization

In CKD3/4 ND patients, baseline levels of hepcidin are raised compared to healthy subjects, but to a lesser extent than CKD5 HD patients (202+/-123 mcg/l vs 1081+/-304 mcg/l). With daprodustat, hepcidin levels are reduced in CKD3/4 ND patients, in a less pronounced way than CKD5 HD patients, without clear dose-dependency (PHI115573). In CKD5 HD patients, baseline levels of hepcidin are markedly elevated, and on daprodustat in a dose-range of 0.5 to 25 mg OD or 10-30 mg TIW, hepcidin levels are reduced in a dose-dependent way (studies PHI115573, 204837). In CKD5 HD, at 5 mg OD for 14 days, hepcidin was reduced by approximately 20% (study 115573). In patients with CKD5 undergoing peritoneal dialysis, baseline plasma hepcidin concentrations were similar between CAPD and APD peritoneal dialysis subjects; baseline values were comparable to the values in CKD5 patients on hemodialysis (200942).

In 2 single-dose studies and 6 multiple-dose studies, daprodustat resulted in a dose-dependent reduction of ferritin and TSAT, and increases of TIBC and transferrin, from 48 to 96 hours post-dose in all categories of CKD patients, including CKD5 HD, in a wide dose-range (from 0.5-100 mg OD and 8-48 mg TIW), compared to baseline and (to a lesser extent) compared to rh-EPO. The ferritin level was reduced by 7.6 to 119.5 mcg/l in a OD dosing scheme (1-12 mg OD), and by 16.9 to 69.9% in a TIW dosing scheme (10-30 mg). There were notable reductions in serum iron at daprodustat-doses of 50 mg and above alongside mean increases in TIBC and UIBC values in healthy subjects and ND and HD-dependent subjects. The decreases in hepcidin, accompanied by decreases in ferritin and TSAT, are probably indicative of decreases in available iron stores due to a shift from serum iron stores to developing erythrocytes. These results are consistent with the expected mechanism of action of daprodustat. However, interpretation of data is complicated by potential confounding by co-administration of iron, iv or orally.

Secondary pharmacology

VEGF (Vascular endothelial growth factor)

VEGF, a biomarker associated with angiogenesis, was also monitored. In healthy subjects, daprodustat at a single dosage of 150-300 mg causes a rise in VEGF at 6-10 hours post-dose (2-4 fold), returning

towards baseline at 24 hours. In patients with CKD3,4 VEGF is increased by 2.4 to 4.3-fold after a single dose of 50 to 150 mg. In healthy volunteers (15-100 mg) and patients with CKD 3/4 ND (10-100 mg) and CKD 5HD (0.5- 25 mg OD), on repeat dosage of daprodustat, no consistent change of VEGF was seen. In patients with CKD5 HD at a dose range of 4 to 12 mg once daily for 24 weeks, a rise of VEGF post-dose up to 1.8-fold versus baseline was seen, without accumulation (PHI113633). In a dosing scheme of 8 to 48 mg TIW VEGF values tended to decrease, but to a lesser extent as compared to rhEPO (study 204837). In the studies performed, no consistent effect was demonstrated when comparing daprodustat with rhEPO.

Lipid-parameters

Dose-dependent reductions in total cholesterol, LDL-c and HDL-c are seen over the first 4 weeks of treatment, with total cholesterol (-5.7% at 4 mg and -12.5% at 12 mg), LDL (-7.7% at 4 mg and -19.6% at 12 mg), and HDL (-4.7% at 4 mg and -11.6% at 12 mg) in patients with CKD5 HD receiving daprodustat doses up to 12 mg OD (PHI113633), maintained at 24 weeks. In study PHI113747 in CKD3,4,5 ND patients, where the final median maintenance dose for daprodustat was 1 mg OD, no effect on the lipid levels was found.

Additional pharmacodynamic biomarkers:

Daprodustat in a dose of 50 to 100 mg OD in CKD 3-5 ND patients was associated with elevated glucose levels (PHI112844). In CKD 3-5 ND patients treated with daprodustat in a dose range of 4-12 mg OD, the glycated albumin level in the daprodustat-group was not raised compared to controls (PHI113633). In the studies performed, no consistent effects were seen of daprodustat on a marker of inflammation, hsCRP.
Fibroblast Growth Factor(FGF)-23 was increased in both the daprodustat- and the control group. Due to a large variability, no consistent pattern was observed (PHI113747). FGF-23 is produced in bone and is an important regulator of phosphate homeostasis. Also, FGF-23 has a role in iron homeostasis and anaemia in CKD (Noonan, Physiological Reports, 2020).

Cardiac depolarisation

No meaningful clinical impact of daprodustat on QTcF has been observed at a single tested dose ranging from 75 to 500 mg in a thorough QT study, including moxifloxacin as a positive control. The predicted mean (90% CI) ΔΔQTcF at Cmax for the 75 mg dose was -0.48 (-2.16, 1.13) msec and -0.51 (-2.29, 1.17) msec for the GSK1278863 model and M13 model, respectively, remaining within the margins of 5 msec, with upper-boundary of the 90% confidence interval not exceeding 10 msec.

Effect on Blood Pressure

Daprodustat at a (single) dose of 24 mg did not show an acute change (during 6 hours ABM) in either systolic, diastolic or mean blood pressure or heart rate, compared to rhEPO, in dialysis patients at first dose, and following 57 days of maintenance-treatment with daprodustat in the specific ASCEND=BP study. Further data are presented in the phase 3 program.

Pulmonary artery hypertension

At a dosage range between 5 and 100 mg daprodustat for 5 days, no effect on PASP (pulmonary artery systolic blood pressure) is seen, both under normoxic (room air) and hypoxic (13% O_2 for 30 min) conditions, in 45 healthy subjects with mild-moderate baseline tricuspid regurgitation. No effect on endothelin-1 was seen.

Pharmacodynamic interactions with other medicinal products or substances

No information was provided on PD interactions with other medicinal products.

Genetic differences in PD response

No information was provided on potential genetic differences in PD response.

2.5.3. Discussion on clinical pharmacology

Methods: Appropriately validated and sufficiently sensitive bioanalytical methods were used to analyse the concentration of daprodustat. Four studies (205767, 201771, 200884, and PWH115760) were mentioned in the presented tables, but the bioanalytical reports were not found. The applicant appropriately explained that these studies did not contain relevant PK samples and are not considered relevant for the current application.

Overall, three PopPK models were developed sequentially. However, due to methodological limitations the Phase II/III study Pop PK Model 3 is not acceptable. Based on non-compartmental analysis (NCA) and Pop PK Model 1 results, there is no indication of any major differences in PK of daprodustat between populations, not between healthy volunteers and CKD patients, nor between non-dialysis and dialysis patients. Despite this, in Model 3, the Applicant has identified two sub-populations with very different PK profiles. According to Model 3, subjects in the Phase 2b study have a relative bioavailability that is less than 40% of the relative bioavailability for a subject in any of the Phase 3 studies. This is an artefact of bad modelling practice, and therefore Model 3 cannot be used to support label claims for daprodustat. Since the daprodustat data package is rich and the dose is titrated based on haemoglobin (i.e., PK is of less importance), claims in the SmPC can be appropriately supported by NCA results in combination with data on efficacy and safety (covering patients with a broad distribution of intrinsic and extrinsic factors). Therefore, no new Phase III PK model is needed.

Pharmaceutical development: During clinical development, several different formulations and manufacturing processes were used, and bioequivalence between different formulations has been shown. From a clinical point of view, the application for the two parallel manufacturing processes is acceptable as bioequivalence between commercial formulation produced via Process 1 and commercial formulation produced via Process 2 has been appropriately shown. In study 207727 Part 1, bioequivalence was shown between the 2 mg and 4 mg strength, upon request the applicant explained that the study was performed to meet the Japanese guideline.

Absorption, distribution, metabolism and elimination: The Applicant has appropriately characterised the absorption, distribution, metabolism and excretion characteristics of daprodustat, following single and multiple doses. Daprodustat is extensively metabolised. *In vitro* data showed that daprodustat is mainly metabolised by CYP2C8 and to a lesser extent by CYP3A4. *In vivo* data indicates that main human metabolite M13 is most likely formed by CYP2C8 from metabolite M4 and/or M2. The pharmacokinetics of the metabolites M2, M3, M4, M5, M6 and M13 were extensively investigated and the potential for drug-drug interactions was characterised. M2, M3 and M13 were the main metabolites in CKD patients, and therefore the assessment is focused on the DDI potential for these metabolites.

Special populations: The influence of renal impairment, hepatic impairment and race was investigated in three dedicated studies. CYP2C8 has genetic polymorphisms affecting the activity and may lead to decreased or increased activity of CYP2C8; complete loss of function of CYP2C8 is not observed with *2 and *3, the most common polymorphisms. The Applicant performed a post hoc study to evaluate the impact of CYP2C8 genetic polymorphisms. No difference was observed between CYP2C8 "extensive metaboliser" and "intermediate metaboliser" status. The effect of CYP2C8 poor metabolising status on the PK remains unclear as only one patient with CYP2C* "poor metaboliser" status had PK data available.

Renal elimination is the minor route of elimination, and renal impairment and haemodialysis had no clinically relevant impact on the PK of daprodustat. In patients with mild to moderate hepatic impairment, an approximate 1.5- to 2-fold higher exposure of daprodustat in both AUC and C_{max} was observed. Since there is a frequent monitoring of Hgb levels during the start of daprodustat treatment, specific adjustments of the starting dose in patients with mild and moderate hepatic impairment are not needed.

In a pharmacokinetic study evaluating the effect of race modest PK differences were observed between Japanese and Caucasian subjects, which were mainly attributable to differences in body weight between ethnic groups.

The effects of age, gender, and body weight on the pharmacokinetics of daprodustat were not studied specifically; however, there is no indication that any of these factors are clinically relevant.

The Applicant has evaluated daprodustat in CKD patients ranging in age in from 22 to 93 years, and provided the standard age table. A total of 24.5% of the subjects was aged 65-74 years, 13.9% was aged 75-84% and 2.6% was aged 85 years and older.

Interactions: The potential for interaction of daprodustat was evaluated in several *in vitro* and clinical DDI studies.

Upon request, the Applicant discussed the clinical consequences of the interaction with gemfibrozil. Concomitant administration with gemfibrozil resulted in a 19-fold increase in AUC. When aiming for similar exposure, a 20-fold reduction in dose should be used in the presence of a strong CYP2C8 inhibitor; this is not deemed to be practical and a viable option. Therefore, concomitant administration with gemfibrozil is contraindicated as stated in section 4.3 of the SmPC.

The Applicant provided information on the systemic exposure, dose adjustments and incidence of AEs in subjects treated with clopidogrel and daprodustat as compared to daprodustat alone. Overall, the data indicate that there is potentially no need for dose adjustment for daprodustat when used in combination with clopidogrel. Since the classification of CYP2C8 inhibitors is not as well-established as for CYP3A4 inhibitors and daprodustat is a sensitive CYP2C8 substrate, a larger increase in exposure can be expected when co-administered with moderate CYP2C8 inhibitors. Therefore, as a precautionary measure, intense monitoring of Hgb levels is recommended in section 4.2 of the SmPC.

Currently, no clinical DDI study can be conducted with rifampicin, a strong inducer of CYP2C8 and 3A4. A reduction of 81 to 93% in daprodustat exposure was predicted when given in the presence of a strong CYP2C8 and 3A4 inducer, which may result in loss of erythropoietic response. Co-administration with CYP2C8 inducers should be avoided.

Daprodustat is a substrate for OATP1B1. No clinical study was conducted with a selective OATP1B1 inhibitor. Although CYP metabolism is most likely the rate limiting step and it cannot be excluded that hepatic uptake via OATP1B1 plays a role, especially when considering the large impact of the interaction with gemfibrozil (CYP2C8 and OATP1B1 inhibitor). A potential for increased daprodustat exposure when co-administered with an OATP1B1 inhibitor cannot be excluded. As a precautionary measure, Hgb monitoring should be performed when concomitant treatment with an OATP1B1 inhibitor.

The applicant discussed potential interactions with daprodustat metabolites. The results for M4 appeared inconsistent between studies. The applicant explained that different assays were used. Screening study (report 2013N167801) used recombinant enzymes and fluorescent probes and definitive study (report 2014N223000), used human liver microsomes and clinically relevant probe substrates. This later study is most relevant and indicated that M4 is not an inhibitor of CYP2C8, 2C19 and 3A4.

In vitro tests for CYP 2B6 were only conducted for daprodustat and major metabolite M3 and not for M2 and M13. The Applicant is committed to investigate if metabolites M2 and M13 may be inhibitors of CYP2B6. The study report will be submitted Q3 2023. Until data from the *in vitro* study is available, SmPC restrictions are implemented in section 4.5 regarding co-administration with CYP2B6 substrates.

The applicant evaluated the potential for interactions when there is concomitant use of daprodustat with several classes of drugs that may be frequently co-administered in CKD patients with aneamia. Non-compartmental analysis (NCA) drug-drug interaction (DDI) assessments were performed for phosphate binders, oral iron, phosphate binders + oral iron and clopidogrel sevelamer, and the different classes of Acid Reducing Agents (ARAs: proton pump inhibitors, H2 blockers and antacids) using observed dose-normalised C_{max} (DNC_{max}).

No interaction with Acid Reducing Agents is anticipated based on clinical data, solubility and bioavailability characteristics of daprodustat. Based on ad-hoc data acid reducing agents do not have an effect on the daprodustat PK or Hgb profile.

Further, based on the solubility and bioavailability characteristics of daprodustat, an increase in pH is expected to have a limited effect on systemic exposure. The solubility of daprodustat is pH-dependent; a higher solubility is observed at higher pH. A large fraction of daprodustat (fa=80%) is absorbed from the gastrointestinal tract into the blood. Consequently, an increase in pH could only have a limited effect on systemic exposure. Thus, concomitant treatment with acid-reducing agents does have a clinically relevant impact on the pharmacokinetics of daprodustat.

However, since it is unclear whether oral iron/phosphate binders were taken at the same time as daprodustat, the provided data cannot be used to rule out that no dose-adjustments are needed for daprodustat when co-administered with these substances. Therefore, it is recommended to take daprodustat at a consistent time relative to these other medicinal products.

In conclusion, the pharmacokinetics of daprodustat in healthy volunteers was investigated following a single dose over a dosing range from 2 mg to 500 mg and following multiple dosing over a dose range of 5 mg to 100 mg once daily and 25 mg twice daily once daily for 5 to 15 days. In addition, the PK was investigated in patients with CKD over the clinical dose range of 1 mg to 24 mg once daily. Limited PK data is available following 2 mg to 48 mg three-times per week.

Pharmacodynamics

Primary Pharmacology

The applicant has demonstrated a dose-dependent effect of daprodustat on EPO, one of the main factors causing the rise in Hb concentration, without accumulation, as demonstrated in single-dose studies in healthy subjects and CKD3,4 ND and CKD5 HD (range 10-300 mg), and repeat-dose studies in healthy subjects and CKD3,4 ND as well as in CKD5 patients treated with hemodialysis or peritoneal dialysis.

In CKD3,4 ND, EPO peak levels are augmented compared to healthy controls at 50 to 100 mg single-dose. At a dose of 10 to 25 mg OD for 4 weeks, no difference was seen in peak EPO levels between patients with CKD3,4 ND and CKD5 HD. In CDK3,4 ND and CKD5 HD, a dose-dependent increase in peak levels for EPO is seen, exceeding physiological levels at the higher part of the proposed maintenance dose ranges (1 mg to 24 mg OD and 2 mg to 48 mg TIW). EPO-peak levels on daprodustat are substantially reduced compared to rhEPO at a dose equivalent to maintaining Hb at the target level in patients with CKD5 HD.

The sequential effect of daprodustat on erythropoiesis has been demonstrated. Reticulocytes increase from day 3, reaching a maximum on day 7 to 9, and remaining stable until discontinuation of daprodustat. At day 7, Hct, Hb and RBC start to rise. In the proposed dose-range, in phase I and II

studies, a dose-related effect of daprodustat up to 50 mg was demonstrated. At higher doses, the reticulocyte count reached a plateau.

Hepcidin is a hormone responsible for the regulation of iron mobilisation. There are non-clinical data demonstrating effects on hepcidin and iron parameters. Measurement of hepcidin levels has not been shown to be clinically useful or superior to more standard iron status tests in patients with CKD, but Hepcidin levels can provide insight in the pathophysiology of anaemia and in pharmacodynamical aspects of medication. In CKD5 HD, baseline levels of hepcidin are markedly elevated, and upon daprodustat in a dose-range of 0.5 to 25 mg OD or 8-48 mg TIW, hepcidin levels are reduced in a dose-dependent way. In CKD3,4, hepcidin is also elevated, but to a lesser extent in comparison with CKD5. Upon daprodustat, hepcidin levels are decreased, though in a less pronounced way compared to CKD5 and without clear dose-dependency.

The serum ferritin is the most commonly used test for evaluation of storage iron and the transferrin saturation (TSAT) is the most commonly used measure of the availability of iron to support erythropoiesis. The serum ferritin is affected by inflammation and is an 'acute phase reactant'; thus, in CKD patients, ferritin values have to be interpreted with caution, especially those on dialysis in whom subclinical inflammation may be present. Daprodustat resulted in a dose-dependent reduction of ferritin and TSAT, and increases of transferrin, from 48 to 96 hours post-dose in all categories of CKD patients, in a wide dose range (from 0.5-100 mg OD and 8-48 mg TIW), compared to baseline and (to a lesser extent) compared to rh-EPO. There were notable reductions in serum iron at doses of 50 mg and in healthy subjects and ND and HD-dependent subjects.

The decreases in hepcidin, accompanied by decreases in ferritin and TSAT in a wide dose-range from 0.5-100 mg OD and 8-48 mg TIW, compared to baseline and (to a lesser extent) compared to rh-EPO, could probably be indicative of decreases in available iron stores due to a shift from serum iron stores to developing erythrocytes. These results are consistent with the expected mechanism of action of daprodustat.

Secondary pharmacology

Daprodustat causes a rise in VEGF at 6-10 hours post-dose, returning towards baseline at 24 hours, in healthy subjects as well as patients with CKD, at a dosage of 150-300 mg. In patients with CKD 3,4 ND, daprodustat in a dose range of 0.5 to 100 mg, no consistent change of VEGF was seen. In patients with CKD5 HD at a dose range of 4 to 12 mg once daily for 24 weeks, a rise of VEGF post-dose up to 1.8-fold was seen, without accumulation. In a dosing scheme of 2 to 48 mg TIW, values tended to decrease during 52 weeks of follow-up, though at a lesser extent than rhEPO. In conclusion, although several studies indicate post-dose increases in VEGF levels, no consistent effect of daprodustat, dosed in the therapeutic range, on VEGF has been demonstrated.

The studies performed did no demonstrate a consistent effect of daprodustat on VEGF. A potential pharmacodynamic interaction between daprodustat and VEGF inhibitors is therefore unlikely. In addition, daprodustat is not recommended to be used in active malignancy as stated in section 4.4 of the SmPC.

Dose-dependent reductions in total cholesterol (-5.7% at 4 mg and -12.5% at 12 mg), LDL-c (-5.7% at 4 mg and -12.5% at 12 mg) and HDL-c (-4.7% at 4 mg and -11.6% at 12 mg) have been demonstrated. However, in CKD5 HD, daprodustat (at a final median dose of 6 mg OD) and rhEPO treatment groups (at doses effective in correction of anaemia) had similar decreases from baseline, though slightly greater changes were observed for daprodustat (PHI113633). In CKD3,4,5 ND, where the final median maintenance dose for daprodustat was 1 mg OD, no effect on the lipid levels was found (PHI113747).

Daprodustat reassuringly did not demonstrate any relevant effects on glucose by potential genes encoding for glycolated enzymes, anti-inflammatory effects (as measured by hsCRP) or bone turnover (measured by FGF23 also involved in iron homeostasis).

Any effects on QT prolongation have not been observed as clinically evaluated in a thorough QT study, and no indication of QT prolongation could be seen in the non-clinical evaluation.

Daprodustat at a (single) dose of 24 mg did not show an acute change (during 6 hours ABM) in either systolic, diastolic or mean blood pressure or heart rate, compared to rhEPO, in patients with CKD5 HD converted from ESA at first dose, and following 57 days of maintenance-treatment to maintain a stable haemoglobin level. Blood pressure has further been evaluated in the phase 3 studies.

No effect on PASP (pulmonary artery systolic blood pressure) is seen under both normoxic and hypoxic conditions. However, the performed study evaluated the short-term effect of daprodustat on PASP, and long-term effects cannot be excluded. In addition, in the active-controlled studies performed (ASCEND-D, ASCEND-ND, ASCEND-TD and ASCEND-ID) as well as in the placebo-controlled study ASCEND-NHQ, no signal of increased frequency of pulmonary artery hypertension was reported.

Exposure response

In clinical studies, pharmacokinetic exposure (C_T, C_{max}) of daprodustat did not have a direct relationship with attainment of stable target Hgb values. This may be due to the large interindividual variability in Hgb response, and because the mechanism of action of daprodustat is governed by HIF transcription factors leading to subsequent haematopoiesis. Starting doses of daprodustat were determined by either prior ESA doses or baseline Hgb.

2.5.4. Conclusions on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of daprodustat has been adequately investigated in healthy volunteers and patients with CKD. No clear exposure response relationship has been observed for daprodustat.

Pharmacodynamics

Based on phase I and phase II studies, including patients in the proposed target population, the pharmacodynamics of daprodustat has sufficiently been investigated. The evaluation included EPO, Hb and markers of iron metabolism in support of the mechanism of action of daprodustat. Moreover, several potential secondary effects have also been evaluated. Doses up to 300 mg were explored in early Phase I and Phase II clinical studies, which are well beyond the proposed maintenance dose ranges of 1 mg to 24 mg once daily and 2 mg to 48 mg TIW. Overall, the PD program is considered sufficiently comprehensive.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

Dose-Hgb model

The starting dose and dosing algorithm for the pivotal global phase III studies were developed using a population PK/PD model with plasma PK and PD measurements from previously conducted clinical

studies with daprodustat. Hgb-time profiles from 6 Phase 2 studies in subjects with anaemia of CKD (PHI112844, PHI116581, PHI116582, PHI116099, PHI113633, and PHI113747) were pooled to generate the 2015 Dose-Hgb Model. Subsequently, this initial model was modified by including 2 additional Phase II studies (PHI114837, 204836) and 3 Japan Phase III studies (PHI204716, PHI201754, PHI201753), referred to as 2019 Dose-Hgb model. The 2019 Dose-Hgb model was utilized via clinical trial simulations (CTS) to support dose strength development.

A longitudinal nonlinear mixed-effects model was developed to describe the Hgb time course after treatment with a once-daily placebo or 0.5 to 25 mg daprodustat. Covariate analyses elucidated that *baseline Hgb, body weight, and prior ESA dose* were the most relevant covariates of Hgb response to daprodustat. No other covariates, including race or ethnicity appeared to have impact on Hgb response.

Population-based simulations were performed to determine the median doses that would achieve a steady-state:

- 0 g/dL change from baseline in ESA users and

- 1 or 2 g/dL increases from baseline Hgb in ESA non-users.

Rapid increases in Hgb (>2 g/dL after 4 weeks of therapy) were also taken into account when assessing the simulation results.

A total of 11,810 Hgb observation records from 710 subjects that received either daprodustat (81%) or placebo (19%, including standard of care other than ESA) was used. Most subjects were White Caucasian (59%), followed by Japanese (21%) and African American (10%). The population contained approximately equal numbers of male and female subjects and ND and HD subjects; 48% of subjects had used an ESA within the last 4 weeks.

The effect of body weight was smaller on daprodustat exposure (Cmax and AUC) than the effect of inter-individual variability in response to daprodustat and did not justify adding complexity when choosing the starting doses. Thus, the starting dose of daprodustat was stratified according to baseline Hgb (ESA non-users) or prior ESA dose (ESA users).

There were no peritoneal dialysis subjects in the population used for the Dose-Hgb model development. Therefore, simulations were not explicitly performed for this population. The pathophysiology of peritoneal dialysis patients is very similar to that of ND CKD subjects because hemoconcentration occurs due to fluid removal during HD and there is no such mechanism of hemoconcentration in peritoneal dialysis or ND (Yamamoto 2017). Additionally, as most peritoneal dialysis patients will be ESA user patients, the starting dose recommendation was the same as for the ND ESA user population in the Phase III trials.

Once per day, starting and maintenance dose

Based on the clinical trial simulations, assuming the Hgb target range is harmonized across all regions and populations to 10 to 11 g/dL, suggested starting doses for daprodustat Phase III program were provided and ranged between 1-4 mg for ESA non-users and 1-12 for ESA user. The Dose-Hgb model simulation results indicated that the response to daprodustat varied greatly among different subjects, and the doses required to achieve the centre of the target Hgb range could range from 1 to 24 mg. Individual dose adjustments are required to achieve and maintain the target Hgb in patients; hence, 9 different once-daily maintenance doses (1, 2, 4, 6, 8, 10, 12, 16, 24 mg) were selected for the global Phase III studies. Dose adjustments are made 1 dose step at a time, generally once every 4 weeks. Please see more details below under "Treatments".

A fraction of patients seems to receive a decreased dose, or even no dose, compared to the starting dose from Week 2 and onwards. From the pharmacokinetic data, there are indications that patient weight may impact C_{max} and AUC, and body weight is also a covariate in the dose-response model, indicating that a patient with a lower body weight would require a lower dose (including starting dose) than a patient with a higher body weight, to achieve the same Hb response.

Three times per week dosing (TIW Regimen)

TIW was assessed for daprodustat in studies 204836 and 204837/ASCEND TD. Because the daprodustat dose-response with Hgb is generally linear between 1 to 24 mg once daily, it was anticipated that a similar time proportional efficacy relationship would exist for daprodustat at dosing TIW. A three-parameter Bayesian Emax dose-response model using data from 204836 (GSK Report 2016N309671_00) produced the most consistent dose conversion ratio estimates across the studied dose range, and the ratio was approximately 2.0, which was used to calculate the TIW doses for

2.5.5.2. Main study(ies)

The pivotal efficacy and safety data of daprodustat come from 5 global Phase III studies (*Table 7*):

In addition, 2 Phase III studies conducted in Japan provide supportive efficacy: One 1 year, double-blind, active-controlled study in HD patients (201754) and a 1-year, open-label, active-controlled study in non-dialysis patients (201753).

Table 7 Global Phase III Studies Overview of Study Design (Studies 205270/ASCEND NHQ, 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD)

	Non-dialysis Studies		***Dialysis Studies***		
	205270/ASCEND-NHQ	***200808/ASCEND-ND***	***201410/ASCEND-ID***	***200807/ASCEND-D***	***204837/ASCEND-TD***
Population	*ND*	*ND rhEPO user or non-user*	*ID rhEPO non-user*	*HD or PD rhEPO user*	*HD rhEPO user*
Daprodustat dosing Frequency	*Once daily*	*Once daily*	*Once daily*	*Once daily*	*TIW*
Control	*Oral placebo*	*SC darbepoetin alfa*	*SC or IV darbepoetin alfa*	*IV epoetin alfa for HD participants or SC darbepoetin alfa for PD participants*	*IV epoetin alfa*
Number of participants	*614*	*3872*	*312*	*2964*	*407*
Study duration	*28 Weeks*	*Event driven. Dependent upon the accumulation of 664 adjudicated first MACE*	*52 weeks*	*Event driven. Dependent upon the accumulation of 664 adjudicated first MACE*	*52 weeks*
Blinding	*Double-blind*	*Open-label (sponsor-blind)*	*Open-label (sponsor-blind)*	*Open-label (sponsor-blind)*	*Double-blind, double dummy*
Randomization	*1:1*	*1:1*	*1:1*	*1:1*	*2:1 (daprodustat:epoetin)*

	Non-dialysis Studies		***Dialysis Studies***		
	205270/ASCEND-NHQ	***200808/ASCEND-ND***	***201410/ASCEND-ID***	***200807/ASCEND-D***	***204837/ASCEND-TD***
Stratification	*Region*	*Region Current rhEPO use (yes/no) Participation in the ABPM sub-study*	*Dialysis type (HD or PD) Dialysis start planned or unplanned (urgent)*	*Dialysis type (HD or PD) Region Participation in the ABPM sub-study*	*Region*
Evaluation Period	*Weeks 24 to 28*	*Weeks 28 to 52*	*Weeks 28 to 52*	*Weeks 28 to 52*	*Weeks 28 to 52*
Primary endpoint	*Mean change in Hgb between Baseline and EP*	*Mean change in Hgb between Baseline and EP AND Time to first occurrence of adjudicated MACE*	*Mean change in Hgb between Baseline and EP*	*Mean change in Hgb between Baseline and EP AND Time to first occurrence of adjudicated MACE*	*Mean change in Hgb between Baseline and EP*
Hgb target range	*11.0 to 12.0 g/dL*	*10 to 11 g/dL*	*10 to 11 g/dL*	*10 to 11 g/dL*	*10 to 11 g/dL*
Hgb analysis range	*11.0 to 12.0 g/dL*	*10 to 11.5 g/dL*	*10 to 11.5 g/dL*	*10 to 11.5 g/dL*	*10 to 11.5 g/dL*

ABPM = ambulatory blood pressure monitoring; ND= non-dialysis; SC= subcutaneous

Study periods

The studies comprised a 4 week screening period and a treatment period. The treatment period was divided in a stabilisation phase when the dose of treatment was titrated to target Hb levels (24 weeks in placebo-controlled study 205270/ASCEND-NHQ and 28 weeks in other studies) and evaluation period (EP, 24-28 weeks in placebo-controlled study 205270/ASCEND-NHQ and 28-52 weeks in 200808/ASCEND-ND study) that was part of a maintenance period (MP) till the end of the study.

Methods

- **Study Participants**

Patient were generally included with > 18 years of age. Patients in the non-dialysis studies were to be CKD stage 3, 4, or 5 (< 60 ml/min/1.73 m2) and not on dialysis. In dialysis studies, patients had to be on HD: ≥2 x/Wk; PD: ≥4 x/Wk or planning to initiate dialysis in the coming 6 weeks (201410/ASCEND-ID), to be on HD: ≥2 x/Wk; PD: ≥5 x/Wk (200807/ASCEND-D) or on HD (in-centre): ≥3 x/Wk (204837/ASCEND-TD).

In the non-dialysis studies, non-ESA patients were included with Hb from 8.5 to 10.0 g/dL or 8.0 to 10.0 g/dL at randomization in the study 205270/ASCEND-NHQ and study 200808/ASCEND-ND, respectively. ESA users in the non-dialysis study 200808/ASCEND-ND and all three dialysis studies were included with Hb from 8 to 11.0 g/dL at randomization. In the studies, 200807/ASCEND-D and 204837/ASCEND-TD, patients with Hgb >11 to 11.5 g/dL were allowed to enrol if receiving greater than the minimum rhEPO or analogue dose.

Ferritin and TSAT levels could be ≥ 50 ng/mL and ≥ 15%, respectively, for the placebo-controlled NDD studies, and > 100 ng/mL and > 20% for the ESA comparator studies. ESA non-users should not be using ESA for at least 6-8 weeks prior screening, depending on the study. ESA users should not be on ESA for at least 6-8 weeks prior screening, depending on the study. In the dialysis initiation study (201410/ASCEND-ID) patients should not use ESA within 8 weeks prior to screening except for limited use as part of dialysis initiation.

Relevant exclusion criteria were transfusions within 8 weeks prior to randomisation for the placebo-controlled study 205270/ASCEND-NHQ. No pregnant or lactating women were included in the study. Also, patients with history of aplasia, other type of anaemia, history of malignancy within the 2 years prior to screening, liver disease, active GI bleeding, patients with acute cardiovascular event within the past 4 weeks for two CVOT trials and 8 or 10 weeks for other studies. Patients with a planned kidney transplant within 52 weeks (28 weeks for 205270) after study start were excluded.

- **Treatments**

In the placebo-controlled Study 205270/ASCEND-NHQ daprodustat and placebo tablets were used. In the active-controlled studies 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D, and 204837/ASCEND-TD, daprodustat tablets and rhEPO (darbepoetin alfa or epoetin alfa).

Daprodustat

The dose of daprodustat in all studies was titrated to reach the target Hb levels (11-12 g/dL in the placebo-controlled Study 205270/ASCEND-NHQ and 10-11 g/dL in the active-controlled studies). For participants assigned to daprodustat, the **starting dose** of daprodustat in the Global Phase III studies was assigned, for ESA users, based on a participant's prior rhEPO or analogue dose at randomization (Day 1) or, for ESA non-users, HemoCue Hgb concentration at randomization (Day 1) (*Table 7*).

Table 8 Daprodustat Starting Dose (Studies 205270/ASCEND-NHQ, 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD)

	Daprodustat Starting Dose				
	Non-dialysis Studies		**Dialysis Studies**		
	205270/ASCEND-NHQ (once daily)	**200808/ASCEND-ND (once daily)**	**201410/ASCEND-ID (once daily)**	**200807/ASCEND-D (once daily)**	**204837/ASCEND-TD (TIW)**
rhEPO Users – rhEPO Dose at Randomization (Day 1)					
Epoetins (including biosimilars) (U/week IV) a					
1500 to 2000		1 mg		4 mg	8 mg
>2000 to <10000		2 mg		6 mg	12 mg
≥10000 to <20000		2 mg		8 mg	16 mg
≥20000		4 mg		12 mg	24 mg
Darbepoetin (μg/4week SC/IV) b					
20 to 30		1 mg		4 mg	8 mg
>30-150		2 mg		6 mg	12 mg

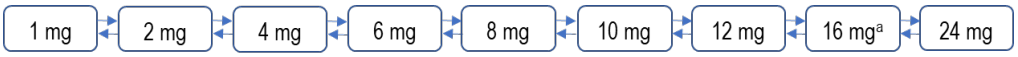
	Daprodustat Starting Dose				
	Non-dialysis Studies		Dialysis Studies		
	205270/ASCEND-NHQ (once daily)	200808/ASCEND-ND (once daily)	201410/ASCEND-ID (once daily)	200807/ASCEND-D (once daily)	204837/ASCEND-TD (TIW)
>150-300		2 mg		8 mg	16 mg
>300		4 mg		12 mg	24 mg
Methoxy PEG-epoetin beta (μg/month SC/IV) c, d					
30 to 40		1 mg		4 mg	8 mg
>40 to 180		2 mg		6 mg	12 mg
>180 to 360		2 mg		8 mg	16 mg
>360		4 mg		12 mg	24 mg
rhEPO Non-user: HemoCue Hgb (g/dL) at Randomization (Day 1)					
≥8 to <9	4 mg	4 mg	4 mg		
≥9 to ≤10	2 mg	2 mg	2 mg		
>10			1 mg		

a. Standardized rhEPO IV dose (U/week) = 161/113 * (epoetin SC dose (units)) / (frequency) [Beserab, 2002]
b. Conversion of 250 U:1 μg (epoetin IV: darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008]
c. Conversion of 1:1.2 μg (darbepoetin alfa: methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [Choi, 2013]
d. Conversion of 208 U:1 μg (epoetin IV: methoxy PEG-epoetin beta)

The available **dose steps** of daprodustat are outlined below. Dose adjustments resulted were performed at least every 4 weeks according to the protocol criteria, if needed, by 1 dose step at a time.

Once Daily Dosing

Studies 205270/ASCEND NHQ, 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D dose steps:



TIW dosing

Study 204837/ASCEND-TD dose steps:

Placebo

Matching 7 mm and 9 mm tablets were used in the placebo group in Study 205270/ASCEND NHQ.

Active Comparator (rhEPO)

ESA non-users (200808/ASCEND-ND and 201410/ASCEND-ID)

- The starting dose of the active comparator was determined based on a participant's weight and HemoCue Hgb concentration at randomization (Day 1).

ESA users (200808/ASCEND-ND, 200807/ASCEND-D and 204837/ASCEND TD)

- For participants already on the active comparator, the starting dose was the same as their currently scheduled dose, rounded to the nearest study dose.

