Study design and baseline characteristics of patients on dialysis in the ASCEND-D trial

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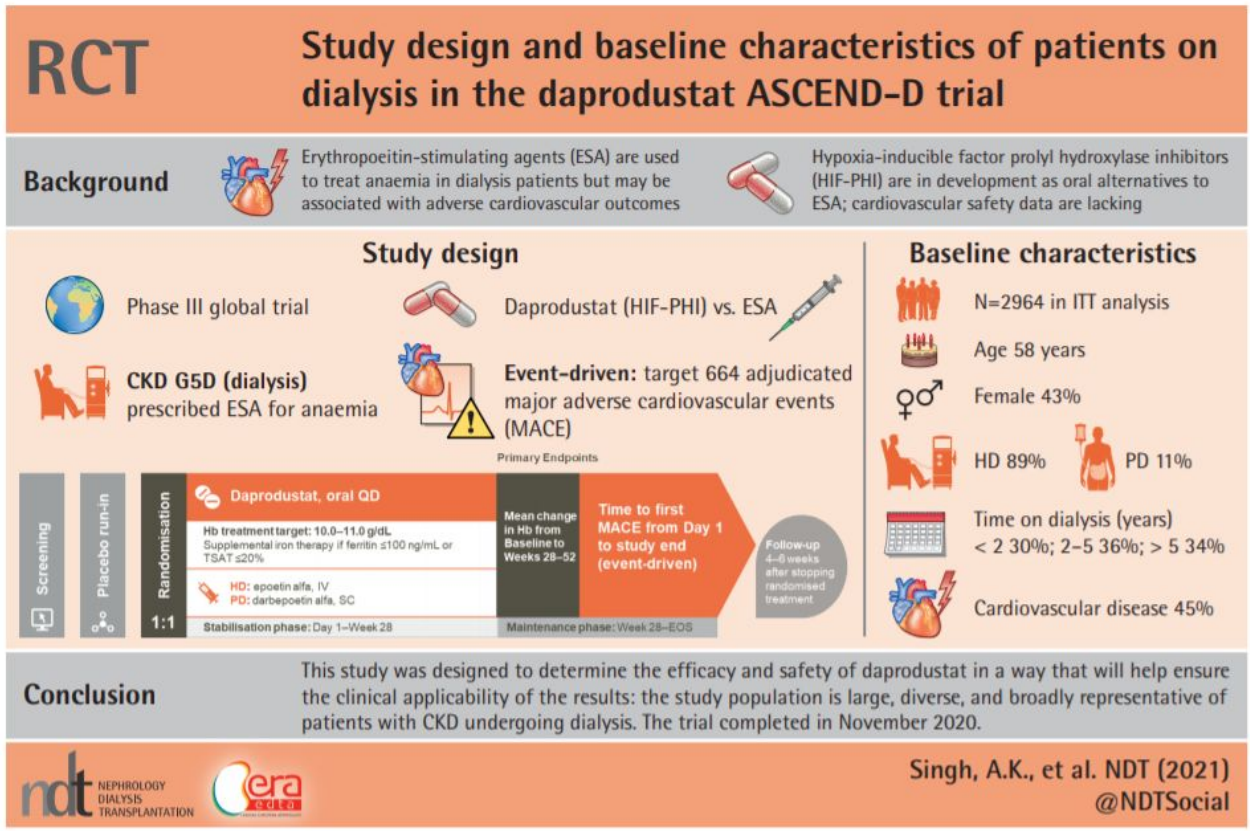
Running head: ASCEND-D trial design and baseline characteristics

GRAPHICAL ABSTRACT



ABSTRACT

Background. The Anemia Studies in chronic kidney disease (CKD): Erythropoiesis via a Novel prolyl hydroxylase inhibitor (PHI) Daprodustat-Dialysis (ASCEND-D) trial will test the hypothesis that daprodustat is non-inferior to comparator epoetin alfa or darbepoetin alfa for two co-primary endpoints: haemoglobin efficacy and cardiovascular safety.

Methods. We report the trial design, key demographic, clinical, and laboratory findings, and baseline therapies of 2964 patients randomised in the open-label (sponsor-blinded) active-controlled, parallel-group, randomised ASCEND-D clinical trial. We also compare baseline characteristics of ASCEND-D patients with patients who are on dialysis (CKD G5D) enrolled in other large cardiovascular outcome trials (CVOTs) and in the most relevant registries.

Results. The median age of patients was 58 years, 43% were female; 67% were white and 16% were black. The median haemoglobin at baseline was 10.4 g/dL. Among randomised patients, 89% were receiving haemodialysis and 11% peritoneal dialysis. Among key co-morbidities, 42% reported a history of diabetes mellitus, and 45% a history of cardiovascular disease. Median blood pressure was 134/74 mmHg. The median weekly dose of epoetin was 5751 units. Intravenous and oral iron use was noted in 64% and 11% of patients, respectively. Baseline demographics were similar to patients with CKD G5D enrolled in other CVOTs and renal patient registries.

Conclusion. ASCEND-D will evaluate the efficacy and safety of daprodustat compared with epoetin alfa or darbepoetin alfa in the treatment of patients with anaemia with CKD G5D.

Keywords: anaemia; baseline data; daprodustat; dialysis; recombinant human erythropoietin

This trial is registered with ClinicalTrials.gov: NCT02879305. EudraCT Number: 2016-000541-31; Sponsor Protocol Number: 200807

KEY LEARNING POINTS

What is already known about this subject?

- Anaemia is a common complication in patients with chronic kidney disease (CKD); untreated, it is ubiquitous in patients with CKD who are on dialysis.
- Treatment of anaemia with erythropoiesis stimulating agents (ESAs) successfully corrects haemoglobin levels; however, ESAs can be associated with adverse cardiovascular (CV) outcomes.
- This large study is needed to evaluate whether daprodustat – a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) – is non-inferior to comparator epoetin alfa or darbepoetin alfa for two co-primary endpoints: haemoglobin efficacy and cardiovascular safety in patients with chronic kidney disease who are on dialysis.

What this study adds?

- This is one of the largest anaemia studies in dialysis patients (N=2964) being performed in 35 countries across Europe, North America, Latin America and Asia Pacific. Baseline characteristics were similar to patients enrolled in other large cardiovascular outcome trials and relevant patient registries, thus supporting the generalisability of this study population.
- A high proportion of the study population have a history of CV disease and/or diabetes mellitus; however, on average, control of diabetes and blood pressure were consistent with Kidney Disease Improving Global Outcomes (KDIGO) guidelines or local equivalents.
- Standardising the doses of randomised treatment, along with utilizing the same dose adjustment algorithm, iron management criteria and anaemia rescue algorithm allow for a more unbiased comparison between the groups.

What impact this may have on practice or policy?

- This study was designed to determine the efficacy and safety of daprodustat in a way that will help ensure the clinical applicability of the results: the study population is large, diverse, and broadly representative of patients with CKD undergoing dialysis.
- If daprodustat is non-inferior to ESAs, it may provide an alternative oral dosing regimen to existing treatment options which may be preferable among certain patients.

INTRODUCTION

Anaemia is ubiquitous among patients with chronic kidney disease who are on dialysis (CKD G5D) [1]. The introduction of recombinant human erythropoietin (rhEPO) treatment in 1989 was one of the most important advances in the treatment of patients on dialysis and other patients with CKD. In the past, severe anaemia was common, diminishing patients' quality of life and resulting in the need for frequent blood transfusions [2]. Treatment with rhEPO and its analogues (erythropoiesis stimulating agents [ESAs]) to partially correct anaemia has improved patients' lives and substantially reduced requirements for blood transfusion. However, several randomised trials have demonstrated either no benefit or even harm in relation to cardiovascular (CV) and other outcomes when treatment with rhEPO and its analogues were used to normalise haemoglobin (Hb) in patients with CKD [3-6]. Indeed, post hoc analyses have suggested that exposure to high doses of exogenous rhEPO may present a possible increase in CV and mortality risk in these patients [7-9].