- For participants receiving other types of rhEPOs, the starting dose was an equivalent dose of the active comparator, rounded to the nearest study dose. Prior rhEPOs dose was converted to an equivalent dose of the active comparator using standardized conversion factors [Beserab, 2002; Sterner, 2008; Choi, 2013].
- In Studies 200807/ASCEND-D and 204837/ASCEND TD if a participant's HemoCue Hgb concentration at randomization (Day 1) was Hgb >11.0 g/dL and ≤11.5 g/dL the starting dose of active comparator was reduced to the next lowest starting dose to maintain Hgb within the target range of 10-11 g/dL.

Dose-steps and frequency of rhEPO administration were pre-defined:

Darbepoetin alfa (200808/ASCEND-ND, 201410/ASCEND-ID and 200807/ASCEND ND)

- The dose steps for SC darbepoetin alfa dose were 20 µg every 4 weeks, followed by, 30, 40, 50, 60, 80, 100, 130, 150, 200, 300 µg.

Epoetin alfa (200807/ASCEND-D and 204837/ASCEND TD)

- The dose steps for IV epoetin alfa were 1000 U per week followed by 2000, 3000, 4000, 5000, 6000, 8000, 10000, 12000, and then an increase of 3000 U weekly for each next step (e.g. 15000, 18000, 21000, etc.).

Standard of care

Iron. In the placebo-controlled Study 205270/ASCEND-NHQ, iron therapy was administered, starting with oral iron, if ferritin was <50 ng/mL and/or TSAT was <15%. In all other active-controlled studies, iron therapy was administered if ferritin was ≤100 ng/mL and/or TSAT was ≤20%.

Rescue. Rescue therapy was initiated as per protocol and included the use of IV iron, blood transfusions or rhEPO. In the placebo-controlled study, rescue was started if HemoCue Hgb is <7.5 g/dL, or HemoCue Hgb is <8.5 g/dL, and participant is symptomatic, or HemoCue Hgb is <8.5 g/dL on three consecutive visits. In the active-controlled studies, rescue was started if HemoCue Hgb remains <9 g/dL (at a scheduled study visit, Week 4 onwards) despite 3 consecutive dose increases above the starting or post-rescue dose (where HemoCue Hgb is <9 g/dL prior to each dose increase), or HemoCue Hgb is <7.5 g/dL despite a dose increase at the prior study visit.

- **Objectives**

Primary objectives of the studies are specified in *Table 9* below.

Table 9 Primary objective of pivotal studies

Study	Primary objective
205270	To compare the efficacy of daprodustat to placebo on mean change in Hgb levels (superiority)
200808	To compare daprodustat to darbepoetin alfa for cardiovascular (CV) safety and Hgb efficacy (noninferiority)
200807	To compare daprodustat to rhEPO for CV safety and Hgb efficacy (non-inferiority)
201410	To compare daprodustat to rhEPO for Hgb efficacy (non-inferiority)
204837	To compare the effect of daprodustat to epoetin alfa on Hgb efficacy when administered TIW to HD-dependent participants (non-inferiority)

- **Outcomes/endpoints**

Primary and secondary efficacy endpoints for the global Phase III studies are provided in Table 10.

Table 10 Key Efficacy Endpoints for Global Phase III Studies (205270/ASCEND-NHQ, 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD)

	Non-dialysis Studies		**Dialysis Studies**		
	205270/ ASCEND-NHQ	**200808/ ASCEND-ND**	**201410/ ASCEND-ID**	**200807/ ASCEND-D**	**204837/ ASCEND-TD**
Primary Endpoint					
Mean change in Hgb between Baseline and EP (mean over Weeks 28 to 52[a] for all studies except 205270/ASCEND-NHQ where the EP is Weeks 24 to 28)	X		X		X
Mean change in Hgb between Baseline and EP (mean over Weeks 28 to 52 **AND** Time to first occurrence of adjudicated MACE (composite of all-cause mortality, non-fatal MI and non-fatal stroke)		X		X	
Principal Secondary Efficacy Endpoints					
% of participants having a Hgb increase of ≥1.0 g/dL from Baseline to EP	X				
Mean change in SF-36 Vitality Domain between Baseline and Week 28	X				
Average monthly IV iron dose (mg)/participant to Week 52			X	X	X
Secondary Efficacy Endpoints					
Hgb change from Baseline to Week 52[b] (Week 28 in 205270/ASCEND-NHQ)	X	X	X	X	X
N (%) responders, defined as mean Hgb within the Hgb analysis range 10 to 11.5 g/dL during EP (11.0 to 12.0 g/dL for 205270/ASCEND-NHQ)	X	X	X	X	X
% time Hgb in analysis range during the EP (all studies) and during the MP (Week 28 to end of trial) (200808/ASCEND-ND and 200807 ASCEND-D only)[c]	X	X	X	X	X
Time to stopping randomized treatment due to meeting rescue criteria	X	X	X	X	X

SF-36 = Short Form -36

a. The primary endpoint was assessed using an alternative EP (Week 28 to 36) as a supportive analysis

b. In studies 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD Hgb change from Baseline was tested for non-inferiority, using the -0.75 g/dL margin used in the primary analysis.

c. % time Hgb in analysis range was tested first for non-inferiority, then for superiority. The non-inferiority analysis used a margin of 15% less time in range and if non-inferiority was established, nominal superiority was achieved if the one-sided p-value is <0.025.

Various other secondary and exploratory endpoints were assessed in the studies, which are mentioned in detail in the study reports. Some of them included changes in QoL measures, blood pressure, and progression to CKD.

- **Sample size**

The sample size for study 205270/ASCEND-NHQ was based on the second principle secondary endpoint, SF-36 Vitality scores, which is indeed the endpoint with the lowest anticipated effect size and

leads to a study being more than sufficiently powered for the primary endpoint. For studies 200808/ASCEND-ND and 200807/ASCEND-D, the sample size was based on the co-primary CV safety endpoint on an ITT analysis to reach 664 MACE events. The sample size for studies 201410/ASCEND-ID and 204837/ASCEND-TD was based on reaching sufficient patient exposure according to ICH E1 and having at least 90% power on the primary endpoint.

- **Randomisation and Blinding (masking)**

Participants were randomized 1:1 to receive either daprodustat or placebo in the placebo-controlled study or active treatment (rhEPO) in the active-controlled study. In the study 204837/ASCEND-TD, 2:1 (daprodustat: epoetin) was applied. Subject randomization was stratified by region (all studies except 201410/ASCEND-ID), current rhEPO use (200808/ASCEND-ND), participation in the ABPM sub-study (200808/ASCEND-ND and 200807/ASCEND-D), dialysis type HD or PD (201410/ASCEND-ID and 200807/ASCEND-D) and dialysis type planned or unplanned (201410/ASCEND-ID). A central randomization approach with an Interactive Response Technology (IRT) system was used to protect against potential selection bias due to the open-label design.

Two studies were double-blind studies; the placebo-controlled study 205270/ASCEND-NHQ in non-dialysis patients and the active-controlled TIW study 204837/ASCEND-TD in dialysis patients. Both patients and investigators were blinded to the study treatment. In the study 205270/ASCEND-NHQ, participants would remain blinded to the dose being administered, while the dose level of each study treatment (tablet and IV formulations) was not blinded in the study 204837/ASCEND-TD, where the patient received both oral and IV formulation (one dummy and one with active substance). In this study, several site staff members (e.g., study coordinator, nurse, or pharmacist) were unblinded and responsible for the handling, dispensing, and preparing of unblinded study treatment (i.e., IV). In the study 205270/ASCEND-NHQ, participants were not provided with the results of the HemoCue Hgb assessment during their participation in the study. Additionally, investigators, investigational site staff, and participants were also blinded to some of the central laboratory results (i.e., Hgb, hematocrit, hepcidin, RBC count, and reticulocyte count).

Three other studies, 200808/ASCEND-ND, 201410/ASCEND-ID and 200807/ASCEND-D, were open-label studies. The sponsor was blinded to randomized assignment until database lock. To increase the reliability of the important MACE data, an external independent Clinical Events Classification group (CEC) blinded to randomized treatment allocation adjudicated all events reported during the global Phase III studies that constitute events of MACE, thromboembolic events and hospitalization for heart failure. In addition, in 200808/ASCEND-ND, two components of progression of CKD were adjudicated (initiating dialysis for <90 days and not initiating dialysis when dialysis was indicated).

- **Statistical methods**

For all Phase III studies, the primary **efficacy analysis population** was the All Randomized Intent-to-Treat (ITT) Population, consisting of all randomized participants and analysed according to the treatment to which they were randomized. A supportive analysis of the primary efficacy endpoint was performed on the Per-Protocol (PP) Population, which consisted of all ITT participants without PP Population exclusions.

The primary efficacy **estimand** (treatment policy estimand) is the effect of daprodustat treatment relative to rhEPO on the change in Hgb from Baseline to the average of all values in the EP, regardless of adherence to treatment, use of non-randomized ESA medication, or use of blood transfusions, in patients with anaemia secondary to CKD and assuming patients do not die before the end of the EP.

Placebo-controlled study ASCEND-NHQ

The **primary efficacy analysis** of mean change from baseline in Hgb was based on the ITT Population and used an analysis of covariance (ANCOVA) model, including prognostic randomization stratification factors (region). A MNAR assumption was used to impute missing Hgb values according to a participant's treatment status (on vs off). Superiority was established if the one-sided p-value was <0.025.

Supportive and sensitivity analyses included: a "while on-treatment" estimand (on-treatment Hgb values and not taken within the 8 weeks following a red blood cell or whole blood transfusion or post-randomisation non-randomized ESA treatment); and a post-hoc an observed-cases analysis using all observed post-randomization Hgb values.

The first **principal secondary endpoint** for ASCEND-NHQ was the % of participants having a Hgb increase of ≥1.0 g/dL from Baseline to EP (Weeks 24 to 28), and the comparison between treatment groups was made using a Cochran-Mantel-Haenszel (CMH) chi-squared test, adjusting for treatment, and region. The second principal secondary endpoint of mean change from baseline in SF-36 Vitality Domain was analyzed using an ANCOVA model including stratification factors. Missing measurements were imputed based on MAR assumption.

As **multiplicity strategy**, the primary endpoint of mean change in Hgb between Baseline and EP (mean over Weeks 24 to 28) was tested first for superiority using a one-sided 2.5% significance level. Conditional on achieving statistical significance, principal secondary endpoints of % of participants having a Hgb increase of ≥1.0 g/dL from Baseline to EP and mean change in SF-36 Vitality Domain between Baseline and Week 28 were hierarchically tested for superiority using a one-sided 2.5% significance level.

Active controlled studies 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD

Non-inferiority for the mean change from baseline in Hgb value was defined as being achieved if the lower limit of the 2 sided 95% confidence interval (CI) of the treatment difference was greater than the **non-inferiority margin** of -0.75 g/dL. This margin was determined based on clinical judgment and statistical reasoning, considering the following factors: Hgb changes that would result in a clinically meaningful difference to a patient, the percentage of the rhEPO efficacy preserved by the margin, consideration of changes that could be due to variability, and precedent for margins used in past rhEPO dialysis and non-dialysis pivotal trials.

The **primary efficacy analysis** was based on the ITT Population and used an ANCOVA model, including prognostic randomisation stratification factors. The analysis population used all available participant data regardless of treatment adherence. Missing data were imputed using multiple imputations and Rubin's rules [Rubin, 1987]. A missing at random (MAR) assumption was considered appropriate, as off-treatment Hgb values were expected to be similar to on-treatment Hgb values since patients would usually take non-randomized ESA medication during such times to control their Hgb.

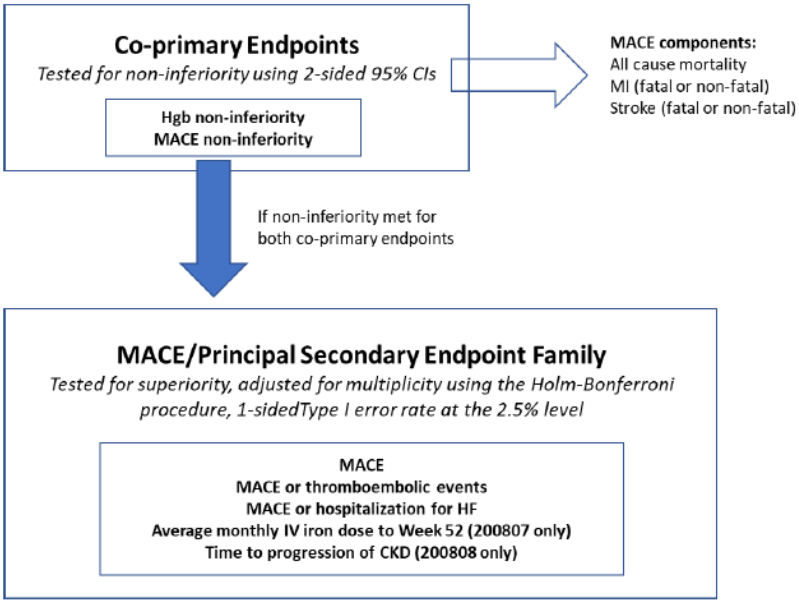
Sensitivity and supportive analyses included: a "while on-treatment" estimand using only evaluable Hgb data (on-treatment Hgb values and not taken within the 8 weeks following a red blood cell or whole blood transfusion or post-randomisation non-randomized ESA treatment); an observed-cases analysis using all observed post-randomization Hgb values. This analysis was performed post-hoc in ASCEND-ID and ASCEND-TD; a PP population analysis; a tipping point analysis including a range of MNAR assumptions and either using all observed values or only "while on treatment" values; and an

alternative EP period (Week 28 to 36) and either using all observed values or only "while on treatment" values.

For the principal secondary endpoint for studies ASCEND-D, ASCEND-ID and ASCEND-TD of average monthly IV iron dose (mg)/participant to Week 52, an ANCOVA model, adjusting for stratification factors, was used to compare the difference between arms.

For studies ASCEND-ND and ASCEND-D, the **multiplicity strategy** used a combination of a gatekeeper approach on the co-primary endpoints, followed by a closed-test multiplicity procedure wrapped around the family of superiority hypotheses consisting of MACE and the principal secondary endpoints. Figure 8 illustrates the structure of the statistical testing plan. MACE and the principal secondary endpoints were formally tested for superiority using the Holm-Bonferroni procedure [Holm, 1979].

Figure 8 Multiplicity Controlled Statistical Testing Plan for Studies 200808/ASCEND-ND and 200807/ASCEND-D



In studies 204837/ASCEND-TD and 201410/ASCEND-ID, the primary endpoint of mean change in Hgb between Baseline and EP (mean over Weeks 28 to 52) was tested first for non-inferiority, using the lower limit of the two-sided 95% CI. Conditional on achieving statistical significance (i.e., establishing non-inferiority) the single principal secondary endpoint of average monthly IV iron dose (mg)/participant to Week 52 was tested for superiority using a one-sided 2.5% significance level.

For all studies, placebo- and active-controlled, the primary endpoint and principal secondary endpoints were evaluated for a set of pre-specified **subgroups** to support the proposed indication. Subgroups included demographic and baseline characteristics, prior history of selected diseases/events, and use of specified medication at Baseline.

Of note, the NI-margin for MACE was changed during the study from 1.2 (hazard ratio) to 1.25, due to COVID-19 outbreak and expected lower number of events (664). CHMP has agreed to the proposal (EMA/CHMP/SAWP/372682/2020; Q3), but indicated that the sponsor blinding is crucial.

Results

- **Participant flow**

Table 11 Participant flow in pivotal studies

	Non-dialysis patients				Dialysis patients					
	205270/ASCEND-NHQ		**200808/ASCEND-ND**		**201410/ASCEND-ID**		**200807/ASCEND-D**		**204837/ASCEND-TD**	
	D (307)	*PB (307)*	*D (1937)*	*ESA (1935)*	*D (157)*	*ESA (155)*	*D (1487)*	*ESA (1477)*	*D (270)*	*ESA (137)*
Completed study	*98% (300)*	*94% (290)*	*97% (1873)*	*97% (1870)*	*99% (155)*	*97% (151)*	*94% (1358)*	*95% (1364)*	*>99% (269)*	*98% (135)*
Completed treatment	*83% (254)*	*69% (211)*	*62% (1210)*	*62% (1207)*	*71% (112)*	*75% (116)*	*48% (697)*	*48% (693)*	*71% (192)*	*71% (97)*
Overall Primary reason for all study treatment discontinuation: n (%)										
Adverse event	*7% (22)*	*8% (24)*	*13% (254)*	*11% (222)*	*12% (19)*	*6% (9)*	*15% (222)*	*16% (235)*	*10% (28)*	*8% (11)*
Participant reached protocol-defined stopping criteria	*5% (14)*	*13% (41)*	*8% (151)*	*8% (161)*	*5% (8)*	*6% (9)*	*16% (232)*	*15% (218)*	*9% (23)*	*10% (14)*
Decision by participant or proxy	*3% (10)*	*8% (25)*	*15% (281)*	*15% (288)*	*11% (17)*	*9% (14)*	*16% (236)*	*17% (250)*	*9% (23)*	*8% (11)*

- **Recruitment**

The study 205270/ASCEND-NHQ was initiated on 05-Mar-2018 (first participant, first visit) and completed on 07-Oct-2020 (last participant, last visit. In the study 200808/ASCEND-ND, the first participant was screened on 27-SEP-2016 and the last participant completed on 19-APR-2021. In the study 201410/ASCEND-ID, the first participant's first visit was on 11-May-2017; the last participant completed their last visit on 24-Sep-2020. In the study 200807/ASCEND-D, the first participant was screened on 28-Sep-2016 and the last participant completed on 9-Nov-2020. In the study 204837/ASCEND-TD, the first participant was screened on 05-Sep-2018 and the last participant completed on 19-Jun-2020.

- **Conduct of the study**

Protocol amendments: Several protocol amendments occurred in all studies except study 204837/ASCEND-TD. Some of the amendments concerned study objectives and secondary/exploratory endpoints, entry criteria and statistical methods and require further clarification.

Protocol violations: Significant protocol deviations were reported for 50% of participants in the daprodustat group and 53% in the placebo group in the study 205270/ASCEND-NHQ, for 66% in the daprodustat group and 68% in the darbepoetin alfa group in the study 200808/ASCEND-ND, for 73% in the daprodustat group and 72% in the darbepoetin alfa group in the study 201410/ASCEND-ID, for 75% of the participants in the daprodustat group and 81% of participants in the rhEPO group in the study 200807/ASCEND-D and for 72% of the participants in the daprodustat group and 79% of participants in the rhEPO group in the study 204837/ASCEND-TD. The most frequently reported significant deviations were related to assessment performance/timing, study procedures, visit

completion, failure to report safety events per protocol, study treatment administration/dispense (e.g. 49% in the ASCEND-TD study), other GCP deviation, informed consent form process/timing, assessment or time point completion.
GCP violations: In the study 205270/ASCEND-NHQ, no GCP non-compliance issues were identified by monitoring or audit in the study. In the study 200808/ASCEND-ND and 200807/ASCEND-D, three and eight sites were closed early due to GCP non-compliance issues, including suspected fraud at one and three sites, respectively; participants from these sites are excluded from the results presented.

Data on 17 study participants (1 randomized) and 10 participants, respectively, were excluded from all analyses as valid informed consent was never obtained. Several individual GCP noncompliance issues were identified at several other sites and corrective actions taken. In the study 201410/ASCEND-ID and 204837/ASCEND-TD only one GCP non-compliance issue was reported related to quality and study drug administration, respectively.

- **Baseline data**

Non-dialyses studies

205270/ASCEND-NHQ

Baseline demographic characteristics, renal characteristics, Hgb levels, CV and diabetes characteristics, blood pressure values, and markers of iron metabolism were generally similar between treatment groups in the placebo-controlled non-dialysis Study 205270/ASCEND-NHQ.

Baseline demographic characteristics and Baseline renal function and Hgb levels are summarized in Table 12 *and* Table 13*,* respectively.

Table 12 Summary of Demographic Characteristics (Study 205270/ASCEND-NHQ, ITT Population)

	Placebo (N=307)	**Dapro (N=307)**
Age (years), n	307	307
Mean (SD)	66.6 (12.93)	65.3 (13.43)
Median	67.0	66.0
Min to max	22 to 91	23 to 89
Age category, n (%)	307	307
<65 years	121 (39)	135 (44)
65 - <75 years	96 (31)	82 (27)
≥75 years	90 (29)	90 (29)
Gender, n (%)	307	307
Female	178 (58)	176 (57)
Male	129 (42)	131 (43)
Ethnicity, n (%)	307	307
Hispanic or Latino	103 (34)	104 (34)
Not Hispanic or Latino	204 (66)	203 (66)
Race, n (%)	307	307
Black or African American	47 (15)	44 (14)
American Indian or Alaska Native	34 (11)	34 (11)
Asian	28 (9)	30 (10)
Native Hawaiian or other Pacific Islander	1 (<1)	0
White	195 (64)	197 (64)
Mixed race	2 (<1)	2 (<1)
Baseline weight (kg), n (%)	307	307
<75 kg	150 (49)	157 (51)
≥75 kg	157 (51)	150 (49)
Baseline hsCRP (mg/L), n	300	302
Mean (SD)	6.98 (12.604)	7.19 (14.760)
Median	2.80	2.30
Min to max	0.2 to 126.4	0.2 to 118.3

Source: Study 205270/ASCEND-NHQ CSR Table 1.09
hsCRP=high sensitivity C-reactive protein

Table 13 Summary of Baseline Renal Function and Hgb Levels (Study 205270/ASCEND-NHQ, ITT Population)

	Placebo (N=307)	Dapro (N=307)
Baseline CKD stage		
Stage 2 (eGFR ≥60<90mL/min/1.73m^2)	2 (<1)	3 (<1)
Stage 3 (eGFR 30-<60 mL/min/1.73m^2)	87 (28)	92 (30)
Stage 4 (eGFR 15-<30 mL/min/1.73m^2)	137 (45)	139 (45)
Stage 5 (eGFR <15 mL/min/1.73m^2)	81 (26)	73 (24)
Baseline Hgb (g/dL)	307	307
Mean (SD)	9.71 (0.729)	9.73 (0.635)
Median	9.70	9.80
Min to max	7.9 to 14.2	6.9 to 12.1
Baseline Hgb group 1[a], n (%)	307	307
<9 g/dL	46 (15)	28 (9)
≥9 and <10 g/dL	151 (49)	168 (55)
≥10 and ≤11 g/dL	99 (32)	106 (35)
>11 g/dL	11 (4)	5 (2)
Baseline Hgb group 2[b], n (%)	307	307
<8.5 g/dL	5 (2)	5 (2)
≥8.5 and <9 g/dL	41 (13)	23 (7)
≥9 and ≤10 g/dL	172 (56)	194 (63)
>10 g/dL	89 (29)	85 (28)

Source: Study 205270/ASCEND-NHQ CSR Table 1.09 and ad-hoc Table 1.28
eGFR= estimated glomerular filtration rate
a. Hgb subgroup categories used in the other daprodustat Phase III studies in the ASCEND program in which the Hgb target range was 10-11 g/dL (Study 200807/ASCEND-D, Study 200808/ASCEND-ND, Study 201410/ASCEND-ID, and Study 204837/ASCEND-TD).
b. Hgb subgroup categories used in Study 205270/ASCEND-NHQ in which the Hgb target range was 11-12 g/dL.

200808/ASCEND-ND

Except for mean Baseline Hgb, which was higher in ESA users compared with ESA non-users, Baseline demographic characteristics, renal characteristics, CV and diabetes characteristics, blood pressure values, and markers of iron metabolism were generally similar between treatment groups and between Baseline ESA users and non-users in the active-controlled non-dialysis study 200808/ASCEND-D. Baseline demographic characteristics, Baseline renal function and Hgb levels overall by Baseline ESA use are summarized in Table 13 and Table 14, respectively.

Table 14 Summary of Demographic Characteristics Overall and by Baseline ESA Use (Study 200808/ASCEND-ND, ITT Population)

	Baseline ESA Users		Baseline ESA Non-Users		Overall	
	Dapro (N=907)	Darbe (N=903)	Dapro (N=1030)	Darbe (N=1032)	Dapro (N=1937)	Darbe (N=1935)
Age (years), n	907	903	1030	1032	1937	1935
Mean (SD)	65.4 (14.41)	65.1 (14.11)	64.3 (13.68)	64.7 (13.59)	64.8 (14.03)	64.9 (13.83)
Median	68.0	68.0	66.0	66.0	67.0	67.0
Min, Max	19, 94	18, 94	20, 94	22, 98	19, 94	18, 98
Age category, n (%)	907	903	1030	1032	1937	1935
< 65 years	366 (40)	378 (42)	470 (46)	464 (45)	836 (43)	842 (44)
65-<75 years	284 (31)	294 (33)	315 (31)	317 (31)	599 (31)	611 (32)
≥75 years	257 (28)	231 (26)	245 (24)	251 (24)	502 (26)	482 (25)
Gender, n (%)	907	903	1030	1032	1937	1935
Female	534 (59)	507 (56)	568 (55)	564 (55)	1102 (57)	1071 (55)
Male	373 (41)	396 (44)	462 (45)	468	835 (43)	864 (45)
Ethnicity, n (%)	907	903	1030	1032	1937	1935

	Baseline ESA Users		Baseline ESA Non-Users		Overall	
	Dapro (N=907)	**Darbe (N=903)**	**Dapro (N=1030)**	**Darbe (N=1032)**	**Dapro (N=1937)**	**Darbe (N=1935)**
Hispanic or Latino	225 (25)	255 (28)	205 (20)	212 (21)	430 (22)	467 (24)
Not Hispanic or Latino	682 (75)	648 (72)	825 (80)	820 (79)	1507 (78)	1468 (76)
Race, n (%)	907	903	1030	1032	1937	1935
American Indian or Alaskan Native	62 (7)	66 (7)	26 (3)	34 (3)	88 (5)	100 (5)
Asian	244 (27)	242 (27)	281 (27)	295 (29)	525 (27)	537 (28)
Black or African American	52 (6)	44 (5)	131 (13)	141 (14)	183 (9)	185 (10)
Native Hawaiian or Other Pacific Islander	2 (<1)	3 (<1)	5 (<1)	4 (<1)	7 (<1)	7 (<1)
White	528 (58)	520 (58)	570 (55)	535 (52)	1098 (57)	1055 (55)
Mixed Race	19 (2)	28 (3)	17 (2)	23 (2)	36 (2)	51 (3)
Baseline weight (kg)	907	903	1030	1032	1937	1935
Mean (SD)	72.86 (18.909)	72.18 (17.483)	75.29 (21.005)	74.75 (20.446)	74.16 (20.083)	73.551(9.159)
Median	70.40	71.00	71.65	71.40	71.00	71.30
Min, Max	35.3, 160.7	35.0, 143.0	36.4, 172.0	34.7, 185.9	35.3, 172.0	34.7, 185.9
Baseline weight (kg), n (%)	907	903	1030	1032	1937	1935
<75 kg	538 (59)	529 (59)	577 (56%)	586 (57%)	1115 (58)	1115 (58)
≥75 kg	369 (41)	374 (41)	453 (44%)	446 (43%)	822 (42)	820 (42)
Baseline hsCRP (mg/L)	899	900	1024	1030	1923	1930
Mean (SD)	5.94 (15.340)	6.30 (14.180)	5.20 (10.296)	6.08 (13.776)	5.54 (12.904)	6.18 (13.692)
Median	2.00	2.10	2.00	1.90	2.00	2.00
Min, Max	0.1, 255.8	0.1, 185.9	0.1, 121.0	0.1, 206.8	0.1, 255.8	0.1, 206.8

Source: Study 200808/ASCEND-D CSR Table 1.021 and Table 1.022

Table 15 Summary of Baseline Renal Function, ESA Dose and Hgb Levels Overall and by Baseline ESA Use (Study 200808/ASCEND-ND, ITT Population)

	Baseline ESA Users		**Baseline ESA Non-Users**		**Overall**	
	Dapro (N=907)	**Darbe (N=903)**	**Dapro (N=1030)**	**Darbe (N=1032)**	**Dapro (N=1937)**	**Darbe (N=1935)**
Baseline eGFR, n (mL/min/1.73m2)	906	903	1030	1032	1936	1935
Mean (SD)	20.11 (11.215)	20.79 (11.205)	20.14 (11.339)	20.57 (10.914)	20.12 (11.278)	20.67 (11.048)
Median	17.00	19.00	17.00	18.00	17.00	18.00
Min, Max	2.0, 66.0	3.0, 70.0	2.0, 71.0	3.0, 68.0	2.0, 71.0	3.0, 70.0
Baseline CKD stage	907	903	1030	1032	1937	1935
Stage 2 (eGFR ≥60<89mL/min/1.73m2)	6 (<1)	6 (<1)	3 (<1)	2 (<1)	9 (<1)	8 (<1)
Stage 3 (eGFR 30-<60 mL/min/1.73m2)	157 (17)	164 (18)	179 (17)	199 (19)	336 (17)	363 (19)
Stage 4 (eGFR 15-<30 mL/min/1.73m2)	412 (45)	430 (48)	463 (45)	464 (45)	875 (45)	894 (46)
Stage 5 (eGFR <15 mL/min/1.73m2)	331 (36)	303 (34)	385 (37)	367 (36)	716 (37)	670 (35)
Missing	1 (<1)	0	0	0	1 (<1)	0
Standardized prior ESA dose (U/week)	907	903	-	-	-	-
Mean (SD)	5471.9 (5146.24)	5394.5 (4559.13)	-	-	-	-
Median	3943.6	3920.5	-	-	-	-
Min, Max	102, 55779	307, 41871	-	-	-	-
Baseline Hgb (g/dL)	907	903	1030	1032	1937	1935
Mean (SD)	10.29 (0.922)	10.29 (0.932)	9.49 (0.787)	9.47 (0.782)	9.87 (0.940)	9.85 (0.948)
Median	10.40	10.40	9.50	9.50	9.80	9.90
Min to max	6.6, 13.8	7.2, 15.9	3.6, 12.5	5.7, 14.1	3.6, 13.8	5.7, 15.9
Baseline Hgb group (g/dL)	907	903	1030	1032	1937	1935
<9 g/dL	69 (8)	81 (9)	236 (23)	257 (25)	305 (16)	338 (17)
≥9 and <10 g/dL	240 (26)	213 (24)	502 (49)	504 (49)	742 (38)	717 (37)
≥10 and ≤11 g/dL	420 (46)	456 (50)	269 (26)	248 (24)	689 (36)	704 (36)
>11 g/dL	178 (20)	153 (17)	23 (2)	23 (2)	201 (10)	176 (9)

Source: Study 200808/ASCEND-D CSR Table 1.021 and Table 1.022

Dialyses studies

201410/ASCEND-ID, 200807/ASCEND-D, 204837/ASCEND-TD

Baseline demographic characteristics, renal characteristics, ESA use, Hgb levels, CV and diabetes characteristics, blood pressure values, and markers of iron metabolism were generally similar between treatment groups for each of the active-controlled dialysis studies. Baseline demographic characteristics and Baseline renal characteristics, ESA use and Hgb levels are summarised in Table 15 and Table 16, respectively.

Table 16 Summary of Demographic Characteristics (201410/ASCEND-ID, 200807/ASCEND-D, 204837/ASCEND-TD, ITT Population)

	201410/ASCEND-ID		200807/ASCEND-D		204837/ASCEND-TD	
	Dapro (N=157)	**Darbe (N=155)**	**Dapro (N=1438)**	**rhEPO[b] (N=1438)**	**Dapro TIW (N=270)**	**Epoetin (N=137)**
Age (years), n	157	155	1438	1438	270	136
Mean (SD)	53.7 (14.31)	55.8 (15.70)	57.0 (14.31)	57.3 (14.67)	59.4 (14.16)	55.8 (15.34)
Median	52.0	56.0	58.0	59.0	60.0	56.0
Min, max	22, 84	20, 86	18, 95	20, 94	21, 90	22, 87
Age category, n (%)	157	155	1438	1438	270	137
<65 years	119 (76)	110 (71)	980 (68)	951 (66)	167 (62)	96 (70)
65 - 74 years	22 (14)	28 (18)	307 (21)	321 (22)	66 (24)	24 (18)
≥75 years	16 (10)	17 (11)	151 (11)	166 (12)	37 (14)	16 (12)
Missing	0	0	0	0	0	1 (<1)
Gender, n (%)	157	155	1438	1438	270	137
Female	61 (39)	57 (37)	614 (43)	618 (43)	121 (45)	56 (41)
Male	96 (61)	98 (63)	824 (57)	820 (57)	149 (55)	81 (59)
Ethnicity, n (%)	157	155	1438	1438	270	137
Hispanic or Latino	50 (32)	50 (32)	343 (24)	338 (24)	69 (26)	33 (24)
Not Hispanic or Latino	107 (68)	105 (68)	1095 (76)	1100 (76)	198 (73)	104 (76)
Missing	0	0	0	0	3 (1)	0
Race, n (%)	157	155	1438	1438	270	137
American Indian or Alaska native	5 (3)	2 (1)	19 (1)	32 (2)	1 (<1)	1 (<1)
Asian	26 (17)	31 (20)	171 (12)	180 (13)	20 (7)	9 (7)
Black or African American	16 (10)	13 (8)	215 (15)	228 (16)	49 (18)	32 (23)
Native Hawaiian or other Pacific Islander	0	0	25 (2)	25 (2)	1 (<1)	0
White	110 (70)	107 (69)	965 (67)	949 (66)	195 (72)	94 (69)
Mixed race	0	2 (1)	43 (3)	24 (2)	1 (<1)	1 (<1)
Missing	0	0	0	0	3 (1)	0
Baseline weight (kg)[a]	155	153	1425	1422	270	137
Mean (SD)	76.01 (18.909)	77.20 (21.658)	77.65 (21.518)	77.46 (20.291)	76.51 (18.996)	77.48 (19.290)
Median	75.00	74.00	74.40	74.85	74.00	75.40
Min, Max	45.0, 136.8	37.4, 173.2	36.0, 193.8	29.0, 176.5	36.1, 138.3	38.5, 131.3
Baseline weight group, n (%)[a]	157	155	1438	1438	270	137
<75 kg	77 (49)	82 (53)	726 (50)	714 (50)	143 (53)	68 (50)
≥75 kg	78 (50)	71 (46)	699 (49)	708 (49)	127 (47)	69 (50)
Missing	2 (1)	2 (1)	13 (<1)	16 (1)	0	0
Baseline hsCRP	155	152	1427	1427	266	136
Mean (SD)	10.29 (23.100)	10.83 (23.076)	10.36 (21.675)	9.97 (20.312)	8.85 (14.482)	11.82 (16.376)
Median	2.80	3.65	3.90	4.00	4.30	4.65
Min, max	0.1, 173.9	0.2, 163.1	0.1, 328.5	0.1, 288.9	0.2, 119.6	0.2, 97.5

Source: Study 201410/ASCEND-ID CSR Table 1.021; Study 200807/ASCEND-D CSR Table 1.049 and Study 204837/ASCEND-TD CSR Table 1.017
hsCRP = high sensitivity C-reactive protein

a. Post dialysis weight for participants with in-clinic dialysis in Study 201410/ASCEND-ID and for all participants in Study 200807/ASCEND-D and Study 204837/ASCEND-TD CSR

b. Epoetin alfa in HD participants or darbepoetin alfa in PD participants

Table 17 Summary of Baseline Renal Characteristics, ESA Dose and Hgb Levels (201410/ASCEND-ID, 200807/ASCEND-D, 204837/ASCEND-TD, ITT Population)

	201410/ASCEND-ID		200807/ASCEND-D		204837/ASCEND-TD	
	Dapro (N=157)	**Darbe (N=155)**	**Dapro (N=1438)**	**rhEPO[b] (N=1438)**	**Dapro TIW (N=270)**	**Epoetin (N=137)**
Dialysis vintage at Screening, n (%)			1438	1438	270	137
<2 Years	-	-	433 (30)	443 (31)	82 (30)	42 (31)
⩾2 and <5 Years	-	-	512 (36)	512 (36)	95 (35)	52 (38)
⩾5 Years	-	-	493 (34)	483 (34)	93 (34)	43 (31)
Dialysis type at Screening, n (%)	157	155	1438	1438	270	137
Hemodialysis conventional	125 (80)	119 (77)	1216 (85)	1213 (84)	237 (88)	120 (88)
Hemofiltration / hemodiafiltration	1 (<1)	7(5)	51 (4)	56 (4)	33 (12)	17 (12)
Peritoneal dialysis	31 (20)	29 (19)	171 (12)	169 (12)	0	0
Standardized prior ESA dose (U/week)			1437	1436	270	137
Mean (SD)	-	-	7980.9 (7301.08)	7659.7 (6449.91)	8462.072(6282.8805)	7958.157 (6635.0920)
Median	-	-	5846.5	5699.1	6297.367	5943.363
Min, Max	-	-	270, 69958	147, 69958	464.29, 43995.00	199.71, 44941.43
rhEPO hyporesponder, n (%) [a]			1438	1438	270	137
No	-	-	1243 (86)	1244 (87)	233 (86)	116 (85)
Yes	-	-	175 (12)	176 (12)	37 (14)	21 (15)
Missing	-	-	20 (1)	18 (1)	0	0
Baseline Hgb (g/dL)	157	155	1438	1438	270	137
Mean (SD)	9.46 (1.002)	9.49 (0.970)	10.36 (0.963)	10.40 (0.976)	10.44 (0.830)	10.59 (0.926)
Median	9.40	9.50	10.40	10.50	10.50	10.70
Min, max	5.9, 12.3	6.4, 14.6	7.1, 13.3	5.3, 17.8	8.1, 13.4	5.3, 12.3
Baseline Hgb group, n (%)	157	155	1438	1438	270	137
<9 g/dL	54 (34)	41 (26)	127 (9)	117 (8)	15 (6)	6 (4)
⩾9 and <10 g/dL	52 (33)	69 (45)	342 (24)	316 (22)	51 (19)	20 (15)
⩾10 and ⩽11 g/dL	44 (28)	42 (27)	596 (41)	629 (44)	141 (52)	60 (44)
>11 g/dL	7 (4)	3 (2)	373 (26)	376 (26)	63 (23)	51 (37)

Source: Study 201410/ASCEND-ID CSR Table 1.021; Study 200807/ASCEND-D CSR Table 1.049 and Study 204837/ASCEND-TD CSR Table 1.017

a. Participants with ERI ⩾2.0 U/kg/wk/g/L (prior epoetin) or ⩾0.008 ug/kg/wk/g/L (prior darbepoetin alfa) or ⩾0.01 mg/kg/wk/g/L (prior methoxy-PEG-epoetin), or if treated with the equivalent of ⩾450 U/kg/week IV epoetin alfa. ERI is calculated as ESA (e.g. epoetin alfa or other ESAs) dose per week (in U or ug) during the 4-week Screening period divided by Baseline dry weight at Day 1 and then divided by the achieved Day 1 Hgb.

b. Epoetin alfa in HD participants or darbepoetin alfa in PD participants.

The number of participants in the ITT and PP populations is summarized in Table 18.

Table 18 Efficacy Analysis Populations

Study	Treatment Group	ITT Population[a] n (%)	PP Population[b] n (%)
Non-dialysis Studies			
205270/ ASCEND-NHQ	Daprodustat	307 (100)	-
	Placebo	307 (100)	-
200808/ASCEND-ND	Daprodustat	1937 (100)	982 (51)
	Darbepoetin alfa	1935 (100)	1083 (56)
201753 (Japanese)	Daprodustat	108 (72)	84 (56)
	Epoetin beta pegol	109(73)	81 (54)
Dialysis Studies			
201410/ASCEND-ID	Daprodustat	157 (100)	77 (49)
	Darbepoetin alfa	155 (100)	101 (65)
200807/ASCEND-D	Daprodustat	1438 (100)	922 (64)
	Epoetin alfa or darbepoetin alfa	1438 (100)	935 (65)
204837/ASCEND-TD	Daprodustat	270 (100)	143 (53)
	Epoetin alfa	137 (100)	82 (60)
201754 (Japanese)	Daprodustat	133 (98)	113 (83)
	Darbepoetin alfa	134 (>99)	121 (90)

c. Defined as all randomized participants for studies 205270/ASCEND-NHQ, 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD; and as all randomized participants with a Hgb assessment at Baseline and at least 1 scheduled visit after Baseline for studies 201754 and 201753.

d. Defined as all ITT participants without PP population exclusions in studies 200808/ASCEND-ND, 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD; and ITT participants who had at least 1 Hgb measurement during the EP period and who were not major protocol violators for studies 201754 and 201753

Exclusions from the PP population included mostly events that, if they should occur, might directly impact the haemoglobin efficacy endpoint; or lead to permanent discontinuation of study treatment or study withdrawal and hence indirectly impact the efficacy endpoint by causing data to be missing.

Of note, 88 subjects from three sites were excluded from all analyses in the ASCEND-D study, since the sites were closed due to suspected fraud.

Outcomes and estimation

Main efficacy outcomes from all five pivotal studies are mentioned in Table 19.

Table 19 Main efficacy outcomes

	Non-dialysis patients		Dialysis patients		
Study	**205270/ ASCEND-NHQ**	**200808/ ASCEND-ND**	**201410/ ASCEND-ID**	**200807/ ASCEND-D**	**204837/ ASCEND-TD**
Primary endpoint					
Hgb Change from Baseline to the EP *	**[1]** 1.58 vs 0.19 1.4 (1.23, 1.56) superiority met	**[1]** 0.74 vs 0.66 0.08 (0.03, 0.13) non-inferiority met	**[1]** 1.02 vs 1.12 -0.10 (-0.34, 0.14) non-inferiority met	**[1]** 0.29 vs 0.11 0.18 (0.12, 0.24) non-inferiority met	**[1]** -0.04 vs 0.02 -0.05 (-0.21, 0.10) non-inferiority met
Hb effects (secondary)					

	Non-dialysis patients		Dialysis patients		
Study	**205270/ ASCEND-NHQ**	**200808/ ASCEND-ND**	**201410/ ASCEND-ID**	**200807/ ASCEND-D**	**204837/ ASCEND-TD**
Proportion of participants with a ≥1 g/dL increase in Hgb between Baseline and over the EP*	**[2]** 235 (77%) vs 54 (18%) 0.56 (0.49, 0.63) superiority met	NA	NA	NA	NA
Hgb change from Baseline to Week 52b (Week 28 in 205270/ASCEND-NHQ) (g/dL) – difference (95%CI)	**[4]** **1.56 vs 0.20** **1.36 (1.16, 1.55)** superiority met	**[3]** 0.76 vs 0.73 0.03 (-0.05, 0.11) non-inferiority met not formally tested	**[3]** 1.17 vs 1.13 0.04 (-0.29, 0.36) non-inferiority met, not formally tested	**[3]** 0.26 vs 0.14 0.12 (0.03, 0.21) non-inferiority met not formally tested	**[3]** -0.03 vs 0.11 -0.14 (-0.37, 0.10) non-inferiority met not formally tested
N (%) responders, defined as mean Hgb within the Hgb analysis range 10 to 11.5 g/dL during EP (11.0 to 12.0 g/dL for 205270/ASCEND-NHQ) – (%) difference (95%CI)	**[5]** 132 (52) vs 17 (8) 0.45 (0.37, 0.52) superiority met	**[4]** 1167 (78.3) vs 1063 (69.9) 8.3 (5.2, 11.4) non-inferiority and superiority met not formally tested	**[4]** 86 (64.7) vs 87 (65.4) -0.8 (-12.2, 10.7) non-inferiority met not formally tested	**[4]** 888 (73.2) vs 853 (70.0) 3.2 (-0.4, 6.8) non-inferiority and superiority met not formally tested	**[4]** 172 (80) vs 68 (63.6) 16.5 (5.9, 27.0) non-inferiority and superiority met not formally tested
% time Hgb in analysis range during the EP (all studies) and during the MP (Week 28 to end of trial) (200808/ASCEND-ND and 200807 ASCEND-D only) (%) – difference (95%CI)	**[6]** 50.08 vs 8.18 38.8 (25.0, 54.55) Superior	**[5]** 70.5 vs 63.2 4.57 (2.04, 7.11) not formally tested	**[5]** 57.0 vs 54.7 2.05 (-4.45, 11.27) not formally tested	**[5]** 61.4 vs 59.5 0.96 (0.0, 3.76) not formally tested	**[5]** 70.83 vs 61.76 11.18 (2.83 vs 19.56) not formally tested
Patient-reported outcomes (secondary)					
Mean change in SF-36 Vitality Domain between Baseline and Week 52 (Week 28 for205270/ ASCEND-NHQ) (score) – difference	**[3]** 7.29 vs 1.93 5.36 (2.17, 8.56) superiority met	-0.14 vs 0.35 -0.49 (-1.19, 0.21) not formally tested	0.16 vs 1.61 -1.45 (-4.03, 1.14) not formally tested	-1.16 vs -1.05 -0.11 (-0.87, 0.65) not formally tested	-
Mean change from baseline to Week 28	8.72 vs 2.81	0.20 vs 1.77 -1.57 (-3.11, -0.03)	-2.36 vs 4.07	-	-

	Non-dialysis patients		Dialysis patients		
Study	**205270/ ASCEND-NHQ**	**200808/ ASCEND-ND**	**201410/ ASCEND-ID**	**200807/ ASCEND-D**	**204837/ ASCEND-TD**
in CKD-AQ Tired/Low Energy/Weak domain (score_ - difference	5.91 (2.83, 9.00) superiority met	not formally tested	-6.43 (-5.51, 1.42) not formally tested		
Patient Global Impression of Change by week 28 (205270/ ASCEND-NHQ), week 52 (204837/ASCEND-TD) or end of treatment (other studies)	Very much improved 20% vs 17% Moderately improved 31% vs 24% Minimally improved 21% vs 27 No change 25% vs 29% not formally tested	Very much improved 12% vs 12% Moderately improved 24% vs 25% Minimally improved 24% vs 23 No change 29% vs 29% not formally tested	Very much improved 19% vs 15% Moderately improved 23% vs 28% Minimally improved 23% vs 24 No change 25% vs 28% not formally tested	Very much improved 11% vs 11% Moderately improved 21% vs 21% Minimally improved 18% vs 16% No change 43% vs 45% not formally tested	Very much improved 11% vs 10% Moderately improved 16% vs 14% Minimally improved 25% vs 16% No change 46% vs 54% not formally tested
Rescue therapy and iv iron use (secondary, unless stated otherwise)					
Adjusted mean average monthly IV iron dose during day 1 to Week 52 (to week 28 in study 205270/ASCEND-NHQ) (mg) – difference	151.1 (IQR 43.2, 153.0) vs 142.2 (IQR 35.8, 245.8) exploratory, not formally tested	NA	**[2]** 144.7 vs 125.3 19.4 (-11.0, 49.9) superiority not met	**[2]** 91.0 vs 99.3 -8.3 (-17.6, 1.1 superiority not met	**[2]** 97.19 vs 101.93 -4.75 (-42.26, 32.77) superiority not met
Rescue therapy (N,%) –HR (95% CI)	2 (<1%) vs 26 (8%) 0.07 (0.02, 0.3) nominal significance, not formally tested	39 (2.0%) vs 64 (3.3%) 0.63 (0.42, 0.94) not formally tested	5 (3%) vs 5 (3%) 1.06 (0.31, 3.66) not formally tested	49 (3.4) vs 50 (3.5) 1.02 (0.69, 1.51) not formally tested	6 (2.2%) vs 3 (2.2%) 1.06 (0.26, 4.22) not formally tested
Blood transfusions (N,%) – HR (95% CI)	4 (1.3%) 15 (4.9%) exploratory, not formally tested	247 (12.8%) vs 261 (13.5%) 0.96 (0.8, 1.1) exploratory, not formally tested	18 (11.5%) vs 21 (13.5%) 0.08 (0.47, 1.66) not formally tested	227 (15.8) vs 266 (18.5) 0.85 (0.71, 1.01) not formally tested	21 (7.8%) vs 16 (11.8%) 0.61 (0.32 vs 1.18) not formally tested
Effect on renal function decline					

	Non-dialysis patients		Dialysis patients		
Study	**205270/ ASCEND-NHQ**	**200808/ ASCEND-ND**	**201410/ ASCEND-ID**	**200807/ ASCEND-D**	**204837/ ASCEND-TD**
Time to progression of CKD (N,%) – HR (95% CI)	NA	**[2]** 343 (28.1%) vs 359 (28.4%) 0.98 (0.84, 1.13) superiority not met	NA	NA	NA
eGFR change from Baseline at Week 52 (mL/min/1.73m2) – difference	-0.3 vs -2.3 exploratory, not formally tested	-3.14 vs -2.87 -0.27 (-0.82, 0.29) not formally tested	NA	NA	NA
Effect on blood pressure					
SBP (mm) - difference	-0.23 vs -0.63 0.40 (-2.4, 3.2) not formally tested	-0.62 vs -1.17 0.56 (-0.79, 1.90) not formally tested	-0.61 vs -0.93 0.33 (-1.28, 1.94) not formally tested	-0.47 vs-0.91 0.43 (-1.18, 2.05) not formally tested	-3.18 vs 0.55 -3.73 (-9.03, 1.56) not formally tested
DBP (mm) – difference	0.84 vs -0.96 1.8 (0.12, 3.49) not formally tested	0.06 vs -0.59 0.65 (-0.09, 1.38) not formally tested	-1.04 vs -0.58 -0.46 (-1.36, 0.44) not formally tested	-1.00 vs-0.60 -0.39 (-1.30, 0.51) not formally tested	-2.52 vs -0.29 -2.23 (-4.99, 0.54) not formally tested
MAP (mm) – difference	0.49 vs -0.82 1.31 (-0.51, 3.13) not formally tested	-0.17 vs -0.77 0.60 (-0.22, 1.43) not formally tested	-0.89 vs -0.71 -0.18 (-1.20, 0.84) not formally tested	-0.82 vs -0.72 -0.10 -1.13, 0.93) not formally tested	-2.72 vs -0.12 -2.60 (-5.86, 0.67) not formally tested

***** Weeks 28 to 52 in all studies except Weeks 24 to 28 in study 205270/ASCEND-NHQ. The numbers in parentheses represent the sequence in which the endpoints were tested i.e., [1] represents the primary endpoint and [2] to [6] represent the secondary endpoints that were formally tested sequentially in a fixed sequence testing procedure. Endpoints indicated as 'not formally tested' refer to where the fixed sequential testing procedure was stopped based on pre-specified criteria.

CKD: chronic kidney disease; CKD-AQ: Chronic Kidney Disease - Anaemia Questionnaire; DAP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; MAP: mean arterial pressure; SAP: systolic blood pressure; SF-36: Short Form 36; ULN: upper limit of normal

Other exploratory endpoints

Hb excursions

Across the placebo and active-controlled studies, the proportion of participants with evaluable central laboratory Hgb values <7.5 g/dL and ≥12 or 13 g/dL during the EP was measured. Also, across the active-controlled studies, the proportion of participants with a rapid increase (>1g/dL increase over 2

weeks or >2g/dL increase over 4 weeks) or decrease in Hgb (>1g/dL decrease over 2 weeks or >2g/dL decrease over 4 weeks) was assessed. See Table 20 below.

Iron metabolism

Markers of iron metabolism, i.e. TSAT, TIBC, ferritin and hepcidin, were measured in all five studies as exploratory endpoints and are presented below in Table 20. IV or oral (for non-dialysis studies) iron use was generally similar between treatment groups.

Table 20 Exploratory endpoints

	Non-dialysis patients		**Dialysis patients**		
Study	**205270/ ASCEND-NHQ**	**200808/ASCEND-ND**	**201410/ASCEND-ID**	**200807/ASCEND-D**	**204837/ASCEND-TD**
Hb excursions (exploratory)					
number (%) of participants with a Hgb <7.5 g/dL	<1% vs 1%	1% vs 1%	4% vs 4%	2% vs 2%	1% vs 2%
number (%) of participants with a Hgb value ≥12 g/dL (or ≥13 g/dL in study 205270/ ASCEND-NHQ)	10% vs 1%	23% vs 23%	27% vs 37%	35% vs 27%	14% vs 21%
% of time Hgb ≥12 g/dL	-	14.6 % vs 16.7%	20% vs 21.2%	21.7% vs 19.9%	8.6% vs 19.5%
Participants with >1g/dL increase in Hgb	NA	8% vs 13% in week 2 10% vs 8% in week 4	14% vs 13% in week 2 18% vs 8% in week 4	12% vs 7% in week 2 11% vs 6% in week 4	10% vs 6% in week 2 2% vs 3% in week 4
Participants with >2g/dL increase in Hgb in any 4-week period through Week 52	NA	10% vs 7%	15% vs 13%	15% vs 10%	-
Participants with >1g/dL decrease in Hgb	NA	5% vs 2% in week 2 3% vs 4% in week 4	6% vs 7% in week 2 3% vs 6% in week 4	5% vs 6% in week 2 7% vs 6% in week 4	6% vs 7% in week 2 5% vs 11% in week 4
Participants with >2g/dL decrease in Hgb in any 4-week	NA	10% vs 9%	13% vs 13%	17% vs 17%	-

	Non-dialysis patients		Dialysis patients		
Study	**205270/ ASCEND-NHQ**	**200808/ASCEND-ND**	**201410/ASCEND-ID**	**200807/ASCEND-D**	**204837/ASCEND-TD**
period through Week 52					
Markers of Iron Metabolism (exploratory)					
Mean change from baseline to end of study or treatment in TSAT (%; mean, SD)	-0.8 (10.59) vs 0.5 (10.56)	-1.20 (13.118) vs 1.66 (15.067)	-0.7 (15.61) vs 1.2 (15.37)	-4.2 (15.81) vs -2.7 (16.68)	-2.7 (15.79) vs -3.9 (16.73)
Mean change from baseline to end of study in TIBC (umol/L;mean, SD)	7.2 (7.43) vs -0.4 (5.73)	4.9 (8.78) vs -0.4 (7.04)	4.7 (9.52) vs 0.1 (7.88)	6.6 (8.48) vs 0.3 (6.55)	4.9 (6.03) vs 1.1 (5.70)
Mean % change from baseline to end of study in ferritin (95% CI)	-34.67 (-39.45, -29.51) vs 0.37 (-6.60, 7.86)	-18.8 (-22.6, -14.8) vs -11.9 (-16.1, -7.6)	-21.8 (-32.7, -9.1) vs -24.7 (-34.2, -13.9)	-35.6 (-40.0, -30.7) vs -24.3 (-29.0, -19.2)	-29.1 (-35.3, -22.3) vs -25.8 (-35.2, -15.2)
Mean % change from baseline to end of treatment in hepcidin (95% CI)	-40.47 (-45.32, -35.19) vs -4.62 (-11.17, 2.43)	-24.7 (-27.5, -21.7) vs 6.8 (2.8, 10.9)	-28.9 (-39.9, -15.9) vs -8.6 (-22.6, 8.0)	-32.3 (-35.7, -28.8) vs -15.8 (-19.6, -11.8)	-19.7 (-27.0, -11.7) vs -20.7 (-33.1, -5.9)

Ancillary analyses

The primary endpoint for each global Phase III study was evaluated for a set of pre-specified subgroups to support the proposed indication. Subgroups included demographic and baseline characteristics, prior history of selected diseases/events, and use of specified medication at Baseline.

Results of the subgroup analyses were generally consistent with the primary analyses. A small number of subgroups had interaction p values <0.1 (Table 21).

Table 21 Subgroups for Analysis of the Primary Endpoint Mean Change in Post Randomization Hgb Between Baseline and Over the EP

Subgroup	**205270/ ASCEND-NHQ**	**200808/ ASCEND-ND**	**201410/ ASCEND-ID**	**200807/ ASCEND-D**	**204837/ ASCEND-TD**
	Interaction p-values <0.1[d]				
Demographic Subgroups					
Age	X	X	X	X	0.0839
Gender	X	X	X	X	X
Ethnicity	X	0.0194	X	X	X
Race	X	0.0342	X	X	X

Region	X	0.0057	X	X	X
Region combined (US vs non-US)		X	X	X	X
Hgb Categories					
Hgb category at Baseline 1[b]	0.0451[a]	X	X	X	X
Hgb category at Baseline 2[c]	0.0761[a]				
ESA Users, rhEPO Hyporesponders and hsCRP					
Standardized prior ESA dose		0.0001		0.0084 [a]	X
Current ESA-user at randomization		0.0025			
rhEPO hyporesponder				0.0468 [a]	X
hsCRP at Baseline	X	X	X	X	0.0119
Weight Subgroups					
BMI at Baseline	X	X	X		
Post-dialysis BMI at Baseline				X	X
Weight at Baseline	X	X	X		
Post-dialysis weight at Baseline				X	X
Renal Disease Subgroups					
Dialysis vintage at Randomization				X	X
Dialysis type at Baseline			X	X	
Dialysis start manner			X		
Baseline CKD stage		X			
eGFR	X				
Transfusion w.6 mo. Screening		X	X	X	
Serum iron level at Baseline	X				
Iron replete participants	X				
Cardiovascular Disease Subgroups					
History of diabetes	X	X	X	X	X
History of stroke		0.0911[a]	X	X	X
History of MI		X	X	X	X
History of heart failure	0.0021[a]	X	X	X	X
History of cancer		X	X	X	
History of thromboembolic events		X	X	X	X
Hospitalization w.6 mo. Screening		0.0250[a]	X	X	X
ACEI/ARB use at Baseline		X		X	X
Smoking history					X
Dosing					
Dosing algorithm at Baseline				X	

Source: Study 205270/ASCEND-NHQ CSR Table 2.009 and Figure 2.026; Study 200808/ASCEND-ND CSR Table 2.016 and Figure 2.009; Study 201410/ASCEND-ID CSR Table 2.163 and Figure 2.051; Study 200807/ASCEND-D Table 67.400011; Study 204837/ASCEND-TD CSR ad hoc Table 952.021 and ad hoc Figure 952.010

e. For these subgroups, the results trended in the same direction across all subgroup categories. Adjusted mean treatment difference (daprodustat - rhEPO) for each subgroup category was >0

f. Hgb subgroup categories used in the active-controlled studies. Target Hgb target range was 10 to 11 g/dL.

g. Hgb subgroup categories used in placebo-controlled study 205270/ASCEND-NHQ. Hgb target range was 11 to 12 g/dL.

h. P-value is only shown for those subgroups where the interaction p-value is <0.1.

Treatment differences between groups of selected studies and endpoints are shown below.

In the study 205270/ASCEND-NHQ:

- Baseline Hb <9 g/dL 1.89 (1.39, 2.40); Hb ≥9 and ≤ 10 g/dL 1.46 (1.22, 1.70), Hb ≥10 and ≤ 11 g/dL 1.15 (0.86, 1.43), Hb >11 g/dL 0.76 (-0.36, 1.88)

In the study 200808/ASCEND-ND:

- ESA non-users 0.16 (0.08; 0.23) and ESA users -0.01 (-0.08, 0.07)
- Standardized prior ESA dose <3000 U/week 0.19 (0.06, 0.31) and ≥3000 U/week -0.12 (-0.21,0.02)

In the study 200807/ASCEND-D:

- Standardized prior ESA dose < 7000 U/week 0.25 (0.17, 0.33), ≥ 7000 U/week 0.08 (-0.02, 0.18)
- rhEPO hyporesponder "no" 0.21 (0.14, 0.27), "yes" 0.01 (-0.17, 0.19).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 Summary of efficacy for the phase 3 trials

Non-dialysis patients

Title: A 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, study in recombinant human erythropoietin (rhEPO) naïve nondialysis participants with aneamia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo			
Study identifier	205270/ASCEND-NHQ		
Design	A 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, study in recombinant human erythropoietin (rhEPO) naïve nondialysis participants with aneamia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 weeks 4 weeks screening period 4 weeks follow-up period
Hypothesis	Superiority		
Treatments groups	Daprodustat		Once daily (1, 2, 4, 6, 8, 10, 12, 16 mg) based on Hb level
	Placebo		Matching to daprodustat
Endpoints and definitions	Primary endpoint	Hb response	Mean change in Hb between baseline and over the evaluation period of weeks 24 to 28 inclusive
	Secondary endpoint	Hb increase proportion	Participants with a Hgb Increase of ≥1.0 g/dL from Baseline to EP
	Secondary endpoint	Quality of Life (SF-36VT)	Mean change in SF-36 Vitality domain-score between baseline and week 28
	Secondary endpoint	Rescue therapy	Time to rescue therapy (from week 4 onward) (criteria for rescue included HemoCue Hgb was <7.5 g/dL, Hgb <8.5 g/dL with symptoms, or Hgb <8.5 g/dL on 3 consecutive visits)
	Secondary endpoint	Blood pressure	Change from baseline to week 28 in on-treatment BP parameters (SBP, DBP, MAP)
	Other secondary endpoints		Other secondary endpoints included: effect on additional Hb endpoints, improving symptoms of anaemia of CKD, severity and change in symptoms, improving HRQoL, improving work productivity and regular daily activity impairment, improving health status.
Database lock	07-Oct-2020		

Title: A 28-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, study in recombinant human erythropoietin (rhEPO) naïve nondialysis participants with aneamia associated with chronic kidney disease to evaluate the efficacy, safety and effects on quality of life of daprodustat compared to placebo				
Study identifier	205270/ASCEND-NHQ			
Results and Analysis				
Analysis description	**Primary Analysis (ITT)**			
Analysis population and time point description			Intent to treat	
Descriptive statistics and estimate variability	Treatment group	Daprodustat	Placebo	Difference (95%CI)
	Number of subject	307	307	
	Hb response (g/dL)	1.58 (0.06)	0.19 (0.06)	1.40 (1.23, 1.56) P<0.0001
	Secondary Analyses (ITT)			
Descriptive statistics and estimate variability	Hb increase proportion (%)	235 (77%)	54 (18%)	0.56 (0.49, 0.63) P<0.0001
	Quality of Life score change (SF36-VT)	7.29 (1.1)	1.93 (1.2)	5.36 (2.2, 8.6) P=0.0005
	Rescue therapy (%)	2 (<1%)	26 (8%)	0.07 (0.20, 0.30) P=0.0002
	Blood pressure (mmHg)	-0.63	-0.23	0.40 (-2.4, 3.2)

Title: A phase 3 randomized, open-label (sponsor-blind), activecontrolled, parallel-group, multi-center, event driven study in non-dialysis subjects with aneamia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa.			
Study identifier	200808/ASCEND-ND		
Design	A phase 3 randomized, open-label (sponsor-blind), active controlled, parallel-group, multi-center, event driven study in non-dialysis subjects with aneamia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Endpoint driven (mean 17 months) 4 weeks screening period, placebo run-in 4 weeks, stabilisation period 28 weeks 4 to 6 weeks follow-up period	
Hypothesis	Inferiority		
Treatments groups	Daprodustat	Once daily (1, 2, 4, 6, 8, 10, 12, 16 mg) based on Hb level; starting dose 4 mg with Hb <9, 2 mg with Hb 9-10	
	ESA (darpoetin alpha)	Matching to daprodustat for ESA users	
Endpoints and	CoPrimary endpoint	Hb response	Mean change in Hb between baseline and over the evaluation period of weeks 28 to 52

Prior ESA Dose at Randomization (Day 1)			Daprodustat Starting Dose
epoetins (incl biosimilars) (convert SC to IV U/week) [a]	darbepoetin alfa (µg /4wk SC/IV) [b]	methoxy PEG-epoetin beta (µg /month SC/IV) [c,d]	(mg, once daily)
1500 to 2000	20 to 30	30 to 40	1
>2000 to <20000	>30 to 300	>40 to 360	2
≥20000	>300	>360	4

PEG=polyethylene glycol
a. Standardized rhEPO IV dose (U/week) = 161/113 * (epoetin SC dose (units)) / (frequency) [Beserab, 2002]
b. Conversion of 250 U:1 µg (epoetin IV: darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008]
c. Conversion of 1:1.2 µg (darbepoetin alfa: methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [Choi, 2013]
d. Conversion of 208 U:1 µg (epoetin IV: methoxy PEG-epoetin beta)

Title: A phase 3 randomized, open-label (sponsor-blind), activecontrolled, parallel-group, multi-center, event driven study in non-dialysis subjects with aneamia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa.					
Study identifier	200808/ASCEND-ND				
definitions	CoPrimary endpoint	MACE	Time to occurrence of adjudicated MACE (composite of mortality, non-fatal MI, non-fatal stroke) (post-hoc on-treatment)		
	Secondary endpoint	CV safety endpoints	MACE or thrombotic event (vascular access thrombosis, symptomatic deep vein thrombosis, symptomatic pulmonary embolism MACE or hospitalisation for heart failure (HF)		
	Secondary endpoint	CKD progression	Time to progression of CKD (40% decline eGFR, ESRD)		
	Secondary endpoint	Hb variability	Responders during evaluation period (week 28-52) % time within Hb range (10-11.5 g/dL)		
	Secondary endpoint	Rescue therapy	Time to rescue therapy		
	Secondary endpoint	Quality of life	Mean change in 36-Item Short Form Health Survey (SF-36) HRQOL scores (Physical Component Score [PCS], Mental Component Score [MCS] and 8 health domains) between Baseline and Weeks 8, 12, 28, 52, of particular interest are the changes from Baseline in the vitality and physical functioning domains at Weeks 28 and 52		
	Secondary endpoint	Blood pressure	Change from baseline to week 28 in on-treatment BP parameters (SBP, DBP, MAP) BP exacerbation/100PY		
	Other secondary endpoints		Additional CV endpoints, symptom severity and change, renal function.		
Database lock	19-April-2021				
Results and Analysis					
Analysis description	**Primary Analysis (ITT)**				
Analysis population and time point description			Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Daprodustat	Darpoetin alpha	HR (95%CI)	
	Number of subject	1937	1935		
	Hb response (g/dL)	0.74 (0.02)	0.66 (0.02)	0.08 (0.03,0.13) non-inferiority met	
	MACE (ITT)	378 (19.5)	371 (19.2)	1.03 (0.89, 1.19)	
	MACE (LDD +DF)	192 (9.9)	189 (9.8)	1.09 (0.89, 1.33)	
	Secondary Analyses (ITT)				
Descriptive statistics and estimate variability	MACE+thrombo-embolic (ITT)	422 (21.8%)	405 (20.9%)	1.06 (0.93, 1.22)	
	MACE+thrombo-embolic (LDD +DF)	230 (11.9%)	220 (11.4%)	1.13 (0.94, 1.36)	
	MACE+HF (ITT)	444 (22.9%)	417 (21.6%)	1.09 (0.95,1.24)	
	MACE+HF (LDD+DF)	253 (13.1%)	248 (12.8%)	1.09 (0.92, 1.30)	

Title: A phase 3 randomized, open-label (sponsor-blind), activecontrolled, parallel-group, multi-center, event driven study in non-dialysis subjects with aneamia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to darbepoetin alfa.				
Study identifier	200808/ASCEND-ND			
	CKD progression (Incidence rate per 100 PY)(ITT)	17.55	17.76	-0.21 (-2.82, 2.40)
	Hb variability (responders)	1167 (78.3%)	1063 (69.9%)	8.3 (5.2, 11.4) P<0.0001
	Hb variability (time within range)	70.5%	63.2%	0.55 (0.53, 0.57) P<0.0001
	Rescue therapy	39 (2.0%)	64 (3.3%)	0.63 (0.42, 0.94)
	QoL SF36 (52 weeks) PCS MCS Vitality	 -0.32 -0.71 -0.14	 -0.12 -0.35 0.35	 -0.20 (-0.81, 0.41) -0.35 (-1.16, 0.46) -0.49 (-1.19, 0.21)
	Blood pressure SBP DBP MAP	 -0.62 0.06 -0.17	 -1.17 -0.59 -0.77	 0.56 (-0.79, 1.90) 0.65 (-0.09, 1.38) 0.60 (-0.22, 1.43)

Dialysis patients

Title: A 52-week open-label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with aneamia associated with chronic kidney disease who are initiating dialysis			
Study identifier	201410/ASCEND-ID		
Design	A 52-week open-label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with aneamia associated with chronic kidney disease who are initiating dialysis.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks 2 weeks screening period 4 to 6 weeks follow-up period	
Hypothesis	Inferiority		
Treatments groups	Daprodustat		Once daily (1 to 24 mg); starting dose 1 with Hb > 10 g/dL, 2 with Hb 9-10 g/dL or 4 mg with Hb 8-9 g/dL
	ESA (darpoetin alpha)		Starting dose Weight / Darbe Starting Dose <60 kg: 40 µg every 4 weeks ≥60 kg to <90 kg: 60 µg every 4 weeks ≥90 kg to <120 kg: 40 µg every 2 weeks ≥120 kg: 60 µg every 2 weeks Highest dose 400 µg total 4-weekkly dose
Endpoints and	Primary endpoint	Hb response	Mean change in Hb between baseline and over the evaluation period of weeks 28 to 52

Title: A 52-week open-label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with aneamia associated with chronic kidney disease who are initiating dialysis			
Study identifier	201410/ASCEND-ID		
definitions	Secondary endpoint	IV iron use	Average monthly IV iron (mg)/participant to week 52
	Secondary endpoint	Blood pressure	Change from baseline to week 28 in on-treatment BP parameters (SBP, DBP, MAP) BP exacerbation/100PY
	Secondary endpoint	Hb variability	Responders during evaluation period (week 28-52) % time within Hb range (10-11.5 g/dL)
	Secondary endpoint	Rescue therapy	Time to rescue therapy (permanent stopping)
	Secondary endpoint	Quality of life	Mean change in 36-Item Short Form Health Survey (SF-36) HRQOL scores (Physical Component Score [PCS], Mental Component Score [MCS] and 8 health domains) between Baseline and Weeks 8, 12, 28, 52, of particular interest are the changes from Baseline in the vitality and physical functioning domains at Weeks 28 and 52
	Other Secondary endpoint		Symptom severity and change (CKD-AQ and PGI-S)
Database lock	24-Sep-2020		

Results and Analysis

Analysis description	**Primary Analysis (ITT)**			
Analysis population and time point description			Intent to treat	
Descriptive statistics and estimate variability	Treatment group	Daprodustat	ESA	Difference (95%CI)
	Number of subject	1487	1477	
	Hb response (g/dL)	1.02 (0.09)	1.12 (0.09)	-0.10 (-0.34, 0.14) non-inferiority met
	Secondary Analyses (ITT)			
	IV iron use	144.7 (11)	125.3 (11)	19.4 (-11.0, 49.9) P=0.8949
	Blood pressure SBP DBP MAP	 -0.61 -1.04 -0.89	 -0.93 -0.58 -0.71	 -0.33 (-1.28, 1.94) -0.46 (-1.36, 0.44) -0.18 (-1.20, 0.84)
	Hb variability (responders)	86 (64.7%)	87 (65.4%)	-0.8 (-12.2, 10.7) P=0.5411
	Hb variability (time within range)	57.0%	54.7%	0.54 (0.46, 0.61) P=0.1538
	Rescue therapy	5 (3%)	5 (3%)	1.06 (0.31, 3.66)
	QoL SF36 Vitality	0.16	1.61	-1.45 (-4.03, 1.14)