The emergence of newer compounds termed hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) to stimulate erythropoiesis through the inhibition of HIF-prolyl hydroxylase (PHD) enzymes PHD1, PHD2, and PHD3 may represent an alternative treatment strategy [10]. Recently approved in China and Japan, these agents are currently in development for the rest of the world [11-13]. PHD inhibition leads to stabilisation of HIF-α transcription factors and expression of HIF-responsive genes involved in adaptation to hypoxia, including EPO and genes that regulate iron uptake, mobilization and transport, as well as resulting in decreased hepcidin production [14, 15]. Given the safety concerns with rhEPO and its analogues and challenges associated with parenteral therapies in some CKD populations, HIF-PHIs such as daprodustat (previously GSK1278863) are being developed to treat anaemia of CKD.

In prior clinical trials of up to 52 weeks in Japan, daprodustat increased Hb to target goals in patients with anaemia as effectively as darbepoetin alfa [16]. However,

unlike rhEPO therapy, daprodustat increased Hb without raising plasma EPO to supraphysiologic levels [17, 18]. Across the trials published to date, daprodustat appears generally well tolerated with the more frequently reported adverse events being common events characteristic of the target populations [16-19]. As an oral alternative to the parenterally administered rhEPOs, daprodustat may also prove to be more convenient to non-dialysis and PD patients, as it is more easily delivered, stored, and administered.

Here we describe the essential design elements and baseline characteristics of patients randomised in the ASCEND-D (Anemia Studies in CKD: Erythropoiesis via a Novel PHI Daprodustat-Dialysis) trial.

MATERIALS AND METHODS

Study design

ASCEND-D is a global, randomised, open-label (sponsor-blind), parallel group, active-controlled, event-driven Phase 3 trial comparing the efficacy and safety of daprodustat in patients with CKD G5D being treated with an ESA for anaemia (ClinicalTrials.gov: NCT02879305. EudraCT Number: 2016-000541-31). The study was approved by the ethics committee at every participating institution and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

ASCEND-D consists of four periods: a screening period, a placebo run-in period, a treatment period, and a follow-up period (**Figure 1**). The 4-week screening period permitted eligibility determination based on laboratory assessments to be confirmed, while the 4-week run-in period was used to establish adherence to daprodustat placebo tablets and study procedures. Prior ESAs were continued during the screening and run-in periods. Subjects were randomised to daprodustat or rhEPO control (intravenous [IV] epoetin alfa for haemodialysis [HD] patients and subcutaneous darbepoetin alfa for peritoneal dialysis [PD] patients). Thereafter, the

treatment period was divided into a stabilisation phase from Day 1 to Week 28, and a maintenance phase from Week 28 to the end of study visit, with dose titration to achieve the prespecified Hb target range (10–11 g/dL). The follow-up period consisted of a visit 4 to 6 weeks after stopping randomised treatment, only for those patients who continued randomised treatment until the end of study visit.

Patients attended routine follow-up at least every 4 weeks during Year 1 of the study and at least every 12 weeks thereafter. Patients who permanently discontinued randomised treatment prior to the end of study were followed at 12-weekly intervals off-treatment until the end of study visit. Serum and plasma samples were collected at baseline, Week 28, and Week 52 for future analysis of biomarkers and iron metabolism.

Eligibility criteria

Eligibility was determined at Week -8, with select criteria confirmed at Day 1 (randomisation). Eligible patients were adults, treated with an approved ESA for ≥6 weeks before screening, had a screening Hb of 8 to 12 g/dL, on a consistent mode of dialysis for >90 days before screening, demonstrated adherence to daprodustat placebo tablets during the run-in period, and able to provide informed consent. The key inclusion and exclusion criteria are provided in **Table 1** and complete entry criteria are outlined in **Supplementary Table 1**.

Study treatments and management strategies

Daprodustat and rhEPO dosing strategies and iron treatment for managing Hb are detailed in **Table 2**. A rescue algorithm was in place to minimise the risk of patients having an inadequate Hb response for an extended period and to enable consistency in the application of rescue therapy across the study (**Table 3**).

Objectives and endpoints

This trial was developed in consultation with the US and European regulatory agencies. The co-primary non-inferiority (NI) objectives of the trial are to compare

Hb efficacy and CV safety among patients receiving daprodustat versus those receiving rhEPO. The NI Hb efficacy objective will be assessed with the co-primary endpoint of mean change in Hb between baseline and the evaluation period (average over Weeks 28 to 52). An external, independent and blinded endpoints committee (Duke Clinical Research Institute) will adjudicate events used to assess the NI CV safety objective with the co-primary endpoint of time to first adjudicated major adverse cardiovascular event (MACE; the composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke). Principal secondary superiority endpoints, including superiority assessment of MACE, and other secondary endpoints are listed in **Table 4**.

Randomisation and stratification

Patients were stratified by dialysis type (HD [including haemodiafiltration and haemofiltration] or PD), by region, and by participation in the ambulatory blood pressure (BP) monitoring sub-study. Following stratification, patients were randomised 1:1 to receive oral daprodustat or rhEPO control. A central randomisation approach was used to protect against selection bias due to the open-label design.

Statistical analysis

A sample size of 3,000 was planned for this event-driven trial based on the co-primary CV safety objective and an event target of 945 adjudicated first MACE. This includes on- and off-treatment MACE in the Intent-to-Treat (ITT) population. This event count provides approximately 90% power to establish NI with a NI margin hazard ratio of 1.20 for daprodustat compared with rhEPO, assuming a true underlying 3% lower relative risk of MACE in favour of daprodustat (i.e. a true underlying hazard ratio of 0.97), and 80% power for NI under the assumption that the true underlying risk of MACE is the same in both groups (i.e. a true underlying hazard ratio of 1.00). The study completed randomisation in August 2018. In August 2020, prior to study unblinding and after discussion with the regulatory authorities, as well as approval with the external steering committees and the Independent Data

Monitoring Committee (IDMC), the MACE NI margin was changed to 1.25, reducing the event target to 664 while maintaining approximately 90% power. The rationale for the NI margin change was to accelerate study closeout in consideration of the COVID-19 pandemic and to align with the NI margin used in other HIF-PHI clinical studies [20]. There are no identified risks to subject safety or data integrity with these changes.

The planned study size provides more than 99% power for the Hb NI test with a NI margin of -0.75 g/dL for the (daprodustat – rhEPO) Hb difference. This includes on and off-treatment Hb values in the ITT population. Multiple imputation will be used to impute missing Hb values. The co-primary endpoints will be tested in parallel for NI at the one-sided 2.5% level, and NI will need to be established for both co-primary endpoints to proceed to evaluate the principal secondary endpoints for superiority. Statistical testing for the principal secondary endpoints will be adjusted for multiplicity using the Holm–Bonferroni for multiplicity adjustment [21].

Descriptive statistics in the form of number and percentage of patients or median and 25th (P25) and 75th (P75) percentiles are provided for baseline variables. Baseline values are presented for the ITT population, overall and by cardiovascular disease (CVD) history, defined as having a history of at least one of the following: angina pectoris, myocardial infarction, stroke, transient ischaemic attack, coronary artery disease, heart failure, atrial fibrillation, cardiac arrest, or valvular heart disease.

Study oversight

ASCEND-D was developed in collaboration with Executive Steering Committee (ESC) and Steering Committee (SC). The ESC provides academic and scientific leadership and ensures that conduct of this study as well the other pivotal studies in the ASCEND programme conform to protocols. The SC provides scientific, medical and operational advice to the ESC. Members of these committees comprised Hb and iron,

standard of care, and regional recruitment and retention sub-committees to review in-stream, blinded, aggregate data on an ongoing basis to identify potential issues, and to escalate to the SC and ESC as required. An IDMC reviews safety and efficacy data as defined in the protocols and makes recommendations for additions or adjustments, as well as evaluates the co-primary MACE endpoint at a planned interim analysis to assess for futility of achieving non-inferiority at study completion. An external, independent and blinded Clinical Events Classification (CEC) group, led by the Duke Clinical Research Institute, in collaboration with George Clinical, was in charge of adjudicating predefined events (all-cause mortality, myocardial infarction, stroke, hospitalisation for heart failure, and thromboembolic events). Committee members and their respective affiliations, along with the CEC Primary Investigator, are presented in **Supplementary Table 2.**

Comparison with other large CVOTs and relevant registries

To assess generalisability, we compared baseline characteristics of ASCEND-D patients with those enrolled in two other large, randomised, controlled, trials, the $INNO_2VATE$ prevalent trial [20] and the PIVOTAL trial [22, 23] that evaluated anemia treatment in maintenance dialysis patients. A comparison of the ASCEND-D population was also made with more contemporaneous registry data sets with sufficient patient information to allow meaningful comparison, i.e., Dialysis Outcomes and Practice Patterns Study (DOPPS), United States Renal Data System (USRDS) [24, 25].

RESULTS

ASCEND-D is being conducted in 431 centres in 35 countries. The country-level patient distribution is listed in **Supplementary Table 3**. In total, 44% of patients originated in Europe Middle East Africa (EMEA), 29% in North America (predominantly USA), 14% in Latin America, and 13% in the Asia Pacific region.

Screening, run-in, and randomisation

A total of 5436 patients were screened, including patients who were re-screened and 2472 (45%) who did not meet entry criteria and were not randomised. The reasons for screen failure are listed in **Supplementary Table 4**. A total of 2964 patients were randomised. One additional patient was randomised but had not provided valid informed consent so was removed from the randomised count.

Demographic characteristics

Baseline characteristics are summarised in **Table 5**. The ITT cohort has a median age of 58 years with 43% being female. Eighty-nine percent of patients were treated with HD and 11% with PD.

Clinical Characteristics

Forty-five percent of patients reported a history of CVD (**Table 5**). A history of stroke was reported by 7% and transient ischaemic attack by 4%. Among patients with CVD, 51% had a history of coronary artery disease, 22% angina pectoris, and 19% myocardial infarction. More patients with CVD had diabetes mellitus than patients without CVD (49% vs 35%, respectively). Likewise, use of beta-blockers, statins, vitamin K antagonists, and aspirin was higher among patients with a history of CVD. Patients with and without reported CVD had similar BPs; approximately 46% were taking angiotensin converting enzyme inhibitors or angiotensin receptor II blockers.

A functioning arterio-venous fistula (AVF) was present in approximately 69% of patients; 9% had an AV graft (AVG); a tunneled or non-tunneled central venous catheter (CVC) was present in 9% and 1%, respectively.

ASCEND-D compared with other large CVOTs

Patients enrolled in ASCEND-D generally had similar demographic characteristics as patients in the other CVOTs (**Table 6**). The ASCEND-D and the $INNO_2VATE$ prevalent trials, the latter investigating another HIF-PHI, vadadustat, were of similar trial design utilising an rhEPO active control, while PIVOTAL investigated high

versus low-dose IV iron. Both $INNO_2VATE$ and ASCEND-D were global trials, however ASCEND-D included more patients in EMEA and less in North America than $INNO_2VATE$; in contrast, PIVOTAL was conducted in the United Kingdom. The HIF-PHI patient populations were of similar racial composition, while PIVOTAL overwhelmingly enrolled white patients. There were similar rates for CVD history (utilising similar definitions) for both the ASCEND-D and the $INNO_2VATE$ trials (not reported for PIVOTAL), while diabetes history was similar for all trials. ASCEND-D had higher rates of hypertension than PIVOTAL and $INNO_2VATE$) and higher rates of heart failure than PIVOTAL (not reported for $INNO_2VATE$).

Both $INNO_2VATE$ and PIVOTAL had slightly higher baseline BP measures than ASCEND-D (**Table 6**) but similar Hb levels. Concomitant medications were similar for the HIF-PHI trials; however, PIVOTAL reported lower ACEi/ARB use and higher antiplatelet therapy and lipid-lowering use. Interestingly, prior ESA dose was lower in ASCEND-D than in the other CVOTs, while the proportion of subjects using IV iron was higher in ASCEND-D than in $INNO_2VATE$ (not reported in PIVOTAL) .

ASCEND-D compared with registry data sets

To assess generalisability, we compared demographic and clinical characteristics of patients enrolled in the ASCEND-D study with several contemporaneous, real-world, global registry data sets, including DOPPS [24, 26] and USRDS [25] **(Table 7)** with DOPPS including patients from the USA and Europe. Other global registries were explored but excluded from comparison due to the sparsity of the pertinent data. Data from DOPPS and USRDS were generally similar to the ASCEND-D population. Notable differences included race where a larger Black population was reported in the USRDS than ASCEND-D which only comprised 29% of patients from USA. Hb levels were higher in the global DOPPS data set than ASCEND-D where subjects were dosed to achieve Hb concentrations within the range of 10 to 11 g/dL; interestingly, higher ESA doses were seen in the USA data sets relative to ASCEND-D.

DISCUSSION

ASCEND-D was designed to include a broad population as representative of the overall dialysis population as possible, with the appropriate measures to enable valid efficacy and safety comparisons across treatment groups. Sites were selected to achieve a balance in recruitment across EMEA, North and, Latin America and Asia Pacific. Entry criteria were developed to identify a stable, maintenance, and adequately treated dialysis population. A placebo run-in period was established to confirm compliance with an oral medication and to minimise withdrawal of consent post-randomisation seen in a prior daprodustat HD study [18]. Exclusions ensured events that could impact the safety analysis were not present, including anaemia due to causes other than CKD, recent CV events or cancer and uncontrolled hypertension.

The Hb target range of 10 to 11 g/dL was selected to accommodate the varying anaemia guidelines and ESA labelling worldwide. The selection of rhEPO control was based on pragmatic clinical dialysis practice. In earlier daprodustat clinical trials, investigators were responsible for managing rhEPO dosing in the control group which led to higher Hb values than targeted [27]. Therefore, a decision was made to apply the same dose adjustment algorithm for both treatment groups, as well as to provide the study rhEPO and develop a standard set of dose steps which were aligned with rhEPO labelling. Similarly, iron management criteria and an anaemia rescue algorithm have been developed and used for both treatment groups. For the latter, only IV iron and/or transfusions were allowed, in addition to randomised treatment, as an early intervention to improve Hb before considering a patient to have met the rescue endpoint and to permanently discontinue randomised treatment. Standardising the doses of randomised treatment, along with utilising the same dose adjustment algorithm, iron management criteria and anaemia rescue algorithm allow for a more unbiased comparison between the groups.

The baseline characteristics of dialysis patients recruited in ASCEND-D were similar to that of other large CVOTs of dialysis patients. The most relevant comparison is between ASCEND-D and the $INNO_2VATE$ prevalent trial which are both investigating HIF-PHIs; trial design, demographic and clinical characteristics were similar. While $INNO_2VATE$ had a higher recruitment in the US, ASCEND-D had a higher recruitment from EMEA. Comparisons with PIVOTAL [22] and other historical CVOTs in dialysis patients also indicate similar baseline characteristics [28-30], with the exception of a lower prior ESA dose and higher rate of IV iron usage for ASCEND-D. Utilization of a lower ESA dose in ASCEND-D likely reflects differences in US recruitment (29% ASCEND-D vs 61% $INNO_2VATE$). In contrast to $INNO_2VATE$, where only 16% of patients had baseline IV iron use, 64% of ASCEND-D patients had baseline IV iron use, comparable with DOPPS data [24].