<table>
<tr><td colspan="4"><u>Title:</u> A 52-week open-label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with aneamia associated with chronic kidney disease who are initiating dialysis</td></tr>
<tr><td>Study identifier</td><td colspan="3">201410/ASCEND-ID</td></tr>
<tr><td colspan="4"><u>Title:</u> A phase 3 randomized, open-label (sponsor-blind), active-controlled, parallel-group, multi-centre, event driven study in dialysis subjects with aneamia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoietin-stimulating agents.</td></tr>
<tr><td>Study identifier</td><td colspan="3">200807/ASCEND-D</td></tr>
<tr><td>Design</td><td colspan="3">A phase 3 randomized, open-label (sponsor-blind), active controlled, parallel-group, multi-center, event driven study in dialysis subjects with aneamia associated with chronic kidney disease to evaluate the safety and efficacy of daprodustat compared to recombinant human erythropoietin, following a switch from erythropoietin-stimulating agents</td></tr>
<tr><td></td><td colspan="2">Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>Endpoint driven (mean 26 months)
4 weeks screening period, placebo run-in 4 weeks, stabilisation period 28 weeks
4 to 6 weeks follow-up period</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Inferiority</td></tr>
<tr><td>Treatments groups</td><td colspan="2">Daprodustat</td><td>Once daily (1, 2, 4, 6, 8, 10, 12, 16 mg)</td></tr>
<tr><td></td><td colspan="2">ESA (darpoetin alpha or epoetin alfa)</td><td>Matching to daprodustat switching from ESA
<table>
<tr><th colspan="3">ESA Dose at Randomization(Day 1)</th><th>Daprodustat Starting Dose</th></tr>
<tr><td>epoetins (incl biosimilars) (U/week IV) [a]</td><td>darbepoetin (µg/4week SC/IV) [b]</td><td>methoxy PEG-epoetin beta (µg/month SC/IV) [c, d]</td><td>(mg, once daily)</td></tr>
<tr><td>1500 to 2000</td><td>20 to 30</td><td>30 to 40</td><td>4</td></tr>
<tr><td>>2000 to <10000</td><td>>30-150</td><td>>40 to 180</td><td>6</td></tr>
<tr><td>≥10000 to <20000</td><td>>150-300</td><td>>180 to 360</td><td>8</td></tr>
<tr><td>≥20000</td><td>>300</td><td>>360</td><td>12</td></tr>
</table>
PEG=polyethylene glycol
a. Standardized rhEPO IV dose (U/week) = 161/113 * (epoetin SC dose (units)) / (frequency) [Beserab, 2002]
b. Conversion of 250 U:1 µg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008]
c. Conversion of 1:1.2 µg (darbepoetin alfa:methoxy PEG-epoetin beta)) utilized and rounded to the nearest available dose strength [Choi, 2013]
d. Conversion of 208 U:1 µg (epoetin IV: methoxy PEG-epoetin beta)</td></tr>
<tr><td>Endpoints and definitions</td><td>CoPrimary endpoint</td><td>Hb response</td><td>Mean change in Hb between baseline and over the evaluation period of weeks 28 to 52</td></tr>
<tr><td></td><td>CoPrimary endpoint</td><td>MACE</td><td>Time to occurrence of adjudicated MACE (composite of mortality, non-fatal MI, non-fatal stroke) (post-hoc on-treatment)</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>CV safety endpoints</td><td>MACE or thrombotic event (vadcular access thrombosis, symptomatic deep vein thrombosis, symptomatic pulmonary embolism MACE or hopitalisation for heart failure (HF)</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>IV iron use</td><td>Average monthly IV iron (mg)/participant to week 52</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>Hb variability</td><td>Responders during evaluation period (week 28-52)
% time within Hb range (10-11.5 g/dL)</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>Rescue therapy</td><td>Time to rescue therapy (permanent stopping)</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>Quality of life</td><td>Mean change in 36-Item Short Form Health Survey (SF-36) HRQOL scores (Physical Component Score [PCS], Mental Component Score [MCS] and 8 health domains) between Baseline and Weeks 8, 12, 28, 52, of particular interest are the changes from Baseline in the vitality and physical functioning domains at Weeks 28 and 52</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>Blood pressure</td><td>Change from baseline to week 28 in on-treatment BP parameters (SBP, DBP, MAP)
BP exacerbation/100PY</td></tr>
<tr><td></td><td>Other secondary endpoints</td><td></td><td>Additional CV endpoints, symptom severity and change.</td></tr>
<tr><td>Database lock</td><td colspan="3">09-Nov-2020</td></tr>
</table>

Title: A 52-week open-label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with aneamia associated with chronic kidney disease who are initiating dialysis				
Study identifier	201410/ASCEND-ID			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Daprodustat	ESA	Difference (95%CI)
	Number of subjects (ITT-88 pts)	1487 (1438)	1477 (1438)	
	Hb response (g/dL) (ITT)	0.28 (0.022)	0.10 (0.022)	0.18 (0.12, 0.24) non-inferiority met
	Hb response (g/dL) (ITT-88 pts)	0.29 (0.022)	0.11 (0.023)	0.18 (0.12, 0.24) non-inferiority met
	MACE (ITT)	355 (24.7%)	389 (27.1%)	0.89 (0.78, 1.03)
	MACE (LDD+DF)	169 (11.8%)	205 (14.3%)	0.85 (0.69, 1.04)
	MACE (LDD+DF+28 OT)	255 (17.2%)	278 (18.9%)	0.94 (0.79, 1.11) non-inferiority met
	Secondary Analyses			
Descriptive statistics and estimate variability	MACE+thrombo-embolic (ITT)	475 (33.0%)	537 (37.3%)	0.85 (0.76, 0.97)) non-inferiority met
	MACE+thrombo-embolic (LDD+DF)	285 (19.9%)	347 (24.2%)	0.83 (0.71, 0.97)
	MACE+HF (ITT)	404 (28.1%)	426 (29.6%)	0.94 (0.82, 1.07)NI was not tested
	MACE+HF (LDD+DF)	225 (15.7%)	246 (17.1%)	0.94 (0.78, 1.13)
	IV iron use	91.0 (3.4)	99.3 (3.4))	-8.3 (-17.6, 1.1)) One-sided P=0.0417
	Hb variability (responders)	888 (73.2%)	853 (70.0%)	3.2% (-0.4, 6.8)One-sided p=0.0488
	Hb variability (time within range) Median, Asymptotic 95% CI	61.4%	59.5%	0.96 (0.00, 3.76) P=0.0952
	Rescue therapy	49 (3.4%)	50 (3.5%)	1.02 (0.69, 1.51)

Title: A 52-week open-label (sponsor-blind), randomized, active-controlled, parallel-group, multi-center study to evaluate the efficacy and safety of daprodustat compared to recombinant human erythropoietin in subjects with aneamia associated with chronic kidney disease who are initiating dialysis_				
Study identifier	201410/ASCEND-ID			
	QoL SF36 (52 weeks) PCS MCS Vitality	 -0.51 -1.52 -1.16	 -1.06 -1.08 -1.05	 -0.55 (-0.15, 1.25) -0.44 (-1.31, 0.43) -0.11 (-0.87, 0.65)
	Blood pressure SBP DBP MAP	 -0.47 -1.00 -0.82	 -0.91 -0.60 -0.72	 -0.43 (-1.18, 2.05) -0.39 (-1.30, 0.51) -0.10 (-1.13, 0.93)

Title: A Phase 3 randomized, double-blind, active-controlled, parallel-group, multi-centre study in haemodialysis participants with anaemia of chronic kidney disease to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of daprodustat compared to recombinant human erythropoietin, following a switch from recombinant human erythropoietin or its analogues.			
Study identifier	204837/ASCEND-TD		
Design	A Phase 3 randomized, double-blind, active-controlled, parallel-group, multi-centre study in haemodialysis participants with anaemia of chronic kidney disease to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of daprodustat compared to recombinant human erythropoietin, following a switch from recombinant human erythropoietin or its analogues.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks 4 weeks screening period 4 to 6 weeks follow-up period	
Hypothesis	Inferiority		
Treatments groups	Daprodustat	Three times weekly (TIW) (2 to 48 mg); starting dose 8-24 mg	
	ESA (epoetin alfa)	Once weekly or TIW Starting dose	
Endpoints and definitions	Primary endpoint	Hb response	Mean change in Hb between baseline and over the evaluation period of weeks 28 to 52
	Secondary endpoint	IV iron use	Average monthly IV iron (mg)/participant to week 52
	Secondary endpoint	Hb variability	Responders during evaluation period (week 28-52) % time within Hb range (10-11.5 g/dL)

RhEPO or Analogue Dose at Randomization (Day 1)			Daprodustat Dose
Epoetins (including biosimilars) (U/week IV) [a]	Darbepoetin (µg/4week SC/IV) [b]	Methoxy PEG-Epoetin beta (µg/month SC/IV) [c, d]	(mg, TIW)
1500 to 2000	20 to 30	30 to 40	8
> 2000 to < 10000	>30 to 150	>40 to 180	12
≥ 10,000 to < 20000	>150 to 300	>180 to 360	16
≥ 20,000	>300	>360	24

a. Standardized rhEPO IV dose (U/week) = 161/113 * (epoetin SC dose (units) / (frequency) [Beserab, 2002]
b. Conversion of 250 U:1 µg (epoetin IV:darbepoetin alfa) utilized and rounded to the nearest available dose strength [Sterner, 2008]
c. Conversion of 1:1.2 µg (darbepoetin alfa:methoxy PEG-epoetin beta) utilized and rounded to the nearest available dose strength [Choi, 2013]
d. Conversion of 208 U:1 µg (epoetin IV: methoxy PEG-epoetin beta)

Title: A Phase 3 randomized, double-blind, active-controlled, parallel-group, multi-centre study in haemodialysis participants with anaemia of chronic kidney disease to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of daprodustat compared to recombinant human erythropoietin, following a switch from recombinant human erythropoietin or its analogues.			
Study identifier	204837/ASCEND-TD		
	Secondary endpoint	Rescue therapy	Time to rescue therapy (permanent stopping)
	Secondary endpoint	Blood pressure	Change from baseline to week 28 in on-treatment BP parameters (SBP, DBP, MAP) BP exacerbation/100PY
	Secondary endpoint	Global symptom severity	Change from Baseline at Weeks 8,12, 28, and 52 in Patient Global Impression of Change (PGI-S)
Database lock	19-June-2020		

Results and Analysis

Analysis description	**Primary Analysis (ITT)**			
Analysis population and time point description			Intent to treat	
Descriptive statistics and estimate variability	Treatment group	Daprodustat	ESA	Difference (95%CI)
	Number of subject	1487	1477	
	Hb response (g/dL)	-0.04 (0.05)	0.02 (0.07)	-0.05 (-0.21, 0.10) non-inferiority met
	Secondary Analyses (ITT)			
	IV iron use	99.0 (187)	104.4 (211)	-8.12 (-45.7, 29.4) P=0.3354
	Hb variability (responders)	172 (80.0%)	68 (63.6%)	0.165 (0.06, 0.027) P=0.0007
	Hb variability (time within range)	70.8%	61.8%	0.59 (0.52, 0.66) P=0.0034
	Rescue therapy	6 (2%)	3 (2%)	1.06 (0.26, 4.22)
	Blood pressure SBP DBP MAP	 -3.18 -2.52 -2.72	 0.55 -0.29 -0.12	 -3.73 (-9.03, 1.56) -2.23 (-4.99, 0.54) -2.60 (-5.86, 0.67)
	QoL PGi-S Very much improved Moderately improved Minimally improved No change	 20 (11%) 31 (16) 47 (25) 87 (46)	 10 (10%) 13 (14) 15 (16) 52 (54)	NA

2.5.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	2684/9820	1573/9820	360/9820
Non Controlled trials	15/43	3/43	0/43

2.5.5.4. Supportive study(ies)

Japanese Study 201753

Study 201753 was a 1-year (52-week), open-label, active-controlled, parallel-group, multi-centre study which included Japanese non-dialysis participants with anaemia associated with CKD. The study assessed the safety and efficacy of daprodustat once daily compared to rhEPO (epoetin beta pegol). In Study 201753, the starting dose of daprodustat was 4mg for rhEPO users and either 2 or 4 mg for rhEPO non-users. The target Hgb range was 10.0 to 12.0 g/dL.

Efficacy Result Non-dialysis Cohort: For the primary analysis of mean Hgb during the primary efficacy EP (Weeks 40 to 52) daprodustat was non-inferior to epoetin beta pegol. The estimated treatment difference between the groups was 0.10 g/dL (95% CI: 0.07 to 0.28 g/dL). Results of sensitivity analyses support the primary analysis.

Japanese Study 201754

201754 was a Japanese, 1-year (52 Week), randomized, double-blind, active-controlled, parallel-group, multi-centre study in HD-dependent participants who had anaemia of CKD and were being treated with rhEPO or its analogues. The starting dose of daprodustat was 4mg, and the target Hgb range was 10.0 to 12.0 g/dL.

Primary Efficacy Result: For the primary analysis of mean Hgb during the primary efficacy EP (Weeks 40 to 52) daprodustat was non-inferior to darbepoetin alfa. The estimated treatment difference between groups was 0.06 g/dL (95% CI: 0.11 to 0.23 g/dL). Results of sensitivity analyses support the primary analysis.

2.5.6. Discussion on clinical efficacy

Main efficacy data of daprodustat come from 5 pivotal trials: two trials in non-dialysis patients (205270/ASCEND-NHQ and 200808/ASCEND-ND) and three trials in dialysis patients (201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD). The data from numerous phase 1/2 studies were used for dose determination for the Phase 3 study.

Dose selection

The starting dose and dosing algorithm for the pivotal global phase III studies were developed using a population PK/PD model with plasma PK and PD measurements from previously conducted Phase 1/2 clinical studies with daprodustat. This can be considered acceptable. Hgb-time profiles from 6 studies in subjects with anaemia of CKD (PHI112844, PHI116581, PHI116582, PHI116099, PHI113633, and PHI113747) were pooled to generate the 2015 Dose-Hgb Model. Subsequently, 2 additional Phase II studies and 3 Japan Phase III studies were added to the model (referred as the 2019 Dose-Hgb model).

Covariate analyses elucidated that baseline Hgb, body weight, and prior ESA dose were the most relevant covariates of Hgb response to daprodustat. The effect of body weight was smaller on daprodustat exposure (Cmax and AUC) than the effect of inter-individual variability in response to daprodustat and did not justify adding complexity when choosing the starting doses. Thus, the starting dose of daprodustat was stratified according to baseline Hgb (ESA non-users) or prior ESA dose (ESA users).

The Dose-Hgb model simulation results indicated that the response to daprodustat varied greatly among different subjects, and the doses required to achieve the centre of the target Hgb range could range from 1 to 24 mg. Individual dose adjustments are required to achieve and maintain the target Hgb in patients. Dose adjustments are made 1 dose step at a time. For the TIW regiment in study 204837/ASCEND-TD, a three-parameter Bayesian Emax dose-response model using data from 204836 (GSK Report 2016N309671_00) produced the most consistent dose conversion ratio estimates across the studied dose range, and the ratio was approximately 2.0, which was used to calculate the TIW doses.

In the summaries of Assigned daprodustat dose per visit, a fraction of the patients seems to receive a decreased dose, or even no dose, compared to the starting dose from Week 2 and onwards. This raises some concerns that there may be a subpopulation in need of a lower starting dose. From the pharmacokinetic data, there are indications that patient weight may impact C_{max} and AUC, and body weight is also a covariate in the dose-response model, indicating that a patient with a lower body weight would require a lower dose than a patient with a higher body weight, to achieve the same Hb response. Upon request, the Applicant has provided ad-hoc analyses of changes in dosing from the starting dose in non-ESA-user dialysis and non-dialysis subjects at Week 4. Data indicates that despite the Applicant's intentions, the starting dose in non-ESA-users was less conservative in the daprodustat compared to the darbepoetin arm, irrespective of weight, even though there was a trend-to-weight correlation. Dose changes did not correlate to the starting dose. However, since most of the subjects, irrespective of weight, (67-84% in the different weight quartiles in ASCEND-ID [n=157 in the daprodustat arm] and 79-86% in ASCEND-ND [n=1030 in the daprodustat arm]) had unchanged or increased dose at Week 4, no action is considered warranted.

In summary, the pivotal global phase III studies used a starting dose of 1 to 12 mg OD or 8 to 24 mg TIW, and maintenance doses of between 1 to 24 mg OD and 2-48 mg TIW, with dose adjustments made every 4 weeks to maintain Hb levels.

Design and conduct of clinical studies

Non-dialysis patients

Study **205270/ASCEND-NHQ** was a 28-week double-blind placebo-controlled study in non-dialysis patients to show the superiority of daprodustat against placebo. The study **200808/ASCEND-ND** in non-dialysis patients was an event-driven, open-label, active-controlled cardiovascular outcome trial

(CVOT) to show non-inferiority of daprodustat versus rhEPO for Hgb and CV outcomes. Blinding of double-blind studies and strategies to mitigate any potential bias in the open-label studies can be considered appropriate.

Studies were global, with a sufficient number of centres in the EU. The studies were in general, well-designed and comprised a 4 week screening period and a treatment period. The treatment period was divided in stabilization phase when the dose of treatment was titrated to target Hb levels (24 weeks in placebo-controlled study 205270/ASCEND-NHQ and 28 weeks in 200808/ASCEND-ND study) and evaluation period (EP, 24-28 weeks in placebo-controlled study 205270/ASCEND-NHQ and 28-52 weeks in 200808/ASCEND-ND study) that was part of a maintenance period (MP) till the end of the study.

The study 205270/ASCEND-NHQ used placebo as **comparator**, while 200808/ASCEND-ND study used rhEPO as a comparator (SC darbepoetin alfa). Placebo control was used in one study in order to show a (clean) effect of daprodustat on Hb in the absence of another treatment as well as this would potentially allow for measuring effects on quality of life (QoL) due to the double-blind design. rhEPO is considered a standard of care for patients with anaemia due to CKD and, therefore, is acceptable as a comparator in the comparator study. Subjects were randomly assigned to receive daprodustat or a comparator (placebo/rhEPO) in a ratio 1:1 in both studies. Subject **randomization** was stratified by region (both studies), current rhEPO use (200808/ASCEND-ND) and participation in the ABPM sub-study (200808/ASCEND-ND), which seems relevant considering the possible implications of these factors on study findings.

Population. The placebo-controlled trial 205270/ASCEND-NHQ included patients with anaemia due to CKD who were not receiving ESA, and trial 200808/ASCEND-ND included patients who are receiving rhEPO or its analogues (ESA-users), as well as those who are not currently receiving rhEPO or its analogues (ESA non-users). ESA non-users should not have used ESA in the past 6-8 weeks. Patients had to be > 18 years of age, have CKD stages 3, 4, or 5 and being not on dialysis. Including CKD stages 3-5 in non-dialysis studies is acceptable, although those with stage 5 are likely to be dialysed within the near future. Only a small percentage of patients started dialysis while on study (6% in daprodustat and 9% in placebo), which is not expected to importantly interfere with the study findings. In the study 200808/ASCEND-ND, however, 35 and 34% of the patients in daprodustat and rhEPO groups initiated dialysis post-baseline. Inclusion criteria for baseline Hb were 8.5 to 10 g/dL for rhEPO naïve or Hb 8 to 11 g/dL if they were on rhEPO-therapy, which is appropriate and follows KDIGO guideline recommendations. Exclusion criteria were generally acceptable to minimise potential safety and integrity issues for both studies. However, rather extensive exclusion criteria regarding cardiovascular morbidity applied in the clinical studies and information regarding limited experience in certain populations. This limitation is reflected in section 4.4 of the SmPC. Patients who were not iron-replete were excluded from the studies. However, the iron target levels are considered low, especially in the placebo-controlled study (see discussion below under *Iron therapy*). However, most subjects in the placebo-controlled study were iron-replete according to the KDIGO (65%) and would likely qualify for ESA treatment initiation. Further, patients with a history of aplasia, another type of anaemia, a history of malignancy within the 2 years prior to screening, liver disease, active GI bleeding, patients with an acute cardiovascular event within the past 4 weeks for CVOT trials and 8 or 10 weeks for other studies were excluded, which is agreed. In order to reduce the bias of prior transfusion or rhEPO use, their use was not allowed 8 weeks prior to the start of the placebo-controlled trial, which is supported.

The **sample size** for study 205270/ASCEND-NHQ of 600 participants was based on the second principle secondary endpoint, SF-36 Vitality scores, which is the endpoint with the smallest anticipated effect size and leads to the study being more than sufficiently powered for the primary endpoint. For study 200808/ASCEND-ND, the sample size was based on the co-primary CV safety endpoint and determined by a fixed event target of 664 adjudicated the first MACE. However, the calculation did not

take into account treatment discontinuation and was based on an ITT analysis, while an on-treatment analysis is preferred. This is further pursued in the safety assessment.

Dialysis patients

The study **200807/ASCEND-D** was an event-driven, open-label, active-controlled CVOT to show non-inferiority of daprodustat versus rhEPO for Hgb and CV outcomes. Studies **201410/ASCEND-ID** and **204837/ASCEND-TD** were 52-week, active-controlled studies to show non-inferiority of daprodustat versus rhEPO for Hgb outcome. Study 201410/ASCEND-ID was an open-label study performed in incident dialysis (ID) patients who recently started with dialysis, while study 204837/ASCEND-TD was a double-blind study performed in haemodialysis patients to test three times per week (TIW) dosing regimen of daprodustat versus ESA.

Studies were global, with a sufficient number of centres in the EU. The studies were in general, well-designed in a similar manner as the 200808/ASCEND-ND study described above. All three studies used rhEPO as a **comparator** (SC darbepoetin alfa or IV epoetin alfa). Subjects were randomly assigned to receive daprodustat or rhEPO in ratio 1:1 in all but one study 204837/ASCEND-TD, where 2:1 randomization was applied. Subject **randomization** was stratified by region (all studies except 201410/ASCEND-ID), dialysis type (201410/ASCEND-ID and 200807/ASCEND-D), dialysis start (201410/ASCEND-ID) and participation in the ABPM sub-study (200807/ASCEND-D), which seems relevant considering the possible implications of these factors on study findings.

The trials included a broad **population** of patients with anaemia due to CKD: participants on long-term dialysis (HD and PD) and those newly starting dialysis (ID). Patients had to be > 18 years of age and being on HD or PD. Patients were included if their Hb levels were from 8 to 11 g/dL for 201410/ASCEND-ID study or from 8 to 11.5 for 200807/ASCEND-D and 204837/ASCEND-TD studies. This is acceptable and in accord with KDIGO guideline recommendations. Exclusion criteria were in general similar to the non-dialysis studies described above (see further discussion in non-dialysis section).

The **sample size** for study 200807/ASCEND-D was based on the co-primary CV safety endpoint and determined by a fixed event target of 664 adjudicated first MACE. The sample size for studies 201410/ASCEND-ID (300 subjects) and 204837/ASCEND-TD (402 subjects) was based on reaching sufficient patient exposure according to ICH E1 and to have at least 90% power on the primary endpoint. This is acceptable.

All studies

Dose. For participants assigned to daprodustat, the starting dose of daprodustat was assigned for ESA users based on a participant's prior rhEPO or analogue dose at randomization or for ESA non-users, local laboratory HemoCue Hgb concentration at randomization. Matching placebo tablets were used in the placebo group in the study 205270/ASCEND NHQ. The starting dose of rhEPO was determined based on a participant's weight and HemoCue Hgb concentration at randomization for ESA non-users and based on the currently scheduled dose, rounded to the nearest study dose, for ESA users. Daprodustat tablets were administered orally every day, except in the study 204837/ASCEND-TD, where a TIW regiment was tested. rhEPO was administered as per the patient's current treatment route or standard of care. Dose adjustment steps for all treatments were pre-specified.

The dose of all treatments was titrated to reach **Hb target ranges** of 10.0 – 11.0 g/dL in the active-controlled trials and 11.0 to 12.0 g/dL in placebo-controlled trial.

The treatment had to be stopped if one of the protocol-defined **stopping criteria** were met, such as receiving renal transplant, transition to dialysis, getting rescue, cancer event etc.

Iron therapy was allowed during the study as the standard of care. In the placebo-controlled study205270/ASCEND-NHQ, oral iron was used or IV in case of intolerance. In the ESA comparative studies, the route of iron administration was decided by a treating physician and local practices. According to the protocol, iron supplementation was indicated if ferritin was <50 ng/mL and/or TSAT was <15% in the placebo-controlled study or if ferritin was ≤100 ng/mL and/or TSAT was ≤20% in the active-controlled studies. However, these iron levels are on the low side when compared to the targets aimed at in clinical practice and treatment guidelines (e.g. KDIGO).

Rescue therapy (IV iron, transfusion, rhEPO) was allowed as per protocol. The criteria for rescue were quite similar between studies and included HemoCue Hgb is <7.5 g/dL (plus "despite a dose increase at the prior visit" in 200808/ASCEND-ND study), HemoCue Hgb is <8.5 g/dL and participant is symptomatic (only 205270/ASCEND-NHQ study), HemoCue Hgb is <8.5 g/dL or <9 g/dL on three consecutive visits in study 205270/ASCEND-NHQ and 200808/ASCEND-ND, respectively (plus "despite 3 consecutive dose increases above the starting or post-rescue dose" in study 200808/ASCEND-ND). Blood transfusions are considered of particular interest, as such treatment have a direct impact on haemoglobin levels and thereby on the primary analysis. Upon request, the Applicant has summarised the number of blood transfusion based on whether they were given due to insufficient effect or due to acute or subacute event for each study. Taken together, the proportion of blood transfusions given as part of the rescue algorithm initial intervention was largely consistent between the treatment arms in the two large studies (6% versus 9% for daprodustat and rhEPO, respectively in ASCEND-D and 10% vs 11% for daprodustat and darbepoetin, respectively, in ASCEND-ND). This is in line with the supportive analyses showing that 'Evaluable Hgb' excluding on-treatment Hgb values taken within the 8 weeks following a red blood cell transfusion, or a whole blood transfusion were consistent with the non-inferiority conclusion from the co-primary Hgb analysis for all studies. The rescue algorithms did not apply for acute or subacute events with an identifiable cause. In this context, it is noted that the analysis of the use of rhEPO and transfusion in study ASCEND-NHQ were included after approximately half of the study period. The data that informed these endpoints was however prospectively collected in all subjects.

The **primary endpoint** was similar between studies. All studies measured mean change in Hgb between Baseline and EP (mean over Weeks 28 to 52 for all studies except 205270/ASCEND-NHQ where the EP is Weeks 24 to 28), with two CVOT trials in non-dialysis and dialysis patients having an additional co-primary endpoint of time to first occurrence of adjudicated MACE events. Principal **secondary endpoints** included the percentage of patients having an increase of ≥1.0 g/dL from Baseline to EP. Further, QoL (SF-36 questionnaire) was a key secondary endpoint in the placebo-controlled trial 205270/ASCEND-NHQ, which is considered important, as treating anaemia by increasing Hb is generally believed to improve this. In the active-controlled dialysis trial, the average monthly IV iron dose was studied, which is also an important parameter of therapy effect and indirectly reflects iron mobilisation (amongst measuring other iron storage markers). Also, in all trials, some additional confirmatory effects on hemoglobin were evaluated including Hgb change from Baseline to Week 52b (Week 28 in 205270/ASCEND-NHQ), percentage responders, defined as mean Hgb within the Hgb analysis range 10 to 11.5 g/dL during EP (11.0 to 12.0 g/dL for 205270/ASCEND-NHQ), percentage of time Hgb in the analysis range during the EP (all studies) and during the MP (Week 28 to end of trial) (200808/ASCEND-ND and 200807 ASCEND-D only), time to stopping randomized treatment due to meeting rescue criteria were assessed, which are all important endpoints and allow sufficiently understand the full Hb treatment effect. The proportion of patients above a certain threshold Hb level is of interest for the risk of overshooting and potentially safety aspects. In addition to the above-mentioned endpoints, several other endpoints were assessed in the trials concerning the clinical implications of increasing Hb levels, such as additional PRO's, progression of CKD or eGFR function, and based on known effects of ESA therapy, such as the effect of on blood pressure.

Analysis sets and the **statistical analysis.** The definition of the **populations** for the efficacy analyses (ITT and PP) are considered standard and acceptable.

The **primary estimand** uses a treatment policy strategy, using effect measurements regardless of adherence, discontinuations, and rescue therapy. This follows the intention to treat principle and can be acceptable for the primary analysis. However, this also assumes that the intercurrent events were not treatment-related and did not affect subsequent measurements, which may not be realistic in all cases, e.g. death, and can introduce a bias towards no difference, which may lead to falsely concluding non-inferiority. Therefore, the while on-treatment estimand and the PP population analysis should lead to the same conclusion. Death was handled using a hypothetical strategy using multiple imputation, assuming missing at random. Post-hoc a sensitivity analysis was performed using worst-case imputation (Hgb value of 6), which is considered more realistic and led to similar results and conclusions.

The **primary efficacy analyses** in all studies were conducted with ANCOVA, including the stratification factors and baseline value, which is appropriate. The non-inferiority margin of -0.75 g/dL, used in the active-controlled studies, was statistically and clinically justified. Notwithstanding, for this to be informative, the setting needs to be sensitive to differences between treatments. The following aspects of the active-controlled studies might make them less sensitive to differences: treatment to a target Hb level and the use of a mean value over an evaluation period might smoothen out any differences; the use of rescue medication; a large number of treatment discontinuations and protocol violations; the imputation method for missing Hb values assumes off-treatment Hb values to be similar to on-treatment Hb values, indicating low sensitivity to differences between treatments. However, the Applicant has sufficiently addressed those aspects of the active-controlled non-inferiority studies.

Missing data in the analysis was handled by multiple imputations. In the placebo-controlled study, imputation was assumed to be missing not at random and was based on retrieved data of patients with the same treatment status (on or off). In the active-controlled studies, data was imputed and assumed missing at random. Since it is likely that patients discontinuing study treatment will be using off-study ESA treatment, this is acceptable. To assess sensitivity, analyses were performed using a while on-treatment estimand, the PP population, observed cases and tipping point analyses.
The tipping point sensitivity analyses are considered valuable. However, it is difficult to interpret the clinical meaning of the observed tipping point. In some of the studies, steps of 0.5 g/dL per 4-week period were used in the tipping point model and in some studies, steps of 0.1 g/dL were used. In the ASCEND-ND study, for example, the larger steps were used, and only one step was possible before the tipping-point was reached. In the ASCEND ID study, a smaller interval was used, and this tipping point is seemingly more reassuring; however, the tipping point appears to be in the same magnitude, although allowing more steps before it is reached.

The applicant has provided tipping point analyses for the NI to no longer hold, which suggests the robustness of the data.
Secondary endpoints were analysed using ANCOVA or Cochrane-Mantel-Haenszel as appropriate, including the stratification factors and baseline value.

Multiplicity in studies 205270/ASCEND-NHQ, 204837/ASCEND-TD and 201410/ASCEND-ID used a hierarchical testing strategy, which preserved the type I error rate across the primary and principle secondary endpoints and is acceptable. Studies 200808/ASCEND-ND and 200807/ASCEND-D first tested the two co-primary endpoints and, if both were statistically significant, proceeded to the principal secondary endpoints, using a Holm-Bonferroni procedure, as well as the MACE components. The first part (co-primary, then principle secondary endpoints) is acceptable and will provide type I error control. The latter part, also proceeding to the MACE components, is not considered multiplicity controlled.

The study conduct appears to be in general in order. However, four sites in two CVOT trials were closed preliminary due to **suspected fraud**. The Applicant has provided analyses excluding data from these sites. The analyses showed minimal impact on the primary endpoint. Even though the impact of the suspected fraud seems to be limited, site closure due to research misconduct, including suspected fraud, is considered a serious issue. Upon request, the Applicant has provided a comprehensive summary comparing the primary and adjusted analyses for the most relevant endpoints and study outcome of the respective trials, as well as a clarification of the circumstances leading to site closure. One subject was randomised at the affected site for the ASCEND-ND study. No actions are considered necessary for this study. For the ASCEND-D study, 88 subjects were randomised at three sites, 49 to the daprodustat arm and 39 to the rhEPO arm. There were no meaningful differences between the primary and adjusted analyses for the most relevant endpoints and study outcome of the ASCEND-D study. However, the detailed information on the nature of the issues at the three sites confirmed a high suspicion of fraud, including the alleged fabrication of data. The Applicant's actions concerning the findings, i.e., closure of three sites, is considered acceptable. However, it is considered most correct to present the results with data from the closed sites excluded in the EPAR and SmPC. All tables and figures in the SmPC and/or EPAR containing data from the ASCEND-D study have been substituted with tables and figures with data from the 88 subjects affected by the site closure excluded. Furthermore, a large number of **protocol deviations** (50-81%) were reported in the treatment arms of all five studies. The Applicant has presented factors that could indicate an increased probability for protocol deviations, such as long studies with frequent visits, the double dummy-design of the ASCEND-TD study and the COVID-19 pandemic affecting three out of five studies. Notwithstanding, the number of protocol deviations was unusually high in the studies. However, the Applicant has presented an acceptable protocol for how protocol deviations were taken care of. The Applicant also performed a PP-analysis, excluding participants who experienced events that would directly impact the haemoglobin efficacy endpoint, which was consistent with the primary results for all studies. The issue is, therefore not pursued.

Two **supportive studies** in Japanese subjects were provided, although the relevance may be limited for the EU setting. Study 201754 was a Japanese, 52 Week, randomized, double-blind, active-controlled, parallel-group, multi-centre study in HD-dependent participants who had anaemia of CKD and were being treated with rhEPO (darbepoetin alfa). The study aimed to compare the efficacy and safety of daprodustat to rhEPO. The starting dose of daprodustat was 4mg, and the target Hgb range was 10.0 to 12.0 g/dL. Study 201753 Study was a 52-week, open-label, active-controlled, parallel-group, multi-centre study that included Japanese non-dialysis participants with anaemia associated with CKD to compare the efficacy and safety of daprodustat to rhEPO (epoetin beta pegol). In Study 201753, the starting dose of daprodustat was 4mg for rhEPO users and either 2 or 4 mg for rhEPO non-users. The target Hgb range was 10.0 to 12.0 g/dL.

Efficacy data and additional analyses

Non-dialysis patients

The percentage of subjects who completed the study was high (96 and 97%). The percentage of patients who remained on treatment was 76% in the placebo-controlled study 205270/ASCEND-NHQ and 62% in the 200808/ASCEND-ND study and comparable between treatment groups. The most common reasons for discontinuation were adverse events (7-13%), a decision by proxy (3-15%) and meeting protocol-specified stopping criteria (5-13%). In general, the primary reasons for discontinuation were similar in both treatment groups across the studies, except for 'participant reached protocol-defined stopping criteria (rescue)' and 'decision by proxy', which were higher in the placebo group in study 205270/ASCEND-NHQ: 13 vs 5% and 8 vs 3%, respectively. However, it is not

believed that this has substantially affected the primary endpoint evaluation. The Applicant was asked to provide reasons to discontinue study/study treatment in ASCEND-ND was not presented for ESA-treated and non-ESA-treated subjects separately in ASCEND-ND. This was based on the observation that the dialysis study ASCEND-ID, with only ESA naïve subjects, was the only study with differences between the treatment arms in subjects discontinuing study treatment due to adverse events, disfavouring daprodustat. However, there were no meaningful differences in the percentage of subjects discontinuing early by any cause or adverse events between baseline ESA users and non-users or by treatment arm in ASCEND-ND, indicating that baseline ESA status did not affect the risk of discontinuing study treatment due to adverse events. Of note, ASCEND-ND is almost seven-fold larger than the ASCEND-ID; therefore, the ASCEND-ND data is considered more robust.

The **baseline characteristics** of the patients in all studies were generally balanced between treatment groups. The majority of patients were > 66 years of age, of not Hispanic or Latino ethnicity (≥1/3) and had CKD stage 4 (~45%). Median baseline Hb was 9.7-9.8 g/dL in study 205270/ASCEND-NHQ, and 9.8-9.9 g/dL (with median Hb being higher in ESA-user subgroup compared to ESA-non-user: 10.4 vs 9.5 g/dL) in study 200808/ASCEND-ND, appropriately reflecting the inclusion criteria. However, some patients had baseline Hb levels above the inclusion criteria that require discussion, as mentioned above.

The **primary Hb efficacy endpoint was met in both studies.** Daprodustat showed a clear effect on Hb levels in both trials. In the placebo-controlled study, daprodustat was shown to be superior to placebo, with the adjusted mean treatment difference (daprodustat- placebo) being 1.40 g/dL (95% CI: 1.23, 1.56; p <0.0001). The stable Hb levels were reached at approximately 12-16 weeks and remained stable till the end of the study. In the active-controlled study 200808/ASCEND-ND, daprodustat was non-inferior to rhEPO in both prior ESA users and non-users: the adjusted mean treatment difference (dapro-rhEPO) was 0.08 (0.03, 0.13).

As expected, the **secondary** Hb endpoints supported the primary endpoint analysis, including the **proportion of participants with a ≥1 g/dL increase in Hgb of 77% in the daprodustat group and 18% in placebo** (0.56 (95% CI: 0.49, 0.63; one-sided p<0.0001)), change in Hb from Baseline to Week 28 (1.36 (95% CI: 1.16, 1.55; p<0.0001)) and a higher proportion of patients had mean Hgb within the analysis range (11-12 g/dL) during the EP compared to the placebo group (52% vs 8%). However, a substantially higher percentage of patients in the daprodustat group had Hb > 12 g/dL during the EP than in the placebo group (20% vs 2%), which should be avoided.