Registry data provided an additional way to compare patient characteristics with ASCEND-D to determine generalisability. Because of its global nature, DOPPS is arguably a better comparator than country-based registries. ASCEND-D compares favourably with DOPPS with respect to demographic and clinical characteristics [26], thus supporting the generalisability of this study population, with the exception of a higher Hb in DOPPS given the practice pattern outside of the US to treat to higher Hb targets than the prespecified target in ASCEND-D which was developed in line with worldwide ESA labelling. Comparisons with US data sets from DOPPS [26] and USRDS [25] demonstrated baseline characteristics were generally similar with only a few accountable differences (e.g. race and Hb level).

The main limitation of the ASCEND-D trial is the open-label design. Blinding dialysis patients to randomised treatment is challenging because the active comparator is either administered intravenously or subcutaneously, whereas daprodustat is an oral medication and would have introduced a number of complexities and potential limitations to the study, including limiting the generalizability of the study. Importantly, the adjudication of clinical outcomes is blinded to the treatment assignment minimising the risk of ascertainment bias [31]. Likewise, the sponsor

remained blind to treatment assignment throughout the trial. Although study patient population is younger than the average age of dialysis patients, it is common for trials to recruit younger patients given that older patients are frailer and less likely to participate in trials. Additionally, the selection of rhEPO type, dose steps and frequency of administration were prespecified in the comparator group and may differ from local ESA protocols. Likewise, a common dose adjustment algorithm across treatment groups was implemented which may differ from local practice.

These limitations are balanced by other strengths. ASCEND-D is a prospective randomised CVOT with one of the largest number of patients recruited worldwide. Patients were recruited not only from academic centres but also from community practices. It is notable that the racial and ethnic composition of ASCEND-D, although similar to other large trials, is more diverse than often seen in trials enrolling dialysis patients. The standard of care for patients on dialysis (e.g., diabetes, BP control, dialysis adequacy) was consistent with Kidney Disease Improving Global Outcomes guidelines or local equivalent [32]. Overall, the study population, including patients on PD, and prevalence of CVD appears typical of global patients undergoing dialysis, ideal for determining the safety and efficacy of daprodustat.

In conclusion, ASCEND-D enrolled 2964 patients who are broadly representative of patients with anaemia of CKD on dialysis. The study will test the hypothesis that daprodustat is non-inferior to comparator epoetin-alfa for two co-primary endpoints, Hb efficacy and CV safety. Results from ASCEND-D, expected in late 2021, will inform on an alternative option to treat anaemia in dialysis patients.

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CONFLICT OF INTEREST STATEMENT

AKS reports consultancy fees from GlaxoSmithKline and stock in Gilead.

KC reports consultancy fees from GlaxoSmithKline.

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IMD reports research grants, consultancy fees and honoraria from GlaxoSmithKline and Vifor Pharma.

JMcM reports personal fees from Abbott, Hickma, Sun Pharmaceuticals, Servier, and that his employer received fees from Alnylam Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardurion, Cytokinetics, Dal-Cor, GlaxoSmithKline, Ionis, Novartis, Pfizer, Theracos.

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VP reports consultancy agreements with AbbVie, Bayer, Boehringer Ingelheim, Chinook, GlaxoSmithKline, Janssen, and Pfizer; Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pharmalink, Relypsa, Retrophin, Roche, Sanofi, Servier, and Vitae. Research funding from Pfizer (supplied drug and seed funding for TESTING trial) and, GSK. Honoraria from AbbVie, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Pfizer; Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Chinook, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi, Tanabe, Mundipharma, Novartis, Novo

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SS reports grants and consultancy fees from Alnylam, AstraZeneca, Bayer, Bristol Myers Squibb, Cytokinetics, Gilead, GlaxoSmithKline, Lilly, MyoKardia, Novartis, Respicardia, Sanofi Pasteur, and Theracos, grants from Bellerophon, Celladon, Eidos, Ionis, Lone Star Heart, Mesoblast, NIH/NHLBI, and Neurotronik, and consultancy fees from Akros, Amgen, Arena, Cardior, Cardurion, Corvia, Daiichi-Sankyo, Ironwood, Merck Sharp Dohme, Roche, Takeda, Quantum Genetics, AoBiome, Janssen, Cardiac Dimensions, Tenaya, Dinaqor, Tremeau, CellProThera, Moderna.

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AUTHORS' CONTRIBUTIONS

AKS contributed to the design, interpretation of data, supervision, and management of the research, writing, and critical review of this manuscript. All authors contributed to the design, interpretation of data, management of research, writing, and critical review of this manuscript.

All authors affirm that authorship is merited based on the International Committee of Medical Journal Editors authorship criteria. AKS was the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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DATA AVAILABILITY STATEMENT

Anonymised individual patient data and study documents can be requested for further research from www.clinicalstudydatarequest.com

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TABLES

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Age: 18 to ≤99 years of age **ESAs:** Use of any approved ESA for at ≥6 weeks before screening and between screening and randomisation **Hb concentration:** *On Week -8*: • Hb 8 to 12 g/dL[1] *On randomisation (Day 1)*: • Hb 8 to 11 g/dL and receiving at least the minimum rhEPO dose[2] • Hb >11 g/dL to 11.5 g/dL and receiving greater than the minimum rhEPO dose[2] **Dialysis:** On dialysis >90 days before screening[3] **Frequency of dialysis:** HD ≥2 times/week and PD ≥5 times/week. Home HD ≥2 times/week	**Kidney transplant:** Planned living kidney transplant within 52 weeks after study start (Day 1) **Iron:** Ferritin ≤100 ng/mL (≤100 µg/L), TSAT ≤20%, at screening **Evidence of non-renal anaemia:** Aplasias**,** untreated pernicious anaemia, thalassemia major, sickle cell disease or myelodysplastic syndrome, GI bleeding **Cardiovascular comorbidities:** MI or acute coronary syndrome stroke, TIA, heart failure, uncontrolled hypertension (contraindicating rhEPO use) **Liver disease** (any one of the following): • *Alanine transaminase:* >2x ULN at screening • *Bilirubin:* >1.5x ULN at screening • Current unstable liver or biliary disease per investigator assessment **Malignancy:** History of malignancy within the 2 years before screening through to randomisation (Day 1) or currently receiving treatment for cancer, or complex kidney cyst

Compliance with placebo (randomisation [Day 1] only]): ≥80% and ≤120% compliance with placebo during run-in period	**Females only:** Pregnancy (as confirmed by a positive serum human chorionic gonadotrophin test), breastfeeding, or subject is of reproductive potential and does not agree to follow one of the contraceptive options listed in the List of Highly Effective Methods for Avoiding Pregnancy **Other conditions:** Any other condition, clinical or laboratory abnormality, or examination finding that the investigator considers would put the subject at unacceptable risk, which may affect study compliance (e.g., intolerance to rhEPO) or prevent understanding of the aims or investigational procedures or possible consequences of the study

[1] Determined using HemoCue, a point of care test

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

[3] Patients receiving PD were restricted to <15% of the overall study population.

ESA, erythropoiesis stimulating agent; GI, gastrointestinal; Hb, haemoglobin; HD, haemodialysis; MI, myocardial infarction; PD, peritoneal dialysis; rhEPO, recombinant human erythropoietin; TIA, transient ischaemic attack; TSAT, transferrin saturation; ULN, upper limit of normal

NOTE: Ophthalmological exclusions were not included given completed studies with daprodustat did not identify any clinically meaningful changes in proliferative retinopathy, macular edema, or choroidal neovascularization with daprodustat [16, 18].

Table 2. Study treatments and management strategies

	Initiation	Protocol-specified dose adjustment algorithm[1]
Daprodustat	• Starting dose 4–12 mg based on prior ESA dose at randomisation • Nine dose steps available (1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg, 16 mg, and 24 mg)	• Dose adjustments (i.e., increase, decrease, maintain, or withhold if Hb ≥12 g/dL) are implemented by the IRT system to maintain Hb concentrations within the range of 10–11 g/dL[2] - Hb value measured at least every 4 weeks (Day 1 through Week 52) or at least every 12 weeks (post-Week 52 until the end of treatment) - From Week 52 onward, additional 4-weekly study visits to check Hb and dispense randomised treatment are required if 1. Hb is outside the target range 2. Dose has changed 3. A moderate CYP2C8 inhibitor has been started/stopped/changed 4. Patient has changed from HD to PD 5. Per investigator discretion to allow for an early dose adjustment.
rhEPO	• Starting dose based on patients' prior ESA dose (converted to the study ESA type) and Hb at the time of randomisation • Pre-defined Dose-steps[3]: - IV epoetin alfa: stepwise increases or decreases in weekly dose from 20% to 33% for most steps (when patients were receiving from 1500 U to 60,000 U IV as a total weekly dose; doses ≤10,000 U are administered once a week; doses >10,000 U are administered three times a week) - Darbepoetin alfa: stepwise increases or decreases in weekly dose from 20% to 33% for most steps (20 µg to 400 µg as a total 4-weekly dose; doses ≤150 µg are administered every 4 weeks; 200 µg and 300 µg are divided and administered every 2 weeks; 400 µg is divided and administered once a week).	
Iron	• Started if TSAT is ≤20% and/or ferritin is ≤100 ng/mL - Type of iron, dose, and route is determined by the investigator based on local clinical practice and the patient's iron status	• Iron must be stopped if values of ferritin >800 ng/mL and TSAT >20% or if TSAT >40% are present - Investigators are to be guided by local/regional guidelines and may stop administration of iron at a lower ferritin or TSAT level if clinically indicated - The framework for starting and stopping iron is based on a review of global and regional iron guidelines, as well as input from the ASCEND Steering Committees
The Hb and Iron sub-committee of the Steering Committee is monitoring blinded patient Hb and iron data during the trial Assessment of the quality of clinical care provided to patients was monitored by the Standard of Care sub-committee of the Steering Committee.		

ESA, erythropoiesis stimulating agent; Hb, haemoglobin; HD, haemodialysis; IRT Interactive Response Technology; IV intravenous; PD, peritoneal dialysis; rhEPO recombinant human erythropoietin; TSAT, transferrin saturation

[1]During the trial, overrides of the dose adjustment algorithm for exceptional circumstances associated with a safety concern are permitted if approved by the sponsor

[2]Based on the HemoCue Hb value

[3]Complete details of rhEPO dose steps (dose and frequency) are outlined in **Supplementary Table 5**.

Table 3. Rescue Algorithm for Anaemia Management

Evaluate Subject for Rescue if: HemoCue Hb remains <9 g/dL (at a scheduled study visit, Week 4 onwards) despite three[1] consecutive dose increases above the starting[2] or post-rescue[3] dose (where HemoCue Hb is <9 g/dL before each dose increase) OR HemoCue Hb is <7.5 g/dL despite a dose increase at the prior study visit	
Step 1: **Initial Intervention**	While continuing randomised treatment (increase dose if HemoCue Hb <7.5 g/dL; otherwise maintain current dose), intervene with <u>one or more</u> of the following as dictated by clinical comorbidities • Single course of IV iron up to 1000 mg (in addition to the iron management criteria) • Transfusion of up to two units of PRBC if clinically indicated • Allow additional 4 weeks on randomised treatment (NOTE: this is a required choice; can be combined with either or both of the above)
Step 2: **Rescue**	Check HemoCue Hb 4 weeks ±1 week from last study visit; earlier checks of Hb may be obtained to advise further intervention as clinically indicated **Randomised treatment should be permanently discontinued, and the subject should be rescued according to local clinical practice if either,** • If HemoCue Hb remains <9 g/dL despite initial intervention based on the average of two HemoCue Hb values[4] ***OR*** • More than two units of PRBC were needed for transfusion (and was not related to acute bleeding)

Hb, haemoglobin; HD, haemodialysis; IV, intravenous; PD, peritoneal dialysis; PRBC, packed red blood cells; rhEPO, recombinant human erythropoietin.

[1]Two consecutive dose increases if starting/post-rescue dose is daprodustat 12 mg, epoetin alfa 42000 U per week, or darbepoetin alfa 200 µg over 4 weeks; one dose increase if starting/post-rescue dose is daprodustat 16 mg, epoetin alfa 48000 U per week, or darbepoetin alfa 300 µg over 4 weeks; and no prior dose increase if starting/post-rescue dose is daprodustat 24 mg, epoetin alfa 60000 U per week, or darbepoetin alfa 400 µg over 4 weeks (top dose).
[2]For patients who have switched from HD to PD who are randomised to rhEPO, the baseline dose for the purposes of the rescue algorithm is the new darbepoetin alfa dose.
[3]For patients who previously were evaluated for rescue and who can continue in the trial, "post-rescue" dose is the dose of randomised treatment that a subject is receiving at the study visit after initial intervention.
[4]Repeat HemoCue Hb at the same study visit to confirm Hb (using the same sample); take average of 2 values.

Table 4. Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Co-primary objectives	**Co-primary endpoints (tested in parallel for non-inferiority)**
• To compare daprodustat with rhEPO for CV safety (non-inferiority) • To compare daprodustat with rhEPO for Hb efficacy (non-inferiority)	• Time to first occurrence of **adjudicated** MACE (composite of all-cause mortality, non-fatal MI and non-fatal stroke) • Mean change in Hb between baseline and EP (mean over Weeks 28 to 52)
Principal secondary objectives	**Principal secondary endpoints (tested for superiority, adjusted for multiplicity)**
• To compare daprodustat with rhEPO on CV safety endpoints • To compare daprodustat with rhEPO on the use of IV iron	• Time to first occurrence of adjudicated - MACE - MACE or a thromboembolic event (vascular access thrombosis, symptomatic deep vein thrombosis or symptomatic pulmonary embolism) - MACE or a hospitalisation for heart failure • Average monthly IV iron dose (mg)/subject to Week 52
Secondary objectives	**Secondary endpoints (tested for superiority[1], no multiplicity adjustment)**
• To compare daprodustat with rhEPO on additional CV safety endpoints	• All-cause mortality, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke[2] • MACE or hospitalisation for heart failure[2] (recurrent events analysis) • CV mortality or non-fatal MI[2] • All-cause hospitalisation • All cause hospital re-admission within 30 days • MACE or hospitalisation for heart failure or thromboembolic events[2] • Hospitalisation for heart failure[2] • Thromboembolic events[2]
• To compare daprodustat with rhEPO on Hb variability	• Hb change from baseline to Week 52[1] • N (%) responders, defined as mean Hb within the Hb analysis range 10-11.5 g/dL during EP[2] • % time Hb in analysis range (10-11.5 g/dL) during the evaluation period (EP, Week 28 to 52) and during the maintenance period (MP; Week 28 to

	end of trial) (non-inferiority analysis that will use a margin of 15% less time in range) [1]
• To compare daprodustat with rhEPO on BP	• Change from baseline in SBP, DBP and MAP at Week 52 and at end of treatment • Number of BP exacerbation events per 100 patient years • N (%) with at least one BP exacerbation event during study
• To compare daprodustat with rhEPO on the time to rescue (defined as permanently stopping randomised treatment due to meeting rescue criteria)	• Time to stopping randomised treatment due to meeting rescue criteria
• To compare daprodustat with rhEPO on HRQoL and utility score	• Mean change in SF-36 HRQoL scores PCS, 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 Wk 28 and 52 • Change from baseline in Health Utility (EQ-5D-5L) score at Week 52 • Change from baseline in EQ VAS at Week 52
• To compare daprodustat with rhEPO on the symptom severity and change	• Change from Baseline at Week 8,12, 28, 52 in PGI-S