This also applied to the comparator study with nominally non-inferior results for change in Hb from Baseline to Week52 (0.03 (95% CI: -0.05, 0.11)), similar Hb responder rates (78.3 % in daprodustat group and 70% in rhEPO group) and proportion of time that Hgb was within the analysis range (10-11.5 g/dL) during the EP (70.5% in daprodustat group and 63.2% in rhEPO group), in line with the primary endpoint analysis. Concerning **Hb excursions**, the proportion of participants with Hgb values <7.5 g/dL was small (≤1%) and similar across treatment groups in both studies. The proportion of participants with Hgb values ≥13 g/dL during the treatment period in the 205270/ASCEND-NHQ study was expectedly higher in the daprodustat group compared with the placebo group (10% vs 1%), and the proportion of participants with Hgb values ≥12 g/dL during the treatment period in 200808/ASCEND-ND comparator study was in daprodustat group compared to rhEPO (23%). The percentage of time Hgb ≥12 g/dL during the EP was similar in both groups in the 200808/ASCEND-ND study (14.6% in the daprodustat group and 16.7% in rhEPO). The proportion of participants with a rapid increase or decrease in Hgb, that should be avoided were also similar in the daprodustat and the rhEPO treatment groups and varied between 7-13% for increases and 2-10% for decreases.

In the placebo-controlled study, the number of patients who received **transfusions** or **rescue** was small in both groups but higher in placebo (4.9% vs 1.3% and 8% vs <1%, respectively), which is

expected in line with increased Hb levels in daprodustat group. In the study 200808/ASCEND-ND, the proportion of participants who received RBC or whole blood transfusions or another rescue was similar between the treatment groups (2.0% vs 3.3%).

Markers of iron metabolism showed expected trends with daprodustat treatment. TSAT and ferritin levels decreased upon daprodustat initiation compared to placebo, which is indicative of decreases in available iron stores due to a shift from serum iron stores to developing erythrocytes. Ferritin levels were also decreased in the active-controlled study. TIBC, on the other hand, increased in all studies, which is in line with decreased TSAT. Hepcidin levels also decreased with daprodustat treatment in all studies, which is in line with a known effect of these types of drugs on hepcidin suppression. Iron use (oral and IV) was generally similar between groups in both studies, questioning the clinical relevance of the effects on iron markers.

Quality of life (QoL) measures (SF-36 questionnaire, CKD-AQ) showed improvement in the daprodustat group compared to placebo, supporting the effectiveness of increasing Hb for patients' wellbeing. No effect of daprodustat on other PROs, i.e. PGI-S, PGI-C, EQ-5D-5L, was observed compared to placebo. The effect on PROs was comparable between daprodustat and rhEPO.

The decline in **renal function** (progression in CKD stage or decline in eGFR) was similar in the daprodustat group and rhEPO. No effects of daprodustat on **blood pressure** was observed in any of the studies.

Dialysis patients

The percentage of subjects who completed the study was high (95-99%) in all studies and similar between treatment groups. The percentage of patients who remained on treatment varied per study and was the highest in the shorter dialysis study 201410/ASCEND-ID (73%) and 204837/ASCEND-TD (71%) and lowest in the CVOT trial 200807/ASCEND-D (48%), but similar between treatment groups. The most common reasons for discontinuation were adverse events (6-16%), the decision by proxy (8-19%) and meeting protocol-specified stopping criteria (5-16%). In general, the primary reasons for discontinuation were similar in both treatment groups across the studies, except for discontinuation due to an 'AE', which were higher reported in the daprodustat group (12%) compared to the darbepoetin alfa group (6%) in study 201410/ASCEND-ID.

The **baseline characteristics** of the patients in all studies were generally balanced between treatment groups. The majority of patients were > 52 years of age in dialysis studies, of not Hispanic or Latino ethnicity (≥1/3), were on HD (>77%), with the number of patients relatively evenly distributed between groups on dialysis <2 years, ≥2 and <5 years, ≥5 years. Median baseline Hb was 9.4-9.5 g/dL in study 201410/ASCEND-ID, 10.4 g/dL in study 200807/ASCEND-D and 10.5-10.7 g/dL in study 204837/ASCEND-TD. This appropriately reflects the inclusion criteria as applied to these studies.

The **primary Hb efficacy endpoint was met.** Daprodustat was shown to be non-inferior to rhEPO in dialysis-dependent patients. The adjusted mean treatment difference (dapro-rhEPO) was -0.10 (-0.34, 0.14) in study 201410/ASCEND-ID, 0.18 (0.12, 0.24) in study 200807/ASCEND-D and -0.05 (-0.21, 0.10) in study 204837/ASCEND-TD. Therefore, daprodustat has demonstrated non-inferiority to rhEPO in achieving Hgb in the target range, whether dosed once daily (200807/ASCEND-D) or TIW (204837/ASCEND TD) in dialysis-dependent participants. Various sensitivity and supportive analyses were in line with the primary analysis.

Other **secondary** Hb endpoints supported the primary endpoint in all 3 studies, including **change in Hb from Baseline to Week52**, **Hb responders and percentage of time Hb was within the target range** (10-11.5 g/dL) that was similar between treatment groups**.**, Although with the TIW regiment 204837/ASCEND-TD, the proportion of participants with mean Hgb within the analysis range

was somewhat higher during the EP in the daprodustat group compared to the epoetin alfa group (80% vs 64%). Concerning **Hb excursions**, the proportion of participants with Hgb values <7.5 g/dL during the EP was small (≤4%) and similar across treatment groups. The proportion of participants with Hgb values ≥12 g/dL during the treatment period was rather comparable in both groups and varied between 27% vs 37%, 35% vs 27%, 14% vs 21% in the daprodustat vs rhEPO group in studies 201410/ASCEND-ID, 200807/ASCEND-D and 204837/ASCEND-TD, respectively. Percentage of time Hgb ≥12 g/dL during the EP was similar between groups in two dialysis studies (20-21.2% and 19.9-21.7%) and lower in study 204837/ASCEND TD with TIW daprodustat regiment (19.5 vs 8.6%). Rapid increases or decreases in Hgb (>2 g/dL per four weeks) were similar in the daprodustat and the rhEPO treatment groups and varied between 2-18% for increases and 3-17% for decreases depending on the study.

The proportion of participants who received RBC or whole blood **transfusions**, or **rescue** was similar between the treatment groups.

The average **monthly IV iron** dose to Week 52 was generally similar in daprodustat groups compared to rhEPO in any of the active-controlled dialysis studies. **Markers of iron metabolism** showed expected trends with daprodustat treatment, similar to what was observed in non-dialysis studies. However, in dialysis studies, while TSAT and TIBC remained generally stable in rhEPO groups, ferritin and hepcidin levels decreased substantially).

Expectedly, no statistically significant improvement in **QoL** was observed for daprodustat when compared to rhEPO.

The **subgroup analyses** that included demographic and baseline characteristics, prior history of selected diseases/events, and use of specified medication at baseline were generally consistent with the primary analyses. Despite the significant treatment by subgroup interaction in a small number of groups, the subgroups generally met the non-inferiority criterion, and the observed differences are likely to be not clinically meaningful.

The data from the **supportive** studies showed similar results to the pivotal studies. In both studies, daprodustat was shown to be non-inferior to rhEPO for the primary analysis of mean Hgb during the primary efficacy EP (Weeks 40 to 52). In addition, the results of sensitivity analyses support the primary analysis.

2.5.7. Conclusions on the clinical efficacy

Non-dialysis patients

Treatment with daprodustat shows a clear improvement in increasing Hb levels versus placebo and similar effects on maintaining Hb levels in the target ranges compared to rhEPO in non-dialysis patients, including ESA users and ESA non-users. The effects of daprodustat were associated with an improvement in patient-reported outcomes of SF-36 and a reduction in rescue therapy or transfusions compared to placebo. In the non-dialysis active-controlled study, the effects of daprodustat on IV iron use, rescue therapy or QoL measures were similar to ESA.

Dialysis patients

In dialysis patients, treatment with daprodustat shows comparable efficacy for stabilisation and maintaining Hb levels versus ESA therapy in the target ranges over time, whether used daily or TIW regiment, in HD or PD patients. QoL measures, IV iron and rescue therapy were similar between daprodustat and ESA.

2.5.8. Clinical safety

The primary evidence for the safety of daprodustat in the treatment of anaemia associated with CKD is provided by the 5 global Phase III studies. The 2 event-driven, randomized, open-label (sponsor-blind), active-controlled cardiovascular outcomes studies individually provide the primary evidence of noninferiority (NI) of daprodustat versus rhEPO for adjudicated cardiovascular events in dialysis (200807/ASCEND D) and non-dialysis (200808/ASCEND-ND) patients, respectively.

2.5.8.1. Patient exposure

The exposure to daprodustat across the clinical program has exceeded 6600 PY across 34 studies (Table 23*)*. The median duration of exposure in the large active-controlled CV outcomes study for those on dialysis (ASCEND-D, n= 1433 vs 1435)) was 26 months and 17 months for those not on dialysis (ASCEND-ND, n=1937 vs 1933). Additionally, the phase 3 program included the 28 weeks placebo-controlled ASCEND-NHQ study (307 ND patients on daprodustat vs 308 on placebo) and the ASCEND-ID study (incidence dialysis patients (n= 157 vs 155) treated for 52 weeks) and ASCEND-TD (n=270 vs 137) using a TIW dosing and treated for 52 weeks.

Table 23 Summary of Extent of Exposure to Daprodustat for All Studies (All Studies, Safety Population)

Duration of exposure	**Persons N=5984**
<1 month	1226
≥1 month	4758
≥3 months	4427
≥6 months	3678
≥12 months	2396
≥24 months	1485
≥36 months	317
Total person time (person-years)	6651.8

Source: Table 2.001
Note: Includes exposure data from all studies in healthy volunteers and participants with anaemia associated with CKD .
Note: Duration of exposure to daprodustat in months is calculated as treatment stop date minus treatment start date+1, divided by 30.4375 (daprodustat treatment periods only for cross over studies).
Note: Total person-time (person-years) is calculated as total of treatment stop date minus treatment start date+1 day for all participants, divided by 365.25.
Note: Participants are counted in each applicable row.

2.5.8.2. Adverse events

Adverse events (AEs) are displayed according to a general AE overview, common AEs, and AEs of special interest, including some more in-depth discussion of some of the Adverse events of special interest (AESIs).

Incidences are displayed as treatment-emergent based on an on-treatment analysis. As dose-frequencies are substantially different between daprodustat (once daily) and ESA (once every week to 4 weeks) a dose-frequency adjusted post-hoc analyses have been presented (except for the placebo-controlled data). The post-hoc dose-frequency adjusted period for each patient is defined as events from the treatment start date to the last non-zero dose date + dosing frequency, which is described as dosing frequency-adjusted treatment emergent in the source tables *(dosing frequency for daily doses = 1 day; TIW doses = 2 days; weekly doses = 7 days; every 2 weeks = 14 days; every 4 weeks = 28*

days). The performed post hoc on-treatment correction may be more appropriate than the pre-specified OT analysis (OT of last dose date +1 day) given that the prespecified analysis introduced bias (although bias can also not be entirely excluded with DF correction (see safety discussion further below)).

Treatment-Emergent Adverse events (TEAEs)

Non-dialysis patients

In both placebo-controlled study and the ESA comparator study, the incidences of TEAEs were generally similar between the daprodustat and the placebo or comparator groups; see tables below.

Table 24 Overview of Adverse Events (205270/ASCEND-NHQ, Safety Population)

	Placebo (N=306) n (%)	**Daprodustat (N=308) n (%)**
Treatment-emergent AEs		
Any treatment-emergent AE	216 (71)	213 (69)
Severe treatment-emergent AEs	52 (17)	50 (16)
Drug-related treatment-emergent AEs	14 (5)	15 (5)
Treatment-emergent SAEs		
Any SAE (fatal and non-fatal)	68 (22)	62 (20)
Fatal SAEs	7 (2)	4 (1)
Drug-related SAEs	1 (<1)	6 (2)
Treatment-emergent AEs leading to withdrawal from the study	5 (2)	3 (<1)
Treatment-emergent AEs leading to permanent discontinuation of study treatment	28 (9)	22 (7)
Follow-up Period AEs		
Any follow-up AEs	69 (23)	54 (18)
Follow-up SAEs	40 (13)	23 (7)

Source: m5.3.5.1 205270/ASCEND-NHQ CSR Table 57
Note: Treatment-emergent AEs are defined as AEs with onset date or AE worsening date on or after treatment start date and on or before the last non-zero dose date plus 1 day.
Note: Follow-up AEs are defined as AEs with onset date or AE worsening date after the last non-zero dose date plus 1 day.

Table 25 Overview of Treatment-emergent AEs adjusted for dose frequency (post-hoc analysis) (200808/ASCEND-ND, Safety Population)

	Pre-specified[a]		Post-hoc[b]	
	Dapro (N=1937)	Darbe (N=1933)	Dapro (N=1937)	Darbe (N=1933)
Treatment-emergent AEs, n (%)				
Any treatment-emergent AE	1545 (80)	1487 (77)	1545 (80)	1559 (81)
Severe treatment-emergent AEs	589 (30)	456 (24)	589 (30)	554 (29)
Drug-related treatment-emergent AEs	119 (6)	69 (4)	119 (6)	71 (4)
Treatment-emergent SAEs, n (%)				
Any SAE (fatal and non-fatal)	850 (44)	703 (36)	850 (44)	817 (42)
Drug-related SAEs	35 (2)	10 (<1)	35 (2)	12 (<1)
Fatal SAEs	153 (8)	59 (3)	153 (8)	146 (8)
Treatment-emergent AEs leading to permanent discontinuation of randomized treatment	247 (13)	94 (5)	247 (13)	201 (10)

Source: Table 3.106, Table 3.296, Table 3.159, Table 3.312, Table 3.120, Table 3.303, Table 3.125, Table 3.304, Table 3.130, Table 3.307, Table 3.134, Table 3.311, Table 3.132, Table 3.309

a. Pre-specified definition of treatment-emergent: Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Last Non-Zero Dose Date + 1 day.

b. Post-hoc definition of treatment-emergent: Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Last Non-Zero Dose Date + dosing frequency.

Dialysis patients

The general AEs incidence profile in dialysis patients is provided in the tables below. The post-hoc analysis is the relevant data source as the on-treatment period has been adjusted for the dose frequency of the ESA comparator. TEAEs were generally similar between the daprodustat and the placebo groups in the prespecified- as well in the post-hoc comparisons; see tables below.

Table 26 Overview of Treatment-emergent AEs adjusted for dose frequency (post-hoc analysis) (200807/ASCEND-D, Safety Population)

	Daprodustat (N=1433) n (%)	rhEPO (N=1435) n (%)
Treatment-emergent AEs		
Any treatment-emergent AE	1272 (89)	1247 (87)
Severe treatment-emergent AEs	494 (34)	524 (37)
Drug-related treatment-emergent AEs	103 (7)	80 (6)
Treatment-emergent SAEs		
Any SAE (fatal and non-fatal)	748 (52)	777 (54)
Drug-related SAEs	26 (2)	28 (2)
Fatal SAEs	125 (9)	143 (10)
Treatment-emergent AEs leading to permanent discontinuation of randomized treatment	208 (15)	194 (14)

Source: Table 68.400003, Table 68.400004,Table 68.400005, Table 68.400006, Table 68.400007, Table 68.400008, Table 68.400009

Post-hoc definition of treatment-emergent: Treatment Start Date ≤AE Start Date/Worsening Date ≤Last Non-Zero Dose date + dosing frequency

Table 27 Overview of Dosing Frequency Adjusted Treatment-emergent AEs (post-hoc analysis) (204837/ASCEND-TD, 201410/ASCEND-ID)

	204837/ASCEND-TD (N=406)				201410/ASCEND-ID (N=312)			
	Dapro N=270		rhEPO N=136		Dapro N=157		Darbe N=155	
	n (%)	Rate per 100 PY	n (%)	Rate per 100 PY	n (%)	Rate per 100 PY	n (%)	Rate per 100 PY
Any TEAE	**205 (76)**	**212.92**	**108 (79)**	**259.38**	**120 (76)**	**240.64**	**116 (75)**	**224.70**
Drug-related TEAEs	40 (15)	19.81	20 (15)	21.04	5 (3)	4.25	8 (5)	6.15
TEAEs leading to disc. of RT	23 (9)	10.46	10 (7)	9.53	14 (9)	11.89	7 (5)	5.21
Severe TEAEs	52 (19)	25.71	31 (23)	33.32	25 (16)	22.45	34 (22)	28.29
Any serious TEAEs	**82 (30)**	**43.63**	**49 (36)**	**59.39**	**52 (33)**	**53.08**	**57 (37)**	**53.92**
Drug-related serious TEAEs	3 (1)	1.36	4 (3)	3.81	0	-	2 (1)	1.49
Fatal TEAEs	8 (3)	3.62	5 (4)	4.75	8 (5)	6.75	8 (5)	5.97

Dosing frequency adjusted treatment-emergent AEs were defined as all events from first dose of randomized study treatment to last non-zero dose date + dosing frequency in days
Abbreviations: Disc of RT = Discontinuation of Randomized Treatment; TEAE = Treatment-emergent Adverse Event

Common adverse events (≥5%)

Non-dialysis patients

Table 28 Common (≥5%) Treatment-Emergent AEs by Overall Frequency (Study 205270/ASCEND-NHQ, Safety Population)

Preferred Term	Placebo (N=306)		Daprodustat (N=308)	
	n (%)	Rate per 100 PY	n (%)	Rate per 100 PY
Any event	**216 (71)**	285.95	**213 (69)**	266.96
Diarrhoea	17 (6)	12.83	25 (8)	17.61
Hypertension	16 (5)	11.93	23 (7)	16.00
Oedema peripheral	21 (7)	16.00	12 (4)	8.24

Table 29 Summary of Common (≥5%) Treatment-emergent AEs by Overall Frequency (adjusted for dose frequency (post-hoc analysis)) (200808/ASCEND-ND, Safety Population)

Preferred Term	Pre-specified[a]		Post-hoc[b]	
	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)
Any event	**1545 (80)**	**1487 (77)**	**1545 (80)**	**1559 (81)**
Hypertension	257 (13)	272 (14)	257 (13)	279 (14)
Urinary tract infection	187 (10)	179 (9)	187 (10)	190 (10)
Oedema peripheral	199 (10)	166 (9)	199 (10)	176 (9)
Hyperkalaemia	151 (8)	144 (7)	151 (8)	153 (8)
Diarrhoea	150 (8)	139 (7)	150 (8)	151 (8)
Chronic kidney disease	134 (7)	113 (6)	134 (7)	129 (7)
Nasopharyngitis	118 (6)	133 (7)	118 (6)	134 (7)
Pneumonia	109 (6)	109 (6)	109 (6)	124 (6)
Constipation	128 (7)	90 (5)	128 (7)	96 (5)
Fall	111 (6)	91 (5)	111 (6)	95 (5)
Anaemia	109 (6)	79 (4)	109 (6)	86 (4)
Back pain	85 (4)	109 (6)	85 (4)	110 (6)
Nausea	103 (5)	84 (4)	103 (5)	87 (5)
Upper respiratory tract infection	98 (5)	91 (5)	98 (5)	92 (5)
Acute kidney injury	102 (5)	81 (4)	102 (5)	87 (5)

Source: Table 3.118, Table 3.301

a. Pre-specified definition of treatment-emergent: Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Last Non-Zero Dose Date + 1 day.

b. Post-hoc definition of treatment-emergent: Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Last Non-Zero Dose Date + dosing frequency.

The adverse events profile according to SOC has been presented in the section 3.3.7.6. according to age group for the pooled largest ND and DD studies.

Dialysis patients

Table 30 Summary of Common (≥5%) Dosing Frequency Adjusted Treatment-emergent AEs by Overall Frequency (200807/ASCEND-D, Safety Population (LDD+DF; (Post-hoc Analysis)

Preferred Term	Dapro (N=1433) n (%)	rhEPO (N=1435) n (%)
Any Event	1272 (89)	1247 (87)
Hypertension	241 (17)	239 (17)
Diarrhoea	166 (12)	183 (13)
Dialysis hypotension	140 (10)	112 (8)
Hypotension	120 (8)	110 (8)
Pneumonia	119 (8)	124 (9)
Headache	115 (8)	135 (9)
Nasopharyngitis	114 (8)	102 (7)
Upper respiratory tract infection	102 (7)	99 (7)
Arthralgia	101 (7)	111 (8)
Cough	98 (7)	100 (7)
Fluid overload	96 (7)	108 (8)
Bronchitis	93 (6)	100 (7)

Preferred Term	Dapro (N=1433) n (%)	rhEPO (N=1435) n (%)
Hyperkalaemia	90 (6)	90 (6)
Arteriovenous fistula thrombosis	84 (6)	97 (7)
Vomiting	84 (6)	83 (6)
Pain in extremity	84 (6)	74 (5)
Fall	83 (6)	90 (6)
Urinary tract infection	82 (6)	87 (6)
Nausea	81 (6)	85 (6)
Anemia	76 (5)	103 (7)
Arteriovenous fistula site complication	67 (5)	97 (7)
Dyspnoea	67 (5)	83 (6)
Back pain	66 (5)	89 (6)
Atrial fibrillation	57 (4)	81 (6)
Pyrexia	56 (4)	77 (5)

Source: Study 200808/ASCEND-D Table 68.400010

Table 31 Common (≥5%) Dosing Frequency Adjusted (post-hoc analysis) Treatment-emergent AEs by SOC and PT (204837/ASCEND-TD, 201410/ASCEND-ID)

System Organ Class Preferred Term	204837/ASCEND-TD (N=406)		201410/ASCEND-ID (N=312)	
	Dapro (N=270)	rhEPO (N=136)	Dapro (N=157)	Darbe (N=155)
	n (%)	n (%)	n (%)	n (%)
Any Event	**205 (76)**	**108 (79)**	**120 (76)**	**116 (75)**
Infections/ infestations	40 (15)	19 (14)	25 (16)	40 (26)
Urinary tract infection	9 (3)	3 (2)	5 (3)	8 (5)
Pneumonia	15 (6)	8 (6)	4 (3)	12 (8)
Nasopharyngitis	10 (4)	4 (3)	7 (4)	9 (6)
Upper respiratory tract infection	6 (2)	6 (4)	7 (4)	12 (8)
Catheter site infection	1 (<1)	0	5 (3)	9 (6)
Vascular disorders	38 (14)	26 (19)	48 (31)	44 (28)
Hypertension	24 (9)	16 (12)	29 (18)	27 (17)
Hypotension	13 (5)	10 (7)	7 (4)	9 (6)
Dialysis hypotension	6 (2)	3 (2)	21 (13)	16 (10)
Gastrointestinal disorders	47 (17)	26 (19)	25 (16)	30 (19)
Diarrhoea	24 (9)	14 (10)	14 (9)	11 (7)
Nausea	7 (3)	12 (9)	8 (5)	7 (5)
Constipation	8 (3)	0	4 (3)	5 (3)
Vomiting	15 (6)	14 (10)	11 (7)	7 (5)
Abdominal pain	8 (3)	9 (7)	3 (2)	5 (3)
Musculoskeletal and connective tissue disorders	24 (9)	14 (10)	18 (11)	21 (14)
Arthralgia	10 (4)	5 (4)	7 (4)	9 (6)
Back pain	7 (3)	4 (3)	7 (4)	8 (5)
Muscle spasms	8 (3)	5 (4)	7 (4)	9 (6)
Metabolism and nutrition disorders	14 (5)	7 (5)	16 (10)	12 (8)
Hyperkalaemia	9 (3)	5 (4)	3 (2)	4 (3)
Fluid overload	5 (2)	2 (1)	14 (9)	9 (6)
General disorders and administration site conditions	13 (5)	10 (7)	7 (4)	13 (8)
Oedema peripheral	4 (1)	1 (<1)	4 (3)	6 (4)
Pyrexia	9 (3)	9 (7)	3 (2)	8 (5)
Respiratory, thoracic and mediastinal disorders	17 (6)	14 (10)	11 (7)	10 (6)

System Organ Class Preferred Term	204837/ASCEND-TD (N=406)		201410/ASCEND-ID (N=312)	
	Dapro (N=270)	rhEPO (N=136)	Dapro (N=157)	Darbe (N=155)
	n (%)	n (%)	n (%)	n (%)
Cough	9 (3)	5 (4)	7 (4)	5 (3)
Dyspnoea	10 (4)	9 (7)	4 (3)	6 (4)
Injury, poisoning and procedural complications	20 (7)	9 (7)	6 (4)	12 (8)
Fall	8 (3)	6 (4)	2 (1)	2 (1)
Arteriovenous fistula site complication	13 (5)	3 (2)	4 (3)	10 (6)
Nervous system disorders	12 (4)	13 (10)	12 (8)	9 (6)
Headache	12 (4)	13 (10)	12 (8)	9 (6)
Blood and lymphatic system disorders	7 (3)	5 (4)	5 (3)	3 (2)
Anaemia	7 (3)	5 (4)	5 (3)	3 (2)

Adverse events of special interest (AESIs)

Safety data for AESIs have been presented overall and separately, including worsening of hypertension, thrombotic events, revascularisation, oesophageal and gastric erosion, cancer-related events, pulmonary arterial hypertension, and exacerbation of rheumatoid arthritis. An overview of AESI is provided below, followed by a presentation of the AESI thrombosis, cancer-related AEs, and revascularisation.

Non-dialysis patients

Table 32 Overview of Treatment-emergent Potential AESI (205270/ASCEND-NHQ, Safety Population)

Category	Placebo (N=306)	Daprodustat (N=308)
	n (%)	n (%)
Worsening of hypertension	26 (8)	31 (10)
Death, MI, stroke, heart failure, pulmonary embolism, DVT, thromboembolic events, thrombosis of vascular access	23 (8)	26 (8)
Proliferative retinopathy, macular edema, choroidal neovascularization	9 (3)	3 (<1)
Esophageal and gastric erosions	3 (<1)	2 (<1)
Cancer-related mortality and tumor progression and recurrence	2 (<1)	1 (<1)
Pulmonary artery hypertension	0	3 (<1)
Exacerbation of rheumatoid arthritis	0	2 (<1)

Table 33 Summary of Dosing Frequency Adjusted (post-hoc analysis) Treatment Emergent AESIs(ASCEND-ND)

Adverse Event of Special Interest	Dapro (N=1937) n (%)	Dapro (N=1937) Rate per 100 PY	Darbe (N=1933) n (%)	Darbe (N=1933) Rate per 100 PY	Dapro vs Darbe RR (Two-sided 95% CI) [1]	Two-sided p-value [2]
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	5 (0.3%)	0.18	3 (0.2%)	0.10	1.66 (0.40, 6.95)	0.481
Cardiomyopathy	6 (0.3%)	0.22	7 (0.4%)	0.24	0.86 (0.29, 2.54)	0.778
Pulmonary Artery Hypertension	15 (0.8%)	0.56	9 (0.5%)	0.31	1.66 (0.73, 3.79)	0.221
Cancer-related mortality and tumor progression and recurrence	72 (3.7%)	2.70	68 (3.5%)	2.39	1.06 (0.76, 1.46)	0.740
Esophageal and gastric erosions	70 (3.6%)	2.63	48 (2.5%)	1.69	1.46 (1.01, 2.09)	0.041
Proliferative retinopathy, macular edema, choroidal neovascularization	54 (2.8%)	2.04	46 (2.4%)	1.63	1.17 (0.79, 1.73)	0.424
Exacerbation of rheumatoid arthritis	2 (0.1%)	0.07	4 (0.2%)	0.14	0.50 (0.09, 2.72)	0.412
Worsening of Hypertension	344 (17.8%)	14.72	372 (19.2%)	15.21	0.92 (0.81, 1.05)	0.234

Dialysis patients

Table 34 Summary of Dosing Frequency Adjusted (post-hoc analysis) Treatment Emergent AESIs (ASCEND-D)

Adverse Event of Special Interest	Dapro (N=1433) n (%)	Dapro (N=1433) Rate per 100 PY	rhEPO (N=1435) n (%)	rhEPO (N=1435) Rate per 100 PY	Dapro vs rhEPO RR (Two-sided 95% CI) [1]	Two-sided p-value [2]
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	20 (1.4%)	0.79	11 (0.8%)	0.42	1.82 (0.88, 3.79)	0.103
Cardiomyopathy	15 (1.0%)	0.59	16 (1.1%)	0.61	0.94 (0.47, 1.89)	0.860
Pulmonary Artery Hypertension	9 (0.6%)	0.36	12 (0.8%)	0.46	0.75 (0.32, 1.78)	0.513
Cancer-related mortality and tumor progression and recurrence	46 (3.2%)	1.82	53 (3.7%)	2.05	0.87 (0.59, 1.28)	0.478
Esophageal and gastric erosions	58 (4.0%)	2.33	82 (5.7%)	3.25	0.71 (0.51, 0.98)	0.038
Proliferative retinopathy, macular edema, choroidal neovascularization	38 (2.7%)	1.53	36 (2.5%)	1.39	1.06 (0.67, 1.66)	0.809
Exacerbation of rheumatoid arthritis	2 (0.1%)	0.08	1 (0.1%)	0.04	2.00 (0.18, 22.06)	0.563
Worsening of Hypertension	291 (20.3%)	13.48	299 (20.8%)	13.54	0.97 (0.84, 1.13)	0.726

Table 35 Overview of Dosing Frequency Adjusted (post-hoc analysis) Treatment-emergent Potential AESI (204837/ASCEND-TD, 201410/ASCEND-ID)

Adverse Event of Special Interest	204837/ASCEND-TD (N=406)		201410/ASCEND-ID (N=312)	
	Dapro (N=270)	rhEPO (N=136)	Dapro (N=157)	Darbe (N=155)
	n (%)	n (%)	n (%)	n (%)
Thrombosis and/or tissue ischemia secondary to excessive erythropoiesis	1 (<1)	0	0	1 (<1)
Cardiomyopathy	1 (<1)	1 (<1)	0	2 (1)
Pulmonary artery hypertension	1 (<1)	1 (<1)	1 (<1)	0
Cancer-related mortality and tumor progression and recurrence	3 (1)	2 (1)	1 (<1)	4 (3)
Esophageal and gastric erosions	7 (3)	2 (1)	1 (<1)	3 (2)
Proliferative retinopathy, macular edema, choroidal neovascularization	5 (2)	1 (<1)	4 (3)	1 (<1)
Exacerbation of rheumatoid arthritis	0	0	0	0
Worsening of hypertension	33 (12)	21 (15)	38 (24)	32 (21)

- **Thrombosis and/or tissue ischemia (both ND and DD patients)**

Table 36 Summary of Treatment-emergent Potential AESI of Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis (200808/ASCEND-ND, Safety Population)

Preferred Term	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)
Any event	5 (<1)	3 (<1)
Device occlusion	2 (<1)	0
Acute myocardial infarction	0	1 (<1)
Arteriovenous fistula thrombosis	0	1 (<1)
Arteriovenous graft thrombosis	1 (<1)	0
Deep vein thrombosis	1 (<1)	0
Monoparesis	0	1 (<1)
Phlebitis	1 (<1)	0

Table 37 Summary of Dosing Frequency Adjusted Treatment-emergent Potential AESI of Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis (200807/ASCEND-D, Safety Population)

Preferred Term	Dapro (N=1433) n (%)	rhEPO (N=1435) n (%)
Any event	20 (1)	11 (<1)
Arteriovenous fistula thrombosis	4 (<1)	2 (<1)
Acute myocardial infarction	2 (<1)	2 (<1)
Vascular access site thrombosis	3 (<1)	1 (<1)
Arteriovenous graft thrombosis	2 (<1)	1 (<1)
Thrombosis in device	2 (<1)	1 (<1)
Transient ischaemic attack	2 (<1)	1 (<1)
Ischaemic stroke	2 (<1)	0
Vascular access site complication	1 (<1)	1 (<1)
Arteriovenous fistula occlusion	1 (<1)	0
Cardiac ventricular thrombosis	1 (<1)	0
Graft thrombosis	0	1 (<1)
Myocardial ischaemia	1 (<1)	0
Peripheral arterial occlusive disease	1 (<1)	0
Peripheral artery occlusion	1 (<1)	0
Peripheral artery thrombosis	1 (<1)	0
Peripheral ischaemia	1 (<1)	0
Vascular graft occlusion	0	1 (<1)
Vena cava thrombosis	0	1 (<1)
Venous thrombosis	1 (<1)	0

Source: Table 68.400012

Few cases of the AESI "Thrombosis and/or Tissue Ischemia Secondary to Excessive Erythropoiesis" were reported, however the rate was slightly increased in the Dapro group compared to the rhEPO control (0.48 vs 0.26 per 100PY, i.e. 25 and 14 cases respectively in the pooled non-dialysis/dialysis populations). No pattern among the PTs was observed. The SmPC contains a warning under section 4.4 that thrombotic events have been observed.

- **Cancer-related mortality, tumour progression, and/or recurrence (both ND and DD patients)**

In the active-controlled non-dialysis study, the number/proportion of participants with a history of cancer at Baseline for daprodustat was 101 participants, 5% and for darbepoetin alfa was 86 participants, 4%. The incidence of treatment-emergent potential AESI of cancer-related mortality and tumour progression and recurrence was generally more common in the daprodustat group compared with the darbepoetin alfa group.

Table 38 Summary of Dosing Frequency Adjusted Treatment-emergent Potential AESI of Cancer-related Mortality and Tumour Progression and Recurrence (200808/ASCEND-ND, Safety Population).

Preferred Term	Dapro (N=1937)	Darbe (N=1933)
Any event	72 (4)	68 (4)
Basal cell carcinoma	12 (<1)	7 (<1)
Squamous cell carcinoma	6 (<1)	5 (<1)
Squamous cell carcinoma of skin	7 (<1)	4 (<1)
Breast cancer	5 (<1)	2 (<1)

Preferred Term	Dapro (N=1937)	Darbe (N=1933)
Pancytopenia	3 (<1)	4 (<1)
Transitional cell carcinoma	1 (<1)	4 (<1)
Monoclonal gammopathy	4 (<1)	0
Plasma cell myeloma	1 (<1)	5 (<1)
Myelodysplastic syndrome	2 (<1)	1 (<1)
Pancreatic carcinoma	2 (<1)	2 (<1)
Prostatic specific antigen increased	3 (<1)	0
Skin cancer	1 (<1)	3 (<1)
Adenocarinoma of colon	2 (<1)	1 (1)
Colon Cancer	0	3 (<1)
Gastric Cancer	1 (<1)	2 (<1)
Myelodysplastic syndrome	2 (<1)	1 (<1)
Renal Cell Carcenoma	0	3 (<1)

Source: Table:3.313
Note: Preferred terms for AEs reported by at least 3 participants are presented

In the active-controlled dialysis study, the proportion of participants with a history of cancer at Baseline was similar between the treatment groups (5% daprodustat, 5% rhEPO). The incidence of treatment-emergent potential AESI of cancer-related mortality and tumour progression and recurrence was generally similar between the treatment groups, and there was no obvious trend in the type or location of cancer.

Table 39 Summary of Treatment-emergent Potential AESI of Cancer-related Mortality and Tumour Progression and Recurrence (200807/ASCEND-D, Safety Population)(LDD+DF)

Preferred Term	Dapro (N=1433) n (%)	rhEPO (N=1435) n (%)
Any event	46 (3)	53 (4)
Basal cell carcinoma	3 (<1)	9 (<1)
Squamous cell carcinoma of skin	3 (<1)	5 (<1)
Renal cancer	3 (<1)	2 (<1)
Squamous cell carcinoma	2 (<1)	3 (<1)
Pancytopenia	2 (<1)	2 (<1)
Bladder cancer	1 (<1)	2 (<1)
Hepatic cancer	0	3 (<1)
Renal neoplasm	2 (<1)	1 (<1)
Superior vena cava syndrome	1 (<1)	2 (<1)
Aplastic anaemia	2 (<1)	0
Breast cancer	0	2 (<1)
Colon cancer	1 (<1)	1 (<1)
Papillary renal cell carcinoma	2 (<1)	0
Papillary thyroid cancer	2 (<1)	0
Plasma cell myeloma	1 (<1)	1 (<1)
Prostatic specific antigen increased	0	2 (<1)
Renal cell carcinoma	1 (<1)	1 (<1)
Transitional cell carcinoma	2 (<1)	0

Source: Study 200807/ASCEND-D Table 68,400012
Note: Events occurring in at least 2 participants are presented.