BP, blood pressure; CV, cardiovascular; DBP, diastolic BP; EP, evaluation phase; EQ-5D-5L, EuroQoL 5-dimension 5-level; EQ VAS, EuroQoL visual analogue scale; Hb, haemoglobin; HRQoL, health related quality of life; IV, intravenous; MACE, major adverse cardiac event; MAP, mean arterial pressure; MCS, Mental Component Score; MI, myocardial infarction; MP, maintenance phase; PCS, Physical Component Score; PGI-S, patient global impression of severity; rhEPO, recombinant human erythropoietin; SBP, systolic BP; SF-36, short form-36 item.
Conversion factors from g/dL to g/L is 10 and from g/dL to mmol/L is 0.6206 (e.g. Hb of 10–11 g/dL is equivalent to 100–110 g/L or 6.2 to 6.8 mmol/L

[1]Hb change from baseline to Wk 52 is tested for non-inferiority, using the -0.75 g/dL margin used in the co-primary analysis. % time in range is tested first for non-inferiority, then for superiority. [2]Events adjudicated.
[2]To account for within-subject variability, 0.5 g/dL was added to the upper end of the target range to create a defined analysis range of 10.0–11.5 g/dL

Table 5. Baseline Characteristics of the Overall ITT Population and by Cardiovascular Disease History

	ITT Population (N=2964)	Cardiovascular Disease History[2]	
		Yes (n=1320)	No (n=1644)
Age (y)	58.0 (47.0–68.0)	63.0 (54.0–71.0)	54.0 (43.0–64.0)
Women (%)	43	40	45
Race (%)			
White	67	69	65
Black	16	17	15
Asian	12	10	14
American Indian or Alaska Native	2	1	2
Native Hawaiian or other Pacific Islander	2	2	1
Multiple	2	<1	4
Time since initiation of dialysis at screening (%)			
0 – <2 years	30	30	31
2 – <5 years	36	35	36
≥ 5 years	34	34	33
Dialysis modality at randomisation (%)			
HD	89	91	86
HD – conventional	85	88	82
HDF/HF	4	3	4
PD	11	9	14
Missing	<1	-	<1
Dialysis access type used at randomisation (%)			
Arteriovenous fistula	69	71	67
Arteriovenous graft	9	9	8
Central venous catheter – tunneled	9	10	7
Central venous catheter – non-tunneled	1	<1	2
Peritoneal catheter	11	8	13
Other	1	<1	2
Missing	<1	<1	<1
Baseline dialysis adequacy			
Kt/V urea for HD patients	1.50 (1.31–1.72)	1.50 (1.31–1.70)	1.50 (1.31–1.73)
URR for HD patients (%)	72 (66–77)	72 (67–78)	72 (66–77)
Kt/V urea for PD patients	1.96 (1.70–2.22)	1.92 (1.74–2.17)	1.97 (1.68–2.26)

Baseline post-dialysis weight (kg)	74.7 (63.0–88.5)	76.5 (64.0–90.7)	73.0 (62.0–86.5)
Baseline estimated dry weight (kg)	74.5 (62.7–88.0)	76.1 (64.0–90.5)	73.0 (61.8–86.0)
Baseline post-dialysis body mass index (kg/m^2)	26.8 (23.1–31.3)	27.3 (23.4–31.8)	26.3 (22.8–30.9)
Cardiovascular disease history (%)[1,2]	45	100	-
Coronary artery disease	23	51	-
Heart failure	17	39	-
Valvular heart disease	11	26	-
Angina pectoris	10	22	-
Atrial fibrillation	9	20	-
Myocardial infarction	9	19	-
Stroke	7	15	-
Transient ischaemic attack	4	10	-
Cardiac arrest	1	3	-
Thromboembolic events (%)[3]	17	21	14
Diabetes (%)	42	49	35
Cancer (%)	5	6	4
Smoking status			
Current smoker (%)	9	9	9
Former smoker (%)	21	26	17
Baseline post-dialysis blood pressure (mmHg)			
Systolic	134.0 (120.0–150.0)	134.0 (120.0–150.0)	134.0 (120.0–150.0)
Diastolic	74.0 (65.0–82.0)	71.0 (62.0–80.0)	76.0 (67.0–83.3)
Mean arterial pressure	93.7 (84.0–103.3)	92.6 (83.3–102.0)	95.3 (85.6–104.7)
Baseline laboratory values			
hsCRP (mg/L)	4.0 (1.5–10.4)	4.5 (1.7–12.2)	3.6 (1.4–9.3)
Albumin (g/dL)	3.90 (3.60–4.10)	3.90 (3.60–4.10)	3.90 (3.70–4.10)
Haemoglobin (g/dL)	10.40 (9.70–11.10)	10.40 (9.80–11.00)	10.45 (9.70–11.10)
<10g/dL (%)	32	31	32
10-11g/dL (%)	43	44	41
>11g/dL (%)	26	25	27
Haemoglobin A1c (%) (in patients with diabetes)	6.40 (5.40–7.70)	6.50 (5.60–7.80)	6.30 (5.30–7.50)
White blood cells (x 10^9/L)	6.30 (5.10–7.60)	6.40 (5.20–7.60)	6.20 (5.10–7.60)
Platelets (x 10^9/L)	194.0 (157.0–238.0)	190.0 (153.0–234.0)	198.0 (161.0–242.0)
Transferrin saturation (%)	33.0 (26.0–41.0)	32.0 (25.0–41.0)	33.0 (26.0–42.0)
Ferritin (µg/L)	595.0 (343.5–961.5)	627.5 (367.0–990.5)	578.0 (331.0–932.0)

Hepcidin (µg/L)	178.5 (110.9–257.5)	179.5 (111.3–259.3)	177.9 (110.9–256.1)
Total cholesterol (mg/dL)	152.5 (125.5–183.4)	148.6 (121.6–179.5)	154.4 (129.3–185.3)
Low-density lipoprotein cholesterol	81.1 (61.0–103.1)	79.9 (57.9–102.3)	83.0 (62.9–103.9)
High-density lipoprotein cholesterol	40.5 (32.8–52.1)	40.5 (32.8–50.2)	40.5 (32.8–52.1)
Medications (%)			
Diabetes medications	30	37	25
Insulin	23	28	19
ACE inhibitor or ARB	46	46	46
Beta Blocker	54	65	45
Statin	41	51	32
Aspirin	34	48	24
Vitamin K antagonist	5	9	2
Phosphate binders[1]	76	77	75
Iron-based	5	5	4
Calcium-based	48	47	49
Non-calcium and non-iron based	35	36	34
Vitamin D	58	61	55
Calcimimetics	18	20	16
Oral iron[4]	11	11	12
Intravenous iron	64	65	63
Standardised IV iron dose iron (mg/month)	194 (100–272)	190 (100–260)	200 (100–272)
Prior ESA use (%)	>99	>99	>99
Prior ESA type at randomisation (%)			
Darbepoetin alfa only	20	21	19
Epoetin only	68	66	69
Methoxy PEG-epoetin beta only	11	12	10
Multiple	1	1	2
Missing	<1	<1	<1
Standardised prior ESA dose (U/week)[5]	5751 (3155–9694)	5500 (3018–9166)	5886 (3371–10268)
Baseline ERI (U/kg/wk/g/L)[6]	0.74 (0.41–1.31)	0.68 (0.40–1.20)	0.78 (0.43–1.38)

Results are based on the in-stream database as of 20 April 2020. Until the time of database lock, data entered into the electronic case report form may be updated by investigator site staff. Therefore, final data may change with continued data updates.
Continuous variables are expressed as median (25th and 75th percentiles). All baseline laboratory tests were performed by central laboratory except for haemoglobin, which uses central laboratory values if available, or a point of care HemoCue value if the central

laboratory value is missing. If Kt/V urea values were not available, URR values were recorded. Haemoglobin A1C was only collected for patients with diabetes. Standardised IV iron doses are provided only for patients using IV iron at baseline.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ERI, erythropoietin resistance index; ESA, erythropoiesis stimulating agent; HD, haemodialysis; HDF/HF, haemodiafiltration or haemofiltration; hsCRP, high-sensitivity C-reactive protein; ITT, intent-to-treat; PD, peritoneal dialysis; URR, urea reduction ratio.
[1]Subjects may be counted in multiple rows
[2]CVD in ASCEND-D was defined as angina pectoris, myocardial infarction, stroke, coronary artery disease, transient ischaemic attack, heart failure, atrial fibrillation, cardiac arrest, and valvular heart disease.
[3]Thromboembolic events include pulmonary embolism, deep vein thrombosis, retinal vein occlusion, arteriovenous graft thrombosis, arteriovenous fistula thrombosis, and central venous catheter thrombosis.
[4]Includes ferric citrate
[5]See **Supplementary Table 6** for ESA dose conversion details.
[6]ERI is defined as the standardised prior ESA dose (U/week) divided by the screening estimated dry weight (kg), then divided by the haemoglobin (g/L) achieved at randomisation.

Table 6. Comparison of ASCEND-D Baseline Characteristics with Characteristics of Patients Enrolled in Large Cardiovascular Outcome Trials in a Dialysis Population

	ASCEND-D (N=2964)	$INNO_2VATE$ prevalent trial (N=3554) [16]	PIVOTAL (N=2141)[22, 23]
Design			
Population	Dialysis (>90 days) with anaemia of CKD	Dialysis (≥12 weeks) with anaemia of CKD	Haemodialysis (≤1 year) treated with ESA and ferritin <400 µg/l and TSAT <30%
Blinding	Open-label (sponsor-blind)	Open-label (sponsor-blind)	Open-label
Intervention	Daprodustat	Vadadustat	IV Iron
Control	Active-controlled (rhEPO)-HD, darbepoetin alfa -PD	Active-controlled (darbepoetin alfa)	Active controlled
Location	44% EMEA; 29% NA (predominantly USA); 14% LA; 13% APAC	61% USA; 11% Europe; 27% rest of regions	United Kingdom
Demographics			
Age, years	58	58	65
Women, %	43	44	35
BMI, kg/m²	26.8	28.6	28
Race, %			
White	67	63	79
Black	16	25	9
Asian	12	5	9
Other	6	5	3
History, %			
Cardiovascular disease	45	50	NR
Diabetes	42	45	44
Heart failure	17	NR	4

Hypertension	92	51	73
Myocardial infarction	9	NR	9
Stroke	7	NR	8
Blood pressure, mm Hg			
Systolic	134	143	144
Diastolic	74	76	73
Haemoglobin, g/dL	10.4	10.2	10.6
Concomitant medications, %			
ACEi/ARB	46	20 (ACEi), 23 (ARB)	27.8
Antiplatelet therapy	34 (aspirin)	37 (aspirin)	45.4
Phosphate binders	76	NR	38.4
Statin	41	42	59.7 (lipid-lowering)
ESA use, %	>99	100[1]	100
ESA dose (standardised to epoetin, Units per kg/week)	5751 (77 U/kg/week)[2]	114 U/kg/week	8000 (100 U/kg/week)[2]
IV iron (%)	64	16.2	NR

Continuous variables are expressed as medians (ASCEND-D & PIVOTAL) and means ($INNO_2VATE$). CVD definition varies by study [ASCEND-D: angina pectoris, myocardial infarction, stroke, coronary artery disease, transient ischaemic attack, heart failure, atrial fibrillation, cardiac arrest, and valvular heart disease; $INNO_2VATE$ prevalent trial: coronary artery disease, myocardial infarction, stroke and heart failure].

APAC, Asia Pacific; BMI, body mass index; CKD, chronic kidney disease; EMEA, Europe Middle East Africa; ESA, erythropoiesis stimulating agent; IV, intravenous; LA, Latin America; NA, North America; NR, Not Reported; PIVOTAL, the Proactive IV Iron Therapy in Hemodialysis Patients; rhEPO, recombinant human erythropoietin; TIA, transient ischaemic attack; TSAT, transferrin saturation.

[1]Assumption based on eligibility criteria.

[2]ESA dose standardised to epoetin Units per kg/week calculated using baseline weight

Table 7. Comparison of ASCEND-D Baseline Characteristics with Characteristics of Patients on Haemodialysis Registered on Global Databases

	ASCEND-D	DOPPS [26]	DOPPS Practice Monitor Feb 2020 [24]	USRDS [25]
Population	Dialysis (>90 days) with anaemia of CKD	Patients on HD with ESRD who survived ≥12 months after enrollment in DOPPs (2005-2015)	Patients on HD; DOPPS 7: ~35 facilities randomly selected utilising the Visonex EHR software (Green Bay, WI)[1]	Prevalent ESRD [2018 data]
Region/Countries	NA, EMEA, APAC, LA (see Supplementary Table 3 for country-level patient distribution)	Europe[2], Canada, USA	USA	USA
Demographics				
Age (years)	58	63.6	63	60
Women (%)	43	43	41	42
BMI (kg/m^2)	26.8	27.9	28.5	NR
Race (%)				
White	67	NR	NR	62
Black or African American	16	36 USA; NR non-USA	36	30
Asian	12	NR	NR	5
Other	6	NR	NR	3
Haemoglobin (g/dL)	10.4	11.3	10.7	HD: 10.7 PD: 10.9

ESA dose standardized to epoetin	5751 (median) (U/week)	NR	10271 (U/week)	9784 U/w epoetin alfa (HD) 145 ug/month darbepoetin (HD) 146 ug/month Mircera (HD) 9019 U/w epoetin alfa (PD) 144 ug/month darbepoetin (PD) 145 ug/month Mircera (PD)
Transferrin saturation, %	33	NR	29.5	HD: ≥20 in 82.0% PD: ≥20 in 86.1%
Ferritin, µg/L	595.0	NR	829.0	HD: >200 in 93.8% PD: >200 in 86.0%
Kt/V urea for HD patients	1.5	1.6	1.62	HD: ≥1.2 (96.9%) PD: Weekly ≥1.7 (94.7%)
Dialysis access type (%)	At randomisation			
Arteriovenous fistula	69	NR	65	66
Arteriovenous graft	9	NR	18	17
Central venous catheter	10	NR	17 (catheter, NS)	18 (catheter, NS)
Peritoneal catheter	11	NR	NR	NR
Other	1	NR	NR	NR
Missing	<1	NR	NR	NR