In summary, cancer-related mortality and tumour progression and recurrence were slightly increased in the ND study (72 (3.7%) vs 68 (3.5%); RR 1.06, p=0.740); however, no such increase could be noticed in the dialysis study (46 (3.2%) vs 53 (3.7%)l; RR 0.87, p=0.478), which does not translate into a clear signal for cancer risk. No signal for any specific cancer type could be noticed. In pooled data from the actively controlled studies using the post hoc analysis adjustment, no difference in the frequency of malignancies between the treatment arms were found (3.5% vs. 3.6% in daprodustat vs the rhEPO control).

- **Proliferative retinopathy, macular oedema, and choroidal neovascularization (both ND and DD patients)**

Table 40 Summary of Dosing Frequency Adjusted Treatment-emergent Potential AESI of Proliferative Retinopathy, Macular Edema, Choroidal Neovascularization (200808/ASCEND-ND, Safety Population)

Preferred Term	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)
Any event	54 (3)	46 (2)
Diabetic retinopathy	13 (<1)	13 (<1)
Vitreous haemorrhage	8 (<1)	7 (<1)
Eye haemorrhage	9 (<1)	2 (<1)
Retinal detachment	4 (<1)	7 (<1)
Retinal haemorrhage	4 (<1)	3 (<1)
Vision blurred	2 (<1)	4 (<1)
Retinopathy proliferative	2 (<1)	3 (<1)
Visual acuity reduced	2 (<1)	2 (<1)
Diabetic retinal oedema	3 (<1)	0
Macular degeneration	2 (<1)	1 (<1)
Visual impairment	1 (<1)	2 (<1)
Vitreous detachment	2 (<1)	1 (<1)
Vitreous floaters	3 (<1)	0
Cystoid macular oedema	2 (<1)	0
Maculopathy	2 (<1)	0
Retinopathy hypertensive	2 (<1)	0
Age-related macular degeneration	1 (<1)	0
Macular fibrosis	0	1 (<1)
Macular oedema	1 (<1)	0
Non-proliferative retinopathy	0	1 (<1)
Photophobia	0	1 (<1)
Photopsia	0	1 (<1)
Retinal scar	1 (<1)	0
Retinal tear	0	1 (<1)
Retinal vein occlusion	0	1 (<1)
Retinopathy	1 (<1)	0
Rhegmatogenous retinal detachment	0	1 (<1)
Vitreoretinal traction syndrome	1 (<1)	0
Xanthopsia	0	1 (<1)

Source: Table 3.313

In the active-controlled non-dialysis study, post-hoc dosing frequency adjusted treatment-emergent potential AESIs of "proliferative retinopathy, macular oedema, choroidal neovascularization" were reported in 100 participants (54 daprodustat-treated and 46 darbepoetin alfa-treated). In order to

better understand the relative risk for ocular adverse events, an external ophthalmology expert reviewed each potential ocular AESI (including AE, concomitant medication, medical history, and randomized treatment allocation). An assessment was made on a per participant basis to determine whether the participant had at least one reported event that was likely to represent an ocular AESI(i.e., proliferative retinopathy, macular oedema, or choroidal neovascularization). Of the 100 participant cases reviewed, 42 participants were likely to have experienced an ocular AESI (26 daprodustat, 16 darbepoetin alfa) based on reported diagnoses, medical history, and/or concomitant medications (e.g., documented treatment with an anti-VEGF medication). Of the 42 participants who experienced a likely ocular AESI, all but two were related to diabetic disease (both in the daprodustat group).

Based on the review of available information, the remaining 58 participants were considered not likely to have experienced an ocular event of special interest (28 daprodustat and 30 darbepoetin alfa).

The types of AEs and AESIs noted in the participants in this study, particularly with regard to the extent of underlying diabetes, are expected in this population of patients with CKD.

Table 41 Summary of Treatment-emergent Potential AESI of Proliferative Retinopathy, Macular Edema, Choroidal Neovascularization (200807/ASCEND-D, Safety Population) (LDD+DF)

Preferred Term	Dapro (N=1433) n (%)	rhEPO (N=1435) n (%)
Any event	38 (3)	36 (3)
Diabetic retinopathy	9 (<1)	6 (<1)
Vitreous haemorrhage	8 (<1)	5 (<1)
Vision blurred	3 (<1)	6 (<1)
Eye haemorrhage	1 (<1)	5 (<1)
Retinal haemorrhage	2 (<1)	3 (<1)
Macular fibrosis	2 (<1)	2 (<1)
Macular oedema	1 (<1)	2 (<1)
Retinal artery occlusion	2 (<1)	1 (<1)
Retinal detachment	3 (<1)	0
Retinal vein occlusion	1 (<1)	2 (<1)
Visual acuity reduced	2 (<1)	1 (<1)
Blindness unilateral	1 (<1)	1 (<1)
Diabetic retinal oedema	1 (<1)	1 (<1)
Vitreous detachment	1 (<1)	1 (<1)

Source: Study 200807/ASCEND-D Table 68.400012
Note: Events occurring in at least 2 participants are presented.

In the active-controlled dialysis study, post hoc dosing frequency adjusted potential treatment-emergent AESIs of "proliferative retinopathy, macular oedema, choroidal neovascularization" were reported in 74 participants (38 daprodustat-treated and 36 rhEPO-treated). An external ophthalmology expert reviewed each potential ocular AESI (including AE, concomitant medication, medical history, and randomized treatment allocation). An assessment was made on a per-participant basis to determine whether the participant had at least one reported event that was likely to represent an ocular AESI.

Of the 74 participant cases reviewed, 23 participants were likely to have experienced an ocular event of special interest (11 daprodustat and 12 rhEPO) based on reported diagnoses, medical history, and/or concomitant medications (e.g., documented treatment with an anti-VEGF therapy temporally related to study treatment exposure). Of the 23 participants who experienced a likely ocular AESI, all but 3 cases were related to diabetic disease. In the rhEPO group, there was one case of neovascular

age-related macular degeneration (choroidal neovascularization) and one case of branch retinal vein occlusion in which Avastin was utilized, suggesting either retinal neovascularization or macular oedema was present. In the daprodustat group, there was one case of vitreous haemorrhage without a documented history of diabetes or prior eye disease; although there was no treatment with an anti-VEGF medication, this case was included to be conservative in the determination of likely AESIs because hypertension, advanced renal disease, and atrial fibrillation may have contributed to an undiagnosed or unreported new retinal neovascular process that bled into the vitreous.

Based on the review of available information, the remaining 51 participants were considered to not likely have experienced an ocular event of interest (27 daprodustat and 24 rhEPO).

In summary, based on a biological hypothesis, the association with HIF induction and Proliferative Retinopathy, Macular Oedema, Choroidal Neovascularization was investigated. The phase IIb studies included an ophthalmic assessment however no effect of daprodustat was found. AEs in the placebo and actively controlled studies revealed no association.

2.5.8.3. Serious adverse event/deaths/other significant events

Non-dialysis patients

Serious adverse events were comparable between daprodustat and placebo.

Table 42 Treatment-emergent SAEs (≥2 Participants in Either Treatment Group) (205270/ASCEND-NHQ, Safety Population)

System Organ Class Preferred Term	Placebo (N=306) n (%)	Daprodustat (N=308) n (%)
Number of Participants with SAEs	**68 (22)**	**62 (20)**
Number of SAEs	**113**	**96**
Renal and urinary disorders	21 (7)	14 (5)
Acute kidney injury	5 (2)	5 (2)
Renal failure	6 (2)	2 (<1)
End stage renal disease	2 (<1)	2 (<1)
Renal impairment	2 (<1)	1 (<1)
Urinary retention	2 (<1)	0
Cardiac disorders	12 (4)	17 (6)
Cardiac failure	1 (<1)	4 (1)
Cardiac failure congestive	2 (<1)	3 (<1)
Cardiac failure acute	4 (1)	0
Acute coronary syndrome	2 (<1)	1 (<1)
Atrial fibrillation	0	3 (<1)
Bradycardia	2 (<1)	0
Left ventricular failure	0	2 (<1)
Infections and infestations	15 (5)	14 (5)
Urinary tract infection	4 (1)	2 (<1)
Sepsis	2 (<1)	2 (<1)
Cellulitis	2 (<1)	1 (<1)
Pneumonia	1 (<1)	2 (<1)
Septic shock	2 (<1)	0
Urosepsis	0	2 (<1)
Gastrointestinal disorders	10 (3)	6 (2)
Gastrointestinal haemorrhage	2 (<1)	1 (<1)
Vomiting	1 (<1)	2 (<1)
Constipation	2 (<1)	0

System Organ Class Preferred Term	Placebo (N=306) n (%)	Daprodustat (N=308) n (%)
Respiratory, thoracic and mediastinal disorders	5 (2)	7 (2)
Acute pulmonary oedema	1 (<1)	3 (<1)
Injury, poisoning and procedural complications	5 (2)	6 (2)
Femur fracture	0	2 (<1)
Vascular disorders	7 (2)	4 (1)
Hypertension	2 (<1)	2 (<1)
Hypotension	3 (<1)	0
Blood and lymphatic system disorders	8 (3)	2 (<1)
Anaemia	8 (3)	2 (<1)
Metabolism and nutrition disorders	4 (1)	5 (2)
Hypoglycaemia	1 (<1)	2 (<1)
Nervous system disorders	3 (<1)	4 (1)
Syncope	0	3 (<1)

Serious adverse events were higher for daprodustat compared to ESA therapy.

Table 43 Summary of Dosing Frequency Adjusted Treatment-emergent SAEs (⩾1% Participants in Either Treatment Group) (200808/ASCEND-ND, Safety Population)

Preferred Term	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)
Any event	850 (44)	817 (42)
Pneumonia	78 (4)	89 (5)
Chronic kidney disease	86 (4)	60 (3)
Acute kidney injury	70 (4)	50 (3)
Azotaemia	54 (3)	42 (2)
End stage renal disease	48 (2)	41 (2)
COVID-19	39 (2)	41 (2)
Urinary tract infection	33 (2)	40 (2)
Anaemia	33 (2)	34 (2)
Acute myocardial infarction	37 (2)	31 (2)
Hyperkalaemia	26 (1)	26 (1)
Cardiac failure congestive	29 (1)	26 (1)
Fluid overload	25 (1)	26 (1)
Cardiac failure	28 (1)	18 (<1)
Sepsis	14 (<1)	25 (1)
Peritonitis	21 (1)	10 (<1)
Renal impairment	20 (1)	13 (<1)

Source: Table 3.305

Dialysis patients

Table 44 Summary of Treatment-emergent SAEs (≥1% Participants in Either Treatment Group) (200807/ASCEND-D, Safety Population) (LDD+DF)

Preferred Term	Dapro (N=1433) n (%)	rhEPO (N=1435) n (%)
Any event	748 (52)	777 (54)
Pneumonia	83 (6)	86 (6)
Arteriovenous fistula thrombosis	36 (3)	58 (4)
Fluid overload	42 (3)	44 (3)
Anaemia	25 (2)	42 (3)
Sepsis	28 (2)	40 (3)
Acute myocardial infarction	27 (2)	33 (2)
Atrial fibrillation	23 (2)	34 (2)
Hyperkalaemia	18 (1)	36 (3)
Peritonitis	31 (2)	26 (2)
COVID-19	22 (1)	24 (2)
Cellulitis	15 (1)	23 (2)
Cardiac arrest	19 (1)	25 (2)
Angina pectoris	17 (1)	15 (1)
Gangrene	14 (<1)	16 (1)
Cardiac failure	15 (1)	15 (1)
Cardiac failure congestive	17 (1)	15 (1)
Myocardial infarction	10 (<1)	20 (1)
Osteomyelitis	15 (1)	11 (<1)
Hypertension	14 (<1)	9 (<1)
Coronary artery disease	8 (<1)	17 (1)
Non-cardiac chest pain	9 (<1)	15 (1)
Pulmonary oedema	11 (<1)	16 (1)
Acute pulmonary oedema	10 (<1)	15 (1)
Hypotension	5 (<1)	21 (1)
Septic shock	8 (<1)	19 (1)
Arteriovenous graft thrombosis	7 (<1)	15 (1)

Source: Study 200807/ASCEND-D Table 68.400013

Table 45 Dosing Frequency Adjusted (post-hoc analysis) Treatment Emergent SAEs by SOC and PT (204837/ASCEND-TD, 201410/ASCEND-ID)

System Organ Class Preferred Term	204837ASCEND-TD (N=406)		201410/ASCEND-ID (N=312)	
	Dapro (N=270)	rhEPO (N=136)	Dapro (N=157)	Darbe (N=155)
	n (%)	n (%)	n (%)	n (%)
Any event	**82 (30)**	**49 (36)**	**52 (33)**	**57 (37)**
Infections and infestations	34 (13)	14 (10)	21 (13)	27 (17)
Pneumonia	9 (3)	5 (4)	4 (3)	9 (6)
Covid-19	0	0	1 (<1)	1 (<1)
Sepsis	1 (<1)	1 (<1)	0	4 (3)
Urinary tract infection	1 (<1)	0	1 (<1)	1 (<1)
Peritonitis	0	0	1 (<1)	3 (2)
Cellulitis	1 (<1)	0	0	0
Cardiac disorders	14 (5)	8 (6)	13 (8)	9 (6)
Acute myocardial infarction	1 (<1)	1 (<1)	0	3 (2)
Cardiac failure congestive	1 (<1)	0	2 (1)	0
Cardiac failure	2 (<1)	0	1 (<1)	2 (1)

System Organ Class Preferred Term	204837ASCEND-TD (N=406)		201410/ASCEND-ID (N=312)	
	Dapro (N=270)	rhEPO (N=136)	Dapro (N=157)	Darbe (N=155)
	n (%)	n (%)	n (%)	n (%)
Atrial fibrillation	1 (<1)	2 (1)	1 (<1)	0
Cardiac arrest	0	2 (1)	0	0
Renal and urinary disorders	2 (<1)	2 (1)	3 (2)	1 (<1)
Chronic kidney disease	0	0	1 (<1)	0
Acute kidney injury	0	0	0	0
Azotaemia	0	0	1 (<1)	1 (<1)
End stage renal disease	1 (<1)	0	0	0
Injury, poisoning and procedural complications	17 (6)	13 (10)	7 (4)	12 (8)
Arteriovenous fistula thrombosis	7 (3)	3 (2)	1 (<1)	4 (3)
Metabolism and nutrition disorders	8 (3)	5 (4)	6 (4)	7 (5)
Fluid overload	2 (<1)	2 (1)	5 (3)	3 (2)
Hyperkalaemia	3 (1)	1 (<1)	2 (1)	2 (1)
Blood and lymphatic system disorders	3 (1)	3 (2)	0	1 (<1)
Anaemia	2 (<1)	3 (2)	0	0

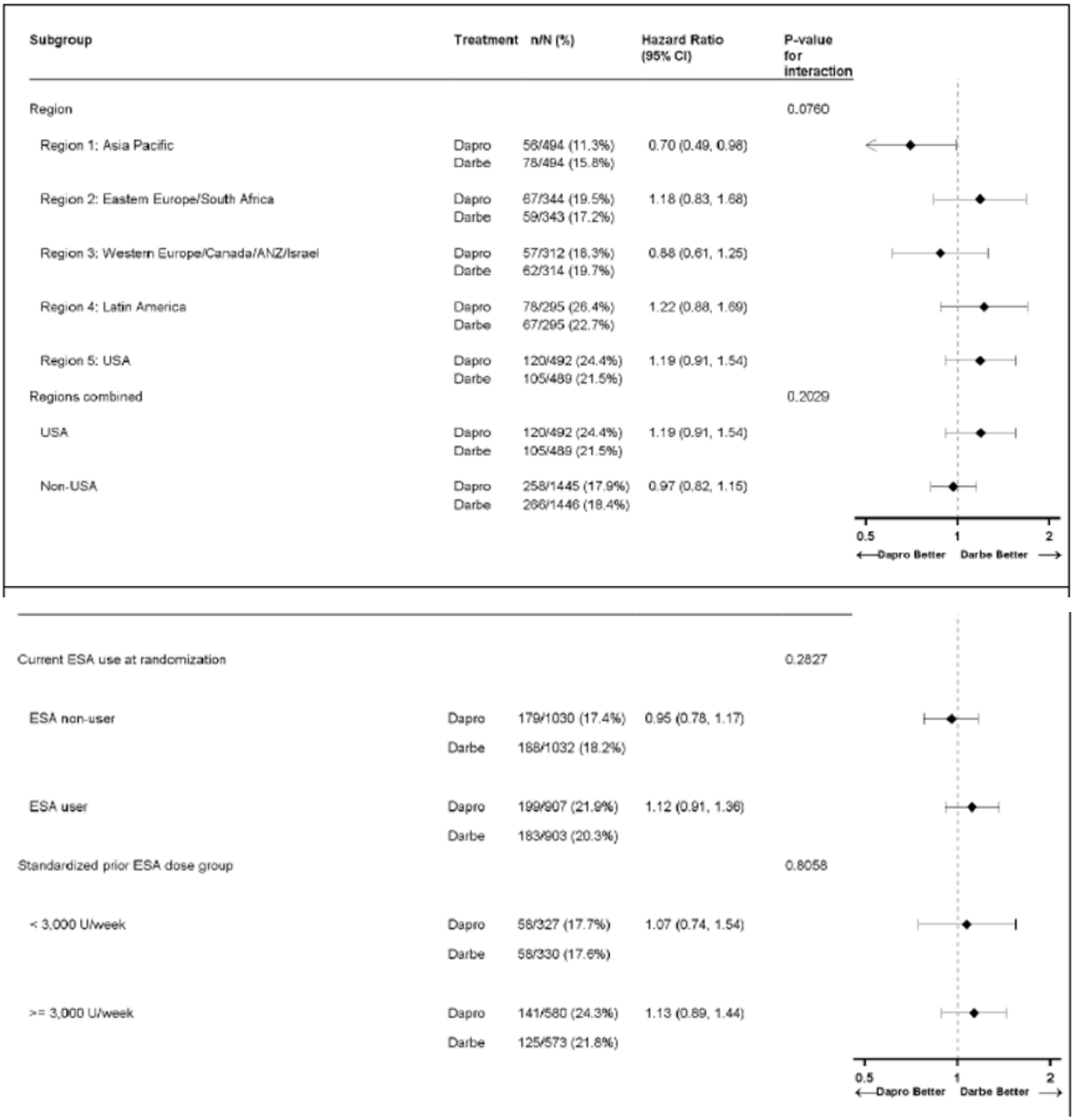
MACE events

Non-dialysis patients

The post-hoc dose frequency adjusted on-treatment MACE was higher for daprodustat vs ESA with HR 1.09 (0.89, 1.33) (192 vs 189 events) (the dose frequency adjusted post-hoc analysis was defined as LDD+ dose frequency correction (due to difference in dose frequency between daprodustat (once daily) and ESA (once every week to 4 weeks) (see results the table further below)). The ITT analysis was HR 1.03 (0.89, 1.19) (378 vs 371) with single components contribution of non-fatal MI (96 vs 91 events), non-fatal stroke (30 vs 21) and all-cause mortality (252 vs 259) (composite endpoint censoring).

In the ASCEND-NHQ study, on-treatment MACE events were 12 (3.9%) vs 15 (4.9%).

Subgroup analyses (ITT analyses) showed a significant p-value for region (p=0.0760) and no other significant differences for other subgroups, including for the stratified prior ESA vs non-ESA use (see figure below for some relevant results).



A time-dependent covariate analysis was performed by dividing each participant's Hgb data into intervals based on Hgb collection schedule, where Hgb was collected every 4 weeks up to Week 52 (or earlier discontinuation of randomized treatment) and every 12 weeks thereafter.

In the daprodustat group in the non-dialysis study (200808/ASCEND-ND), the average change from Baseline in Hgb was associated with MACE risk, with the risk decreasing as the Hgb value increased. The lower (<10 g/dL) Hgb values were associated with higher MACE risk compared to Hgb values between 10 to 11.5 g/dL.

Table 46 Analysis of Effect of Time-Dependent Hemoglobin Data on First Occurrence of Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events (Study 200808/ASCEND-ND, ITT Population)

	Daprodustat			Darbepoetin alfa		
Covariates	**Odds Ratio[a]**	**95% CI**	**p-value**	**Odds Ratio[a]**	**95% CI**	**p-value**
Baseline Hgb	0.69	0.56, 0.85	0.0005	0.72	0.60, 0.86	0.0004
Average 4-week Change in Hgb	0.65	0.52, 0.82	0.0003	0.67	0.55, 0.83	0.0002
High Hgb value (>11.5 g/dL)	1.03	0.69, 1.54	0.8875	1.22	0.81, 1.84	0.3471
Low Hgb value (<10 g/dL)	1.53	1.01, 2.30	0.0493	1.66	1.20, 2.31	0.0031
Recent 4-week Change in Hgb Category (>1 g/dL)	0.85	0.42, 1.71	0.6410	0.84	0.45, 1.58	0.5902
Recent 4-week Change in Hgb Category (>=0 and <1 g/dL)	0.53	0.32, 0.87	0.0130	0.42	0.27, 0.67	0.0002
Recent 4-week Change in Hgb Category (>= -1 and <0 g/dL)	0.48	0.29, 0.77	0.0028	0.47	0.30, 0.74	0.0011

Source: Table 2.103, Table 2.104
Hgb=hemoglobin
Note: Missing Hgb data have been imputed using multiple imputation method assuming missing at random (MAR). Low and high cutoffs at Hgb values of 6 g/dL and 15 g/dL, respectively, were applied to all imputed values. Piecewise exponential model approximated by logistic regression model with forward selection method was performed on 15 imputed datasets to identify the subset of covariates to be included in final model based on remaining 15 imputed datasets. Rubins rules were used to combine results from final model after log - transformation, and then exponentiated back to obtain pooled estimate. The model selection step included covariates baseline Hgb, interval, recent 4-week change, largest 4-week increase and decrease, average 4-week change Hgb category, and recent 4-week change category.
a. Odds ratio is estimated using PROC LOGISTIC with covariates identified at model selection step.

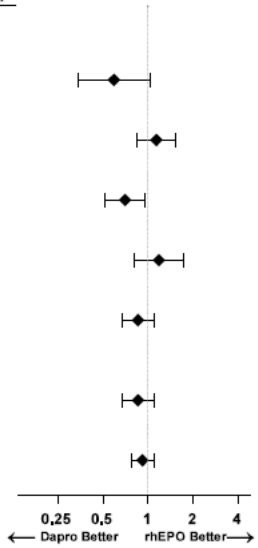
Dialysis patients

The on-treatment MACE was comparable for daprodustat vs ESA with HR 0.94 (0.79, 1.11) (255 vs 278 events) (post-hoc analysis defined as dose frequency correction) (see table below). The ITT analysis was HR 0.89 (0.78, 1.03) (355 vs 389) with single components contribution of non-fatal MI (97 vs 124 events), non-fatal stroke (28 vs 35) and all-cause mortality (230 vs 230) (composite endpoint censoring).

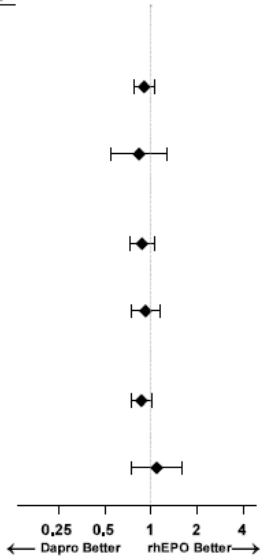
In the ASCEND-ID and ASCEND-TD studies, ITT analysis for MACE events was 19 (12.1%) vs 15 (9.7%) and 33 (12.2%) vs 14 (10.2%).

Subgroup analyses (ITT analyses) showed a significant p-value for region (p=0.0582) and no other significant differences for other subgroups (see figure below for some relevant results).

Subgroup	Treatment	n/N (%)	Hazard Ratio (95% CI)	P-value for interaction
Region				0,0582
Region 1: Asia Pacific	Dapro	20/142 (14,1%)	0,59 (0,34, 1,03)	
	rhEPO	33/143 (23,1%)		
Region 2: Eastern Europe/South Africa	Dapro	92/419 (22,0%)	1,14 (0,84, 1,53)	
	rhEPO	82/416 (19,7%)		
Region 3: Western Europe/Canada/ANZ	Dapro	68/288 (23,6%)	0,70 (0,51, 0,96)	
	rhEPO	92/284 (32,4%)		
Region 4: Latin America	Dapro	57/213 (26,8%)	1,19 (0,81, 1,74)	
	rhEPO	48/213 (22,5%)		
Region 5: USA	Dapro	118/376 (31,4%)	0,86 (0,67, 1,10)	
	rhEPO	134/382 (35,1%)		
Regions combined				0,6517
USA	Dapro	118/376 (31,4%)	0,86 (0,67, 1,10)	
	rhEPO	134/382 (35,1%)		
Non-USA	Dapro	237/1062 (22,3%)	0,92 (0,77, 1,10)	
	rhEPO	255/1056 (24,1%)		



Subgroup	Treatment	n/N (%)	Hazard Ratio (95% CI)	P-value for interaction
Dialysis type at randomization				0,7400
HD	Dapro	315/1267 (24,9%)	0,90 (0,77, 1,05)	
	rhEPO	343/1269 (27,0%)		
PD	Dapro	40/171 (23,4%)	0,84 (0,55, 1,28)	
	rhEPO	46/169 (27,2%)		
Standardized prior ESA dose group				0,7209
< 7,000 U/week	Dapro	202/869 (23,2%)	0,87 (0,72, 1,05)	
	rhEPO	230/879 (26,2%)		
>= 7,000 U/week	Dapro	153/568 (26,9%)	0,92 (0,74, 1,15)	
	rhEPO	159/557 (28,5%)		
rhEPO hyporesponder				0,2683
No	Dapro	291/1243 (23,4%)	0,87 (0,74, 1,01)	
	rhEPO	328/1244 (26,4%)		
Yes	Dapro	56/175 (32,0%)	1,09 (0,75, 1,59)	
	rhEPO	53/176 (30,1%)		



In the daprodustat group in the dialysis study (200807/ASCEND-D), the average change from Baseline and largest 4-week increase in Hgb were associated with MACE risk, with the risk decreasing as these values increased. The lower (<10 g/dL), and to a lesser degree higher Hgb values (>11.5 g/dL) compared with Hgb value between 10 to 11.5 g/dL were associated with higher MACE risk.

Table 47 Analysis of Effect of Time-Dependent Hemoglobin Data on First Occurrence of Adjudicated MACE During the Time Period for Follow-up of Cardiovascular Events (Study 200807/ASCEND-D, ITT Population)

	Daprodustat			rhEPO		
Covariates	**Odds Ratio[a]**	**95% CI**	**p-value**	**Odds Ratio[a]**	**95% CI**	**p-value**
Baseline Hgb	0.77	0.64, 0.93	0.0058	0.82	0.69, 0.98	0.0337
Largest 4-week Increase in Hgb	0.84	0.71, 0.98	0.0313	0.82	0.69. 0.97	0. 0.0176
Average 4-week Change in Hgb	0.83	0.68, 1.00	0.0563	0.80	0.66, 0.97	0.0225
High Hgb value (>11.5 g/dL)	1.15	0.76, 1.75	0.5105	1.09	0.76, 1.56	0.6433
Low Hgb value (<10 g/dL)	1.75	1.21, 2.53	0.0040	1.71	1.23, 2.37	0.0022
Recent 4-week Change in Hgb Category (>1 g/dL)	1.09	0.59, 2.04	0.7816	1.30	0.69, 2.46	0.4213
Recent 4-week Change in Hgb Category (>=0 and <1 g/dL)	0.58	0.35, 0.95	0.0311	0.67	0.42, 1.07	0.0966
Recent 4-week Change in Hgb Category (>= -1 and <0 g/dL)	0.60	0.37, 0.97	0.0364	0.65	0.42, 1.00	0.0490

Source: Table 68.400001, Table 68.400002
Hgb=hemoglobin
Note: Missing Hgb data have been imputed using multiple imputation method assuming missing at random (MAR). Low and high cutoffs at Hgb values of 6 g/dL and 15 g/dL, respectively, were applied to all imputed values. Piecewise exponential model approximated by logistic regression model with forward selection method was performed on 15 imputed datasets to identify the subset of covariates to be included in final model based on remaining 15 imputed datasets. Rubins rules were used to combine results from final model after log - transformation, and then exponentiated back to obtain pooled estimate. The model selection step included covariates baseline Hgb, interval, recent 4-week change, largest 4-week increase and decrease, average 4-week change Hgb category, and recent 4-week change category.
a. Odds ratio is estimated using PROC LOGISTIC with covariates identified at model selection step.

The ITT (first table) and the on-treatment (second table) MACE endpoints are presented below both for the non-dialysis ASCEND-ND study and the dialysis ASCEND-DD study. As dose frequencies are substantially different between daprodustat (once daily) and ESA (once every week to 4 weeks), dose-frequency adjusted post-hoc analyses have been presented (see also legenda of the second table).

Table 48 Overall Summary of Analysis of Time to First Occurrence of Adjudicated MACE and Other CV Events During the Time Period for Follow-up of Cardiovascular Events for the Cardiovascular Outcomes Studies (ITT Population)

	200807/ASCEND-D				200808/ASCEND-ND			
	Dapro N= 1438	**rhEPO N= 1438**	**Dapro vs rhEPO**		**Dapro N=1937**	**Darbe N=1935**	**Dapro vs Darbe**	
	n (%)	**n (%)**	**HR**	**95% CI**	**n (%)**	**n (%)**	**HR**	**95% CI**
Co-primary Safety Endpoints [b]								
MACE	355 (24.7)	389 (27.1)	**0.89**	**0.78, 1.03**	378 (19.5)	371 (19.2)	**1.03**	**0.89, 1.19**
Principal Secondary Endpoints for CV events[c]								
MACE	355 (24.7)	389 (27.1)	**0.89**	**0.78, 1.03**	378 (19.5)	371 (19.2)	**1.03**	**0.89, 1.19**
MACE or TEE	475 (33.0))	537 (30.3)	**0.85**	**0.76, 0.97**	422 (21.8)	405 (20.9)	**1.06**	**0.93, 1.22**
MACE or HHF	404 (28.1)	426 (29.6)	**0.94**	**0.82, 1.07**	444 (22.9)	417 (21.6)	**1.09**	**0.95, 1.24**
Key Individual CV components [d]								
All-cause mortality	276 (19.2)	297 (20.7)	**0.92**	**0.78, 1.08**	301 (15.5)	298 (15.4)	**1.03**	**0.87, 1.20**
CV mortality	112 (7.8)	120 (8.3)	**0.92**	**0.71, 1.19**	109 (5.6)	92 (4.8)	**1.20**	**0.91, 1.58**
Fatal and non-fatal MI	109 (7.6)	135 (9.4)	**0.79**	**0.62, 1.02**	103 (5.3)	97 (5.0)	**1.06**	**0.80, 1.40**
Fatal and non-fatal stroke	39 (2.7)	51 (3.5)	**0.76**	**0.50, 1.15**	45 (2.3)	34 (1.8)	**1.33**	**0.85, 2.07**
TEE	180 (12.5)	213 (14.8)	**0.83**	**0.68, 1.01**	64 (3.3)	51 (2.6)	**1.27**	**0.88, 1.84**
HHF	106 (7.4)	98 (6.8)	**1.08**	**0.82, 1.42**	140 (7.2)	115 (5.9)	**1.22**	**0.95, 1.56**
Other secondary CV endpoints [d]								
MACE or HHF -recurrent events[e]								
First event			**0.94**	**0.82, 1.07**			**1.09**	**0.95, 1.24**
Subsequent events			**0.73**	**0.58, 0.92**			**1.16**	**0.92, 1.46**
CV mortality or non-fatal MI	196 (13.6)	225 (15.6)	**0.86**	**0.71, 1.04**	188 (9.7)	175 (9.0)	**1.08**	**0.88, 1.33**
MACE or TEE or HHF	516 (35.9)	570 (39.6)	**0.88**	**0.78, 0.99**	485 (25.0)	448 (23.2)	**1.11**	**0.97, 1.26**

Table 49 Summary of Analysis of Time to First Occurrence of Adjudicated MACE and other CV Events During the On-treatment Period for Cardiovascular Events for the Cardiovascular Outcomes Studies

	200807/ASCEND-D						200808/ASCEND-ND					
	Dapro N=1438	rhEPO N=1438	Dapro vs rhEPO				Dapro (N=1937	Darbe (N=1935)	Dapro vs Darbe			
	n (%)	n (%)	Rate diff per 100 PY	95% CI for rate diff	HR	95% CI for HR	n (%)	n (%)	Rate diff per 100 PY	95% CI for rate diff	HR	95% CI for HR
Co-primary Safety Endpoint[a]												
MACE												
Post hoc[b]	**169 (11.8)**	**205 (14.3)**	-1.31	-2.84, 0.21	**0.85**	**0.69, 1.04**	**192 (9.9)**	**189 (9.8)**	0.53	-0.88, 1.94	**1.09**	**0.89, 1.33**
Principal Secondary Endpoints for CV events[a]												
MACE or Thromboembolic events												
Post hoc[b]	**285 (19.9)**	**347 (24.2)**	-2.67	-4.80, -0.54	**0.83**	**0.71, 0.97**	**230 (11.9)**	**220 (11.4)**	0.91	-0.65, 2.46	**1.13**	**0.94, 1.36**
MACE or Hospitalization for HF												
Post hoc[b]	**255 (15.7)**	**246 (17.1)**	-0.70	-2.46, 1.05	**0.94**	**0.78, 1.13**	**253 (13.3)**	**248 (12.8)**	0.80	-0.86, 2.45	**1.09**	**0.92, 1.30**
Key Individual CV components[a]												
All-cause mortality												
Post hoc[b]	**80 (5.6)**	**99 (6.9)**	-0.63	-1.65, 0.38	**0.84**	**0.62, 1.12**	**93 (4.8)**	**114 (5.9)**	-0.53	-1.54, 0.48	**0.88**	**0.67, 1.16**
CV mortality												
Post-hoc[c]	**40 (2.8)**	**55 (3.8)**	-0.53	-1.27. 0.21	**0.75**	**0.50, 1.13**	**38 (2.0)**	**47 (2.4)**	-0.23	-0.88, 0.41	**0.88**	**0.57, 1.35**
Fatal and non-fatal MI												
Post-hoc	**76 (5.3)**	**101 (7.0)**	-0.93	-1.97, 0.11	**0.78**	**0.58, 1.05**	**86 (4.4)**	**75 (3.9)**	0.57	-0.34, 1.49	**1.21**	**0.89, 1.65**
Fatal and non-fatal stroke												
Post hoc[b]	**28 (2.0)**	**38 (2.6)**	-0.36	-0.98, 0.27	**0.75**	**0.46, 1.22**	**31 (1.6)**	**21 (1.1)**	0.42	-0.10, 0.93	**1.58**	**0.91. 2.75**
Thromboembolic events												
Post hoc[b]	**144 (10.0)**	**176 (12.3)**	-1.26	-2.73, 0.20	**0.84**	**0.67, 1.04**	**50 (2.6)**	**37 (1.9)**	0.57	-0.09, 1.24	**1.48**	**0.97, 2.27**
Hospitalization for HF												
Post hoc[b]	**81 (5.7)**	**85 (5.9)**	-0.09	-1.10, 0.92	**1.00**	**0.74, 1.35**	**107 (5.5)**	**97 (5.0)**	0.60	-0.44, 1.63	**1.15**	**0.88, 1.52**

a. Co-primary, principal secondaries, and key individual CV were tested for superiority (daprodustat versus rhEPO). No multiplicity adjustments were made. P-values presented are nominal p-values.

b. The post-hoc definition for end of the time period for On-treatment Cardiovascular Events is defined as the earlier of last non-zero dose date + dosing frequency (LDD+DF) and the date of study withdrawal/completion

After further request, the following ITT and OT post-hoc analyses have been provided for both the ND and DD populations.