Continuous variables are expressed as medians (ASCEND-D) and means (DOPPS, DOPPS Practice Monitor, USRDS). APAC, Asia Pacific; BMI, body mass index; CKD, chronic kidney disease; EMEA, Europe Middle East Africa; ESA, erythropoiesis stimulating agent; ESRD, end-stage renal disease; HD, haemodialysis; LA, Latin America; NA, North America; NR, Not Reported; NS, not specified; PD, peritoneal dialysis.
[1]Selection from among each of the two largest dialysis organizations, and ~100 small and medium-chain, independent, and hospital-based facilities
[2]Belgium, France, Germany, Italy, Spain, Sweden, UK

FIGURE LEGENDS

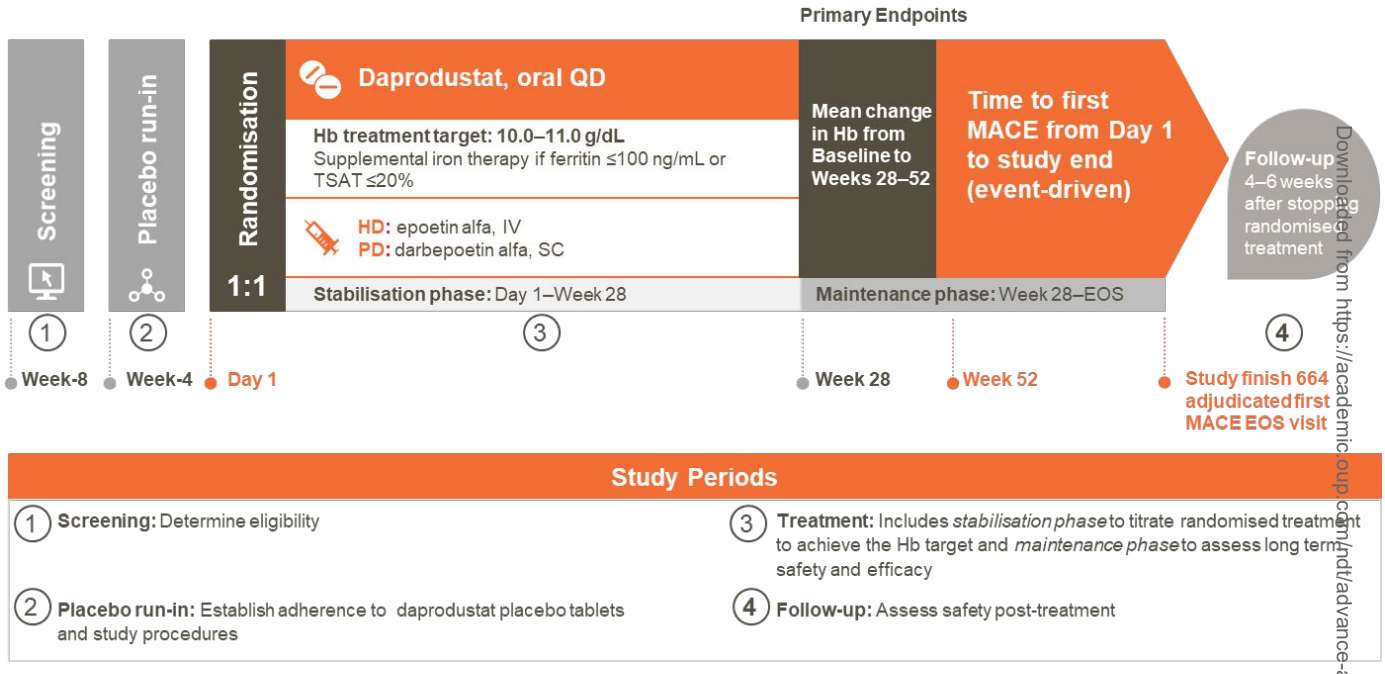
Figure 1. ASCEND-D study design

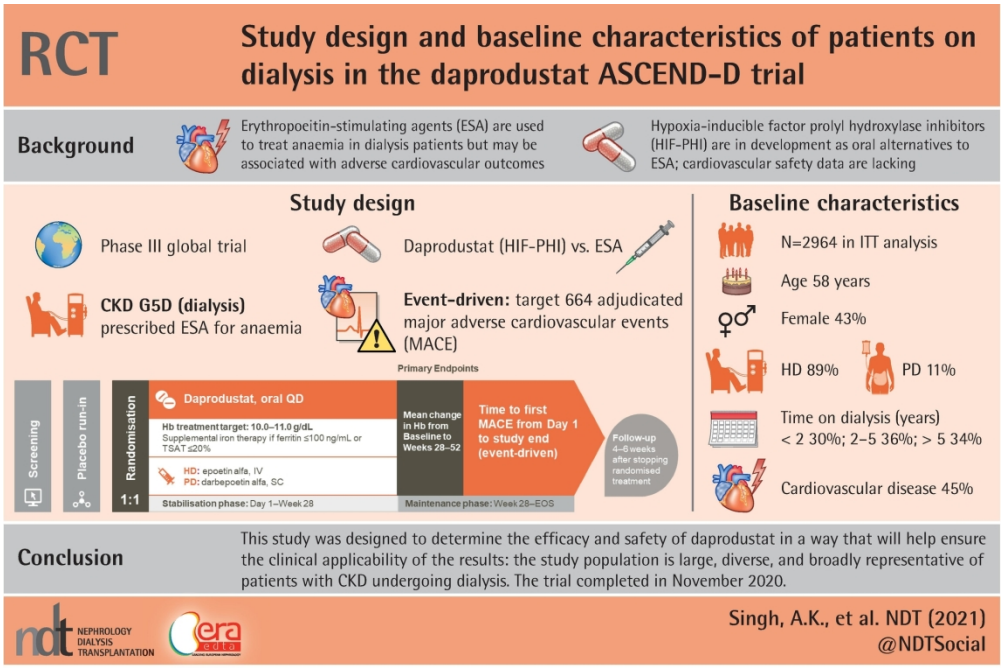
Serum and plasma samples are collected at baseline, Week 28, and Week 52 for future analysis of biomarkers of CV risk and iron metabolism.

CV, cardiovascular; EOS, end of study; Hb, haemoglobin; HD, haemodialysis; IV, intravenous; MACE, major adverse cardiovascular event; PD, peritoneal dialysis; QD, once daily; SC, subcutaneous; TSAT, transferrin saturation

FIGURE

FIGURE 1: ASCEND-D study design





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RCT

Study design and baseline characteristics of patients on dialysis in the daprodustat ASCEND-D trial

Background

Erythropoeitin-stimulating agents (ESA) are used to treat anaemia in dialysis patients but may be associated with adverse cardiovascular outcomes

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) are in development as oral alternatives to ESA; cardiovascular safety data are lacking

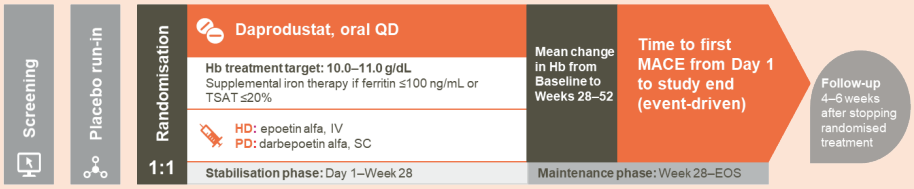
Study design

Phase III global trial

Daprodustat (HIF-PHI) vs. ESA

CKD G5D (dialysis) prescribed ESA for anaemia

Event-driven: target 664 adjudicated major adverse cardiovascular events (MACE)



Baseline characteristics

N=2964 in ITT analysis

Age 58 years

Female 43%

HD 89%

PD 11%

Time on dialysis (years)
< 2 30%; 2–5 36%; > 5 34%

Cardiovascular disease 45%

Conclusion

This study was designed to determine the efficacy and safety of daprodustat in a way that will help ensure the clinical applicability of the results: the study population is large, diverse, and broadly representative of patients with CKD undergoing dialysis. The trial completed in November 2020.

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