Table 50 Summary of Time to First Adjudicated MACE using the Intent-to- Treat Analysis during the Time Period for Follow-up of CV Events (ITT and OT Population)

	200807/ASCEND-D		200808/ASCEND-ND		Dialysis Pool[a]	
Adjudicated Event Type[b]	**Dapro (N=1438)**	**rhEPO (N=1438)**	**Dapro (N=1937)**	**Darbe (N=1935)**	**Dapro (N=1865)**	**Darbe (N=1730)**
MACE Intent-to-Treat (on/off treatment events)						
Number of participants[c]	1438	1438	1937	1935	1865	1730
First adjudicated MACE, n(%)	355 (24.7)	389 (27.1)	378 (19.5)	371 (19.2)	407 (21.8)	418 (24.2)
Hazard ratio (95% CI)[d]	0.89 (0.78, 1.03)		1.03 (0.89, 1.19)		0.92 (0.81, 1.06)	
OT (LDD)						
Number of participants	1433	1435	1937	1933	1860	1726
First adjudicated MACE, n(%)	138 (9.6)	132 (9.2)	158 (8.2)	105 (5.4)	160 (8.6)	141 (8.2)
Hazard ratio (95% CI)[d]	1.07 (0.84, 1.36)		1.54 (1.20, 1.97)		1.11 (0.89, 1.40)	
OT+1 (LDD+1)						
Number of participants	1433	1435	1937	1933	1860	1726
First adjudicated MACE, n(%)	169 (11.8)	142 (9.9)	192 (9.9)	109 (5.6)	193 (10.4)	152 (8.8)
Hazard ratio (95% CI)[d]	1.21 (0.97, 1.52)		1.80 (1.43, 2.28)		1.24 (1.01, 1.54)	
OT+28 (LDD+28)						
Number of participants	1433	1435	1937	1933	1860	1726
First adjudicated MACE, n(%)	242 (16.9)	269 (18.7)	274 (14.1)	202 (10.5)	283 (15.2)	289 (16.7)
Hazard ratio (95% CI)[d]	0.91 (0.77, 1.09)		1.40 (1.17, 1.68)		0.94 (0.80, 1.11)	
OT+28+Dosing Frequency (LDD+28+DF)						
Number of participants	1433	1435	1937	1933	1860	1726
First adjudicated MACE, n(%)	242 (16.9)	275 (19.2)	275 (14.2)	248 (12.8)	283 (15.2)	297 (17.2)
Hazard ratio (95% CI)[d]	0.90 (0.76, 1.07)		1.18 (0.99, 1.40)		0.93 (0.79, 1.09)	
MACE OT+Dosing Frequency (LDD+DF)						
Number of participants	1433	1435	1937	1933	1860	1726
First adjudicated MACE, n(%)	169 (11.8)	205 (14.3)	192 (9.9)	189 (9.8)	198 (10.6)	221 (12.8)
Hazard ratio (95% CI)[d]	0.85 (0.69, 1.04)		1.09 (0.89. 1.33)		0.88 (0.72, 1.07)	

DF=dosing frequency, LDD=last dose date, MACE=major adverse cardiovascular event, OT=on treatment (LDD)

c. Dialysis Pool=ASCEND-D, ASCEND-TD, and ASCEND-ID excluding sites with suspected fraud in ASCEND-D.

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

e. All randomized participants.

f. For D and ND: Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and geographic region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with rhEPO/darbepoetin alfa).
For Dialysis Pool: Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group as covariate and study, region, and dialysis type as stratification factors.

Deaths

Non-dialysis patients

Compared to ESA, 301 vs 298 events were reported for daprodustat vs ESA (see table above, ITT analysis). Fatal SAEs were reported with a comparable incidence of 153 (8%) vs 146 (8%). In the placebo-controlled study, there were 11 patients (4 vs 7) with treatment-emergent fatal AEs.

Dialysis patients

In the largest dialysis study, 276 vs 297 events were reported for daprodustat vs ESA (see table above, ITT analysis). Fatal SAEs were reported with a comparable incidence of 125 (9%) vs 143 (10%). In the ASCEND-ID and ASCEND-TD, the numbers of deaths were limited (8 (5%) vs 8 (5%) and 8 (3%) vs 5 (4%), respectively).

Table 51 Summary of Causes of Death (≥3.0%) of All-Cause Mortality During the Time Period for Vital Status (200807/ASCEND-D, 200808/ASCEND-ND, ITT Population), ITT analysis.

	200807/ASCEND-D		200808/ASCEND-D	
Adjudicated Event Type	**Dapro (N=1438)**	**rhEPO (N=1438)**	**Dapro (N=1937)**	**Darbe (N=1935)**
	n (%)	n (%)	n (%)	n (%)
Death	276	297	301	298
CV mortality [a]	112 (40.6)	120 (40.4)	109 (36.2)	92 (30.9)
Non-CV mortality	128 (46.4)	154 (51.9)	149 (49.5)	148 (49.7)
Unknown death	36 (13.0)	23 (7.7)	43 (14.3)	58 (19.5)
Cause of death				
Cardiovascular	93 (33.7)	90 (30.3)	89 (29.6)	70 (23.5)
Sudden cardiac death	47 (17.0)	38 (12.8)	34 (11.3)	31 (10.4)
Stroke	11 (4.0)	15 (5.1)	14 (4.7)	11 (3.7)
Heart failure/cardiogenic shock	14 (5.1)	11 (3.7)	20 (6.6)	13 (4.4)
Acute myocardial infarction	11 (4.0)	9 (3.0)	9 (3.0)	9 (3.0)
Non-cardiovascular	128 (46.4)	154 (51.9)	149 (49.5)	148 (49.7)
Infection (includes sepsis)	76 (27.5)	90 (30.3)	90 (29.9)	90 (30.2)
Malignancy	14 (5.1)	18 (6.1)	11 (3.7)	14 (4.7)
Renal	14 (5.1)	15 (5.1)	20 (6.6)	22 (7.4)

Source: Study 200807/ASCEND-D Table 68.400025, Study 200808/ASCEND-ND Table 3.043,
Note: Percentages are calculated using the total number of deaths as the denominator.
CV mortality includes all deaths indicated as having a cardiovascular primary cause of death as well as deaths with an undetermined primary cause of death that are indicated to be either presumed sudden death or presumed cardiovascular death.

After further request, the following ITT and OT post-hoc analyses have been provided for both the ND and DD populations.

Table 52 Summary of Time All Cause Mortality using the Intent-to- Treat Analysis during the Time Period for Follow-up of CV Events (ITT and OT Population)

	200807/ASCEND-D		200808/ASCEND-ND		Dialysis Pool[a]	
Adjudicated Event Type[b]	**Dapro (N=1438)**	**rhEPO (N=1438)**	**Dapro (N=1937)**	**Darbe (N=1935)**	**Dapro (N=1865)**	**Darbe (N=1730)**
All-Cause Mortality Intent-to-Treat (on/off treatment events)						
Number of participants[c]	1438	1438	1937	1935	1865	1730
Adjudicated All-Cause Mortality, n(%)	276 (19.2)	297 (20.7)	301 (15.5)	298 (15.4)	311 (16.7)	319 (18.4)
Hazard ratio (95% CI)[d]	0.92 (0.78, 1.08)		1.03 (0.87, 1.20)		0.94 (0.80, 1.10)	
OT (LDD)						
Number of participants	1433	1435	1937	1933	1860	1726
Adjudicated All-Cause Mortality, n(%)	50 (3.5)	16 (1.1)	62 (3.2)	28 (1.4)	57 (3.1)	17 (1.0)
Hazard ratio (95% CI)[d]	3.22 (1.84, 5.66)		2.29 (1.46, 3.58)		3.58 (2.08, 6.16)	
OT+1 (LDD+1)						
Number of participants	1433	1435	1937	1933	1860	1726
Adjudicated All-Cause Mortality, n(%)	80 (5.6)	26 (1.8)	93 (4.8)	32 (1.7)	89 (4.8)	28 (1.6)
Hazard ratio (95% CI)[d]	3.17 (2.04, 4.93)		3.02 (2.02, 4.51)		3.27 (2.14, 5.01)	
OT+28 (LDD+28)						
Number of participants	1433	1435	1937	1933	1860	1726
Adjudicated All-Cause Mortality, n(%)	159 (11.1)	173 (12.1)	183 (9.4)	129 (6.7)	185 (9.9)	183 (10.6)
Hazard ratio (95% CI)[d]	0.94 (0.76, 1.17)		1.47 (1.18, 1.85)		0.99 (0.81, 1.22)	
OT+28+Dosing Frequency (LDD+28+DF)						
Number of participants	1433	1435	1937	1933	1860	1726
Adjudicated All-Cause Mortality, n(%)	159 (11.1)	182 (12.7)	185 (9.6)	175 (9.1)	185 (9.9)	195 (11.3)
Hazard ratio (95% CI)[d]	0.90 (0.73, 1.12)		1.13 (0.92, 1.39)		0.94 (0.77, 1.15)	
All-Cause Mortality OT+Dosing Frequency (LDD+DF)						
Number of participants	1433	1435	1937	1933	1860	1726
Adjudicated All-Cause Mortality, n(%)	80 (5.6)	99 (6.9)	93 (4.8)	114 (5.9)	94 (5.1)	106 (6.1)
Hazard ratio (95% CI)[d]	0.84 (0.62, 1.12)		0.88 (0.67. 1.16)		0.89 (0.68, 1.17)	

DF=dosing frequency, LDD=last dose date, MACE=major adverse cardiovascular event, OT=on treatment (LDD)

g. Dialysis Pool=ASCEND-D, ASCEND-TD, and ASCEND-ID excluding sites with suspected fraud in ASCEND-D.

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

i. All randomized participants.

j. For D and ND: Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group, dialysis type (ASCEND-D only), ESA use at randomization (ASCEND-ND only), and geographic region as covariates. A hazard ratio <1 indicates a lower risk with daprodustat compared with rhEPO/darbepoetin alfa).
For Dialysis Pool: Hazard ratio is estimated using a Cox proportional hazard regression model with treatment group as covariate and study, region, and dialysis type as stratification factors.

2.5.8.4. Laboratory findings

Laboratory evaluation included haematology parameters (leukocytes, lymphocytes, neutrophils, platelets), chemistry parameters (ALT, albumin, AST, bilirubin, calcium, carbon dioxide, eGFR, phosphate, potassium, sodium, lipid parameters (LDL-C, HDL-C, TC), ferritin, TSAT).

Non-dialysis patients

Median baseline *serum creatinine* values were comparable between treatment groups at Week 52 (Median [IQR] change from Baseline: 23.40 [-3.55 to 79.10] µmol/L daprodustat; 22.55 [-6.15 to 79.10] µmol/L darbepoetin alfa).

No relevant differences were observed in *hematology parameters* (within range leukocytes (93% vs 91%), lymphocytes (98% vs 97%), neutrophils (>99% each), and platelets (98% vs 97%) and without relevant difference of too high levels of (less than) 1%). Also, for any of the chemistry markers, no relevant differences were observed (ALT (> 99% each), albumin (93% each), AST (>99% each), bilirubin (>99% each), calcium (74% vs 73%; too high 5% vs 4%), carbon dioxide (74% vs 73%), phosphate (69% vs 71%; too high 28% vs 25%), potassium (94% vs 93%; too high 5% vs 6%), sodium (95% vs 94%).

Lipid parameters were reduced, including LDL-C (week 52 -8.8 mmol/L vs -0.6 mmol/L change) and HDL-C (-4.8 vs 2.2 mmol/L change).

Table 53 Summary of Percent Change from Baseline in On-treatment Lipid Parameters at Week 52, Week 100, and End of Treatment (or Early Treatment Discontinuation) (200808/ASCEND-ND, ITT Population)

Parameter	Treatment	N	Planned Relative Time	n	Percent Change Geometric Mean[a]	95% CI Lower Limit	95% CI Upper Limit
Cholesterol (mmol/L)	Dapro	1937	Baseline	1918	4.10	--	--
			Week 52	1017	-6.9	-8.2	-5.5
			Week 100	535	-9.6	-11.6	-7.6
			Early trt disc	44	-12.2	-18.4	-5.5
			EOT	1082	-8.4	-9.8	-7.0
	Darbe	1935	Baseline	1917	4.13	--	--
			Week 52	1076	-1.8	-3.1	-0.5
			Week 100	586	-4.1	-6.0	-2.1
			Early trt disc	19	-7.7	-19.4	5.8
			EOT	1116	-3.8	-5.2	-2.4
HDL Cholesterol Direct (mmol/L)	Dapro	1937	Baseline	1918	1.19	--	--
			Week 52	1017	-4.8	-6.2	-3.4
			Week 100	535	-4.1	-5.9	-2.2
			Early trt disc	44	-11.2	-17.4	-4.7
			EOT	1082	-4.8	-6.2	-3.4
	Darbe	1935	Baseline	1917	1.19	--	--
			Week 52	1076	2.2	1.0	3.4
			Week 100	586	2.1	0.3	4.0
			Early trt disc	19	-6.3	-15.9	4.3
			EOT	1116	2.1	0.8	3.4
LDL Cholesterol Direct (mmol/L)	Dapro	1937	Baseline	1912	2.16	--	--
			Week 52	1006	-8.8	-10.5	-6.9
			Week 100	527	-11.1	-13.9	-8.2
			Early trt disc	44	-14.0	-22.1	-5.2
			EOT	1077	-10.4	-12.3	-8.5
	Darbe	1935	Baseline	1910	2.16	--	--
			Week 52	1065	-0.6	-2.4	1.3
			Week 100	579	-5.0	-7.7	-2.2
			Early trt disc	18	-9.0	-26.3	12.2
			EOT	1108	-4.0	-5.9	-2.0

Source: Table 3.076 and Table 3.077

Note: Baseline includes only pre-treatment values. Baseline and End of Treatment (EOT) are derived.

a. Baseline values are geometric means of actual values.

One participant had an increase in *ALT > 15xULN* who experienced an SAE of "acute hepatitis B" on the same date. Three cases met ALT and total bilirubin criteria for inclusion in the Hy's Law with alternative explanations (of which details have been provided).

Dialysis patients

No relevant differences were observed in *haematology parameters* (within range leukocytes (86% vs 87%), lymphocytes (96% vs 97%), neutrophils (>99% each), and platelets (96% each) and without relevant differences of too high levels (< 1%)).

Also, for any of the chemistry markers, no relevant differences were observed (ALT (> 99% each), albumin (91% vs 93%), AST (>99% each), bilirubin (>99% each), calcium (79% vs 80%), phosphate (57% vs 53%, too high 36% vs 38%), and potassium (85% each; too high 14% vs 13%).

Table 54 Summary of Percent Change from Baseline in On-treatment Lipid Parameters at Week 52, Week 100, and End of Treatment (or Early Treatment Discontinuation) (200807/ASCEND-D, ITT Population)

Parameter	Treatment	N	Planned Relative Time	n	Percent Change Geometric Mean[a]	95% CI Lower Limit	95% CI Upper Limit
Cholesterol (mmol/L)	Dapro	1438	Baseline	1416	3.91	--	--
			Week 52	1006	-6.5	-7.7	-5.3
			Week 100	722	--8.0	-9.6	-6.3
			Early trt disc	56	-14.4	-17.7	-8.5
			EOT	1054	-8.5	-9.8	-7.2
	rhEPO	1438	Baseline	1425	3.92	--	--
			Week 52	1027	-2.6	-3.8	-1.5
			Week 100	750	-4.4	-5.7	-2.8
			Early trt disc	21	-5.5	-12.7	2.4
			EOT	1062	-4.1	-5.2	-2.8
HDL Cholesterol Direct (mmol/L)	Dapro	1438	Baseline	1416	1.07	--	--
			Week 52	1006	-4.8	-6.3	-3.5
			Week 100	722	-3.5	-5.2	-1.9
			Early trt disc	56	-12.3	-17.9	-5.7
			EOT	1054	-4.7	-6.2	-3.4
	rhEPO	1438	Baseline	1425	1.08	--	--
			Week 52	1027	0.6	-0.8	2.0
			Week 100	750	2.7	1.1	4.4
			Early trt disc	21	0.3	-7.8	9.1
			EOT	1062	2.1	0.8	3.5

Parameter	Treatment	N	Planned Relative Time	n	Percent Change Geometric Mean[a]	95% CI Lower Limit	95% CI Upper Limit
LDL Cholesterol Direct (mmol/L)	Dapro	1438	Baseline	1424	2.03	--	--
			Week 52	1016	-7.5	-9.1	-5.7
			Week 100	722	-9.0	-11.1	-6.7
			Early trt disc	55	-17.6	-21.8	-7.4
			EOT	1061	-9.6	-11.3	-7.7
	rhEPO	1438	Baseline	1430	2.03	--	--
			Week 52	1035	-1.4	-3.2	0.2
			Week 100	746	-2.0	-4.1	0.4
			Early trt disc	21	-4.5	-15.4	7.8
			EOT	1067	-2.1	-3.8	-0.2

Source: Table 68,400026 and Table 68.400027
Note: Baseline includes only pre-treatment values. Baseline and End of Treatment (EOT) are derived.
k. Baseline values are geometric means of actual values.

One participant had an increase in *ALT >20xULN* with an SAE of cardiac failure starting 10 days prior to the SAE of hepatic enzyme increase. The investigator reported, "The liver event of an increase of liver enzymes was probably caused by cardiac failure and decompensation." One case of Hy's Law was identified with an SAE of hepatitis B. The results of the ASCEND-ID and ASCEND-TD studies showed a comparable profile to the ASCEND-D study.

2.5.8.5. In vitro biomarker test for patient selection for safety

N/A

2.5.8.6. Safety in special populations

Table 55 Overview of Treatment-Emergent AEs by Subgroup (Study 205270/ASCEND-NHQ, Safety Population)

	Placebo		Daprodustat	
	N	Any Event, n (%)	N	Any Event, n (%)
Age group				
<65 Years	121	85 (70)	135	92 (68)
65 to <75 Years	96	72 (75)	82	56 (68)
≥75 Years	89	59 (66)	91	65 (71)

The results for comparison to ESA have currently only been described by pooling of the largest ND and DD studies (see table further below).

Dialysis patients

The results for comparison to ESA have currently only been described by pooling of the largest ND and DD studies (see table below).

Table 56 Summary of All Dosing Frequency Adjusted (post-hoc) Treatment-emergent Adverse Events by Age Group and SOC (for events that occurred in ≥10% participants in any group)(Pooled Studies 200807/ASCEND-D + 200808/ASCEND-ND, Safety Population)

System Organ Class	Age Group: <65 Years N=3605		Age Group: 65 to <75 Years N=1834		Age Group: ≥75 Years N=1299	
	Dapro N=1814	rhEPO Control N=1791	Dapro N=903	rhEPO Control N=931	Dapro N=653	rhEPO Control N=646
Any Event, n (%)						
Infections and infestations	866 (48)	887 (50)	429 (48)	422 (45)	307 (47)	303 (47)
Gastrointestinal disorders	584 (32)	598 (33)	332 (37)	306 (33)	206 (32)	196 (30)
Vascular disorders	522 (29)	526 (29)	261 (29)	284 (31)	57 (9) 155 (24)	180 (28)
Injury, poisoning and procedural complications	445 (25)	427 (24)	235 (26)	264 (28)	197 (30)	191 (30)
Metabolism and nutrition disorders	467 (26)	473 (26)	244 (27)	250 (27)	165 (25)	158 (24)
Musculoskeletal and connective tissue disorders	390 (21)	397 (22)	232 (26)	237 (25)	138 (21)	177 (27)
General disorders and administration site conditions	386 (21)	390 (22)	219 (24)	212 (23)	162 (25)	142 (22)
Respiratory, thoracic and mediastinal disorders	329 (18)	372 (21)	192 (21)	217 (23)	125 (19)	122 (19)
Nervous system disorders	356 (20)	338 (19)	193 (21)	199 (21)	124 (19)	140 (22)
Cardiac disorders	289 (16)	268 (15)	187 (21)	194 (21)	143 (22)	154 (24)
Renal and urinary disorders	269 (15)	261 (15)	174 (19)	150 (16)	103 (16)	100 (15)
Skin and subcutaneous tissue disorders	254 (14)	218 (12)	122 (14)	128 (14)	108 (17)	86 (13)
Investigations	199 (11)	230 (13)	112 (12)	95 (10)	57 (9)	68 (11)
Psychiatric disorders	110 (6)	118 (7)	65 (7)	54 (6)	45 (7)	69 (11)

Source: Table 68.396007

Note: Data are presented for SOCs with at least 10% incidence in either treatment group (based on total number of participants and post-hoc summary).

Table 57 Overview of Dosing Frequency Adjusted (post-hoc) Treatment-Emergent AEs by Subgroup (Study 204837/ASCEND-TD, Safety Population)

	Dapro		rhEPO	
	N	Any Event, n (%)	N	Any Event, n (%)
Age group				
<65 Years	167	117 (70)	96	72 (75)
65 to <75 Years	66	54 (82)	24	20 (83)
≥75 Years	37	34 (92)	16	16 (100)

Table 58 Overview of Dosing Frequency Adjusted (post-hoc) Treatment-emergent AEs by Subgroup (Study 201410/ASCEND-ID, Safety Population)

	Dapro		Darbe	
	N	Any Event, n (%)	N	Any Event, n (%)
Age group				
<65 Years	119	90 (76)	110	82 (75)
65 to <75 Years	22	17 (77)	28	19 (68)
≥75 Years	16	13 (81)	17	15 (88)

2.5.8.7. Immunological events

No data on immunological events are available.

2.5.8.8. Safety related to drug-drug interactions and other interactions

No safety-related drug-drug interactions have currently been identified. See also 3.3.1 Clinical pharmacology.

2.5.8.9. Discontinuation due to adverse events

Non-dialysis patients

Discontinuations due to AE were 22 (7%) for daprodustat vs 28 (9%) for placebo in the placebo-controlled study.

For the larger ESA controlled study, the results are shown below.

Table 59 Summary of Treatment-emergent AEs Leading to Permanent Discontinuation of Randomized Treatment (≥3 Participants, Posthoc) by Overall Frequency (200808/ASCEND-ND, Safety Population) (dose frequency adjusted post-hoc analysis)

Preferred Term	Pre-specified[a]		Post-hoc[b]	
	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)	Dapro (N=1937) n (%)	Darbe (N=1933) n (%)
ANY EVENT	247 (13)	94 (5)	247 (13)	201 (10)
Death	11 (<1)	3 (<1)	11 (<1)	12 (<1)
COVID-19	10 (<1)	4 (<1)	10 (<1)	7 (<1)
Pneumonia	9 (<1)	4 (<1)	9 (<1)	8 (<1)
Cardiac arrest	5 (<1)	4 (<1)	5 (<1)	9 (<1)
Acute myocardial infarction	6 (<1)	3 (<1)	6 (<1)	7 (<1)
Myocardial infarction	10 (<1)	0	10 (<1)	3 (<1)
Azotaemia	8 (<1)	2 (<1)	8 (<1)	4 (<1)
Anaemia	8 (<1)	2 (<1)	8 (<1)	2 (<1)
Septic shock	2 (<1)	3 (<1)	2 (<1)	7 (<1)
Chronic kidney disease	7 (<1)	0	7 (<1)	1 (<1)
End stage renal disease	4 (<1)	3 (<1)	4 (<1)	4 (<1)
Sepsis	5 (<1)	0	5 (<1)	3 (<1)
Acute respiratory failure	3 (<1)	1 (<1)	3 (<1)	4 (<1)
Breast cancer	5 (<1)	2 (<1)	5 (<1)	2 (<1)
Cardiac failure	4 (<1)	1 (<1)	4 (<1)	3 (<1)
Multiple organ dysfunction syndrome	6 (<1)	0	6 (<1)	0
Renal failure	3 (<1)	2 (<1)	3 (<1)	3 (<1)
Plasma cell myeloma	1 (<1)	2 (<1)	1 (<1)	4 (<1)
Sudden death	0	2 (<1)	0	5 (<1)
Cardiac failure acute	2 (<1)	1 (<1)	2 (<1)	2 (<1)
Cardiogenic shock	4 (<1)	0	4 (<1)	0
Coronary artery disease	2 (<1)	1 (<1)	2 (<1)	2 (<1)
Pancreatic carcinoma	2 (<1)	1 (<1)	2 (<1)	2 (<1)
Respiratory failure	3 (<1)	0	3 (<1)	1 (<1)
Transitional cell carcinoma	0	4 (<1)	0	4 (<1)
Acute kidney injury	3 (<1)	0	3 (<1)	0
Acute pulmonary oedema	1 (<1)	2 (<1)	1 (<1)	2 (<1)
Adenocarcinoma of colon	2 (<1)	0	2 (<1)	1 (<1)
Arrhythmia	1 (<1)	0	1 (<1)	2 (<1)
Cardiac failure congestive	0	1 (<1)	0	3 (<1)
Cardio-respiratory arrest			0	3 (<1)
COVID-19 pneumonia	2 (<1)	0	2 (<1)	1 (<1)
Dyspnoea	2 (<1)	0	2 (<1)	1 (<1)
Gastric cancer	1 (<1)	0	1 (<1)	2 (<1)
Gastrointestinal haemorrhage	3 (<1)	0	3 (<1)	0
Hyperkalaemia	1 (<1)	2 (<1)	1 (<1)	2 (<1)
Lower respiratory tract infection	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Metabolic acidosis	2 (<1)	0	2 (<1)	1 (<1)
Renal cell carcinoma	0	1 (<1)	0	3 (<1)
Suspected COVID-19	0	1 (<1)	0	3 (<1)
Thrombocytopenia	3 (<1)	0	3 (<1)	0

Source: Table 3.132, Table 3.309

a. Pre-specified definition of treatment-emergent: Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Last Non-Zero Dose Date + 1 day.

b. Post-hoc definition of treatment-emergent: Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Last Non-Zero Dose Date + dosing frequency.

Dialysis patients

Discontinuations due to AE in the largest dialysis study are shown below. For the ASCEND-ID and the ASCEND-TD, discontinuation due to AE were 14 (9%) vs 7 (5%) and 10 (7%) vs 23 (9%), respectively.

Table 60 Summary of Treatment-emergent AEs Leading to Permanent Discontinuation of Randomized Treatment (≥3 Participants, Posthoc) by Overall Frequency Frequency (200807/ASCEND-D, Safety Population) (LDD +DF post-hoc analysis)

Preferred Term	Post-hoc[a]	
	Dapro (N=1433) n (%)	rhEPO (N=1435) n (%)
Any event	208 (15)	194 (14)
Cardiac arrest	17 (1)	16 (1)
Sepsis	12 (<1)	6 (<1)
Death	7 (<1)	6 (<1)
Septic shock	3 (<1)	10 (<1)
Cerebrovascular accident	4 (<1)	7 (<1)
Cardio-respiratory arrest	6 (<1)	4 (<1)
COVID-19	5 (<1)	4 (<1)
Pneumonia	4 (<1)	5 (<1)
Myocardial infarction	2 (<1)	6 (<1)
Respiratory failure	2 (<1)	5 (<1)
Anaemia	5 (<1)	1 (<1)
Sudden death	3 (<1)	3 (<1)
Acute myocardial infarction	2 (<1)	3 (<1)
Cardiac failure	3 (<1)	2 (<1)
Cerebral haemorrhage	2 (<1)	3 (<1)
End stage renal disease	4 (<1)	1 (<1)
Sudden cardiac death	3 (<1)	2 (<1)
Acute respiratory failure	0	3 (<1)
Fatigue	0	4 (<1)
Haemorrhagic stroke	2 (<1)	2 (<1)
Hepatic cirrhosis	3 (<1)	1 (<1)
Hypertension	3(<1)	0
Subdural haematoma	1 (<1)	3 (<1)
Bladder cancer	1 (<1)	2 (<1)
Dyspnoea	1 (<1)	2 (<1)
Endocarditis	2 (<1)	1 (<1)
Haemoglobin decreased	3 (<1)	0
Hepatic cancer	0	3 (<1)
Peritonitis	2 (<1)	1 (<1)
Pulmonary tuberculosis	2 (<1)	1 (<1)
Renal cancer	1 (<1)	2 (<1)
Renal neoplasm	2 (<1)	1 (<1)
Squamous cell carcinoma of skin	1 (<1)	2 (<1)

Source: Table 3.132, Table 68.400009

a. Post-hoc definition of treatment-emergent: Treatment Start Date ≤ AE Start Date/AE Worsening Date ≤ Last Non-Zero Dose Date + dosing frequency.

2.5.8.10. Post marketing experience

GSK received approval of daprodustat on 29 June 2020 in Japan for renal anemia for the tablet strengths 1 mg, 2 mg, 4 mg, and 6 mg. GSK also received approval of daprodustat 1 mg, 2 mg,4 mg, 6 mg, and 8 mg tablets on 1 February 2023 in the US for the treatment of anemia due to CKD in adults who have been receiving dialysis for at least four months. Post marketing data from Japan were submitted. (see also the RMP of the product)

2.5.9. Discussion on clinical safety

Introduction

Daprodustat is used once daily (except for the TIW (3 times a week) dosing in the small TD study in dialysis patients), while ESA therapy is generally dosed less frequently (e.g. once every four weeks for most of the patients in de ASCEND-ND study (78%) and once weekly in the ASCEND-DD study (59%)). Therefore, in the presentation of the adverse events profile, the applicant also provided a post-hoc presentation accounting for dose frequency (not needed for the placebo-controlled ND study). Any discussion of data is primarily based on these post-hoc data; if not, this is explicitly mentioned.

The overall exposure with 6652 patients years, 1485 patients treated for at least 24 months, and 317 patients treated for at least 36 months is considered sufficient to understand the safety profile of daprodustat. The relatively large database is the consequence of the need to assess the cardiovascular (CV) safety profile of daprodustat due to known CV safety issues from ESA therapy, with event-driven studies in both the non-dialysis and dialysis pool for MACE events. The discussion is separated according to the non-dialysis (ND) pool and the dialysis (DD) pool, while for some further safety understanding (e.g. adverse of special interest), an integrated discussion follows to have a proper global understanding of these safety issues. This is allowed for those possible adverse events not directly related to the dialysis status. Given that study ASCEND-D and ASCEND-ND encompassed different study populations (dialysis vs non-dialysis), discussion according to these populations has also been provided.

The largest ASCEND-ND and ASCEND-D contributed the most to the safety database due to the largest exposure in terms of the number of patients and follow-up time. TEAEs in these studies were corrected using a post hoc on-treatment analysis, given that the prespecified analysis did not take into account the different dosing regimens for daprodustat and the ESA control group. The post-hoc method included events from the treatment start date to the last non-zero dose date + dosing frequency (dosing frequency for daily doses = 1 day; TIW doses = 2 days; weekly doses = 7 days; every 2 weeks = 14 days; every 4 weeks = 28 days). The prespecified method added 1 day to last non-zero dose data thereby introducing bias.

Non-dialysis patients

Available study data

In non-dialysis (ND) patients, limited placebo-controlled data and substantial ESA-controlled data are available. The placebo-controlled data are provided by the ASCEN-NHQ study (205270) including 307 ND patients on daprodustat vs 308 on placebo-treated for 28 weeks. In addition, the large ASCEND-ND study provided additional non-dialysis exposure compared to ESA (n=1937 vs 1933) treated for a mean of 17 months.

Overall safety characteristics

In the placebo-controlled ASCEND-NHQ study, the proportion of patients with any adverse event was comparable between the daprodustat vs placebo (69% vs 71%). Moreover, the incidence of serious AEs (20% vs 22%), fatal AEs (1% vs 2%), and patients discontinuing due to AEs (7% vs 9%) was also comparable, which appears reassuring, although the number of daprodustat-treated patients was limited to 308 and follow-up time was limited to 28 weeks. In the substantially larger non-dialysis, ASCEND-ND study comparing daprodustat to ESA, the incidence of any AEs (80% vs 81%) and of fatal SAEs (8% each) were comparable, but serious AEs (44% vs 42%) and discontinuation due to AEs (13% vs 10%) was slightly higher.

Adverse events based on incidence

In the placebo-controlled study, the most notable AEs with a higher incidence in the daprodustat group compared to placebo were diarrhoea (8% vs 6%), nausea (5% vs 2%)), hypertension (7% vs 5%), and headache 4% vs 3%), while oedema peripheral was lower (4% vs 7%)). In the large study comparing daprodustat with ESA, oedema peripheral (10% vs 9%), constipation (7% vs 5%), and anaemia (6% vs 4%) were increased, while hypertension (13% vs 14%), nasopharyngitis (6% vs 7%), and back pain (4% vs 6%) was lower. Of these, hypertension (see also further discussion below), peripheral oedema and constipation are identified as ADRs, which is supported.

Serious adverse events

For the placebo-controlled non-dialysis pool, the incidence of SAEs was high but with a lower incidence for daprodustat (62 (20%)) vs placebo (68 (22%)). Any differentiation, according to SOC, seems difficult due to the limited number of events within each SOC. In the ASCEND-ND study, there was, however, an imbalance in fatal AEs within SOC 'renal and urinary disorders' (1.2% [24 cases] vs 0.6% [11 cases]). There was also an imbalance for SAEs within this SOC (15% vs 12%). Within the PTs, frequencies were increased in dapro vs ESA for chronic kidney disease, acute kidney injury, azotaemia and end-stage renal disease. There was also an imbalance in adverse events that led to treatment discontinuation within this SOC, but the cases were few (28 vs 13 cases). However, in the ACEND-ND study, the principal secondary endpoint, "time to progression to CKD". was generally similar between the treatment groups. Although the reported cases were few in each PT within this SOC, a possible relation between daprodustat and these SAEs can still not be excluded based on the provided data. The applicant has been requested to discuss the causal relationship between daprodustat and the observed AEs within SOC "renal and urinary disorders". No final conclusions could be drawn, but as the indication is not approvable for the ND population this issue is not further pursued.

MACE

The absence of an increase in MACE events (378 vs 371; HR 1.03 [0.89;1.19]) for daprodustat versus ESA therapy in the primary ITT analysis appears not to be robust. Components of first MACE included non-fatal MI (96 vs 91 events), non-fatal stroke (30 vs 21), and all-cause mortality (252 vs 259). Although the endpoint was formally non-inferior to the ESA therapy given that the upper limit of the 95% CI was lower than the non-inferiority margin of 1.25 (amended during study conduct), on-treatment analyses, which are especially of importance in a non-inferiority setting and according to the CV risk reflection paper, could not confirm this. In particular, patients who discontinue treatment are likely to initiate standard-of-care ESA therapy, which is also the comparator treatment group and is likely to dilute any potential difference in MACE between treatment groups in an ITT analysis. The OT analyses caused substantial increases in hazard ratios and differences in the number of total events depending on the on-treatment definition being used. E.g. an increase in MACE (HR 1.09 [0.89, 1.33], 192 vs. 189 events was observed for the post-hoc dose frequency corrected analysis (OT+DF)), due to an imbalance in events between daprodustat vs ESA after

discontinuation, and exceeds the specified 1.25 upper margin for non-inferiority in the study comparing daprodustat vs ESA therapy. Similar results were seen with additional analyses, such as OT + 28 (HR 1.40 [1.17, 1.68] (prespecified) and OT + DF + 28 HR 1.18 [95% CI 0.99; 1.40] (post-hoc in MAA)). Despite additional analyses provided by the applicant, these observations in the ND patients are not understood and still not sufficiently clarified, in contrast to the absence of CV risk findings observed in the DD pool. Overall, any worse GFR imbalance according to the treatment group or effect according to region are not considered a sufficient explanation for the substantial shift in HR as observed. Further, the impact of the lower number of health care contacts does not seem plausible as an explanation due to the not-linear increase in CV events after treatment discontinuation (including dose frequency adjustment and/or ascertainment 28 days period). Information on the clinical management of patients discontinuing study treatment (e.g. whether other treatments were initiated potentially impacting MACE events) was not fully collected in the studies which importantly limits the appropriate understanding of these data. Furthermore, the OT+DF definition does still not account for the disproportional number of events occurring after treatment discontinuation. Also, the explanation that medication can also be discontinued due to clinical adverse effects occurring just before a MACE event has not been supported by data but suggest that any ascertainment period needs to be introduced in the OT definition. Furthermore, a potentially different degree of instability of hemoglobin when switching patients from non-study ESAs to daprodustat and also when initiating non-study ESAs after stopping daprodustat which are known to be a period of increased CV risk, as compared to switching from ESA to ESA, have been raised by the applicant as explanation. This may theoretically be valid, however, the real impact is uncertain due to the following: As initiation of non-ESA therapy has been poorly registered after discontinuation (amongst possible other clinical important decisions with potential impact on the observed MACE events), the impact of dilution of MACE effect between treatment arms due to non-randomised ESA therapy vs randomised ESA therapy during this difference in follow-up time is unknown. Furthermore, such instability-phenomenon should then especially be observed in the dialysis population, however, no such increase in risk was observed. Also, any relationship of daprodustat on MACE risk with Hb extremes (< 10 and >12) could not be demonstrated for overshooting of Hb and remains uncertain, however, such phenomenon as known for ESAs cannot be excluded. Other OT sensitivity analyses including a Rank Preserving Structural Failure Time (RPSFT) analyses accounting for initiation of dialysis of ND patients during the study, or analyses based on the decision to stop study treatment do not meet non-inferiority criteria either. Considering this remaining uncertainty and concern, ND patients should be excluded from the indication.

Of further concern is an increased risk of hospitalisation of HF. These demonstrated an increased risk in the ND for the secondary endpoint of MACE or Hospitalisation HF (HR 1.09 [0.95, 1.24] ITT; HR 1.18 [1.01, 1.37] OT+DF+28), which was mainly explained by an increased risk in the limited patient population with a history of HF (HF + ACM endpoint HR 1.20 [0.89, 1.62]).

Subgroup analysis shows that a difference could be observed for the stratification factor region (p=0.0760), with the highest risk in regions Eastern Europe/South Africa, Latin America, and the USA compared to the Asia Pacific and Western Europe/Canada/ANZ, Israel (largely comparable to observations in the DD pool, except for USA). However, data on the EU region vs other regions showed slightly better results versus the non-EU region (without significant p for interaction). No notable differences could be identified for other subgroups (including the stratification factor of ESA users/non-users). A further effort has been made to identify whether post-randomised Hb level could have impacted CV risk. According to an analysis of time-dependent Hb covariate analyses, a Hb < 10 g/dL was associated with a significantly increased risk (RR 1.66 [1.20, 2.31], p=0.0031) and a Hb > 11.5 g/dL with a numerical increase (RR 1.22 [0.81, 1.84]). Of note, comparable findings were observed for hypo-responsiveness and Hb overshooting in the DD study (RR 1.69

[1.22, 2.36] and RR 1.08 [0.75, 1.55]). Since Hb goals were set relative conservative between 10 and 11.5 g /dL, it is of interest to what extent real overshooting outside the ESC recommended Hb goal range (> 12 and > 13 g/dL) has been observed and the impact of these categories on MACE for both the ND and DD patients. The provided analyses did however not show consistent results, likely due to the type of analyses and the limited number of patients with these levels of Hb. Any further analyses are not considered able to provide further clarification. Furthermore, the consistently increased risk of hypo-responsiveness has been appropriately addressed in the labelling. Such considerations have also been adopted in a previously assessed medicinal product within this class. The provided landmark analysis at week 4 and the post-randomisation quintile analysis on the influence of Hb are less relevant due to the limitation of dividing according to only week 4 Hb values, not addressing Hb values during further follow-up, knowing that stable Hb levels are only achieved after 12 to 16 weeks after initiation of therapy. In addition, dose interruptions have occurred during treatment with daprodustat. The impact of this on the on-treatment definition (assuming no interruptions) is very complex to establish and not further pursued.

The placebo-controlled analysis of MACE does not sufficiently add to further conclude on the MACE risk in non-dialysis patients as the number of MACE events was very limited (15 vs 19 for daprodustat vs placebo ITT, 12 vs 15 on-treatment). While this population largely qualifies for ESA therapy as well, patients who would likely not yet qualify for ESA therapy have only been included in limited numbers (approximately 100 patients in each arm). The indication has appropriately been restricted according to these considerations.

Deaths

In the ASCEND-ND study, adjudicated deaths appear to be comparable in the ITT analysis (RR 1.03 (0.87, 1.20), 301 vs 298 events) but slightly increased based on the on-treatment pre-specified analysis (RR 1.47 (1.18, 1.85) and the dose-adjusted post-hoc analysis (RR 1.13 (0.92, 1.39)), which requests for further understanding, similar to the MACE issues. For the ITT analysis, adjudicated deaths were not consistent across the type of deaths, with an increase in CV mortality (89 (29.6%) vs 70 (23.5%), due to an increase in sudden cardiac death (34 vs 31), stroke (14 vs 11) and HF (20 vs 13)).

Discontinuation due to AEs

In the placebo-controlled study, discontinuations due to AE were comparable between arms (22 (7%) vs 29 (9%)), although the study was only 28 weeks. The active compared ASCEND-ND study was much longer (mean 17 months) and showed a slight increase in discontinuations due to AE versus ESA therapy (247 (13%) vs 201 (10%)), with MI (10 vs 3) azotaemia (8 vs 4), anaemia (8 vs 2), CKD (7 vs 1), multiple organ dysfunction syndrome (6 vs 0), cardiogenic shock (4 vs 0), mostly contributing to this difference.

Laboratory findings and vital signs

For the larger ESA comparator ND study, serum creatinine increase was comparable between studies at week 52 (23.40 [-3.55 to 79.10] µmol/L daprodustat; 22.55 [-6.15 to 79.10] µmol/L darbepoetin alfa), suggesting for no renal function decline between both arms. No relevant differences were observed in haematology parameters with comparable frequencies within range and without relevant differences of too high levels. Also, no relevant differences were observed for any of the chemistry markers. Lipid parameters were reduced, including LDL-C (week 52 -6.9 mmol/L vs -1.8 mmol/L change) and HDL-C (-4.8 vs 2.2 mmol/L change). The overall impact of such a change in lipid profile is difficult to discriminate; however, CV safety has been specifically evaluated. With regard to liver safety, specific stopping rules have been applied in the studies. Daprodustat showed a slightly greater number of patients meeting these stopping rules; however, numbers were limited (12 vs 7 cases). Three cases of Hy's Law were identified (2 on daprodustat vs 1 ESA), but alternative explanations were provided for such abnormal levels. No specific issues in liver safety have

been observed in the non-clinical studies. The far more limited placebo-controlled study did not identify any substantial findings that differentiate from these observations.

Safety according to age

In the placebo-controlled study, no trend towards increased safety issues were noticed for age categories of < 65, 65-75,> 75, and > 85 years of age. Similarly, no such trend could be observed for the large ESA controlled studies (DD and ND combined), which support the use of Jesduvroq in elderly patients.

Dialysis patients

Available study data

For dialysis patients, the database is large, but only comparative data versus ESA is available. In the ASCEND-D study, patients (1433 vs 1435) were treated for a mean of 26 months, in the ASCEND-ID study, the incidence dialysis patients (n= 157 vs 155) were treated for 52 weeks and in the ASCEND-TD study, patients were treated for 52 weeks (n=270 vs 137) using a different dosing strategy (TIW).

Overall safety characteristics

In the dialysis pool, the largest amount of data, as provided by the ASCEND-D study, demonstrated a slightly increased incidence of adverse events (89% vs 87%), while discontinuation due to adverse events (15% vs 14%) and serious AEs (52% vs 54%) was comparable. The overall incidence of adverse events was slightly lower in the ASCEND-TD (76% vs 79%) while slightly increased in the ASCEND-ID study (76% vs 75%). Results on serious adverse events (30% vs 36% and 33% vs 37%, respectively) and discontinuation due to AEs (9% vs 7% and 9% vs 5%, respectively) match with the larger study in terms of imbalance.

Adverse events based on incidence

In the ASCEND-D study, any clear differences in SOCs could not be observed (not greater than 2%), suggesting for comparable safety as to ESA therapy. Only slight differences could be observed on a PT level for most common AEs. Most notable is the slight increase in dialysis hypotension (10% vs 8%), and the lower incidence of anaemia (5% vs 7%). An increase in dialysis hypotension was supported by the ASCEND-TD study but not in the ASCEND-ID study, but these studies were considerably smaller. A pooling of phase 3 dialysis patients did not identify any new findings.

Serious adverse events

Serious AEs were comparable in the largest dialysis study (748 (52%) vs 777 (54%)), without any differences larger than 1%, which appears reassuring. The number of SAEs in the TD and ID studies is substantially smaller and do not importantly contribute to the overall understanding of the SAE profile of daprodustat vs ESA (82 (30%) vs 49 (36%) in the TD study and 52 (33%) vs 57 (37%) in the ID study).

MACE

No increase in MACE events (355 vs 389; RR.0.89 (0.78; 1.03)) was observed for daprodustat versus ESA therapy in the largest dialysis study for the ITT analysis. Also, for the preferred on-treatment analyses, with the pre-specified on-treatment analysis (+28 days) and the post-hoc analyses accounting for the dose frequency, the point estimate was below 1, and the upper confidence interval was well below the NI margin of 1.25 (RR 0.96 (0.81, 1.14) and RR 0.94 (0.79, 1.11), 255 vs 278 events), with minimal differences between the point estimate according to the type of analysis, suggesting for the robustness of the finding. The applicant has only presented the OT analyses for the pooled dialysis population, and not for the ASCEND-D study results (excluding the 88 patients). While this study was powered to estimate the CV safety of

daprodustat versus ESA in dialysis patients, the 2 smaller phase 3 studies in patients on dialysis showed an increase in MACE (19 (12%) vs 15 (10%), RR 2.41 (-4.61, 9.43) and 33 (12%) vs 14 (10%), RR 2.28 (-4.44, 9.00) for the ID and the TD studies, respectively). Considering the difference in absolute numbers, combining these data with the large dialysis study demonstrated similar findings. The increased MACE in the TD study with the TIW dosing is likely due to chance finding as a lower rate of overshooting of Hb > 12 g/dL (14% vs 21%) and time with Hb > 12 (8.6% vs 19.5%), which is also lower than the other dialysis studies, and a comparable exposure to daily dosing does not suggest for factors to increase such risk.

Further, key individual CV event endpoints did not show an increased risk for daprodustat, including all-cause mortality, CV mortality, thrombosis, and hospitalisation for heart failure (RR 1.08 (0.82, 1.42)). The findings seem generally robust across the ITT and on-treatment analyses presented. However, as noted in the ND discussion, hypo-responsiveness seems to have been a factor in increased CV risk in both pools, which likely needs to be appropriately addressed in the labelling. Such trend is also noticed for the subgroup analysis of hyporesponders vs no hyporesponders at baseline (RR of 1.09 (0.75, 1.59) vs RR 0.87 (0.74, 1.01), p for interaction (0.2683)).

Deaths

Adjudicated deaths were not increased both for the ITT analysis (RR 0.92 (0.78, 1.08), 276 vs 297 events) as for the on-treatment pre-specified analysis (RR 1.00 (0.81, 1.230 and the post-hoc analysis (RR 0.95 (0.77, 1.17)). Although, this was not consistent across the CV death (93 (33.7%) vs 90 (30.3%), attributed to sudden death (47 vs 38) and HF (11 vs 9)). The events in the TD and ID studies were discordant but limited, which limits drawing any conclusions on fatal SAEs for these studies.

Discontinuations due to AEs

Also in the largest DD study, a slight increase in discontinuations due to AE was seen (208 (15%) vs 194 (14%)), mostly attributed to sepsis (12 vs 6), anaemia (5 vs 1), and hypertension (3 vs 0). For the TD study and the ID study, also a slight increase in discontinuations due to AE was seen (23 (9%) vs 10 (7%) and 14 (9%) vs 7 (5%), respectively).

Laboratory findings

No relevant differences were observed in haematology parameters with comparable frequencies within range and without relevant differences of too high levels. Also, no relevant differences were observed for any of the chemistry markers. Lipid parameters were reduced, including LDL-C (week 52 -7.5 mmol/L vs -1.4 mmol/L change) and HDL-C (-4.8 vs 0.6 mmol/L change). The overall impact of such a change in lipid profile is difficult to discriminate; however, CV safety has been specifically evaluated. With regard to liver safety, specific stopping rules have been applied in the studies. Daprodustat showed a comparable number of patients meeting these stopping rules as to ESA therapy (14 vs 16 cases). One case of Hy's Law was identified (in the ESA group), but an alternative explanation could have caused such abnormal levels (hepatitis B). No specific issues in liver safety have been observed in the non-clinical studies. The results for the smaller TD and ID studies were in line with these observations.

Safety according to age

For the large ESA-controlled studies (DD and ND combined) no trend according to age could be observed, which seems reassuring.

<u>Other adverse events of interest across the ND and DD patients</u>

Specific adverse events of interest have been monitored given the safety profile of ESA therapy, based on pre-clinical findings or based on the mechanism of action of daprodustat. These included worsening of hypertension, thrombotic events secondary to excessive erythropoeisis, revascularisation, oesophageal and gastric erosion, cancer-related events, pulmonary arterial hypertension, and exacerbation of rheumatoid arthritis. Some of these adverse events need to be considered across both ND and DD pools to better understand any possible relation to daprodustat therapy. This is considered reasonable as several of these AESIs may not be specifically related to the presence or absence of dialysis therapy. In this context, the large ND and DD studies most importantly contributed to these evaluations. In contrast, in the placebo-controlled study in ND patients and the TD and ID studies in dialysis patients, data were generally too limited to contribute in a relevant way to understanding these AESIs.

In the ND patients, for the placebo-controlled patients, of the AESIs only worsening of hypertension was slightly increased (10% vs 8%), although this was not increased versus ESA in the ND study (17.8% vs 19.2%) and the DD study (20.3% vs 20.8%). As already mentioned, AEs of hypertension were also not increased versus ESA (13% vs 14% in ND, 17% vs 17% in DD (prespecified analysis in DD)). Further, blood pressure differences were minimal and not considered clinical relevant between treatment arms both in the ND and DD study (SBP 0.56 mmHg, DBP 0.65 mmHg; SBP -0.43 mmHg, DBP -0.39 mmHg, respectively). Similarly, this was shown for hypertension exacerbation (RR 0.92 (0.81, 1.05); RR 0.97 (0.84, 1.13), respectively). Nevertheless, since hypertension is a known risk of ESA, it is supported that hypertension is identified as ADR, and a warning regarding the worsening of hypertension is included in section 4.4 of the SmPC.

A low incidence through a numerical increase in thrombotic events secondary to excessive erythropoiesis (5 (0.3%) vs 3 (0.2%)) was observed in the ND study, which was confirmed in the dialysis study (20 (1.4% vs 11 (0.8%). However, adjudicated thrombo-embolic events are only observed with possible increased risk in the ND population. This risk is appropriately described in the SmPC and is mitigated by haemoglobin monitoring and dose adjustment algorithms for maintaining haemoglobin within target range.

An important potential safety concern is cancer risk due to the underlying mechanism of daprodustat. Cancer-related mortality and tumour progression and recurrence were slightly increased in the ND study (72 (3.7%) vs 68 (3.5%); RR 1.06, p=0.740); however, no such increase could be noticed in the dialysis study (46 (3.2%) vs 53 (3.7%)l; RR 0.87, p=0.478), which does not translate into a clear signal for cancer risk. No signal for any specific cancer type could be noticed. In pooled data from the actively controlled studies using the post hoc analysis adjustment, no difference in the frequency of malignancies between the treatment arms was found (3.5% vs 3.6% in daprodustat vs the rhEPO control). However, current data may still be limited due to the long latency of cancer progression. This risk will continue to be monitored through routine pharmacovigilance activities. A specific warning has been added in section 4.4 of the SmPC and the use of Jesduvroq is not recommended in patients with active malignancy.

Revascularisation, as examined by proliferative retinopathy, macular oedema, and choroidal neovascularisation, is a potential risk associated with daprodustat therapy due to the mechanism of potential overexpression of VEGF. Revascularisation was lower in the placebo-controlled study based on limited data (3 vs 9), but was slightly numerically increased both in the ND study (54 (2.8%) vs 46 (2.4%)) as the DD study (38 (2.7%) vs 36 (2.5%)). Identified cases have been evaluated and adjudicated in more detail by an ophthalmologist. For the ND population, for 58 cases, a proliferative origin was not likely to be present and may have been inappropriately identified as AESI. For the remainder of 42 cases (26 vs 16), all but 5 (2 vs 3) were associated to diabetic disease. For these 5 cases, any relation to revascularisation could not be excluded. For the DD study, 51 participants may have inappropriately been identified as AESI. For the

remainder of 23 cases (11 vs 12), all but 3 (1 vs 2) were associated to diabetic disease. For these 3 cases, any relation to revascularisation could not be excluded. Overall, this does not identify any signal for revascularisation issues.

For several AESIs any relation to daprodustat seems unlikely due to inconsistent findings across the ND and DD studies including exacerbation of rheumathoid arthritis (2 (0.1%) vs 4 (0.2%) in ND, 2 vs 1 (0.1% each) in DD; oesophageal and gastric erosion (70 (3.6%) vs 48 (2.5%); RR 1.46, p=0.041 in ND, 58 (4.0%) vs 82 (5.7%) in DD, and pulmonary arterial hypertension (15 (0.8%) vs 9 (0.5%) in ND, 9 (0.6%) vs 12 (0.8%) in DD).

On further request, additional quantitative and qualitative evaluation identified headache, nausea and diarrhoea as ADRs and are currently included in the SmPC.

2.5.10. Conclusions on clinical safety

Non-dialysis patients

Considering the inconclusive results on the risk of MACE events in non-dialysis patients, the agreed indication does not cover non-dialysis patients.

Dialysis patients

No increased risk for MACE was observed in dialysis patients, even though hypo-responsiveness and overshooting may also be factors for a possible increased CV risk within this pool.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in Pregnancy and Lactation

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.6.3. Risk minimisation measures

Safety concern	**Risk minimization measures**
Use in Pregnancy and Lactation	Routine risk minimization measures: SmPC section 4.6 PL section 2 Legal status: Prescription only medicine; Restricted medical prescription

	Additional risk minimization measures None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 29 June 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Jesduvroq (daprodustat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Applicant applied for the following indication: "treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD)."

Due to safety issues the indication is restricted only to the DD-CKD patients as follows:.

"treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis."

3.1.2. Available therapies and unmet medical need

Treatments for anaemia associated with dialysis dependent (DD) patients with CKD include iron supplementation, RBC transfusions, treatment with erythropoiesis-stimulating agents (ESA) and/or hypoxia-inducible factor prolyl-hydroxylase inhibitor (roxadustat, vadadustat).

Iron supplementation can increase Hb levels to resolve anaemia in patients with CKD, but iron alone is rarely sufficient when CKD disease advances and thus requires additional treatment to sufficiently raise Hb levels. However, it may be associated with hypotension and dyspnea and rarely results in potentially life-threatening events of acute hypersensitivity reactions, which need specific precautions upon administration (see also New Recommendations to Manage Risk of Allergic Reactions with Intravenous Iron-containing Medicines; EMA/579491/2013).

Erythropoiesis stimulating agents (ESAs) have been regarded as the standard of care, depending on the type of patients (see below), although iron status should be evaluated for all patients prior to and during treatment and iron supplementation is recommended when serum ferritin values are < 100 µg/L or transferrin saturation is < 20% [Aranesp SmPC; Eprex SmPC]. Several options include short-acting epoetin (EPO) alfa or the long-acting darbepoetin alfa (DA) without any preference due to the absence of robust evidence of differences in clinical outcome. While improvement in QoL has been demonstrated, an increase in the risk of CV adverse events (AEs), all-cause mortality, myocardial infarction (MI), stroke and thromboembolic events is observed when high Hb targets of 13 to 15 g/dL are achieved (see also Public statement EMEA/496188/2007). In addition, treatment with rhEPOs has been associated with increased cancer-related morbidity and mortality. In Europe, the SmPC recommends a Hb treatment target of 10 to 12 g/dL and prevents continued Hb levels over 12 g/dL. The US FDA has, for the same concern, set a maximum Hb target of 11 g/dL.

RBC transfusion in CKD patients with anaemia can be seen as a last resort therapy, mostly effective but can be associated with a risk of allo-sensitization, which decrease the availability of obtaining matching organs for patients eligible for kidney transplantation. Other risks can be introducing pathogens, hyperkalemia, and volume overload.

Two oral HIF inhibitors, i.e. roxadustat and vadadustat have recently been authorized for the treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD). Both agents have been associated with cardiovascular or thrombotic events, or inadequate response (similar to ESAs).

3.1.3. Main clinical studies

The pivotal efficacy and safety data of daprodustat in the DD population come from 3 global Phase III studies. The study **200807/ASCEND-D** in dialysis patients was an event-driven, open-label, active-controlled cardiovascular outcome trial (CVOTs) to show non-inferiority of daprodustat versus rhEPO for Hgb and CV outcomes. Studies **201410/ASCEND-ID** and **204837/ASCEND-TD** were 52-week, active-controlled studies in dialysis patients to show non-inferiority of daprodustat versus rhEPO for Hgb outcome. Study 201410/ASCEND-ID was an open-label study performed in incident dialysis (ID) patients who recently started with dialysis, while study 204837/ASCEND-TD was a double-blind study performed in haemodialysis patients to test three times per week (TIW) dosing regimen of daprodustat. The primary endpoint was similar between studies. All studies measured mean change in Hgb between Baseline and EP (mean over Weeks 28 to 52 for all studies), with the CVOT trial having an additional co-primary endpoint of time to first occurrence of adjudicated MACE events. Several other secondary endpoints were included for sequential testing.

3.2. Favourable effects

A comparable effect on **haemoglobin levels** was observed for daprodustat versus ESA therapy in dialysis patients, as shown by the adjusted mean treatment difference (dapro-rhEPO) of -0.10 (95% CI: -0.34, 0.14) in study 201410/ASCEND-ID, 0.18 (95% CI: 0.12, 0.24) in study 200807/ASCEND-D and -0.05 (95% CI: -0.21, 0.10) in study 204837/ASCEND-TD. Therefore, daprodustat has demonstrated non-inferiority to rhEPO in achieving Hgb in the target range, whether dosed once daily (200807/ASCEND-D) or TIW (204837/ASCEND TD) in dialysis-dependent participants. The proportion of patients who achieved Hb response was comparable for daprodustat compared to rhEPO (not formally tested). Effect maintained during a mean of 26 months.

Average monthly **IV iron** dose to Week 52 was similar in daprodustat groups compared to rhEPO in any of the active-controlled dialysis studies: superiority was not met, and the treatment difference was between -4.75 (95%CI -42.26, 32.77) and 19.4 mg (95%CI: -11.0, 49.9), depending on the study. The proportion of participants who received RBC or whole blood **transfusions** (between 7.8% and 15.8%, depending on the study) or **rescue** (between 2.2% and 3.5%, depending on the study) was similar between the treatment groups (not formally tested).

No statistically significant improvement in **QoL** (SF-36) was observed for daprodustat when compared to rhEPO (not formally tested).

3.3. Uncertainties and limitations about favourable effects

Study conduct: In total, three sites were closed in study ASCEND-D due to misconduct and suspected fraud. Upon request, the Applicant has presented the data excluding these patients, as well as a clarification of the circumstances leading to site closure. For the ASCEND-D study, 88 subjects were randomised at three sites, 49 to the daprodustat arm and 39 to the rhEPO arm. There were no meaningful differences between the primary and adjusted analyses for the most relevant endpoints and study outcome of the ASCEND-D study.

However, the detailed information on the nature of the issues at the three sites confirmed a high suspicion of fraud, including the alleged fabrication of data. The Applicant's actions with regard to the findings, i.e., closure of three sites, are considered acceptable. Therefore, the results presented in the SmPC and the EPAR do not contain data from the closed sites.

The number of protocol deviations was unusually high in the studies. However, the Applicant performed a PP-analysis, excluding participants who experienced events that would directly impact the haemoglobin efficacy endpoint, which was consistent with the primary results for all studies. The issue was, therefore, not pursued.

PD patients: The studies included a very limited number of patients on PD. Even though subgroup analyses do not indicate differences in response between HD and PD patients, uncertainty remains.

TIW regiment: TIW dosing regimen was studied only in one small study. Even though the study was powered to show an effect on the primary endpoint, it might not be sufficiently big to show an effect on other important endpoints, e.g. PRO's; iron use etc., or fully assess the risk for Hb overshooting.

Treatment discontinuations: large amounts of patients discontinued study treatment in the ASCEND-D study (53%), even though discontinuations were similar between treatment groups.

3.4. Unfavourable effects

Evaluation of the safety profile is based on the **exposure** to daprodustat of 1433 patients included in the ESA comparator study (ASCEND-D) with a mean follow-up of 26 months, 157 incidence dialysis patients treated for 52 weeks (ACEND-ID), and 270 patients treated with a 3 times weekly dose (TIW) for 52 weeks (ASCEND-TD).

The **general adverse events profile** showed to be largely comparable or slightly increased to ESA therapy for adverse events (89% vs 87%), discontinuation due to adverse events (15% vs 14%), and serious AEs (52% vs 54%). Results were somewhat discordant between the two smaller ASCEND-TD and ID studies with adverse events (76% vs 79%, 76% vs 75%), serious adverse events (30% vs 36%, 33% vs 37%), and discontinuation due to AEs (9% vs 7%, 9% vs 5%), respectively.

Adverse events of abdominal pain (5% vs 4%, not post-hoc) have been identified as ADR and included in the SmPC section 4.8.

No increase in **MACE events** in the prespecified ITT analysis ((355 vs 389; RR 0.89 (0.78;1.03)) was observed, with a NI margin well below 1.25. An on-treatment analysis correcting for dose frequency confirmed these findings (RR 0.85 (0.69, 1.04), 169 vs 205 events, post-hoc).

Serious adverse events were comparable (748 (52%) vs 777 (54%), without any differences larger than 1%. This was also observed in the TD and ID studies, though numbers were substantially smaller (82 (30%) vs 49 (36%) and 52 (33%) vs 57 (37%)).

Laboratory findings were generally comparable between daprodustat and ESA therapy, including haematology parameters and chemistry markers. **Lipid parameters** were reduced, including LDL-C (week 52 -7.5 mmol/L vs -1.4 mmol/L change) and HDL-C (-4.8 vs 0.6 mmol/L change).

With regard to **liver safety**, specific stopping rules have been applied in the studies. Daprodustat showed a slightly greater number of patients meeting these stopping rules of liver enzyme increases; however,

numbers were limited (14 vs 16 cases). One case of Hy's Law was identified (in the ESA group), but an alternative explanation of hepatitis B was provided. The results for the smaller TD and ID studies were in line with these observations. No specific safety signal has been observed in the non-clinical findings.

Revascularisation (AESI "Proliferative Retinopathy, Macular Oedema, Choroidal Neovascularization") was slightly lower versus ESA (38 (2.7%) vs 36 (2.5%)). Identified cases have been evaluated and adjudicated in more detail by an ophthalmologist. For 51 participants, this may have inappropriately been identified as AESI. For the remainder of 23 cases (11 vs 12), all but 3 (1 vs 2) were associated to diabetic disease. For these 3 cases, any relation to revascularisation could not be excluded. VEGF (vascular endothelial growth factor) showed no consistent increase across several phase 1 studies.

For several **other adverse events of special interest,** including exacerbation of rheumatoid arthritis, oesophageal and gastric erosion and pulmonary arterial hypertension, no consistent relations to daprodustat treatment were found.

3.5. Uncertainties and limitations about unfavourable effects

The two phase 3 studies in patients on dialysis showed an **increase in MACE discordant from the largest dialysis study** (19 (12%) vs 15 (10%), RR 2.41 (-4.61, 9.43) and 33 (12%) vs 14 (10%), RR 2.28 (-4.44, 9.00) for the ID and the TD studies, respectively), although these studies were not powered for such an analysis. Moreover, the increased MACE in the TD study with the TIW dosing is likely due to chance finding as a lower rate of overshooting of Hb > 12 g/dL (14% vs 21%) and time with Hb > 12 (8.6% vs 19.5%), which is also lower than the other dialysis studies, and a comparable exposure to daily dosing does not suggest for factors to increase such risk.

In addition, due to the limited number of MACE events, these data are unlikely to change the MACE findings for the substantially larger ASCEND-D study. Key individual CV event endpoints in the largest dialysis study did not show an increased risk for daprodustat, including all-cause mortality, CV mortality, or thrombosis, except for hospitalisation for heart failure (RR 1.08 (0.82, 1,42) but not for MACE or HHF (0.94(0.82, 1.07)). The findings seem generally robust across the ITT and on-treatment analyses presented. However, in a time-dependent Hb covariate analyses, a Hb < 10 g/dL was associated with a significantly increased risk (RR 1.71 (1.23, 2.37)) and a Hb > 11.5 g/dL with a numerical increase (RR 1.09 (0.76, 1.56) (as also observed in the non-dialysis patients). Such a trend is also noticed for the subgroup analysis of **hypo-responders** vs no hypo-responders at baseline (RR of 1.09 (0.75, 1.59) vs RR 0.87 (0.74, 1,01), p for interaction (0.2683)).

A slightly lower incidence of **adjudicated deaths** was observed for daprodustat versus ESA RR 0.92 (0.78, 1.08), 276 vs 297 events ITT and RR 0.84 (0.62, 1.12), 80 (5.6%) vs 99 (6.9%) post-hoc OT+DF). However, this was not consistent across the type of deaths, with CV death somewhat increased (93 (33.7%) vs 90 (30.3%), attributed to sudden death (47 vs 38) and HF (14 vs 11)).

Cancer related mortality and tumour progression and recurrence were lower 46 (3.2%) vs 53 (3.7%)l; RR 0.87, p=0.478). Nevertheless, current data may still be limited due to the long latency of cancer progression;

No trend of increased AEs according to **age** categories of < 65, 65-75, > 75, and > 85 years could be observed.

3.1. Effects Table

Table 61 Effects Table for daprodustat for anaemia associated with CKD (data cut-off: May 2022).

Effect	Short Description	Unit	Daprodustat	ESA	Uncertainties/ Strength of evidence	References
Favourable Effects						
Hb response	Mean change in Hb between baseline and over the evaluation period of weeks 28 to 52 inclusive	g/dL mean (sd)	0.29	0.11	**SoE**: Non-inferiority met (0.18 (0.12, 0.24)). Supported by a comparable proportion of patients with Hb increase (73% vs 70% and proportion of time within the target range (mean values: 59%, 57%). Numerically comparable quality of life outcome (SF36-Physical, Mental, Vitality) cave open-label design. Numerically comparable need for rescue therapy (3.4% vs 3.5%). Large study (n=1438 vs 1438). Effect maintained during a mean of 26 months. Comparable results obtained in studies ASCEND-ID (initiating dialysis) and ASCEND-TD (TIW dosing) **Unc**: 25% and 24% of patients in daprodustat and rhEPO groups discontinued study treatment, respectively, at the time of the measurement of the Hb response.	ASCEND-D
Unfavourable Effects						
MACE	The composite of death, MI, or stroke	N (%)	ITT: 355 (24.7) LDD+DF: 169 (11.8)	ITT: 389 (27.1) LDD+DF: 205 (14.3)	**SoE:** ITT HR 0.89 (0.78, 1.03) supported by HR 0.85 (0.69, 1.04) on-treatment corrected for dose frequency (LDD+DF post-hoc). Also not increased for almost all secondary adjudicated CV endpoints. **Unc**: On-treatment MACE discordant but limited events for the ID and TD studies (19 (12%) vs 15 (10%), Absolute Rate Difference per 100 PYs 2.41 (-4.61, 9.43) and 33 (12%) vs 14 (10%), Absolute Rate Difference per 100 PYs 2.28 (-4.44, 9.00)). In total, 51% of the patients discontinued the treatment during the study.	
Overall mortality		N (%)	ITT: 276 (19.2%) LDD+DF: 80 (5.6%)	ITT: 297 (20.7%) LDD+DF: 99 (6.9%)	**SoE:** ITT 0.92 (0.78, 1.08), 276 vs 297 supported by HR 0.84 (0.62, 1.12) on-treatment corrected for dose frequency (post-hoc).	

Effect	Short Description	Unit	Daprodustat	ESA	Uncertainties/ Strength of evidence	References
Thrombo embolic events (TEE)		N (%)	ITT: 180 (12.5%) LDD+DF: 144 (10.0%)	ITT: 213 (14.8%) LDD+DF: 176 (12.3%)	**SoE**: Known AE from ESAs, likely class-effect. **Unc** For thrombosis secondary to excessive erythropoiesis this was limited but higher in daprodustat group with 20 (1.4%) events vs 11 (0.8%) in ESA group.	
Lipid change at Wk 52	LDL-C % change HDL-C % change	mmol/L	-7.5 -4.8	-1.4 0.6	**Unc:** Contributing impact on CV safety unknown.	

Abbreviations: AE: adverse event, CV: cardiovascular, ESA: erythropoiesis stimulating agents, Hb: haemoglobin, HDL-C: high-density lipoprotein cholesterol, ITT: intention to treat, LDL-C: low-density lipoprotein cholesterol, MI: myocardial infarct, SoE: strength of evidence, SF36: Short Form (36) Health Survey, Unc: uncertainty.

3.2. Benefit-risk assessment and discussion

3.2.1. Importance of favourable and unfavourable effects

Correction and maintaining appropriate haemoglobin levels are considered of clinical relevance. This is generally associated with improved quality of life due to alleviating symptoms such as fatigue, shortness of breath, insomnia, lethargy, headaches, dizziness, and lack of concentration/ cognitive functioning. Further, Hb correction is believed to improve CV morbidity and overall mortality eventually. Furthermore, the use of RBC transfusion may be prevented.

In dialysis patients, ESA therapy is part of standard therapy in a relevant proportion of patients. Daprodustat has shown a comparable effect on Hb correction and maintenance versus ESA therapy. This was associated with comparable effects on QoL indicators, although not formally assessed, thus limiting the drawing of firm conclusions. Although, an appropriate iron status may still be needed for daprodustat to prevent hyporesponsiveness (as known with ESAs with inappropriate iron levels).

Although the current studies were not specifically designed and powered to evaluate a potential improvement in morbidity and mortality, these aspects have been addressed in terms of safety, in particular, as it is known from ESA therapy that too high levels of haemoglobin levels are associated with increased risk for mortality and cardiovascular events.

In the case of roxadustat, an increased mortality and MACE risk was observed in dialysis patients converted from ESA therapy. Dysregulation resulting in increased Hb variability of ESA stabilised patients was assumed (but not demonstrated) to be one of the factors to clarify this increased risk (another is hyporesponsiveness). However, this is unlikely to play a major role in patients converted from ESA to daprodustat, as generally, no increased CV risk has been observed in these dialysis patients in the daprodustat group. In addition, any increased risk has not been reported in dialysis patients in vadadustat either.

Nevertheless, factors that could influence CV risk have been analysed. Hyporesponsiveness appears to be an associated factor, which has currently been addressed in the labelling (sections 4.2, 4.4 and 4.8), as previously done for roxadustat (Evrenzo) and vadadustat (Vafseo), other medicinal products within this class. However, overshooting of haemoglobin levels may be another factor but this could not be shown, possibly considering that conservative Hb goals were applied in the clinical studies (10-11 g/dL instead of 10-12 g/dL). This could previously not be clearly demonstrated for roxadustat either.

Oral administration of daprodustat provides a benefit and convenience over intravenous or subcutaneous use of ESA therapy, especially for the peritoneal dialysis patients without standard (arterio-venous) access, although an increased number of gastro-intestinal events was observed with oral administration of daprodustat both when compared to placebo and ESA therapy. Nevertheless, this seems not importantly result in tolerability issues as discontinuation due to AEs was generally limited and comparable to ESA therapy.

3.2.2. Balance of benefits and risks

The Benefit and Risk balance can be considered positive for the dialysis dependent patient population.

3.3. Conclusions

The benefit /risk balance of Jesduvroq is positive subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jesduvroq is favourable in the following indication:

Jesduvroq is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that daprodustat is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).